MOVING INTO THE FUTURE WITH NEW DIMENSIONS AND STRATEGIES:

A VISION FOR 2020 FOR WOMEN'S HEALTH RESEARCH

OFFICE OF RESEARCH ON WOMEN'S HEALTH
NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

VOLUME II
REGIONAL SCIENTIFIC REPORTS

Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research

Office of Research on Women's Health
National Institutes of Health

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REGIONAL SCIENTIFIC REPORTS

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ORWH also wishes to thank the cochairs of the scientific working and discussion groups, credited in this volume at the beginning of each individual regional scientific meeting report. In addition, the more than 1,500 individuals listed in the Appendices of this volume who participated in the public hearings and scientific workshops provided invaluable input to the strategic planning process.

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APPENDICES

Introduction

The Office of Research on Women's Health (ORWH) was established in September 1990 in response to congressional, scientific, and advocacy concerns that a lack of systemic and consistent inclusion of women in NIH-supported clinical research could result in clinical decisions being made about health care for women based on findings from studies of men—without evidence that they were applicable to women. The Office was further established in statute in the NIH Revitalization Act of 1993 (Public Law 103–43). Congress codified the Office's mission and included directives that expanded its leadership role in identifying and promoting research on women's health.

Since that time, the Office has been the focal point for guiding the national research effort on women's health issues and is responsible for ensuring that women's health research priorities are integrated into the wider NIH research agenda. The mission of ORWH is to:

1. advise the NIH Director on matters relating to research on women's health;
2. strengthen and enhance research related to diseases, disorders, and conditions that affect women;
3. ensure that research conducted and supported by NIH adequately addresses issues regarding women's health;
4. ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH;
5. develop opportunities for and support recruitment, retention, reentry, and advancement of women in biomedical careers; and
6. support research on women's health issues.

To advance a robust research agenda to guide women's health research at the NIH, ORWH previously initiated two intensive planning initiatives, one beginning in 1991 and a second one in 1997. ORWH called upon experts in the fields of basic and clinical sciences, practitioners interested in women's health, and representatives of professional and women's organizations to develop specific and workable recommendations to advance research activities on behalf of the diversity of women and define the research priorities for women's health research at the NIH. The first research agenda from 1991, *The Report of the National Institutes of Health: Opportunities for Research on Women's Health* redefined the parameters of women's health to encompass the life span going beyond the reproductive system and to better understand sex and gender differences between women and men in development, health, and disease. It also brought attention to the need to focus on populations of women that had been underrepresented in clinical research. The 1997 report, *Agenda for Research on Women's Health for the 21st Century*, expanded upon the initial scientific agenda for women's health research and emphasized the relevance of the full spectrum of research from basic to clinical research, epidemiological and population studies, translation into clinical applications and health outcomes, with continued emphasis on sex

and gender comparisons and the introduction of an emphasis on interdisciplinary research on women's health.

Science is dynamic and evolving at a remarkable pace with emerging knowledge from results of investigations and from new concepts of health and disease based on new technologies and approaches to research endeavors. Each decade has brought new discoveries, new understanding of the intricacies of molecular contributions to health and the workings of the totality of the human body, and new opportunities to leverage the knowledge from science to improve human health and, specifically, women's health. The first two reports ensured that women's health rose to prominence within the national psyche, as well as within the research environment. The next 10 years can bring new research advances with improved therapeutics based on sex differences with an expansion of the evidence based clinical application to women's health care. Achieving new dimensions and innovative strategies for research is an important element of the NIH women's health research agenda for the future.

Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research

Ten years after the last women's health research agenda was updated, the ORWH launched a series of five regional scientific workshops and public hearings to ensure that research on women's health continues to be on the cutting edge of science, based upon the most advanced techniques and methodologies. Four of the five regional scientific workshops were held during 2009, and the final was in 2010. The meetings were hosted by five universities:

1. Washington University, St. Louis, Missouri, March 4–6, 2009
2. University of California, San Francisco, May 27–29, 2009
3. Women and Infants Hospital/Brown University, Providence, Rhode Island, September 21–23, 2009
4. Northwestern University, Chicago, Illinois, October 21–23, 2009
5. Emory University, Atlanta, Georgia, February 16–17, 2010

The format of each of the regional scientific workshops was designed to promote an interactive discussion involving leading scientists from across the nation, women's health advocates, public policy experts, health care providers, and the general public. Individuals representing the full spectrum of academic institutions, professional associations, advocacy organizations, health care facilities interested in biomedical and behavioral research on women's health and sex/gender issues, or those wishing to present their personal opinions on these issues were encouraged to provide both written and public testimony at each of the regional meetings. In each of the meetings, the ORWH Director challenged conference attendees to think beyond traditional women's health issues in defining the women's health research agenda of the future. Participants were asked to give attention to new areas of scientific application, innovative technologies, and sex differences research in basic and laboratory investigations. Clinical questions for which documented answers are still not evident were to be considered in determining research priorities, recognizing the importance of new health care and research paradigms that will be facing the Nation in the years ahead.

A total of 37 scientific and career development working groups were cochaired by research scientists representing 44 academic institutions and 19 NIH Institutes, Centers, and the Office of the Director. Participants came from thirty-three states, and scientists from Great Britain and Australia also contributed to the discussions. Scientific panels and concurrent workshops addressed a wide range of topics, from the interplay of research and health care to specific areas of research, resulting in nearly 400 recommendations. The working group reports and recommendations are found in the companion Volume II to the ORWH Strategic Plan.

A key element of each of the regional meetings was the time devoted to receiving public testimony. From its earliest establishment, ORWH has actively welcomed input from advocacy organizations, health and disease interest groups, health care providers, and the general public. Over the years, public testimony has served as an important reality gauge to inform the research agenda-setting process. During the course of the five meetings, 141 organizations and individuals presented written and public testimony, always on the first day of the meeting. The testimonies from the meetings are found in Volume III of the ORWH Strategic Plan.

At the conclusion of the five regional workshops, the working group reports and recommendations were synthesized by ORWH staff and the resulting document (Volume I) was reviewed by three separate groups: (1) the Advisory Committee on Research for Women's Health (the non-Federal advisory committee to the Director of ORWH); (2) an outside group of experts in women's health research convened April 14, 2010 at the NIH; and (3) the Coordinating Committee on Research on Women's Health Research/NIH (composed of NIH Institute and Center directors or their designees). The final document, entitled *Moving Into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research*, represents the conclusion of an intensive 2-year national planning discussion. This new Strategic Plan for research and career development opportunities to guide efforts towards the year 2020 is being unveiled on September 27, 2010 as part of the 20th anniversary celebration of the establishment of the ORWH at the NIH.

Vivian W. Pinn, M.D.
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A Vision for 2020 for Women's Health Research: Moving into the Future with New Dimensions and Strategies
Washington University in St. Louis School of Medicine
St. Louis, Missouri
March 4–6, 2009

DAY 1—PUBLIC HEARING

Location: Eric P. Newman Education Center

12:00–2:00 p.m. — **Registration**

2:00–2:15 p.m. — **Welcome**

Scott Hultgren, Ph.D.
Helen L. Stoever Professor of Molecular Microbiology and Director, Center for Women's Infectious Disease Research, Washington University in St. Louis

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

2:15–3:30 p.m. — **OPENING PANEL: A Common Goal—Engaging the Public, Nonprofit Organizations, and Scientists in the Future of Research on Women's Health**

Susan Wood, Ph.D.
Associate Professor, The George Washington University School of Public Health

Valerie C. Montgomery Rice, M.D.
Sr. Vice President of Health Affairs and Dean, Meharry Medical College

Susan Scanlan
President, Women's Research and Education Institute

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Jeffrey F. Peipert, M.D., Ph.D.
Robert J. Terry Professor and Vice Chair of Clinical Research Department of Obstetrics and Gynecology

3:30–6:00 p.m. — **PUBLIC HEARING**

Interested individuals presented oral testimony to a panel of scientists, clinicians, and NIH representatives.

DAY 2—SCIENTIFIC WORKSHOPS

Location: Eric P. Newman Education Center

7:00–8:00 a.m. — **Registration**

8:00–8:15 a.m. — **Welcome and Opening Remarks**

Samuel L. Stanley, Jr., M.D.
Vice Chancellor for Research, Washington University in St. Louis

8:15–8:45 a.m. — **Realizing the Vision: Advancing Research on Women's Health in the 21st Century**

Vivian W. Pinn, M.D.

8:45–9:15 a.m. — **Keynote Address: Women's Health Research Must Be Part of the National Research Strategy**

Nancy H. Nielsen, M.D., Ph.D.
President, American Medical Association

9:30–10:15 a.m. — **PANEL: Unmet Medical Needs and the Future of Women's Health: Identifying Opportunities for Women's Health Research**

Moderator: Gail H. Cassell, Ph.D.
Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company

Third World Statistics in the USA: What Keeps the Health Commissioner Awake at Night

Judy Monroe, M.D.
Indiana State Health Commissioner

Research in Women's Health Viewed Through the Lens of Health Care Reform

Eve E. Slater, M.D.
Senior Vice President of Worldwide Policy, Pfizer, Inc.

Unmet Needs and Sex and Gender Differences Research

Phyllis Greenberger, M.S.W.
President and CEO, Society for Women's Health Research

10:15–10:30 a.m. — **BREAK**

10:30–11:00 a.m. — **PANEL: A Paradigm for Enhancing Interdisciplinary Science in Women's Health—Research on the Urogenital Tract**

Remarks by Griffin Rodgers, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

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11:00–11:30 a.m. — **Audience Questions and Discussion**

11:30–11:45 a.m. — **Working Group Charge**

Vivian W. Pinn, M.D.

11:45 a.m.–3:15 p.m. — **Lunch and Concurrent Working Groups: Drafting of Recommendations by Area**

- **Bladder and Pelvic Floor Disorders**
- **Brain and Psychiatric Disorders**
- **Chronic Pain Syndromes**
- **Eating Disorders**
- **Genetics and Microbial Communities (Metagenomics/ Microbiome)**
- **Infectious Diseases of the Urinary and Reproductive Tracts**
- **Obesity**
- **Women in Biomedical Careers**

3:15–3:30 p.m.	**BREAK**
3:30–5:30 p.m.	**PANEL: Narrowing the Focus—Applying Emerging Concepts in Science to Women's Health Research** **Moderator: Mary Woolley, M.A.** *President, Research!America* ***Microbes, Genomics, and Premature Labor and Delivery*** **David Relman, M.D.** *Professor of Medicine, Infectious Diseases, Microbiology, and Immunology, Stanford University* ***Biological Engineering Approaches for Women's Health*** **Pamela Kreeger, Ph.D.** *Assistant Professor of Biomedical Engineering, University of Wisconsin–Madison* ***The Human Microbiome Project: Exploring the Microbial Side of Ourselves*** **Jeffrey Gordon, M.D.** *Dr. Robert J. Glaser Distinguished University Professor, Director, Center for Genome Sciences, Washington University in St. Louis*
5:30–6:30 p.m.	**Audience Questions and Discussion**
6:30–8:00 p.m.	**Reception**

DAY 3—SCIENTIFIC WORKSHOPS

Location: Eric P. Newman Education Center

8:00–8:30 a.m.	**Welcome and Opening Remarks** **Vivian W. Pinn, M.D.**
8:30–9:00 a.m.	**Keynote Address: Retaining Women in Academic Medicine** **Phoebe S. Leboy, Ph.D.** *President, Association for Women in Science*

9:00–10:30 a.m.	Concurrent Working Groups: Finalizing of Reports
10:30–10:45 a.m.	BREAK
10:45 a.m.–12:15 p.m.	PANEL: Working Group Results, Audience Questions, and Feedback Moderator: Gail H. Cassell, Ph.D.
12:15–12:45 p.m.	Audience Questions and Discussion
12:45–1:00 p.m.	Closing Remarks Vivian W. Pinn, M.D.

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St. Louis, Missouri
March 4–6, 2009

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WOMEN IN BIOMEDICAL CAREERS

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INTRODUCTION

This report summarizes the first strategic planning meeting, held at the Washington University School of Medicine, St. Louis, Missouri, March 4–6, 2009. The agenda included public hearings, four panels, two keynote speakers, and a presentation in which the ORWH Director provided the charge to eight scientific breakout working groups. Public hearings with testimony were held the first day, and 39 representatives of advocacy and professional organizations, as well as clinicians and private citizens, provided verbal and written statements to a panel of scientists, clinicians, and NIH representatives. On the second and third days of the meeting, working groups addressed scientific challenges, gaps, and opportunities for women's health in breakout sessions on specific areas, which ranged from brain and psychiatric disorders to metagenomics and microbial communities. The recommendations of the working groups, summarized in individual reports, constitute the major portion of this document. Highlights of the panels and presentations are summarized briefly here.

The panels were designed to challenge the audience to think "outside the box" of their discipline, scientific research, clinical specialty, or advocacy interest. The themes ranged from public health, health policy, and health services to models of interdisciplinary research and a vision for the potential application of leading-edge science and technology to women's health. Recurrent themes were the importance of behavioral and societal factors in health and disease and the need to translate science from the research setting to the community setting.

SUMMARIES OF PLENARY PRESENTATIONS

OPENING PANEL: A COMMON GOAL—ENGAGING THE PUBLIC, NONPROFIT ORGANIZATIONS, AND SCIENTISTS IN THE FUTURE OF RESEARCH ON WOMEN'S HEALTH

The theme of the opening session emphasized common ground among the diverse participants in the audience. Speakers addressed the interplay among biomedical science, public health, and public policy. Panelists included:

Susan Wood, Ph.D.
Associate Professor, The George Washington University, School of Public Health and Health Services

Dr. Wood discussed the many policy implications and challenges facing NIH as the research strategy in women's health is developed. The challenges include bringing research from bench to bedside and moving clinically relevant findings to the appropriate level of widespread use. Policy mechanisms for promoting interdisciplinary research are also critical, and it is important to evaluate whether these mechanisms have been used to promote women's health research and have led to increased interdisciplinary research in women's health in the past and envision their impact over the next decade. Likewise, effective communication of NIH research activities and findings on women's health both to the public and to policymakers is critical. The public understanding of both the promise and limitations of NIH-funded research requires proactive outreach and partnerships for success. Reaching women facing health concerns in their daily lives who do not actively seek NIH information requires expanding existing programs and developing new and innovative approaches and partnerships. Finally, as policymakers at the State

and national levels begin to implement health care reform, providing them with relevant data and information stemming from NIH research on women's health will give them the tools they can use for decisions in establishing health policy.

Valerie Montgomery Rice, M.D.
Senior Vice President for Health Affairs, Dean School of Medicine, Meharry Medical College
Dr. Montgomery Rice addressed the special challenges facing women of color in their access to the health care system, health status, and health outcomes. She demonstrated the urgency of health disparity issues by sharing the changing demographics of the United States, which project that women will make up 51 percent of the population in 2050, with population increases of 188 percent in Latinos, 213 percent in Asian-Americans, 71 percent in African Americans, and only 7 percent in Caucasians. Dr. Montgomery Rice presented compelling data related to diseases that impact health disparities, racial differences in access to health care innovations and resource allocation, and the underrepresentation of minorities in health professions. She cautioned that the exclusion of women from clinical studies, or inclusion of women in numbers too small to detect gender differences or to support subgroup analyses, may result in a "male model" of medical treatment that is inappropriate for women. Dr. Montgomery Rice proposed three approaches to eliminate disparities in women's health, including 1) channeling funding and resources to research diseases that disproportionately impact women of color; 2) directing funding to study the social determinants that contribute to health disparities; and 3) increasing the number of women investigators, particularly women of color. She emphasized that, beyond improving access to health care, the benefits of scientific advances and innovations must be equally diffused into all communities. Further health outcomes and the achievement of milestones should be measured indications of success in eliminating health disparities.

Susan Scanlan
President, Women's Research and Education Institute
Ms. Scanlan provided a historical retrospective, beginning in 1977, of the role of the Women's Health Caucus in influencing policy decisions. She aptly characterized the challenges facing legislators in her opening comment that in "Washington, DC, where the decisions get made, you're either at the table or on the menu!" Aided by external advocates and informed by health statistics, dedicated and determined women in Congress—Senators Barbara Mikulski and Olympia Snowe and Congresswomen Lindy Boggs, Yvonne Burke, Martha Keys, and Gladys Noon Spellman, to name a few—awakened a sense of urgency in their congressional colleagues about women's health issues. With a series of historical anecdotes, Ms. Scanlan demonstrated the effectiveness of the Women's Health Caucus in drawing attention to inequities, such as the comparative lack of funding for women's health issues and diseases and the disjuncture between the public health impact of diseases like breast cancer and the NIH investment in researching such diseases. From 1977 onward, the Caucus succeeded in bringing about major changes in funding and legislation that benefited women's health. The Breast and Cervical Cancer Mortality Prevention Act and the Mammography Quality Standards Act are examples of how biomedical science, joined with public health data, can be translated into public policy of far-reaching impact.

PERSPECTIVES FROM WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Kenneth Polonsky, M.D.
Chair, Department of Medicine

Dr. Polonsky provided a perspective on women's health research using the incidence and impact of bone health as an example. One focus of the Washington University Department of Medicine is understanding basic bone biology and developing novel approaches to preventing and treating metabolic bone disease—an area of research addressed by only a few departments of medicine nationally. The research is informed by strong interactions with the departments of orthopedics and pathology. Dr. Polonsky discussed some of the most exciting basic molecular findings in osteoporosis, including some promising research on the inhibition of notch signaling to stimulate bone formation with the potential of reversing osteoporosis. Dr. Polonsky also outlined the research philosophy that characterizes all research conducted by his department and ensures that women's health research continues to flourish. These strategies involved choosing research that is relevant to human health; selecting diseases that are common and have a large impact—or that are relatively rare, but important scientifically; emphasizing the underlying basic science; facilitating the translation of basic findings to applications at the bedside; and promoting training and career development.

Alan Schwartz, M.D., Ph.D.
Chair, Department of Pediatrics

Dr. Schwartz noted that the 750,000 U.S. teens who become pregnant each year are more likely to give birth prematurely and their babies are at greater risk for health problems, long-term disabilities, and death. The consequences can extend to later life, according to the Barker Hypothesis, which holds that reduced fetal growth can increase the risk of developing diseases such as cardiovascular disease and type 2 diabetes in adulthood.

Victoria Fraser, M.D.
Co-Director, Infectious Disease Division, Department of Medicine

Dr. Fraser charted the increasing number of women in biomedical research, but noted that it will require a massive effort to achieve equality. Among the challenges are the disproportionate attrition of women, who leave at double to triple the rate of men. It is important to find out why women leave research and what can be done to keep them. Among her suggestions: have dual PIs for research, use team-based science, develop reentry programs for women who have taken a career break, and develop mentoring programs.

Jeffrey F. Peipert, M.D., Ph.D.
Robert J. Terry Professor and Vice Chair of Clinical Research, Department of Obstetrics and Gynecology

Dr. Peipert discussed the use of the dual contraceptive method as a way to prevent unplanned pregnancy and sexually transmitted diseases (STDs). This requires pairing a long-acting, reversible contraception (such as an IUD or subdermal implant), which effectively prevents pregnancy, with a barrier method (a condom), which effectively prevents STDs. Dr. Peipert also described his ongoing research, the Contraceptive Choice Project, which will provide no-cost, long-acting contraceptives to 10,000 women for 3 years. Among the aims: to determine whether removing

the financial barrier to obtaining contraceptives could increase their use, decrease teen pregnancy, and reduce repeated abortions. Eighteen months into the project they have found significantly increased use of the contraceptives.

KEYNOTE ADDRESS: WOMEN'S HEALTH RESEARCH MUST BE PART OF THE NATIONAL RESEARCH STRATEGY

Nancy Nielsen, M.D., Ph.D.

President, American Medical Association (AMA)

Dr. Nielsen, a member of the ORWH Advisory Committee on Research on Women's Health, addressed the St. Louis meeting participants and attendees by video because her in-person attendance at the White House at a Health Care Summit convened by President Obama prevented her from attending the St. Louis meeting. In her presentation she identified several areas that needed to be a part of the thinking and the discussion during the St. Louis meeting. For example, when identifying the gaps in basic and biomedical research—the traditional purview of NIH—meeting attendees were urged also to consider other knowledge gaps. Dr. Nielsen noted that even effective dissemination of health information does not guarantee that desired behavior change will occur. She expanded on two examples—obesity and heart disease in women. Obesity remains a major epidemic and a major contributing factor to multiple conditions such as diabetes, coronary heart disease and cancers despite widely disseminated information of its risk and ways to reduce weight through diet and exercise. Clearly, behavior change will require new strategies. With heart disease, sometimes clinicians do not behave as they should when women present with atypical symptoms. This represents a gap in care. There are other gaps that need attention—for example, violence against women. This is usually viewed as a societal problem, yet it has significant negative impacts on the health of women, children and families. Research into its causes and strategies for prevention should be included in a comprehensive national research agenda on women's health. Finally, Dr. Nielsen emphasized that the AMA has been in the forefront of advocating for increased funding for research on women's health, as well as urging medical and scientific journals to publish research on women's health issues and insisting that research data be analyzed by sex/gender differences.

PANEL: UNMET MEDICAL NEEDS AND THE FUTURE OF WOMEN'S HEALTH: IDENTIFYING OPPORTUNITIES FOR WOMEN'S HEALTH RESEARCH

A second panel was moderated by Gail H. Cassell, Ph.D., Vice-President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases. In her opening remarks, Dr. Cassell noted that the St. Louis meeting was the beginning of another round of strategic planning that would further women's health nationally and globally, and that women's health was an important barometer of the health of families and communities. Science has a key role in this enterprise, as does the continuing work of public health officials and women's health advocates. Panelists included the following:

Judy Monroe, M.D.

Indiana State Health Commissioner

Dr. Monroe highlighted public health problems such as infant mortality and preterm births that remain at unacceptably high levels in some parts of the United States and among certain

populations. In two counties in Indiana, for example, infant mortality among Black infants is 30 per 1,000 live births, a rate that is comparable to rates in some developing countries. Smoking, obesity, and sexually transmitted diseases among women are also greater than national norms in some U.S. regions. Disparities will not be resolved until public health officials and researchers "drill down" to the local level in databases so they can identify where health indicators fall short of optimal norms. Public health practitioners should work more closely with basic science and clinical researchers to find ways to close the gap between their knowledge of science and population-level health outcomes that continue to fall short of what the United States is capable of achieving. Translation of research is needed across all levels and all communities, with information technology serving as an important conduit.

Eve E. Slater, M.D.
Senior Vice President of Worldwide Policy, Pfizer, Inc.
Viewing American Recovery and Reinvestment Act funds from the perspective of women's health, Dr. Slater said researchers should assess gender, racial, and ethnic differences as they pertain to comparative effectiveness. With respect to investment in health information technology, she recommended that tools to assess quality and outcomes be incorporated in all systems. An important health problem is noncompliance in taking medication; Dr. Slater advocated more extensive use of health information technology, for example, to remind patients to get prescription refills or to make a doctor's appointment.

Phyllis Greenberger, M.S.W.
President and CEO, Society for Women's Health Research
Ms. Greenberger provided a retrospective presentation that looked at how 20 years ago, advocacy, informed by health statistics, moved women's health research forward at the NIH. She cited the 2001 IOM report *Exploring the Biological Contributions to Human Health: Does Sex Matter?* as pivotal in emphasizing the need to carefully evaluate sex-based differences in medical research and incorporate these differences into clinical practice. Ms. Greenberger noted that despite recognized differences, women at risk continue to face uneven care or are not referred for diagnostic testing that would be standard for men. She concluded her presentation by presenting six issues that need to be addressed to change the face of sex differences research and to improve health care for all women: (1) physicians need to be trained and educated in medical school, residencies and in continuing medical education about sex difference in order to communicate the information effectively to their patients; (2) physicians need to be alert to possible "physician bias" in diagnosis and treatment in favor of men; (3) women need to be informed and empower themselves to ask for sex-specific information when consulting physicians or dealing with the health care system; (4) sex should be included as a variable in all basic and clinical research design; the analysis and reporting of results by sex, age, race and ethnicity must be a fundamental requirement; (5) there is a need for a strong patient-centered comparative clinical effectiveness research emphasis that will add value to understanding biologic and physiologic differences that affect disease prevention, diagnosis and treatment; and (6) research and innovation into new diagnostics and imaging tools is critical to our health care system's ability to address new and emerging diseases and illnesses.

PANEL: A PARADIGM FOR ENHANCING INTERDISCIPLINARY SCIENCE IN WOMEN'S HEALTH—RESEARCH ON THE UROGENITAL TRACT

Interdisciplinary research is a model paradigm for achieving progress toward understanding the interplay of biomedical and biopsychosocial factors that influence women's health. Consequently, a third panel highlighted two ORWH-funded interdisciplinary research centers focused on women's urogenital health. Panelists included the following:

Griffin Rodgers, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Rodgers opened this session by asserting that interdisciplinary approaches to research on the urogenital tract can serve as a model for future research in women's health, and he noted the special features of this research—powerful interdisciplinary and multidisciplinary approaches, translational research, and prevention-oriented research tailored to patient needs. To help set the stage for the presentations by Drs. Hultgren and Brown, Dr. Griffin provided some thoughts on past successes and future opportunities for research in women's health, making the following five points. (1) A major element in the success of women's health research at NIH has been the leadership role of ORWH and its "vigorous" director, Dr. Vivian Pinn. The office has brought women's health research to the forefront of science by identifying, articulating, and providing funding for critical research priorities. ORWH has been strategic in designing collaborations across NIH, and NIDDK has been fortunate to be one of those research partners. (2) The Women's Health Initiative (WHI) provided critical information, based on research, that women receiving estrogen plus progestin to treat menopausal symptoms had increased risk for cardiovascular disease. Beyond these specific findings, WHI cast an intense spotlight on women's health research and the need for additional studies in the field. (3) As a result of the NIH policy requiring the inclusion of women in clinical trials and analysis for sex and gender differences, women's health research has become a central element of NIH research efforts. (4) Women's health research has benefited from a range of new technologies that permit more rapid and precise scientific investigation. Of particular note are the new approaches of functional genomics, proteomics, and metabolomics. (5) The emphasis on interdisciplinary and multidisciplinary research has led to a veritable explosion in scientific knowledge and new technologies. More scientists are now working together toward common goals, and women's urologic health is an excellent example of this emphasis upon team science.

Scott Hultgren, Ph.D.
Helen L. Stoever Professor of Molecular Microbiology and Director, Center for Women's Infectious Disease Research, Washington University in St. Louis

Dr. Hultgren, a member of the ORWH Advisory Committee on Research on Women's Health, described the multiple approaches and disciplines represented in his laboratory and among his collaborators in his ORWH-sponsored Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health to study urinary tract infection (UTI) in women at all levels from the clinical to the molecular. The work of Dr. Hultgren and his colleagues is changing the way UTIs are evaluated and spawning the development of novel vaccines and antimicrobial therapeutics to diagnose, treat and/or prevent UTIs and their sequelae. Using his interdisciplinary team as an example, Dr. Hultgren emphasized the great strides that are possible by

examining conditions from many angles simultaneously. He noted that discovery of disease etiology and novel therapeutics are facilitated by a combined approach utilizing clinical samples directly from women, animal models of disease, and basic molecular science. Dr. Hultgren ended by applauding the ORWH for its pivotal role in championing this interdisciplinary and applied scientific approach at the NIH through its SCOR, Advancing Novel Science in Women's Health Research (ANSWHR) and Building Interdisciplinary Research Careers in Women's Health (BIRCWH) programs.

Jeanette Brown, M.D.
Professor, Obstetrics, Gynecology, and Reproductive Sciences, Epidemiology and Biostatistics, and Urology; Director, Women's Continence Center; University of California, San Francisco
Dr. Brown spoke about the SCOR program at UCSF, which focuses on lower urinary tract function in women. The SCOR model promotes collaboration between basic science and clinical researchers, encouraging more rapid translation of research findings to patient care. Obesity and diabetes mellitus are risk factors for urinary incontinence (UI), and the work to study the molecular mechanisms of the condition continues, Dr. Brown said. Losing weight and preventing diabetes can reduce episodes of incontinence. The public health implications are that women may be motivated to lose weight, control diabetes, or to control hyperglycemia as a way to alleviate incontinence.

PANEL: NARROWING THE FOCUS—APPLYING EMERGING CONCEPTS IN SCIENCE TO WOMEN'S HEALTH RESEARCH

A fourth panel highlighted ways in which fundamental science advances and cutting-edge scientific technologies may be used to benefit women's health research. Panelists included the following:

Mary Woolley, M.A.
President, Research!America
Ms. Woolley moderated the panel. Her opening comments reminded the scientists in the audience that no matter how technical or esoteric their research, they must effectively communicate to the public how their research benefits public health. Research saves lives, provides better quality of life, can make health care less costly, and can foster economic growth. Helping the public and legislators see these benefits is critical to building support for biomedical research.

David Relman, M.D.
Professor of Medicine, Infectious Diseases, Microbiology, and Immunology, Stanford University
Dr. Relman discussed his research showing that previously unrecognized intra-amniotic infections caused by cultivation-resistant microbes play a role in preterm births. Molecular methods can detect, characterize, and quantify microbes independently of traditional culture techniques. However, molecular studies on a scale needed to define the diversity and abundance of microbes invading the amniotic fluid were not possible until genomics revolutionized microbiology. The evolving field of bacterial typing and genomic technologies will enable comparative analysis of multiple genomes and the metagenomes of complex microbial environments, and help address problems such as the microbial contribution to risk for preterm birth.

Pamela Kreeger, Ph.D.
Assistant Professor of Biomedical Engineering, University of Wisconsin–Madison
Dr. Kreeger discussed the potential contributions of biological engineering to biomedical research on women's health. Biological engineering includes tissue engineering; biomechanics; and the "omics" (e.g., genomics, proteomics, metabolomics) used to identify and characterize biomarkers for disease. Examples of potential applications to women's health include the development of neuroengineering devices to monitor pain, biomechanical approaches to the study of male-female differences, bioimaging tools to better image breast and bone, and systems engineering to create models of estrogen crosstalk with signaling pathways. She also noted an impediment in narrowing the focus of biomedical advances to problems in women's health—there are very few women engineers, particularly in academic settings.

Jeffrey Gordon, M.D.
Dr. Robert J. Glaser Distinguished University Professor and Director, Center for Genome Sciences; Washington University in St. Louis
Dr. Gordon discussed advances in metagenomics as applied to the study of the microbial composition of the human body. Recently, scientists have come to appreciate that humans are a composite of microbial and human cells—a "supraorganism." In adults, it is estimated that microbial cell populations outnumber human cells by nearly 10 times. The genetic landscape of a human is the sum total of genes in the human genome and the genomes of the microbial partners that inhabit our bodies (the microbiome). Human metabolic features are an amalgam of human and microbial traits. To understand fully human genetic and physiologic diversity, the factors influencing health and illness and the structure and functions of human microbiota and the microbiome need to be characterized.

KEYNOTE ADDRESS: RETAINING WOMEN IN ACADEMIC MEDICINE

Phoebe Leboy, Ph.D.
President, Association for Women in Science
Dr. Leboy gave the keynote address on the challenges of and potential solutions for retaining women in academic medicine. Dr. Leboy informed the audience that despite earning over 40 percent of the M.D. and Ph.D. degrees in the biomedical sciences in the last 15 to 20 years, women are seriously underrepresented among medical and biomedical faculty. She presented striking findings regarding the predominantly male associate-professor status across clinical and tenure-track positions, as well as the disproportionately low application rates of women for tenure-track faculty positions in basic science departments. Dr. Leboy noted that the relative absence of women among medical school faculty is reflected in NIH grant data, with women receiving more NIH-mentored scientist (K) awards than research (R) awards. However, she pointed out that this finding appears to be a result of fewer applications submitted by women rather than lower success rates. Dr. Leboy outlined several possible factors that contribute to the poor retention of women clinician-scientists and biomedical researchers in academic medicine. These included a culture, which is extremely competitive and focused on very high productivity, demanding 24/7 professional effort, with an increasing emphasis on quantity rather than quality of research. She emphasized the link between large numbers of high-quality trainees and increased publication rates and suggested that lower professional prestige is a key factor leading to lower research productivity among women scientists. Dr.

Leboy recommended a three-pronged approach to tackle these issues: 1) acknowledge that existing policies and practices disadvantage women in academic biomedical careers, 2) initiate efforts to change those practices that are particularly unfriendly to women, and 3) provide targeted grant funding for those institutions committed to transforming both their climate and their culture.

CHARGE TO THE WORKING GROUPS

Prior to breaking out into their science working groups, participants were given their charge by Dr. Pinn. NIH women's health research priorities, she noted, must be comprehensive and interdisciplinary. They should include the full spectrum of research, from molecular and genetic studies and translational research to prevention, behavioral, clinical, and outcomes research. A comprehensive National Research Agenda should include the following multiple elements:

- The identification of continuing gaps and emerging science about women's health and sex/gender factors
- The application of new technologies to women's health science
- A program of research that moves from basic science to clinical translation and ranges from molecular to societal factors
- The translation of advocacy concerns to science-based initiatives
- The advancement and sustainability of the careers of women in science and engineering

The working groups were charged with developing recommendations in these areas, which would move women's health research and career development forward, and which also anticipated future cutting-edge women's health research. Reports of the working groups follow.

SCIENTIFIC WORKING AND DISCUSSION GROUPS

BLADDER AND PELVIC FLOOR DISORDERS

Cochairs:

Jeanette Brown, M.D.
University of California, San Francisco

Kimberly Kenton, M.D., M.S.
Loyola University Medical Center

NIH Cochairs:

Chris Mullins, Ph.D.
National Institute of Diabetes and Digestive Kidney Diseases (NIDDK)

Estella Parrott, M.D., M.P.H.
Eunice Kennedy Shriver *National Institute of Child Health and Human Development*

Science Writers:

Ashley Nenninger, Ph.D.
Washington University in St. Louis

Lorry Blath
St. Louis Breast Cancer Coalition

Introduction

The three primary pelvic floor disorders (PFDs) are urinary incontinence (UI), pelvic organ prolapse (POP), and fecal incontinence. These conditions are common among women, with nearly one quarter of all women reporting one or more PFD according to a recent prevalence study.[1] This prevalence results in a significant national burden in the form of health care costs, lost productivity, and decreased quality of life. Despite this prevalence, relatively few studies are conducted on PFDs. Although some PFD risk factors are well described, such as increased age, parity, and weight, a substantial lack of knowledge or progress remains for many key issues, including the following:

- Comparative effectiveness trials of surgical procedures and therapies, including types and methods of procedures, materials used, and the timing of repair
- Development of new therapies, including regenerative therapy
- Elucidation of the biological mechanisms that lead to dysfunction
- Identification of additional risk factors and biological markers to improve diagnosis, prevention, and therapy
- Development and efficacy of prevention strategies
- Dissemination of information to clinicians and the community to increase awareness and to create a common language

The discussions began with brief oral presentations based on prepared statements from experts in the fields of urogynecology, urology, translational/basic science, and primary care. Each speaker highlighted areas of need, with the goal of advancing the understanding and treatment

of PFD. Presentations were followed by questions, comments, and discussion from working group participants. The resulting recommendations fall into four areas of research: basic science, T1 translational research, clinical studies, and T2 translational research.

Summary of the Discussion

Group consensus was that numerous reliable epidemiologic studies consistently report both high prevalence and symptom bother from PFDs, and that future efforts should be directed away from epidemiologic studies and toward identifying risks, treatments, and prevention strategies for PFDs. This was addressed in a September 2008 report in the Journal of the American Medical Association about the prevalence of symptomatic pelvic floor disorders in U.S. women. In this report, PFD prevalence was found to be substantial, with at least one PFD being reported by nearly 24 percent of all women and nearly 50 percent of women 80 years or older, using conservative estimates. Prevalence was found to increase with age, number of children a woman has delivered, and weight.[1] Given the aging population and the probable underestimates of current prevalence due to conservative study design, considerable effort is needed to address the many other knowledge gaps about PFD to better care for these patients.

Biological Mechanisms of PFDs

Although the risk factors for PFDs are known, the biological mechanisms that result in PFDs are less clear. Certain PFDs are associated with maternal changes during pregnancy and delivery. A better understanding of the biological mechanisms associated with these changes may lead to preventive or reparative therapies that promote or accelerate pelvic floor healing to prevent or minimize later development of PFDs.

One potential biological mechanism underlying PFDs is neuromuscular dysfunction. Neuromuscular changes associated with secondary damage to pelvic floor muscles were described in women with UI and POP over two decades ago; these changes are believed to be major contributors to the etiology and pathogenesis of UI and POP. However, few clinician-investigators have explored the impact of neuromuscular dysfunction on disease progression or on symptomatic outcomes after surgery. It is quite plausible that the degree of neuromuscular injury predicts or is associated with development of pelvic floor symptoms with aging or incomplete symptom resolution after reconstructive surgery. Recent advances in neuroregenerative neuroscience, such as application of electrical stimulation, gonadal steroids, or nerve growth factors, could be useful as adjunct preventive or perioperative interventions aimed at symptom improvement. Future studies should not only quantify neuromuscular differences in parous and nulliparous women with and without pelvic floor symptoms across ages, but should identify neural targets at which to direct concomitant therapies. This may have important implications for preventing pelvic floor symptoms with aging, maximizing surgical outcomes, and preventing recurrences.

The following overall research strategies for this area were identified during the discussion.

- Conduct translational and basic research to identify the basic biological processes by which risk factors lead to development of PFDs.
- Conduct translational and basic research to supplement or boost the processes of healing after delivery followed by clinical testing of these treatments. For example, can an

easily administered treatment with nominal side effects be developed for administration to women identified diagnostically to be at greatest risk?

- Conduct translational and basic research to develop neuroregenerative techniques (e.g., electrical stimulation or nerve growth factors) that could be used instead of or in addition to conventional treatments and reconstructive surgery.
- Based on knowledge of the biological processes, conduct translational and basic research to develop a diagnostic test for identifying women at greatest risk for PFD, followed by clinical testing of this test in longitudinal clinical studies as a predictor of PFD and as a way to track a woman's response to treatment.

Needs in Clinical Care

Significant gaps remain in the understanding of numerous aspects of clinical care for patients with PFDs, such as comparative effectiveness of different PFD treatments, factors that predict adherence and response to treatment, an understanding of "normal" pelvic floor function, and standardization of care across clinical specialties.

In particular, improvements are needed in the efficacy and safety of surgical treatments and surgical devices. Reconstructive pelvic surgery is common, with one in nine women undergoing surgery for POP or UI in her lifetime, many women reporting new or persistent symptoms, and 30 percent requiring additional surgery.[2] Similarly, regardless of the procedure, less than 80 percent of stress incontinence surgeries have positive outcomes.[3] Research on surgical treatment efficacy is still lacking, although both the UTI Network and PFD Network are attempting to fill these gaps. Also, there has been a significant increase in new medical devices cleared by the U.S. Food and Drug Administration (FDA) and commonly used for POP and UI, despite minimal safety or efficacy data. Strategies that enable clinical testing of promising devices in a timely fashion are critical to ensure both patient safety and access to new, effective treatments supported by data. Furthermore, the development of better data and resource sharing may allow more timely insight into complications of new medical devices. Collaboration between the UTI and PFD Networks, thought leaders, trial design experts, industrial collaborators, and various Federal agencies can help to standardize treatment assessments of new and promising medical, minimally invasive, and surgical treatments.

The following additional research strategies needed in this area were identified during the discussion.

- Compare effectiveness trials to evaluate UI and POP treatments, including design methods to further our understanding of disease mechanism and predict treatment response.
- Determine the optimal timing and method for initial treatment of uterovaginal prolapse, with or without concomitant stress urinary incontinence.
- Assess the indications for hysterectomy (total or subtotal) and for augmenting surgical materials at the time of surgical treatment of uterovaginal prolapse.
- Advance our understanding of urethral function in women with all types of UI: innovative methods should be incorporated to quantify urethral function (e.g., neurophysiologic

testing and imaging) to enhance the understanding of UI pathophysiology and to predict success.

- Improve the POP–Q system so that the condition of prolapse can be better described, and establish a baseline of "normal" pelvic anatomy/function across groups.
- Increase precision in patient-reported outcomes, which may help to detect small, but significant, differences between interventions.
- Improve patient-physician communication by developing a common language regarding PFD to avoid inconsistencies between surgical expectations and goals.
- Standardize care across geographic and specialty variation for women with PFD.
- Develop more sensitive and specific tests to quantify disease severity, follow disease progression, and predict treatment outcomes.
- Identify factors that determine whether women adhere to, and benefit from, pharmacologic and behavioral therapies for incontinence, to guide clinicians in choosing the optimal strategy for symptom management.

Risk Factors and Prevention

The current understanding of risk factors (including potentially modifiable risk factors) that contribute to the development, progression, and/or recurrence of PFD is incomplete. No primary or secondary preventive strategies for PFD have been proven. Research is needed to determine whether risk factor modification may prevent or delay disease development, decrease the severity of these conditions, or improve treatment outcomes. Identifying risk factors that may exacerbate these conditions after the primary occurrence (i.e., risk factors of recurrence) is also important, and may help improve the specificity of treatments and decrease the number of women requiring multiple procedures.

Concomitant Diseases

Other important factors to consider are comorbidities that may influence the development and severity of PFD, such as obesity, diabetes, and depression, and whether clinical interventions directed at improving these modifiable risk factors can also improve women's urinary tract and pelvic floor symptoms. This goal could be achieved through clinical trials or through ancillary studies in which urinary and pelvic floor symptom assessment measures are incorporated into ongoing studies of clinical interventions to address these comorbid problems.

Biological disease mechanisms of PFD may differ due to these comorbidities. For instance, whereas it is known that incontinence is more common in women with diabetes, mechanisms by which type 2 diabetes may contribute to its development or severity are not well understood. A likely etiology for incontinence is microvascular damage, similar to the disease process involved in development of retinopathy, nephropathy, and peripheral neuropathy. Also, clinical outcomes of common treatments for lower urinary tract dysfunction in women with prediabetes and diabetes have not been critically examined, and randomized controlled trials are needed to assess the efficacy and safety of conservative, pharmacologic, and surgical treatments in the

diabetic population as well as the nondiabetic population because outcomes may vary across these groups.

Incontinence might also be used as a diagnostic marker for diabetes. Recent findings of a similarly high prevalence of incontinence among women with prediabetes and those with diabetes suggests that incontinence may be an earlier and more common consequence of hyperglycemia than other microvascular complications. As the population ages, diabetes and lower urinary tract dysfunction will markedly increase in prevalence. Physicians should be alert for lower urinary tract dysfunction because it is often unrecognized and therefore undertreated among women with diabetes and prediabetes.

Finally, PFD symptoms may be a barrier to treatment of potentially life-threatening conditions that are well recognized, such as heart disease and obesity. For example, a woman with urge incontinence may be less likely to comply with diuretic therapy for underlying heart disease. An obese patient may avoid exercise because of stress incontinence or prolapse. Without advanced understanding of the consequences and optimal treatment strategies for PFD, it is possible that other important areas of women's health will advance more slowly.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Comparative effectiveness trials of surgical and adjuvant treatments to determine optimal methods, materials/devices, indications, timing, and combinations of treatment to improve patient outcome.

Recommendation 2: T1 translational research to develop methods, including the application of stem cells, cytokines, gonadal steroids, and other neurotrophic factors, to promote regeneration and repair of damaged nerves, muscles, and connective tissue after pelvic floor injury.

Recommendation 3: Clinical research to identify modifiable risk factors; characterize "normal" pelvic floor function and anatomy across age, parity, weight, race/ethnicity; and identify factors that predict adherence and response to given treatments.

Recommendation 4: Basic science aimed at understanding the biologic processes and pathophysiology underlying PFD to improve diagnostic, therapeutic, and preventive strategies.

Recommendation 5: T2 translational research to raise awareness and create a common language for improved communication, treatment, and understanding of PFD in the community.

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BRAIN AND PSYCHIATRIC DISORDERS

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Introduction

The global burden of psychiatric disorders is substantial. According to the World Health Organization, four of the top six leading causes of "years lived with disability" are due to neuropsychiatric disorders: depression, substance use disorders (including nicotine, alcohol, and illicit drug abuse), schizophrenia, and bipolar disorders. The costs of these disorders, including health care costs, economic and individual productivity, and family burden, exceed $650 billion per year in the United States.[1,2] Psychiatric disorders are comorbid with nearly every chronic medical disease, multiplying the burden substantially.

There are sex and gender differences in prevalence, expression, and treatment responses regarding depression, anxiety disorders (including post-traumatic stress disorder or PTSD), eating disorders, alcohol and drug-related substance use disorders, schizophrenia, autism, and Alzheimer's disease. New technologies provide novel capabilities for understanding processes that may explain sex/gender differences in ways that were not previously possible. Furthermore, it is important to take a lifespan perspective to identify etiologic mechanisms during fetal development, puberty, adulthood, and aging, with special consideration to time periods specific to women such as childbearing years, perimenopause, and menopause. Time periods in which there are major changes in the hormonal milieu are critical periods for research on vulnerability for developing sex differences in psychiatric disorders. Research findings must be translated into

effective clinical and population-based strategies that meet the needs of women with diverse backgrounds, including those who are underserved and have limited access to health care.

Progress in research on sex and/or gender differences has been impeded by a number of challenges. They include methodological attention to designing studies focused on sex/gender differences, not just separating data by sex/gender after data collection. Two examples of methodological attention include selection issues related to ascertainment of women and men in population studies or in treatment studies and controlling for hormonal status, which is important for both human and animal investigations. Thus, there is a need for methodological development that considers the complexity of the domains of sex and gender in the initial design of the study. Second, there is a need to educate the scientific community that data analyses by sex/gender reflect quality science and that the findings can enhance the understanding of neurobiology and its implications for clinical medicine. This understanding should underlie the training of the next generation of leaders in women's mental health. Furthermore, education regarding the importance of sex and gender differences in clinical medicine is important not only for the scientific community, but also for policymakers and the public, if funding of these important arenas is to be sustained.

Summary of the Discussion

Invited investigators and clinicians presented observations to the working group, and a discussion followed. The following are the major concepts that emerged from the discussion.

1. Regarding genes and psychiatric disorders, it is important to do the following:
   - Determine the genetic contribution to sex differences in psychiatric illnesses.
   - Understand the function of genes associated with psychiatric illnesses, how these genes are regulated, and the relationship between gene expression in the brain and the disease state.
   - Consider that genes on sex chromosomes may play key roles in generating sex differences in brain structure and function beyond their role in gonadal determination.
2. Sex differences in psychiatric illnesses, even when they develop in adulthood, are likely to be the result of brain development during the fetal and postnatal periods. Thus, to understand developmental antecedents to sex differences in adult-onset psychiatric disorders, it is critical to understand the following:
   - What are the sex differences in the development of the healthy human brain?
   - How do they go awry differentially in the female and male brain given specific risk factors?
   - How can research on sex differences in the human brain be integrated with the long history of, and continued work on, preclinical studies of brain sexual differentiation?
3. The onset of many sexually dimorphic disorders occurs during periods of endocrine transitions (e.g., depression and schizophrenia after puberty or pregnancy). Puberty, perimenopause, menopause, and postmenopause can influence the trajectory of a woman's mental health significantly with regard to clinical outcomes. Factors affecting

outcomes (e.g., endocrine states, inflammatory factors, vascular status) need to be better understood.

4. In understanding sex and gender differences in the vulnerability to phenotypic expression of psychiatric disorders, an enhanced appreciation of gene-environment interactions in the expression of psychiatric disorders in women would be critical. Environmental factors would necessarily include those that are intrafamilial, but would also extend to sociocultural factors, exposure to environmental chemicals and neurotoxins, and psychoactive drugs and medications that might enhance or diminish vulnerability. Environmental endocrine disruptors may also differentially influence males and females as they transition through puberty, even after normal fetal development.

5. The impact of sex/gender on the brain through etiologic mechanisms discussed above is shared with other organs and tissues. It is important to understand shared mechanisms for understanding sex/gender biology and pathology across organs and tissues (e.g., heart and brain) to fully understand the mental health of women and men. These shared mechanisms may involve hormones, genes, inflammatory pathways, growth factor signaling, vasculature factors, cell cycle and proliferation, and neuropeptides.

6. It is important to translate clinical and preclinical knowledge of sex differences in the brain into development of sex- and gender-specific treatments and prevention strategies. Sex-specific treatment and prevention strategies for psychiatric disorders must be rigorously tested for efficacy and effectiveness, with focused investigation on mediators and moderators of outcome.

7. Education of the scientific community and the public is an important component of improving women's mental health. An understanding of sex differences in the brain and how this contributes to sex and gender differences in psychiatric illnesses will lead to the development of, and demand for, sex-specific treatments and prevention strategies for psychiatric disorders.

8. Mental health policies are needed at the State and Federal levels that are informed about sex and gender differences in psychiatric disorders, both in underlying predisposing factors to disease as well as differences in treatment response.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Develop New Knowledge: Visualize and manipulate *in vivo* cellular function and communication in the nervous system in humans and animal models to explain sex differences in the pathophysiology of psychiatric disorders. The dream of neuroscience is to see the brain in action: not as a black box, but as vital and functioning in the world. The real world imposes limits on our ability to do this, but the limits are being broken down continuously. Visualization can refer to anything from functional magnetic resonance imaging in

live people to mapping of molecular entities in live tissue slices or postmortem fixed-tissue sections. This recommendation looks forward broadly with an eye toward future innovations. However, the following steps can be initiated now.

- Expand existing brain banks and atlases with a focus on sex differences in normal brain structure and functional processes from development through aging.
- Within these atlases, compare postmortem human tissue, *in vivo* human imaging, and animal postmortem tissue and imaging.
- Create standards for open access of these atlases and the quality of collected brain tissue, including the requirement that all banks/atlases include tissue/images from male and female brains.
- Determine the neural basis of behavior change in treatment outcome research (i.e., use these visualization tools to understand the neural basis of behavior, affect, and cognition and apply this knowledge to understanding individualized treatment outcomes).

Recommendation 2: Develop New Knowledge: Identify biomarkers of sex-specific vulnerabilities in psychiatric disorders. Determining the genetic contribution to sex differences in psychiatric illnesses is important. With the successful mapping of the human genome and increasing molecular knowledge ranging from genomics to proteomics and other emerging disciplines, we are at a new point in time to identify molecular and genetic variability that may be linked to specific psychiatric disorders. It is important to understand the function of specifically linked genes, how these genes are regulated, and the relationship between gene expression in the brain and the disease state. It is also important to integrate population-level studies with preclinical and other clinical studies to advance our knowledge of sex-specific psychiatric disorder biomarkers. For example,

- Identify biosignatures, including behavioral phenotypes, to account for individual differences in risk and resilience, including the interplay of biological factors (including genes, molecular and cellular signaling cascades, race/ethnicity, developmental stage) and environmental variables (including diverse social contexts and health disparities, stress, coping resources).
- Identify the molecular bases for cellular communication and determine if the bases are different for males and females.
- Combine the power of genetics with new tools for phenotyping (e.g., imaging, proteomics) to explain sex differences in variability of psychiatric disorders.
- Develop and validate sex-specific animal models of critical brain processes implicated in the pathophysiology of sex differences in psychiatric disorders.

Recommendation 3: Develop New Knowledge: Exploit neuroengineering approaches to manipulate brain function using viral and/or transgenic approaches, stem cells, or medical devices to understand healthy brain function and treat mental disorders in women and men. Engineering is a discipline that applies technical and scientific knowledge in the context of natural laws and physical resources to design and implement specific outcomes. Neuroengineering applies this approach to problems of nervous system function and disorder. New

tools range from the world of computer science and nanotechnology to the integration of new cellular and genomic material into animal models or humans. For example,

- Antidepressants may alter neurogenesis. Methods are needed to ask whether this occurs in humans (and if so, is there a difference by sex), while using animal models to determine detailed mechanisms to explain sex differences.
- Electrical stimulation of the peripheral and central nervous system may influence psychiatric function. Understanding of the medical device/human-animal interface is needed and, in particular, whether there are differential implications for women and men.
- Stem cells are being proposed as solutions for brain dysfunction. We need to understand the integration and function of such cells in living individuals; the visualization of such cells *in situ* will greatly enhance their utility.

Recommendation 4: Translation to the Clinic: Use the new knowledge obtained from visualization, biomarker identification, and neuroengineering to develop and evaluate novel, sex-specific treatments (including pharmacologic and behavioral) in diverse populations and community contexts. Taking a treatment from the bench to the bedside adds a level of complexity. Animal models show behavior, but they do not communicate mental processes as humans do. Some animals do not experience menopause. As new technologies are developed that provide an ability to look at brain function in live individuals, it may be possible to better match the expectations of the bench to the realities of the bedside. For example,

- Brain treatment targets can be identified by visualizing molecular or activity-based changes.
- Molecular processes as drug targets can be identified as biosignatures unique to selected psychiatric disorders.
- Novel treatments (e.g., stem cells) can be developed by using neuroengineering approaches.
- These studies must test for the specificity of treatment efficacy by sex/gender and hormonal status and compare treatment strategies.

Recommendation 5: Translation to the Community: Develop and test innovative models of health care delivery for women that provide integrated prevention and treatment for mental and physical disorders, emphasizing wellness through the lifespan and including issues of diversity. Integration throughout the health care universe is a desirable goal, but a difficult mission. New strategies are needed that range from arranging physical locations (proximity) to sharing medical records (paper in the past and present to more digital in the future). The emphasis should be on designing ways to test whether these changes improve health outcomes for women in diverse contexts, including those facing health disparities and a variety of social challenges. This integrated approach will replace the fragmented system experienced by most women seeking care for physical and mental health, which is important given the substantial comorbidity of psychiatric disorders with chronic medical diseases. For example,

- Compare outcomes in integrated interdisciplinary practice settings (not just co-localization of disciplines) with standard settings. Incorporate tests of comparative treatment effectiveness.

- Develop and evaluate integrated assessment and treatment protocols for sex-specific, comorbid conditions in psychiatric disorders (e.g., substance use disorders with eating disorders, psychoses, and/or depression) and comorbid psychiatric and physical health conditions (e.g., depression or substance use disorders or psychoses with obesity, diabetes, cardiovascular disease, cancer).
- Increase effectiveness studies of safer sex skills in at-risk women (e.g., women with substance use disorders, depression, PTSD) to decrease transmission of HIV through risky sexual behaviors.

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CHRONIC PAIN SYNDROMES

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Introduction

At the outset, the working group decided that the focus would be on "chronic functional pain" syndromes including, but not limited to, fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis/painful bladder, pelvic pain syndromes, vulvodynia, temporomandibular disorder, and headache disorders. The rationale for this decision was twofold: These conditions are more prevalent in women than in men, and the conditions are not well addressed in clinical settings or by the categorical structure of the NIH institutes.

The discussion then focused on the following areas to assist with formulation of recommendations.

- Identifying areas of progress in research, with acknowledgment that advances both in the understanding of chronic pain syndromes, as well as in sex and gender differences of chronic pain, is limited. Participants provided summaries for recent advances in preclinical and clinical research, and presented patient advocate and industry perspectives.
- Recognizing major obstacles to making progress in future work, participants placed particular emphasis on a general lack of crosstalk between important stakeholders (e.g., between investigators and clinicians, between preclinical and clinical investigators, between investigators from different disciplines, and between patient advocacy organizations representing different syndromes and investigators).

Summary of the Discussion

In discussing the state of pain research, the working group concluded that the lack of a generally accepted organizing hypotheses, or conceptual models, for chronic pain is partly because of a lack of basic understanding of the clinical disease, and specifically how it relates to sex and gender. Several related questions were raised.

- Does chronic pain have a cortical dimension (e.g., cognitive, attentional) not affected by treatments directed at peripheral pain-processing pathways that differs between male and female patients? Cortical dimensions cannot be modeled effectively in rodents; therefore, a more complete understanding of this dimension in humans may be critical for developing effective treatment.
- Can sex or gender differences be organized into a single hypothesis?
- Do sex or gender differences with regard to sleep, diet, enteric microbiota, and anatomy contribute to differences of prevalence among women?
- Are there prepubescent differences between the sexes with respect to pain processing or clinical pain?
- How do culture and society influence the etiology and treatment of chronic pain, including the perceived negative impact on women in both acknowledging chronic pain and seeking necessary medical interventions? If women seek health care at a lower threshold of pain, are they still considered “excessive health care seekers,” and would the development of unbiased biomarkers (e.g., prefrontal imaging) ameliorate this social or cultural issue?

The group discussed how pain research focuses on putative end-organ pathologies or is pursued by respective subspecialties, fragmenting research design to the detriment of crosstalk between interdisciplinary investigators. The future of pain research should move away from categorical syndrome-focused research and move toward the development of neurobiological and neuropsychological endophenotypes. Discussion on this topic led to identification of key needs in both clinical and preclinical research. Problems identified with regard to current and future clinical research of chronic pain include the following:

- A lack of rigor in studies in which, because of the higher prevalence of women with chronic pain, an insufficient or unrepresentative male sample affects the assessment of sex and gender differences in the treatment of pain.

- Clinical trials that do not accurately represent the diversity of symptoms within chronic pain. Several reasons were given for this, including (1) presentation of the mean data without outliers; (2) no broad survey of symptoms to transcend an end organ/subspecialty analysis; and (3) lay vocabulary that is both difficult to use to convey pain accurately, and even more difficult to translate into quantifiable data.
- A heightened biological redundancy during chronic pain in humans as compared to laboratory animals. Although not well understood, this biological redundancy is evidenced by the failure of several high-profile, single-target chemical candidates to show efficacy in clinical trials that previously demonstrated great preclinical promise (e.g., failure of recent clinical trials with antagonists for the substance P and the CRF1 receptor).
- Major variations in placebo rates, ranging between 25 and 60 percent, that have been detrimental to the continuation of several clinical trials into chronic pain pharmacotherapeutics. The variations in placebo may result from the lack of understanding of the true diversity of symptoms, as addressed above.

In addition, the working group brought forth several issues with regard to preclinical animal studies, as follows:

- Use of animal models in chronic pain research presents several inherent problems, related to poor face, construct, and predictive validity. These include (1) a general lack of models for common chronic pain syndromes, including irritable bowel syndrome, fibromyalgia, and migraine; (2) lack of relevant outcome measures of pain, particularly with regard to spontaneous versus evoked pain models, and with regard to reflexive outcome measures versus operant models; (3) the unsuccessful translation of therapeutic targets in knockout/transgenic animals to efficacy in the clinic; and (4) an inability to model social factors that modulate pain perception and efficacy of treatment in the clinic.
- A lack of significant focus on sex and gender differences in chronic pain because the majority of the animal models of pain use male animals only. This situation is, in large part, due to the increased cost of studying sex-related differences, and to the technical challenges in controlling for cyclical hormonal variations in female animals.
- Better rodent models of spontaneous pain and better methods to assess associated pain behaviors are needed.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Focus research on identifying shared mechanisms among different pain syndromes with trans-NIH effort, to support collaborative inquiry into commonalities and differences in chronic pain syndromes. One successful example is NIDDK's Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network approach for head-to-toe phenotyping (clinical as well as biological), using a collaborative effort to identify systemic disease with comorbidity while moving away from an organ-centric approach. One logical area of research, spanning several subspecialty areas, should be sex differences in the central nervous

system that may underlie the observed greater prevalence of chronic pain syndromes in women (including sex differences in cognitive, attentional, and affective mechanisms, and sex differences underlying the lower threshold in women for seeking health care).

Recommendation 2: Encourage the study of clinical programs that promote societal support for individuals, especially women of all socioeconomic and cultural groups, in seeking out and receiving treatment for chronic pain. For example, in positive portrayals of women, a lower threshold in women for seeking medical care for persistent pain should be presented as reflecting an adaptive biological mechanism, that enhances chances for survival of women and their offspring, rather than as a psychological weakness.

Recommendation 3: Encourage funding initiatives that address the issue of the transition of acute into chronic pain, specifically: Does it occur? In which subset of patients does it occur? What are the vulnerability factors for such a transition to occur—such as physical trauma (e.g., infection, injury) and psychological trauma (e.g., traumatic brain injury, rape, stress)? How do psychological factors interact with genetic and other vulnerability factors to influence the development and progression of chronic pain? Preventive programs, starting in childhood, should be designed that focus on early support for vulnerable individuals following acute injury in an effort to minimize the development of chronic pain.

Recommendation 4: Encourage funding initiatives that develop a more "universal" impact scale for chronic pain across endophenotypes, similar to the Patient-Reported Outcomes Measurement Information System (PROMIS) network. PROMIS is a network of NIH-funded primary research sites and coordinating centers working together to develop tools to reliably and validly measure patient-reported outcomes. The development of a similar questionnaire, with an emphasis placed on gender specificity, could be encouraged in all NIH-funded chronic pain research.

Recommendation 5: Undertake an evaluation and subsequent overhaul of clinical trial designs for chronic pain and include advocacy and industry representation.

- Investigate more than one pathology instead of the evidence-based single pathology approaches currently in use.
- Support an environment for chronic pain clinical trials that is not a "one and done" approach. An accepted industry standard is for 10 trials to be undertaken with respect to antidepressant drugs, with only 4 to 5 of these clinical trials showing efficacy. Because chronic pain spans a spectrum of disorders, with high incidence of comorbidity, this approach may be necessary to truly establish efficacy for a particular endophenotype.
- Require the reporting of the full spectrum of results, not just the mean data. This will be particularly beneficial to outliers who may benefit from the drug in question.
- Encourage the exploration of combinations of treatments (combinations of drugs, or combination of a drug with cognitive behavioral approaches).

- Minimize the wide range of placebo effects in current chronic pain clinical trials by incorporating the effective methodology currently used in pediatric trials, including lead-in studies or randomized withdraw.
- Promote the concept of flex dosing, which is not currently used in chronic pain clinical trials, but is used in clinical psychiatry trials with excellent effects.

Recommendation 6: Because of the prevalence of chronic pain in the United States, there should be a call for increased funding for functional pain research to better understand the disease mechanisms in humans, appropriate treatments, and possible preventive measures. This funding initiative should include research of chronic pain across gender and socioeconomic and cultural strata, with emphasis on how life experience modulates resilience and recovery. As a long-range objective, advances in understanding the human etiology of chronic pain, via genetics, biomarkers, neuroimaging, etc., can promote the development of relevant animal models that would more accurately predict the clinical efficacy of therapeutics (reverse translation).

Recommendation 7: Encourage the development and management of repositories for pain-relevant clinical and biological information that spans current end-organ subspecialties. Such repositories could include a centralized database for structural and possibly functional magnetic resonance imaging data. To spearhead the rapid development of this repository, there should be an international call to industry to share clinical data, particularly with regard to failed clinical trials in the area of chronic pain. This should be presented as an ethical and moral imperative, to minimize superfluous experimentation into compounds that are not efficacious, and to promote the possible combination of FDA-approved drugs that may show efficacy in treatment for specific syndromes.

Recommendation 8: Encourage individual fellowships that support a 1-year grant for basic science researchers to work in a clinical setting. With particular regard to chronic pain, understanding how pain presents in the clinic could aid the rapid development of animal models by basic researchers that more accurately reflect the disease.

EATING DISORDERS

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Introduction

The cochairs of the Eating Disorders Working Group presented a review of the current state of research on eating disorders and summarized input from experts they consulted on the gaps in knowledge in the field and needs for future research. The working group discussed research progress to date and current gaps in knowledge regarding the etiology, prevention, and treatment of eating disorders across the lifespan.

Summary of the Discussion

Eating disorders currently recognized in the *DSM-IV* include anorexia nervosa, bulimia nervosa, and "eating disorders not otherwise specified," which includes binge eating disorder. Eating disorders are among the top 10 mental disorders that cause disability among women and are a significant source of morbidity and even mortality.[1,2] For example, morbidity from anorexia nervosa is the highest of all mental disorders, with a 50-fold increase in the relative risk of death from suicide.[3] Common psychiatric comorbidities of eating disorders include depression, anxiety, substance abuse, and impaired social functioning. Serious medical complications include cardiovascular problems (e.g., bradycardia, low blood pressure), electrolyte imbalance, neurological problems (e.g., seizures, disordered cognitions), hormonal changes (e.g., lower estrogen, higher stress hormones), and problems with bone health.

Observations on Anorexia Nervosa

Anorexia nervosa (AN) affects .3 percent to .6 percent of Americans—as many as 1.8 million people—in their lifetime, and 90 percent of the cases are among women.[4,5,6] The disorder presents as a failure to maintain a minimally normal body weight, intense fear of weight gain, and disturbances in the perception of body shape or size. It typically begins during adolescence and is associated with profound, even life-threatening, physiological abnormalities. It can have a variable (e.g., full recovery after a brief episode, chronic illness lasting years, death), but often chronic, course.

The state of current research on AN is the following.

- Evidence suggests that genetic and environmental factors play important roles in the etiology of AN (e.g., studies comparing brain circuitry of normal individuals and individuals with AN have found that although eating produces a calming effect for most people, it elicits anxiety for individuals with AN). However, clear evidence-based etiology and pathophysiology have not been established.
- A small amount of research indicates that the most effective intervention for adolescents with AN is a family-based approach, and several studies of this approach are currently underway.[7] However, no specific treatment, either pharmacological or psychological, has been shown to be consistently effective for adults with AN.[8]

Observations on Bulimia Nervosa

Bulimia nervosa (BN) affects 1 percent of Americans in their lifetime—approximately 3 million people—and occurs primarily among women with body weights that are within normal limits.[4,5,8]

The disorder is characterized by recurrent binge eating (the consumption of an abnormally large amount of food in a discrete period of time), followed by the use of inappropriate compensatory behaviors, particularly self-induced vomiting, to avoid weight gain. It generally begins during adolescence or early adulthood and may be accompanied by potentially serious medical complications, largely as a result of self-induced vomiting or other forms of inappropriate compensatory behaviors, and frequent psychosocial morbidity.

The state of current research on BN is the following.

- The detailed etiology and pathophysiology of BN are not well established, although existing data support the important role that biologic and psychosocial factors play in the development and persistence of this disorder (e.g., research indicates the frontal lobes of individuals with BN exert less inhibitory control than those of normal individuals).[9]
- Significant progress has been made in the last 20 years in the development of several effective psychological and pharmacologic treatment interventions for BN. However, continued progress in treatment development is clearly needed because as many as 50 percent of women treated for BN are resistant to available interventions.[10]
- Although BN often begins in the early teenage years, controlled treatment studies of adolescents with BN are just now getting underway.

Observations on Binge Eating Disorder

Binge eating disorder (BED) affects 2.8 percent of Americans—approximately 8.4 million people—in their lifetime. The majority of cases are women.[5] The disorder is characterized by recurrent binge eating without other frequent inappropriate compensatory behaviors (i.e., binge eating without purging). It develops in adolescence and early adulthood, but treatment seeking does not typically occur until middle age. It is typically associated with obesity and significant psychosocial morbidity.

The state of current research on BED is the following.

- Extensive research has demonstrated the clinical significance and validity of BED, with studies demonstrating that BED is distinct from other eating disorder diagnoses (i.e., AN, BN) and non-BED obese populations.[11]
- BED appears to aggregate in families and to have a significant genetic component, though the etiology and pathophysiology is unclear.[11] It is notable that genetic and biological research on BED has lagged behind that of AN and BN.
- Treatment interventions, such as cognitive behavior therapy and interpersonal psychotherapy, have been shown to achieve long-term reductions in binge eating and have resulted in weight stabilization, with a subset of patients obtaining clinically significant weight loss.[12]

In addition, individuals with clinically significant eating disorder symptoms who do not meet the full diagnostic criteria for AN, BN, or BED are commonly seen for treatment in outpatient settings. However, the diagnostic validity and clinical utility of these other symptom presentations (e.g., purging disorder, night eating syndrome) are not yet well understood.

Recommendations

The working group, consistent with responses by members of the Eating Disorders Research Society (EDRS), believed that the most pressing issue confronting the field is the establishment of the significance of eating disorders as a major public health problem for women. (EDRS is an international organization of researchers in the field of eating disorders interested in AN, BN, BED, and obesity.) Additional issues include advances needed in basic research, intervention/prevention research, and training the next generation of eating disorders scientists. The concern regarding research training is common across many research areas, but the small number of researchers of eating disorders warrants heightened concern.

The following are specific research gaps identified by the working group. The recommendations proposed may help to provide guidance to health administrators, clinicians, scientists and the public as to areas of investigation that merit greater research.

- **The development and testing of effective treatments for persistent AN**. For example, there are many barriers to conducting controlled clinical trials with this population given the relative rarity of this disorder and the egosyntonic nature of the symptoms (e.g., recruitment and retention of individuals with AN to clinical trials is even more difficult and costly than is typical, often requiring multiple treatment sites, which further increases the cost and complexity of conducting research with this population). These challenges are exacerbated by the paucity of clinical research scientists working with AN in particular, and in the field of eating disorders in general.

- **The genetics and pathophysiology of eating disorders and how biological factors interact with behavioral and environmental factors and vice versa**, particularly in view of the increasing cost effectiveness of genetic testing and continuous improvements in neuroimaging techniques. For example, studies of brain circuitry regarding reward and emotion regulation, research on temperament, and research into the differential maturation rates of various brain structures during adolescence and early adulthood are needed to learn more about why some individuals, especially youth, are at risk for developing eating disorders.

- **The roles that gender and life stages play in the development, course, and responsiveness to treatment of eating disorders**. For example, do genetic or hormonal mechanisms contribute to the disproportionate expression of eating disorders in women, but not men? How do events such as pregnancy and menopause affect the development or course of eating disorders?

- **The development of effective methods for early identification, intervention, and prevention of eating disorders**. For example, efficient screening methods need to be developed for identifying individuals most at risk for eating disorders (e.g., women with high weight and shape concerns, with other comorbid psychiatric symptoms, and with loss-of-control eating), and targeted prevention programs need to be developed.

- **The intersection of the fields of obesity and eating disorders research**. For example, obesity prevention programs that emphasize the adoption of healthy lifestyle behaviors (e.g., regular eating patterns) may prevent eating disorders by modifying the unhealthy dieting and dysregulated eating behaviors in which individuals with eating disorders

often engage. Additionally, obesity prevention programs that encourage the adoption of regular, moderate physical activity are associated with improvements in mood and sleep cycles, which may help with body-image enhancement and emotion regulation in overweight individuals and thus may decrease their risk for developing eating disorders.

- **The development of more potent treatments for eating disorders** by examining the mediators and moderators of treatment effects, determining the degree of recovery or of symptom change that is necessary to prevent relapse in these often chronic and recurring disorders, and by using basic and laboratory research findings to help personalize treatments for eating disorders.

Furthermore, a "disconnect" exists between proven treatments for eating disorders, such as BN and BED, and their use by the general treatment community. For example, more than half of the training programs for psychologists and social workers do not require training in evidence-based psychotherapies. More specifically, few formal training opportunities exist at the doctoral level for instruction and practice in providing evidence-based treatments to individuals with eating disorders. In addition, clinical research in the area of eating disorders is most often conducted in specialty clinics within medical school departments of psychiatry. As a result, when women seek treatment for an eating disorder in the community, the treatment they receive is likely to be inconsistent and not necessarily based on evidence.

Intervention designs need to consider the perspectives of consumers and stakeholders (e.g., patients, providers, family members) from the outset so that the most effective interventions can be implemented in "real world" settings in a timely and cost-effective manner. Along these lines, innovative training paradigms need to be explored to allow for training scientists and clinicians to work as part of interdisciplinary teams in order to design studies that evaluate, test, and treat eating disorders across multiple levels (e.g., the biological/genetic, interpersonal, and cultural) and to ensure that the most effective interventions available are provided to women across the age spectrum.

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GENETICS AND MICROBIAL COMMUNITIES (METAGENOMICS/MICROBIOME)

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Introduction

The Genetics and Microbial Communities Working Group discussed strategies and approaches for applying metagenomics technologies to stimulate progress in basic science and clinical research related to women's health. Research on the human microbiome—the sum of those microbial communities found in and on the human body—can be used to define the healthy and diseased states of women throughout life and to better understand women's responses to diseases, medical therapies, and technologies. The most important potential benefit of these studies is an increased understanding of the healthy and diseased states of women and differences among individuals that arise from the interaction of genetic, physiological, socioeconomic, environmental, and other variables. An increased understanding of the healthy human state will enable early disease recognition and prediction, novel therapeutic targets, optimal nutrition, and an increased understanding of drug action.

As a background for the working group discussion, the cochairs presented extensive information about the nature of the human microbiome, the NIH Human Microbiome Project, and research technologies and methodologies for studying the microbiome. Human microbiome research is poised to make significant advances, and considerable preliminary data are available. In addition, rapid progress is being made in the development and application of technical tools for the study of interactions between human hosts and their microbiomes. For example, a current major initiative for microbiome research is the Human Microbiome Project, part of the National Institutes of Health Roadmap for accelerating biomedical research.

The goal of the NIH Human Microbiome Project is to characterize the microbes that inhabit the human body and examine whether changes in the human microbiome can be related to health and disease. Specific goals of the project include (1) sequencing 1,000 microbial reference genomes; (2) performing metagenomic analysis of human clinical samples from five human body sites (vagina, nose, mouth, skin, and gastrointestinal tract) in more than 250 healthy individuals; (3) demonstrating the feasibility of metagenomics to correlate changes in the human microbiome with health or disease phenotypes; and (4) developing new and improved technologies and bioinformatic tools specifically applicable to metagenomic research.

The Human Microbiome Project also supports a reagent repository and a data analysis and coordination center located at the University of Maryland School of Medicine to give the scientific community rapid access to reagents, datasets, and other resources generated by the project. In addition, an International Human Microbiome Consortium has been formed that will internationally coordinate human microbiome initiatives and generate a shared resource of human microbiome data and protocols, coordinate international efforts to reduce redundancy, and provide a venue for international communication of results and strategies.

Summary of the Discussion

The working group discussion centered on four broad issues: (1) investigation of the human microbiome to explore mutualistic relationships that occur with the host, with a focus on health to provide insights into disease; (2) the need to be inclusive in clinical research to understand these interactions as they occur throughout women's lifespans; (3) technical challenges faced in studies of the human microbiome; and (4) the need to recruit and retain women in research

to understand the role of the human microbiome in women's health. Subsequently, the working group developed five broad recommendations for genetics and human microbiome research.

Mutualistic Relationships Between Hosts and Their Microbiomes

The human body has remarkable homeostatic mechanisms that ensure the stability of bodily functions and the survival of individuals; as a result, most humans are healthy most of the time. Understanding these mechanisms, particularly with regard to the mutualistic relationships that exist between the human host and its microbiomes, should receive increased attention so that strategies for the maintenance of human health and the prevention of disease can be improved. Furthermore, it should be recognized that the microbiomes of healthy individuals are in dynamic equilibria, and a certain degree of variability in structure and function over time should be expected. However, changes that exceed certain limits could either increase the risk for disease or be associated with disease symptoms, and this possibility warrants exploration. Thus, there is a need to better understand the temporal dynamics of these systems. This effort should include changes in the host and human microbiome that occur over a human's lifespan. Such studies must be interdisciplinary and must address all three domains of the ecological triad—host, microbiome, and environment.

The recognition that mutualism exists among the hosts, their microbiota, and the environment presents new avenues toward learning about the maintenance of health in individuals. By not simply focusing on disease states, one could envision studies in which microbiomes were deliberately perturbed to explore their resiliency and to better understand the processes, community members, and relationships that are key to homeostasis and the maintenance of health. Such human-provoked perturbations might arise from changes in lifestyle, behavior, pregnancy, diet, birth control practices, or various other habits and practices. However, these perturbations might also occur following chemotherapy, use of antibiotics, and use of other drugs. These studies might also assess whether different microbiota communities are functionally equivalent, determine if new alternative equilibria are established following specific perturbations, or identify indicators of pathology.

Inclusiveness in Clinical Research

Expanding Clinical Research to Include a Woman's Lifespan. Studies on women's health must encompass the entire lifespan. Until recently, there was a dearth of information concerning women of nonreproductive age, and many clinical studies in the past excluded women of childbearing age or who were nursing or pregnant. Information is needed about all stages of life to define the normal progression of acquiring microbiota, to define differences in microbiota that occur independently of reproductive status, to define the roles of interpersonal variation in microbiota composition, and to define the interaction between the human host and the microbiota. Such studies will provide insight about how the host's age affects interactions between the microbiome and a woman's body at all stages and states of a woman's life. Such studies should be extended beyond the cross-sectional studies to include longitudinal studies that accurately reflect the variations in microbial communities that occur in healthy individuals over time. Examples of age-specific issues that warrant further investigation are described briefly below.

Pregnancy. For both the infant and the mother, microbiome changes during and after pregnancy offer a unique opportunity to study changes in host status on microbiome structure and function and to study the effects of those changes on women's health. Such studies might address potential differences in the microbiome before, during, and after pregnancy and during lactation. There are likely to be multiple deterministic and stochastic effects on the acquisition of microbiota and community assembly during the pre- and postpartum periods that are influenced by the mode of childbirth (vaginal versus C-section delivery); the prophylactic use of antibiotics during pregnancy or prior to delivery; breastfeeding; and medical interventions to improve infant health in the short term. This acquisition may be especially important to the development of the microbiome in neonatal intensive care units that could be influenced by the numbers and types of organisms to which infants are exposed and by medications that are administered.

Correlation of health status with factors such as reproductive age, medical interventions during delivery, and normal versus abnormal pregnancy will shed light on the healthy state in women and newborn children. For example, correlation of perinatal effects (C-section, predelivery antibiotic administration, early administration of broad-spectrum antibiotics, health care worker interactions with the infant, etc.) with microbiome structure and function will provide insight into the long-term consequences of these interventions on microbiome.

Adulthood. Gaining information about women across the globe who live in different environments and cultural settings will shed light on how these factors influence the microbiomes of women. Moreover, mapping changes in the microbiome over time, throughout menstrual cycles, and in various anatomic sites will provide information on variation in microbiome structure and function over time. Finally, studies on the effects of medical interventions on women's health should be expanded to include the human microbiome.

Older women. Older women are likely to experience multiple perturbations of the host-environment interaction because of comorbidities and polypharmacy. These perturbations may contribute to adverse effects on a woman's health and susceptibility to additional disease, and alter her response to treatments. These possibilities should be explored through detailed monitoring of the microbiome in the presence of pharmaceuticals and comorbidities, especially in older women.

Policy Barriers to Clinical Research on Women's Health. Changes to current research practices and funding mechanisms are needed to facilitate the long-term longitudinal studies required to address all stages of life, and to study interpersonal variations and behavioral parameters. Such studies to relate the structure and function of the microbiome to women's health must be interdisciplinary and designed to address the host, the microbial communities, and the environment in an integrated manner.

Several policies limit studies of women's health over the lifespan. Research funding and approvals for using human subjects currently focus on time-limited, cross-sectional studies; thereby, longitudinal, intergenerational, and long-term data gathering are largely precluded. The necessity of conducting lifespan research over multiple funding periods conflicts with

current prohibitions against contacting study participants after the end of a study period. Thus, changes to the scientific and funding environment are needed to facilitate recruitment for lifespan studies and to ensure accessibility to samples across multiple funding periods.

Novel protocols and methods will be needed to identify, recruit, and retain women who are willing and able to participate in studies over extended periods. Adequate funding will be required to create sampling protocols that allow data collection on individuals over multiple funding periods and that will produce samples that adequately represent the tremendous interpersonal variation inherent to human populations. Funding should exist that can support long-term studies, including interdisciplinary studies.

Regulatory Barriers to Research on Women's Health. A change in regulations regarding the use of existing women's cohorts and databases (including electronic health records and associated health care information) would facilitate multiple contacts with study participants and the use of existing samples for additional studies. Existing cohorts might provide a valuable source of serial samples (data) to correlate microbiome dynamics with healthy states and help increase the understanding of the role and dynamics of microbial communities in women of all ages. These data would enable wide-ranging multifactorial correlation analyses of the interactions among a woman's body, the microbiome, and the environment. Such retrospective analyses would also enable the development of predictive models for future health predicaments. Access to such cohorts and databases has major implications for the protection of a woman's confidentiality, and addressing ethical issues associated with patient privacy and consent is requisite to the use of existing cohorts and data.

Changes to regulatory control of clinical studies will be required to support studies of the microbiome over a woman's lifespan. These studies must start before birth, which raises specific ethical questions. Standardizing data and specimen collection procedures across institutions and improving the sharing of information among researchers might ease interactions with institutional review boards (IRBs). Uniform standards, such as those of the NIH best practices model program, could provide templates for standardized protocols that will be acceptable for approval by IRBs and other regulatory bodies.

Educating IRBs on such studies will be required. The composition of the IRB is outlined in the Code of Federal Regulations and, historically, has been most concerned with issues of risk management. The concern with liability is so great that it often excludes women of reproductive age, children, and infants from clinical research in spite of NIH directives to include women of all ages. Furthermore, there is no advocate for women or minorities in the codified composition of the IRB. Lifespan research will be facilitated by better communication between IRBs and researchers as well as women themselves. This, coupled with broader representation and increased input to IRB decisions by all parties, particularly ethnic minority communities, will be necessary.

Ethical Issues Affecting Women's Health Research. Former interpretations of ethical issues create barriers to the participation of women, children, and infants in lifespan research, including research before birth. Paternalistic attitudes about who can and cannot participate in

clinical research effectively prevent women at all life stages from participating in important clinical studies. Some researchers and review boards have misconceptions that certain population groups, such as minority women, are not interested in participating in clinical research. Adding members, such as community advocates or bioethicists who specifically represent the interest of women and communities, to IRBs might increase the IRBs' fundamental knowledge of women's health and community attitudes. These members would have a nonvoting status because of the codified composition of IRBs.

Community Education. There is remarkable receptivity among the lay public for women's health research. This is important because their involvement and support is essential to promote lifespan research. To promote research on the human microbiomes of women, the lay public must come to understand that the microbiome is a normal, beneficial part of body, important to each individual. Behavioral research and educational programs must target specific groups of women and must focus on the family in order to communicate why women's health research is important and that clinical research is a tool for community progress. Educational programs and materials must target the community and potential study participants. Researchers should use these educational tools and can take advantage of existing community-based infrastructures to disseminate and use these educational tools. Experience has shown that all truly effective communication is locally based and engages the community. Communication must be established between members of the community and scientists. To further community education, increased support is necessary for those people who know both the science and clinical aspects of women's health research and can also interact effectively with the community.

Technical Challenges to Microbiome Research

Critical technical issues that limit microbiome research must be overcome, such as separating microbial DNA from human DNA. In addition, novel bioinformatic and computational approaches will be required to mine existing and emerging datasets and sources, including electronic health records, pharmacotherapy, comorbidities, and others, while respecting the privacy of participants. Technologies and bioinformatic algorithms must be developed to correlate health or disease with microbiome community characteristics. These studies might remedy the current limited clinical ability to diagnose diseases such as vaginitis or to develop new and improved diagnostics for known etiologic agents.

Career Opportunities in Women's Health Research

Women's health research is an expansive field of study with broad opportunities and a great need for scientists with expertise in a broad range of disciplines. Young students must be encouraged to choose women's health research as a career. Specifically, educational opportunities and training grants for the next generation of researchers must be targeted specifically to women and, most importantly, to women of color. Financial commitments will be required to support the infrastructure necessary at the university level to implement the needed career training in women's health research.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Examine the relationships among host, microbiome, and environment.

- *Host:* Define genotypically or phenotypically well-defined controls and cohorts. Analyze other effects on the host that include, but are not limited to, the effects of socioeconomic status on health.
- *Microbiome:* Correlate microbial community structure and function with the occurrence of disease. Identify appropriate controls and reference microbiomes. Develop advanced technological tools for genome sequencing, data analysis, and translation of microbiome findings to point-of-care applications.
- *Environment:* Determine the influences of environmental factors on immune status, unintentional effects (e.g., diet), stochastic variation, extremes of health, and behaviors that are generally regarded as safe (e.g., methods of birth control).

Recommendation 2: Develop new strategies for community outreach and behavioral research and develop educational materials to increase clinical trial registration and the general public's knowledge of health and the microbiome.

- Disseminate and translate information to the public, K–12 teachers, health care professionals, and the scientific community.
- Interact with communities to improve acceptance of research and to enhance participation in longitudinal genomics research.
- Develop models of preclinical trial preparation to encourage community participation, addressing health care disparities between different racial and ethnic groups.

Recommendation 3: Advance women's health research by addressing lifespan, logistical, and bioethical issues.

- Facilitate longitudinal studies throughout a woman's lifespan through the development of new funding models and institutional review board mechanisms.
- Ensure opportunities for special populations, including infants, children, adolescents, older adults, and underrepresented ethnic groups, to participate in longitudinal studies.
- Encourage open discussion of bioethical issues associated with recruiting populations that have been excluded previously from studies.

Recommendation 4: Apply new technologies to clinical care.

- Address both technical and ethical issues of linking databases on microbial communities to other data sources, including electronic health records and associated health care information, to enhance the understanding of interactions that occur in the host-microbial community-environment triad. Promote the use of emerging information technologies to facilitate transmission of data in real time.
- Encourage the translation of findings into point-of-care applications to facilitate personalized medicine in women's health and wellness.

- Develop software and hardware for database integration.

Recommendation 5: Promote career training of future scientists, especially women, in genomics and bioinformatics.

- Focus on recruitment and training of women and underrepresented minorities.
- Encourage interdisciplinary research training that includes ecology, genomics, systems biology, information technologies, and clinical science.

INFECTIOUS DISEASES OF THE URINARY AND REPRODUCTIVE TRACTS

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Introduction

The Infectious Diseases of the Urinary and Reproductive Tracts Working Group focused on four areas of women's genitourinary health:

1. Urinary tract infections
2. Reproductive tract infections
3. Preterm birth as a consequence of urinary and reproductive tract infections
4. Global impact of women's reproductive and genitourinary tract infections

For each of the four areas, the discussion below provides an overview of the current state of the field and emerging technologies recently developed at the bench that must be integrated into clinical studies and patient care; ways to make disease prevention messages, disease treatments, and health services delivery more efficient by quantifying the impact of the cur-

rent methodologies, and then using the feedback to modify research focus as well as clinical practices; and future work that will be critical for continued progress in these disciplines.

Summary of the Discussion

Urinary Tract Infections

Urinary tract infections are common in women, yet poorly understood. Persistent urinary tract infections can progress to ascending infections, causing disseminated disease (including maternal and neonatal sepsis). However, the determinants of progression are poorly understood. Recent work has overturned classic models of infection by showing that acute, recurring, and chronic infections are part of a continuum of pathophysiology and may provide a new paradigm for infectious diseases of the urinary tract. The growing problem of widespread antimicrobial resistance underscores the importance of developing novel therapeutic strategies.

Basic research has illuminated the involvement of microbial biofilms in disease. New methods have been developed for rapid pathogen-sequencing methods and culture-independent methods for pathogen identification. The challenge now lies in translating these advances into clinical methods for point-of-care screening and individualized therapy. Basic and translational research is needed (1) to enable early, rapid identification of pathogens and drug sensitivity profiles and to identify the type of infection (acute, recurrent, or chronic); and (2) to develop efficient translational therapeutics, for example, biofilm inhibitors and vaccines, with a strong emphasis on more prudent use of antimicrobials, including use of combination therapy to prevent further development of antimicrobial resistance.

Reproductive Tract Infections

Significant progress has been made in detecting and treating reproductive tract infections, for example, urine screening to detect sexually transmitted diseases (STDs), Group B streptococcal screening and prophylaxis, human papillomavirus genotyping and vaccine development, and highly active antiretroviral therapy to reduce mother-to-child HIV transmission. In spite of this, the basic etiology and pathogenesis of most STDs remain poorly understood. Antimicrobial resistance has become a critical public health challenge. Major unexplored questions remain. Does the endogenous (benign) vaginal flora affect STD acquisition? Do various contraceptive methods affect STD acquisition and disease progression? More studies are required to (1) advance genetic/genomic studies of microbial communities in the reproductive tract, and use microbial "omic" data (proteomic, metabolomic, other) to develop point-of-care screening for early, rapid identification of the pathogen, its drug resistance profile, and women at risk; and (2) develop critically needed, novel antimicrobial agents for STD and pelvic inflammatory disease (PID) prophylaxis and treatment, including natural products and immunobiologics.

STDs and PID are occurring at epidemic frequencies among U.S. teens and minorities. Accompanying the unabating problem of sexually transmitted infections in teens is the problem of unintended teen pregnancy, particularly among minority populations. Teen pregnancies account for about 750,000 live births per year and are often complicated by urinary tract infections and STDs.[1] Current advances in this field include development of long-acting reversible contraceptives (LARCs) and Plan B contraception. Focused effort is required to (1) advance research to

more accurately quantify the risk of PID and STDs associated with intrauterine devices and other LARC use; (2) promote dual protection methods, including use of LARC and barrier contraception to prevent both pregnancy and STDs; and (3) develop more effective methods to promote sexual health through better dissemination of information regarding disease and pregnancy prevention. These goals will require multidisciplinary projects that emulate the NIH's Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health program, and projects that strive to include populations that are underserved due to racial, ethnic, cultural, or educational disparities.

Preterm Birth

Urinary tract and reproductive tract infections during pregnancy significantly increase the risk for preterm birth. Preterm birth is the leading cause of infant mortality and long-term disability in the United States, disproportionately affecting African-American and Native American women. Social factors, such as poverty and lower education, also increase a woman's risk of preterm birth. Health care costs for treatment of preterm labor and delivery and subsequent infant care are estimated at $26 billion per year in the United States alone.[2] Little progress has been made in the past decade in the prevention of preterm birth and preterm-related mortality.

Use of 17-hydroxyprogesterone caproate therapy for the prevention of preterm birth in women at high risk and antenatal steroids to promote infant lung maturation represent advancements in the field. Increased use of assisted reproductive technologies for treatment of infertility, often due to chlamydia or other preventable causes, has resulted in increased multiple gestation pregnancies and risk for preterm delivery. Moving forward in this field will require (1) basic research to understand the contribution of genitourinary infections and inflammatory processes that affect risk of preterm birth based on a fundamental understanding of the biology of pregnancy from implantation to delivery; and (2) development of methods to detect women at risk early in pregnancy, such as screening for biomarkers of genetic risk factors, immunologic determinants, and infections that contribute to preterm birth. Advancing these goals will lead to new methods for early detection and prevention of preterm birth and improvement of infant outcomes.

Global Health Burden of Women's Reproductive Tract Infections

The working group came to the consensus that there is an unacceptable gap in the knowledge of the burden of genitourinary infections among women in resource-restricted countries. In the developing world, there is a dearth of projects to assess the epidemiology or etiology of female genitourinary and reproductive tract infections, and few statistics for teen pregnancy, preterm birth, stillbirth, and maternal and infant mortality. Addressing women's health issues in the developing world is directly relevant to women's health care in the United States, particularly regarding women of lower socioeconomic status and immigrant populations. More clinical studies of these populations will provide a universal understanding of women's urinary and reproductive infections as they relate to maternal/fetal health and infant outcomes.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

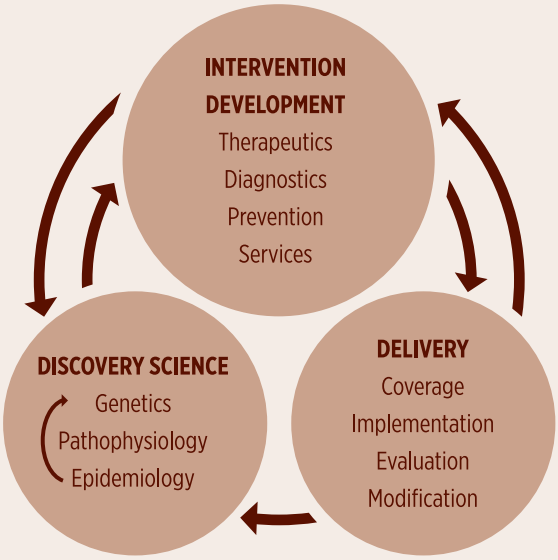
Recommendation 1: Promote multidisciplinary projects that create linkages between medical fields and newer disciplines, such as computational biology and bioengineering to develop cutting-edge tools for clinical applications; biomarker-assisted risk assessment; early diagnostics; and point-of-care pathogen screens, drug-resistance profiling, and infection classification (acute, recurrent, chronic).

Recommendation 2: Use emerging technologies and develop animal models to understand the normal and diseased states of the female urinary and reproductive systems, including during pregnancy. Collect the resulting data in a centralized, open-access database that correlates prospective cohorts with data on patient phenotype, treatment strategy, and outcome with descriptions of the relevant animal models and basic research findings (molecular data) germane to the disease. The database should be structured to support prospective, longitudinal studies of clinical conditions using either human cohorts or animal model systems along with properly collected, processed, and stored specimens collected at appropriate times during clinical assessments and followup, such as during antenatal care.

Recommendation 3: Foster public-private partnerships that use multiethnic cohorts to develop more vaccines and critically needed, novel antimicrobials—such as biofilm inhibitors, chemoprophylactics, natural products, and immunobiologics—against infectious diseases of the female urinary and reproductive tracts. New products must be evaluated for safety during pregnancy and early infancy in humans and relevant animal models.

Recommendation 4: Create a smoother pipeline among basic research, T1 (lab to clinic), and T2 (clinic to community) translational research to more effectively link research findings from bench to bedside. This can be achieved by funding cross-disciplinary projects and centers that combine basic research, translational research, and public health application research. Currently there are significant barriers to effective translation of basic biologic discovery to clinical application at critical points, including invention technology transfer, preclinical development and testing, meeting regulatory (FDA) requirements, and capacity for clinical trials. In addition, attention should be paid to monitoring and evaluation to guide technical refinement and successful implementation and scale-up of new interventions (see pipeline diagram below).

Model: "Pipeline of Discovery to Delivery"—Pipeline priorities dependent on global burden of a particular disease or condition



Feedback loops promote refinement and new science

Recommendation 5: Measure the public health impact of the current strategies used in health education regarding pregnancy prevention and acquisition of genitourinary infections. Measure the impact of current treatment strategies for infections of the female genitourinary tract. Use feedback to improve the effectiveness of current strategies by refining the focus of basic research and modifying clinical research practices, with a strong emphasis on the prudent use of antimicrobials by both clinician and patient.

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OBESITY

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Introduction

Obesity has become a major health problem in the United States because of its high prevalence, causal relationship to serious medical illnesses, and economic impact of more than $100 billion per year in direct (health care expenses) and indirect (lost productivity) costs.[1] The working group identified three primary areas for which targeted research could have a high clinical impact.

- Community-based prevention and treatment of obesity. Special focus was placed on behavior lifestyle change, ethnic and racial disparities, issues specific to children and adults, and community issues.
- The cellular, organ, and whole-body physiological mechanisms responsible for (1) obesity-related cardiometabolic disease, with particular interest in the mechanisms responsible for metabolic differences between men and women and ethnic and racial groups; and (2) the beneficial metabolic effects of weight loss.
- The developmental factors that affect weight status, with specific consideration of factors *in utero* and during infancy that influence childhood and adult body weight.

Summary of the Discussion

Community-based Prevention and Therapy of Obesity

Dr. Gary Bennett of Duke University presented background information to start the discussion in the working group. The most recent National Health and Nutrition Examination Survey data show a 40-year disparity in the prevalence of obesity, which has plateaued in white women, but continues to rise in African-American women and children.[2] This discrepancy cannot be adequately explained by socioeconomic status alone. Sociocultural influences may be an important factor to consider; for example, African Americans have a higher acceptance of larger body size than Whites and often demonstrate common misconceptions regarding the health risks associated with obesity. In fact, the few randomized controlled trials of weight loss that have been conducted with African Americans have had limited success, perhaps because they did not address such sociocultural influences.

The working group began by discussing what steps are required to translate what has been learned in academic centers to the community. The group discussed whether future studies should focus on implementation research or on effective interventions, especially given the fact that some highly controlled trials have shown successful outcomes. The following is a list of the major discussion points and observations of the working group:

Community Interventions

- When considering the best age to intervene, effective models of interventions for children that should be taken into account include Planet Health and Coordinated Approach to Child Health (CATCH). Planet Health is a curriculum that helps middle school teachers guide students in learning about nutrition and physical activity while building skills in language arts, math, science, and social studies; understanding how health behaviors are interrelated; and choosing healthy foods, increasing physical activity, and limiting TV and other screen time. CATCH is an evidence-based, coordinated school health program to promote physical activity and healthy food choices, and to prevent tobacco use in children, preschool through grade 8.

- Long-term studies, greater than 2 years, are needed to track maintenance of weight loss.

- Given the difficulty of losing weight in an obesogenic environment, there should be a stronger focus on implementing an ecological intervention model that would coordinate interventions at multiple social levels. These would include the individual, familial, communal, academic, working, and policy levels. Women strongly influence familial lifestyle choices by purchasing food, preparing meals, and serving as family caretakers. Because childhood obesity tracks into adulthood and women potentially play an important role in managing their children's health, there is a need to develop multigenerational research that examines family interventions. Ideally, these interventions would harness women's roles as family caretakers in order to facilitate healthy familial and personal lifestyle decisions. Furthermore, there is limited information on what specifically motivates women to lose weight. Some suggest that women experience increased incentive to lose weight when they become pregnant, but additional research is warranted. Furthermore, the many roles women take on in the family frequently impede their efforts to lose weight.

- White or wealthy women are more likely to breastfeed than Black or poor women. This has potentially large implications that merit further exploration.[3]

- Information is lacking on how physiologic (e.g., hormonal) and behavioral changes, which occur during transitional phases of female development (menarche, pregnancy, menopause), relate, alone and in combination, to increases in rates of obesity. Why do 60 to 70 percent of American women exceed weight gain recommendations during pregnancy, and how can this trend be countered?[4]

The Physiological Mechanisms Responsible for Obesity-Related Cardiometabolic Disease

The obesity working group concluded that cardiovascular and metabolic (cardiometabolic) disease should be a major focus of future research initiatives regarding obesity because these are the most common complications associated with obesity and habitually result in considerable morbidity, decreased quality of life, and increased mortality. However, other important adverse consequences of obesity in women should also be addressed, specifically reproductive dysfunction and certain cancers. Some key questions that should be addressed by future research follow:

- Why does excess body fat cause metabolic and other chronic diseases in some, but not all, obese persons?

- What mechanisms are responsible for the association between obesity and dysfunction or disease in organ systems that are of particular importance to women, including endocrine function; reproductive system; and cancer (breast, uterus, cervix)?
- Why is the relative risk of certain obesity-related diseases, such as type 2 diabetes and heart failure, greater in women than men?
- What cellular, organ system, and whole-body mechanisms are responsible for metabolic improvements associated with weight loss in obese persons? What are the mechanisms responsible for the metabolic benefits of bariatric surgery? Are there weight-loss-independent effects?

The Developmental Effects of Obesity in Utero and During Infancy

In research studies, high-fat diets fed to mice during pregnancy led to a transgenerational effect—the babies developed glucose intolerance and a propensity to become obese. Are effects on preconception human oocytes related? Are they reversible? What are the long-term effects and how can these studies be translated to humans? Discussion points and specific research questions include the following.

- What types of childcare settings or institutional and parental feeding skills predispose infants to obesity? Do large babies, stressful life circumstances, or excessive crying correlate with the incidence of obesity?
- There is currently a gap in research knowledge regarding epigenetic changes, and studies have rarely focused on *in utero* factors.
- Because the field lacks information about how nutritional patterns and changes affect oocyte metabolism, more research should be conducted to answer these questions as well as an additional focus placed on preconception nutritional counseling for women. There should be identifiable ways of communicating to women the increased risk of obesity derived from specific preconception and pregnancy exposures.
- The following environmental health issues may increase the risk of obesity: exposure to tobacco smoke and antiestrogens showing transgenerational effects on male spermatogenesis and oocytes. Additional research on environmental health issues (e.g., Bisphenol A, plastics) would be useful in identifying the existence of and degree of further risks.

Currently, research efforts regarding pregnant women are often highly constrained by inadequate guidelines from IRBs. IRBs should recognize the importance of studies gleaned from pregnant participants and should change guidelines to allow for research on pregnant women. Guidance is needed for institutions on how basic, clinical, and epidemiologic research can be safely and effectively conducted in this way.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Use multilevel (i.e., ecological model) and multigenerational (e.g., family) interventions for obesity prevention and treatment. The specific levels to be considered are

the individual level, such as determining motivators unique to women, as well as intrapersonal, interpersonal, family, community, societal, institutional, and policy levels. Multigenerational interventions should harness women's status as family gatekeepers and caretakers.

Recommendation 2: Develop a comprehensive, rather than a piecemeal, understanding of the metabolic consequences of excess body fat, by conducting transdisciplinary research (basic, clinical, and public health science) to examine obesity's effects on multiple organ systems simultaneously. The use of animal models is important to provide research directions in humans and to provide a better understanding of the mechanisms responsible for effects observed in humans. Most importantly, advanced clinical and translational research involving collaborations between basic and clinical scientists is urgently needed to make clinically relevant advances in the field.

Recommendation 3: Understand reproductive and further factors during pregnancy that affect obesity-related disease and maternal and fetal obesity. Their immediate and long-term effects also should be considered.

Overall, the working group believed the field would benefit from funding mechanisms, such as was done with the Transdisciplinary Research on Energetics and Cancer (TREC) centers at the National Cancer Institute, which give incentives to researchers conducting related work at different levels (cellular, animal, human) and different phases of translation (bench, bedside, community) to work together to translate findings.

Other research goals are relevant to community-based prevention and therapy of obesity.

- Establish when in specific life-course stages (preconception, *in utero*, childhood, adolescence, adulthood) interventions are most effective at interrupting disparate obesity trajectories. This research should particularly focus on the female developmental time periods of menarche, pregnancy, and menopause.
- Develop interventions that lead to sustained weight loss and improvements in metabolic parameters and health outcomes. This research may include the evaluation of communities with low prevalences of overweight and obesity.
- Develop interventions that prevent weight gain and determine the relative importance of diet and physical activity.
- Implement obesity intervention programs that recognize and study socioeconomic, geographic (e.g., urban/rural), and ethnic/racial disparities with consideration of research findings regarding sociocultural influences.
- Determine the most effective and sustainable methods of implementing, translating, and disseminating evidence-based interventions to communities. Possible methods may include public education programs, use of new technologies such as social networking, and tailored messages.

Other research goals relate to physiological mechanisms responsible for obesity-related cardiometabolic disease.

- Understand the cellular, organ system, and whole-body mechanisms responsible for the metabolic consequences of obesity. These studies should be directed to provide an understanding of (1) why excess body fat causes metabolic and other chronic diseases; (2) why some obese persons are resistant to the adverse metabolic effects of obesity; (3) how obesity affects different organ systems; and (4) why the relative risk of certain obesity-related diseases is different in men and women, particularly type 2 diabetes and heart failure.
- Determine the cellular, organ system, and whole-body mechanisms responsible for metabolic improvements associated with weight loss in obese persons. In addition, provide a better understanding of why these improvements are seen with moderate 5–10 percent weight loss despite the persistence of obesity.
- Other research goals relate to developmental obesity.
- Concentrate on the postpartum health and weight trajectory of women.
- Determine what level of intervention before (e.g., oocyte level, *in utero*) and during pregnancy is required to prevent obesity/metabolic syndrome in infants and how these conditions track into adulthood.
- Develop effective educational programs highlighting the importance of prepregnancy planning (e.g., planned pregnancy, preconception diet, and diet during pregnancy).
- Determine causes of and remedies for racial/ethnic disparities in pregnancy-related outcomes.

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WOMEN IN BIOMEDICAL CAREERS

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Introduction

The participants of the Biomedical Careers Working Group recognized that women today are well represented in life science fields. They have earned more than 40 percent of medical and biomedical doctorates since 1995. By 2006, approximately 50 percent of the new recipients of M.D. and biomedical Ph.D. degrees in the United States were women.[1,2] However, women are underrepresented in positions of research leadership. During the past 5 years, approximately 25 percent of principal investigators (PIs) on NIH research grants have been women and the data suggest that this percentage is increasing, however slowly.[3] The problem, as identified by the working group, is not one of a lack of talent and credentials, but rather one of a non-level playing field.[4] The goal of the discussion, therefore, was to understand why this is the case and what can be done to improve the situation.

Summary of the Discussion

The following were the major issues identified regarding women in biomedical careers.

- Although women have a success rate similar to men in obtaining their first grants, they are less successful in securing subsequent funding.[3]
- Women M.D.s leave academia at a twofold higher rate than men M.D.s.[5,6]
- Women Ph.D.s apply for faculty positions at medical schools in smaller numbers than would be expected by their availability in the Ph.D. and postdoctoral populations.[7]

Initial discussion focused on the reasons for this situation. The following were among the points made.

- Academic health centers undervalue the importance of retaining highly skilled scientists, regardless of gender.
- Tenure and promotion decisions are primarily based on numbers of publications and "weighing the CV" rather than acknowledging the many other ways that scientists contribute.
- The climate in medical schools often leaves women faculty feeling isolated and unwelcome.
- The current structure of academia is not designed for faculty with family responsibilities.
- Researchers who have left academia for a number of years have difficulty regaining a fulltime scientist position.

- Mentoring in medical schools is inadequate and undervalued.
- Many of these problems cannot be corrected simply by NIH actions because they are created and maintained by academic institutions.

During lively discussion, the group returned repeatedly to the five main themes below.

Changing the culture: There is a need for institutional transformation at medical schools and other biomedical institutions.

Efforts must be focused on "changing the game" versus teaching everyone how to play the old game. The group strongly concurred that the culture of academic institutions should change.[4] NIH encourages the development of a diverse workforce at all levels through a variety of programs, including entry programs, but can clearly do more in terms of supporting studies and encouraging institutional transformation. This transformation must be directed toward both increasing equity and improving work-life balance.

Colleges and universities are the biggest players and are directly responsible for the environment in which most biomedical scientists work. Tenure and promotion decisions should not be so heavily based on the number of publications and "weighing the CV," but rather should consider other ways that women contribute, such as team building and participation in collaborative projects. Evaluation mechanisms should emphasize quality rather than quantity.

The world of academia appears to undervalue employee retention, whereas businesses recognize the value of retaining trained people.[8] The need for facilitating career reentry for academic physicians also was discussed, and it was noted that data are needed on how many researchers want to reenter academia. Academia should adopt the attitude of businesses, especially considering the time and resources devoted to predoctoral, doctoral or medical, and postdoctoral or fellowship training.

Family-friendly policies are needed at academic institutions and at NIH.

Policies at academic institutions, as at NIH, should continue to strengthen efforts to promote support for childbearing responsibilities for graduate students, postdoctoral fellows, and medical residents; in the absence of such supportive policies, women may feel compelled to delay this important life choice until they start an academic appointment.[9] Other suggestions included extensions of funding for PIs with children, such as the no-cost extensions that are already available on NIH grants, implementation of part-time faculty positions in medical schools, and, when possible, more flexible grant application deadlines, which might be more convenient for researchers who have family care responsibilities.

There was strong agreement about the importance of institutions and universities providing and subsidizing onsite day care. The group believed the lack of affordable day care is not simply a women's issue or even a biomedical career issue, but truly is a workforce issue of importance to the entire United States. Possible initiatives at the national level were (1) grassroots advocacy for congressional bills that support subsidized day care, and (2) a White House summit on work-life balance. Focusing on biomedical research, the working group reached a consensus that child-care costs should be covered by grants as fringe benefits or indirect costs, and each institution

should be responsible for implementing this. A broader awareness of these Federal policies is needed to help assist them in designing their family-friendly policies.

The group also raised the possibility that day care and K–12 education could be directly associated with universities and health professional schools to improve both work-life balance and educational quality. The group did not define what kinds of educational relationships between elementary education and universities should be built, but these ideas might be explored further.

Mentoring programs within research and teaching institutions need to be evaluated.

There is a need for mentor training, clarity of expectations for both mentor and mentee, and assessment of mentoring methods. Mentors should not only help women identify strategies to advance their careers, but also address issues such as work-life balance. While there was strong consensus that systems need to be in place that promote good mentoring practices and ways of rewarding mentors, whether or not mentoring programs should be mandated remained controversial. One suggestion was that PIs be required to increase their effort on a grant by approximately 5 percent if they have graduate students, postdoctoral fellows, or fellows funded on the grant.

A disputed topic was whether grant scores should take into account the family-friendly policies (or lack thereof) of an applicant's institution. Concerns were that this would be burdensome to study sections or that this could have a negative impact on researchers at a "nonenlightened" institution. Although there might not be an acceptable way to do this in grant applications, nonetheless, there was broad agreement that some kind of mechanisms should be in place that recognize and reward institutions with exemplary mentoring and work-life balance practices.

Level the playing field and promote the prestige of women scientists.

The working group expressed the common belief that because women scientists have a decreased probability of gaining tenure, are PIs on fewer grants, publish less often, and do not receive as many invitations to give lectures as their male peers, ambitious graduate students frequently conclude that men may be better thesis advisers. The result is that most women biomedical faculty do not train as many of the best graduate students as men, leading to a self-fulfilling prophecy: women having fewer publications, fewer grants, and less prestige.

What is good for women is good for everyone.

Programs with a gender-neutral approach are more accepted by institutions and are thus more likely to be sustained.

Recommendations

The group envisions a future in which the proportion of women holding academic positions and receiving NIH grant funding is equivalent to the proportion of women in the postdoctoral medical and biomedical community. All researchers should experience a productive work-life balance. None should feel that work pressures force them to delay or abandon having a family. Furthermore, the tenure decision process should value the quality of contributions, not just the quantity of publications. This will become increasingly important as projects become more collaborative and interdisciplinary. The culture of academia should move away from "survival of the fittest" toward a "rising tide lifts all boats."

To bring about these changes, the working group identified the following recommendations to provide guidance to academic institutions and administrators, the health professions, clinicians, and scientists.

Recommendation 1: Funding agencies should develop funding programs for institutional transformation grants, similar to and building upon the information from the NIH Request for Applications, RFA-GM-09-012, "Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering." These grants would support research into best practices that promote work-life balance in institutions engaged in biomedical research and would support initiatives within those institutions to accomplish changes in the culture, climate, and practices of both clinical and basic science departments.

Recommendation 2: There is a need to change the culture of academic institutions so that they recognize the value of retaining highly trained personnel. The current tenure and promotion processes at many health professional schools rely heavily on the dollar value of grants an investigator has received and the number of papers she has published. These criteria fail to take into account other ways in which investigators contribute to their field, such as participation in interdisciplinary work, mentoring, advocacy, and education. Furthermore, the traditional approach forces many to make the unpalatable choice between working longer hours and spending time with their families or on personal pursuits.

Recommendation 3: Individuals, professional organizations, and funding agencies should support mentoring and faculty development. The "leaky pipe" problem is manifested in a disproportionate loss of women at two critical stages. Many women focused on a career in biomedical research are lost in the transition from postdoctoral status to an independent faculty position. One major reason is the perception that the chance of career success for women in junior faculty positions is unacceptably low, but research is needed to analyze the causes and solutions to this phenomenon. NIH should also expand institutional K awards that provide mentoring and bridging support to physician-scientists as they move between completion of clinical or postdoctoral training and an independent research career.

The second stage in which a disproportionate number of women leave biomedical careers occurs after a woman attains an assistant professor position and a first R01. The women who do achieve faculty positions have as favorable a chance of attaining their first NIH research grant as comparably employed men. However, the odds of receiving a second and third grant decline for women, as do the chances of faculty promotion. Better mentoring of junior faculty can reduce these losses. NIH should expand mentor training programs and should develop programs to evaluate mentors and mentoring systems.

Recommendation 4: Institutions should be more aware of the need for subsidized child care. Many young researchers avoid having children during their training period due to an inability to pay for child care. Some find that they must make a financial choice between staying in academia and starting a family. They are effectively forced to wait until a time when they receive a sufficient salary to afford care for their children. This is a problem plaguing all researchers, not just women. Providing subsidized onsite child care would go a long way toward promoting work-life balance in the lives of researchers, both men and women.

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A Vision for 2020 for Women's Health Research: Moving into the Future with New Dimensions and Strategies
University of California, San Francisco (UCSF)
San Francisco, California
May 27–29, 2009

DAY 1 – PUBLIC HEARING

Location: Mission Bay Conference Center

12:00–1:00 p.m. — **Registration**

1:00–1:15 p.m. — **Welcome**

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Linda C. Giudice, M.D., Ph.D., M.Sc.
Professor and Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences, UCSF

Video Welcome
The Honorable Jackie Speier
Congresswoman, 12th District, California

1:15–2:00 p.m. — **OPENING PANEL: Shaping the Future of Women's Health Research—Two Perspectives**

Moderator: Nancy Milliken, M.D.
Professor and Vice Dean, UCSF

Sally A. Shumaker, Ph.D.
Professor & Associate Dean, Research, Wake Forest University

Surina Khan
Vice President of Programs, Women's Foundation of California

2:00–6:00 p.m. — **PUBLIC HEARING**

Moderator: Linda C. Giudice, M.D., Ph.D., M.Sc.

Receiving Public Testimony: Members of the ORWH Advisory Committee and governmental officials and staffers

DAY 2 – SCIENTIFIC WORKSHOPS

Location: Mission Bay Conference Center

8:30–8:45 a.m.

Welcome and Opening Remarks

Vivian W. Pinn, M.D.

8:45–9:30 a.m.

Keynote Address: Why So Slow— The Advancement of Women in Science and Medicine

Virginia Valian, Ph.D.
Distinguished Professor, Psychology and Linguistics, Hunter College and CUNY Graduate Center

9:30–10:15 a.m.

PANEL: Telomeres and Aging: A Women's Health Issue

Elizabeth H. Blackburn, Ph.D.
Morris Herzstein Professor of Biology and Physiology, Department of Biochemistry and Biophysics, UCSF

Jue Lin, Ph.D.
Assistant Research Biochemist, Department of Biochemistry and Biophysics, UCSF

10:15–10:30 a.m.

Working Group Charge

Vivian W. Pinn, M.D.

10:30–10:45 a.m.

BREAK

10:45 a.m.–3:15 p.m.

Lunch and Concurrent Working Groups: Drafting of Recommendations by Area

- **Global Women's Health**
- **Stem Cells**
- **Women's Health and the Environment**
- **HIV/AIDS and Women**
- **Information Technology**
- **Women in Science and Health Careers**

3:15–3:30 p.m.

BREAK

3:30–5:00 p.m.

PANEL: Role of Community-Based Participatory Research ("T3")

Moderator: Cynthia A. Gómez, Ph.D.
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Ngina Lythcott, Dr.P.H., M.S.W., R.N.
Associate Dean for Students, Boston University School of Public Health

5:00–6:00 p.m. **Conference Reception**

DAY 3 – SCIENTIFIC WORKSHOPS

Location: Mission Bay Conference Center

8:30–8:40 a.m. **Welcome and Opening Remarks**

Vivian W. Pinn, M.D.

8:40–9:15 a.m. **New Pathways for Translational Research: How Science Can Advance Women's Health**

Moderator: Linda C. Giudice, M.D., Ph.D., M.Sc.

Claire Brindis, Dr.P.H.
Director, Philip R. Lee Institute for Health Policy Studies, UCSF

Deborah Grady, M.D., M.P.H.
Director, Women's Health Clinical Research Center, UCSF

9:15–10:45 a.m. **Concurrent Working Groups: Finalization of Recommendations**

10:45–11:00 a.m. **BREAK**

11:00 a.m.–12:30 p.m. **Working Group Presentations**

Moderator: Nancy Milliken, M.D.

Presentations by individual Working Group co-chairs and discussion of Working Group results

12:30–12:45 p.m. **Closing Remarks**

Vivian W. Pinn, M.D.

University of California, San Francisco (UCSF)
San Francisco, California
May 27–29, 2009

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INTRODUCTION

This report summarizes the second regional strategic planning meeting, held May 27-29, 2009, at the University of California, San Francisco (UCSF). The meeting format included welcoming remarks from the ORWH Director and the University sponsor, a video welcome by California Congresswoman Jackie Speier, a keynote address on the advancement of women in science and medicine, public testimony from 45 participants, a charge to participants by the ORWH Director, and six breakout working groups. The groups addressed scientific challenges, gaps, and opportunities for women's health in six areas: global health, HIV/AIDS, careers, environmental risk factors, information technology, and stem cells. Below are highlights from the plenary presentations.

SUMMARIES OF PLENARY PRESENTATIONS

OPENING PANEL: SHAPING THE FUTURE OF WOMEN'S HEALTH RESEARCH—TWO PERSPECTIVES

The opening panel speakers highlighted the progress that has been made in women's health research but noted that there is still much more to do. They called for new research approaches to ensure the equitable representation of underserved populations of women in clinical research. The challenges and potential benefits of community-based participatory research were also discussed.

Nancy Milliken, M.D.

Professor and Vice Dean, University of California, San Francisco

Dr. Milliken moderated the panel and introduced the presenters as leaders committed to communication between academia and the community. She characterized this dialogue as a way to identify the important questions that merit further research and to educate providers to the needs of patients. In addition, such communication can help make leadership positions a possibility for academics and community members who are working on women's health.

Sally A. Shumaker, Ph.D.

Professor and Associate Dean, Research, Wake Forest University

Dr. Shumaker traced the progress of women's health research using the example of the Women's Health Initiative (WHI), the NIH study that began in 1991. At the time, some expressed skepticism that women would participate in clinical studies; others said a hormone trial was not needed because the outcomes were already known. The WHI successfully enrolled large numbers of women, has a retention rate of more than 90 percent, and has produced a number of unexpected findings. In addition, the WHI continues to generate hundreds of papers, new hypotheses, and new ancillary studies on the health of older women; and it opened the door for a large number of women scientists who have become engaged in and are leaders in the biomedical sciences. Although much progress has been made in women's health research, important challenges remain, such as increasing diversity among health researchers and decisionmakers. Research is still needed to address health disparities, women's health issues across the lifespan, and cultural and international differences in women's health. Creative new models are needed to overcome the multiple barriers facing diverse and underrepresented groups.

Surina Khan
Vice President of Programs, Women's Foundation of California
Ms. Khan discussed the important role of community participation in health care research. The traditional central role of women as decisionmakers for the health care of families means that efforts to engage women in research will yield dividends in the improved health of family members. She said that individuals and communities that are most impacted by health disparities are in the best position to help develop solutions. Among the communities she mentioned were elder women, women of color, low-income women, lesbians, women in the military, and women in military families. Among the areas of research Ms. Khan said needed greater attention were environmental health, including women's exposure to workplace toxins; the effect of economic insecurity on the health of elder women; lesbian health; causes and prevention of child sexual abuse; and the effect of trauma on women's health, including from domestic violence, human rights violations, or exposure to HIV. Researchers also need to take into consideration what it takes for communities that experience health disparities to fully participate, including access to childcare and transportation.

KEYNOTE ADDRESS: WHY SO SLOW—THE ADVANCEMENT OF WOMEN IN SCIENCE AND MEDICINE

Virginia Valian, Ph.D.
Distinguished Professor, Psychology and Linguistics, Hunter College and CUNY Graduate Center
Overt discrimination against women has all but disappeared from academic biomedical research settings, and, with a few exceptions, gender equity now exists in hiring for most entry-level biomedical fields. However, women continue to lag behind men in the uppermost rungs of most biomedical academic career ladders. Dr. Valian cited research suggesting that gender-role "schemas" are cognitive barriers to the attainment of leadership positions among women. Schemas of women as helpers and nurturers are consistent with gender roles but inconsistent with the prevailing schemas of the ideal qualities of scientific leaders and innovators, which are more likely to be attributed to men. Furthermore, women who act in ways that are consistent with leadership schemas (and not consistent with helper-nurturer schemas) may risk being viewed negatively by academic decisionmakers and colleagues. The persistence of gender-based schemas leads to an "accumulation of advantage" for men over time. Institutional efforts to reduce structural barriers to women's career advancement will likely not be enough to eliminate inequalities. To achieve that end, efforts are needed to heighten awareness among members of the research community of the effects of schemas on their behavior toward and perceptions of more junior faculty, as these influence their decisionmaking.

PANEL: TELOMERES AND AGING—A WOMEN'S HEALTH ISSUE

Elizabeth H. Blackburn, Ph.D.
Morris Herzstein Professor of Biology and Physiology, Department of Biochemistry and Biophysics, University of California, San Francisco
Dr. Blackburn presented evidence that variations in telomere length are influenced by modifiable environmental factors, and hence may provide a new model for studying environmental influences on aging and age-related diseases. She explained that although telomeres do not contain genes, they play a role in chromosomal replication. They also shorten with repeated cell cycles, so that telomere length is a biomarker for cellular aging. Recent studies have

found a relationship between telomere length and longevity in human samples. While telomere length appears to be highly heritable, there is also evidence that it can be influenced by environmental factors.

Jue Lin, Ph.D.
Assistant Research Biochemist, Department of Biochemistry and Biophysics, UCSF
Dr. Lin discussed reports of telomere shortening in two samples with high psychosocial stress, with one consisting of mothers caring for chronically ill children, and the other of family caregivers of dementia patients. This area of research could lead to the development of new biological and behavioral interventions to promote longevity and ameliorate age-related illnesses. New high-throughput methods for examining telomere lengths on a large scale are available and should facilitate this line of research in human samples.

PANEL: THE ROLE OF COMMUNITY-BASED PARTICIPATORY RESEARCH ("T3")

Cynthia A. Gómez, Ph.D.
Founding Director, San Francisco State University Health Equity Initiatives
Dr. Gómez opened the panel by saying that community-based participatory research (CBPR) can reduce the distance between the people who produce scientific research and the people who use the results. CBPR is an extension of multidisciplinary research and attempts to create mutually beneficial relationships between scientists and the community. The outcomes are better science and increased interest and knowledge of research from the public.

Elena Rios, M.D.
President and CEO, National Hispanic Medical Association (NHMA)
Dr. Rios emphasized that CBPR relies on coalition building. She explained how her organization has been building coalitions to improve the health of the Hispanic community, which, according to the 2006 National Healthcare Disparities Report, has the most problems with disparities in health care of any ethnic group in the United States. New challenges will arise as the Nation's demographics change. The new America will consist of populations that face severe lack of access to health care, lack of trust and knowledge, and are low-income, poorly educated, with strong cultural and family values, limited English proficiency, and living mainly in urban areas. They suffer from high rates of obesity, diabetes, infectious and chronic diseases, and demand health care reform. To address these problems, the NHMA brought together 100 people from disparate organizations—medical schools, foundations, insurance companies, unions, schools, community clinics, Hispanic chambers of commerce, and government—to talk about improving health care for the community. Dr. Rios detailed the recommendations that resulted, broadly falling under the categories of improving access to care and preventing obesity and diabetes.

Karen Pierce, J.D.
Coordinator, Bayview Hunters Point Health and Environmental Assessment Program
Ms. Pierce discussed some of the challenges that can make CBPR more difficult and time-consuming than traditional research. Her program addresses the impact that environmental contaminants have had on the health of the Bayview Hunter's Point community of San Francisco, a predominantly African-American community. One particular challenge was developing a

survey instrument that not only included the key factors that researchers wanted to assess, but also framed questions in a way that community members could understand and to which they could give substantive responses. Translational challenges arose in another project that sought to involve community members with basic science research. The partners in the study continue to examine how the community voice might directly influence the way research is conducted, how to interpret the research findings, and who should be involved in that interpretation. Finding solutions to such challenges takes time and commitment to true collaboration. When applying for funding, researchers should take into account the amount of time that is needed to complete a CBPR project. Ms. Pierce also recommended that funding organizations require a copy of the principles of collaboration agreed upon by all parties as part of all funding applications. In addition, funders should more strongly encourage partnerships between researchers and the community. To encourage dissemination into the community, scientists should consider publication of study results in popular media a respectable goal, and continue to work together with community members to formulate recommendations from their findings.

Caitlin Ryan Ph.D., M.S.W.
Director, Adolescent Health Initiatives, Cesar Chavez Institute at San Francisco State University

Dr. Ryan outlined the benefits of CBPR by describing her research on how family behavior affects the mental health of lesbian, gay, bisexual, and transgender (LGBT) adolescents. The Family Acceptance Project uses a participatory research approach to engage community members, health and mental health providers, social workers, teachers, families, and youth in planning and implementation. Results are being used to develop culturally competent interventions to strengthen families, improve health and mental health outcomes for LGBT youth, and improve the quality of care they receive. The community groups and the participants were instrumental in identifying the 106 family behaviors (positive and negative) that were most important to mental health outcomes. The CBPR method also helped connect the researchers to communities such as farm workers and non-English speakers.

Marj Plumb, Dr.P.H., M.N.A.
Coach, Consultant and Trainer, Plumbline Coaching and Consulting, Inc.

Dr. Plumb highlighted the successes of the community research collaboration (CRC) awards funded by the California Breast Cancer Research Program (CBCRP) and discussed some of the important lessons learned. Community research collaborations produce outcomes that benefit the community, the researcher, and the science. In evaluations of more than 60 CRC projects, CBCRP found that the program encouraged women affected by breast cancer to participate in the research process and fostered the inclusion of diverse participants (including disabled women, lesbians, rural women, Samoans, Koreans, Hmong, Guam immigrants, and hard-of-hearing women). When technical assistance was provided by CBCRP, it was regarded as important and valued. To facilitate successful outcomes, community research teams should focus on fully collaborating through all steps of the research process. Funders must become active participants, providing technical assistance, outreach, and support to both community members and researchers. Thoughtfully written agreements are required to ensure full collaboration throughout all phases of the research process and to reduce barriers to community participation.

Ngina Lythcott, Dr.P.H., M.S.W., R.N.
Associate Dean for Students, Boston University School of Public Health
Dr. Lythcott emphasized the role of CBPR in giving the community a sense of control and providing community members with a chance to develop new skills. Funding organizations should expect researchers to use CBPR in most population-based research, taking into account the additional time needed to truly engage a community in participatory research and the costs associated with these efforts. Dr. Lythcott also recommended that researchers partner with existing community-based organizations to empower community members to take on formal and informal leadership roles. Research funding should support the establishment of a community coalition board to serve in an advisory capacity. Researchers should directly involve community members in the conduct of the research by training them to identify a hypothesis and collect and interpret data. To ensure that the research results provide the maximum benefit to the community, researchers should write a "lay" abstract of the research and community members should be encouraged to help disseminate the findings.

PANEL: NEW PATHWAYS FOR TRANSLATIONAL RESEARCH: HOW SCIENCE CAN ADVANCE WOMEN'S HEALTH

A translational research panel focused on the potential for systems biology research to make possible dramatic advances in women's health research.

Linda C. Giudice, M.D., Ph.D., M.Sc.
Professor and Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences, UCSF
Dr. Giudice defined systems biology as a discipline at the intersection of biology, mathematics, engineering, and the physical sciences. It integrates experimental and computational approaches to study and understand biological processes in cells, tissues, and organisms. The field is holistic and integrative, as opposed to more traditional reductionist scientific paradigms. Its progress has been greatly facilitated by advances in high-throughput technology, computer science, and bioinformatics. Systems biology uses whole-system methods, such as genomics (study of the whole set of genes of a biological system), proteomics (study of the entire set of proteins expressed in a system), transcriptomics (study of the set of RNA transcripts of a system), and metabolomics (study of the set of metabolites in a biological process). Applied to human health, systems biology holds the potential to predict the physiological behavior of a complex system in response to natural and artificial perturbations, and thereby contribute to the understanding of the etiology of disease as well as to the development of new diagnostic and prognostic technologies and identification of new treatments.

Systems biology approaches are applicable to a wide range of conditions and disorders of importance in women's health research. These include breast and gynecological cancers, endometriosis, developmental and regenerative medicine, and systemic diseases, such as immune disorders, cardiovascular disease, and diabetes. A goal for the future is to apply systems biology to the development of personalized medicine. A current example of a personalized medicine application of systems biology is found in the development of MammaPrint, which yields a 70-gene breast cancer expression signature to predict which early-stage breast cancer patients may in fact be at risk for metastasis or recurrence. Challenges to advances in systems biology as applied to women's health include the tasks of identifying and modeling the

biologic, genetic, and hormonal diversity of women. Career development in this highly interdisciplinary field is of the utmost importance. There are dual challenges: to prepare women's health researchers with skills needed to work collaboratively on systems biology problems, and to stimulate increased interest in systems biology approaches to women's health research.

Deborah Grady, M.D., M.P.H.
Director, Women's Health Clinical Research Center, University of California, San Francisco
At a time when comparative effectiveness research is being emphasized, the biomedical research enterprise must consider how to maximize its potential contribution to inform clinical best practices. Dr. Grady noted that it is unrealistic to expect that even large-scale clinical trials will be adequately powered to provide answers to questions of effectiveness for different population subgroups. There is a need to design new models of clinical research to provide more information on effectiveness, and to implement strategies to utilize results from varied and multiple sources. Meta-analysis provides one such standard method for studying effectiveness, and its impact could be enhanced if researchers were to provide more uniform data elements and information about the characteristics of subjects in their studies. Other methods include advanced statistical modeling and repeated measures meta-analysis. Propensity scores may be derived from observational studies to assess causal effects. The combined use of observational and clinical trial designs within one study has merit for yielding more information than could be obtained from stand-alone studies. The next generation of clinical trials will include Web-based recruitment, advanced electronic data collection and management, and access to and pooling of data from multiple clinical sources. ORWH should consider funding methodological research on alternative methods to randomized clinical trials. In its interdisciplinary training and career development programs, it should also consider enhanced efforts to recruit individuals from fields needed to advance data mining and clinical study design, such as information technology and biostatistics.

Claire Brindis, Dr.P.H.
Director, Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco
Dr. Brindis discussed how rapid technological change contributes to information overload, leading to important questions. For example, what is the best method for communicating complex health findings? How can researchers ensure that communication not only is understood but also results in behavior change? Dissemination—that is, the uptake of information—is the communication challenge of the 21st century. For this process to be successful, many partners must be involved, including the media, health care providers, policymakers, and consumer educators. The latter group, in particular, may provide a means of "narrowcasting" messages more effectively to communities experiencing health disparities. Funding organizations could support this process by funding research on implementation science. Likewise, in educating the next generation of scientists, training in core communication competencies may arguably be as important as basic sciences education for maximizing the impact of the biomedical research enterprise.

CHARGE TO THE WORKING GROUPS

Before meeting participants broke out into working groups, the ORWH Director noted that, "if everything is a priority, then nothing is a priority." She urged members to undertake the hard work necessary to narrow their focus to the most pressing women's health issues, while at the same time identifying, within that focused scope, new opportunities for cutting-edge science and technology applications. Finding this intersection of public health needs and science opportunity is what ORWH seeks to achieve as it prepares to update its strategic plan.

SCIENTIFIC WORKING AND DISCUSSION GROUPS

GLOBAL WOMEN'S HEALTH

Cochairs:

Paula Tavrow, Ph.D.
University of California, Los Angeles

Amy Levi, Ph.D., C.N.M.
University of California, San Francisco

Warner Greene, M.D., Ph.D.
University of California, San Francisco

Kirsten Bibbins-Domingo, M.D.
University of California, San Francisco

NIH Cochairs:

F. Gray Handley, M.S.P.H.
National Institute of Allergy and Infectious Diseases

Linda Wright, M.D.
Eunice Kennedy Shriver *National Institute of Child Health and Human Development*

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Simran Sabherwal, M.H.S.
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Carinne Meyer, M.P.H.
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Introduction

Even though 85 percent of excess disability and mortality occurs in the developing world, less than 4 percent of research funding is devoted to identifying the factors and mitigating the conditions that underlie the global disease burden. Biological, social, political, and economic factors combine to put women, especially those in the developing world, at risk for disease, injury, and death across their life course. Pregnancy and childbirth can be life-threatening events for women in developing countries: more than one-half million women die of preventable causes related to pregnancy and childbirth every year, 99 percent of whom are in developing countries. For every woman who dies, another 30 are estimated to suffer long-term disabilities related to maternal reproductive causes. Women in low-resource countries also suffer disproportionately from malnutrition, some infectious diseases, gender-based violence, certain chronic conditions

(such as depression and longevity-related diseases), and unwanted pregnancies. In many cases, women's ill health and death could be avoided through simple, effective, and cheap interventions that are already known, but are not accessible or affordable to women.

The group began by reviewing sex and gender disparities in disease and injury in each stage of women's lives in developing countries, beginning *in utero* and ending in old age. Gender disparities were identified in the areas of health risks (women have less opportunity to enjoy good health); health needs (women have greater needs due to childbearing and longevity); and organization of health care (women may have more responsibilities in providing health services, but the power resides with men). The session highlighted specific areas where global disparities are particularly acute, such as in maternal mortality, unsafe abortion, and maternal disability. Participants also took note of health conditions that almost exclusively affect women in developing countries, such as female genital mutilation, obstetric fistula, chronic conditions (and deaths) associated with indoor cooking fires, and the interaction of infectious diseases like malaria with pregnancy.[1]

Summary of the Discussion

Before the conference, it was decided that the Global Women's Health Working Group would be split into three subgroups: (1) maternal, sexual, and reproductive health, (2) chronic diseases, and (3) infectious diseases. Each subgroup was asked to answer the following questions. What should be the priorities for research in this area? How should the priorities be set? And, how could research be structured to achieve maximum impact on women's health in developing countries? Because the first subgroup had more than 40 participants, it was further divided into two discussion groups—maternal health and sexual/reproductive health—and brought together again to develop priority recommendations.

Maternal, Sexual, and Reproductive Health Subgroup

This subgroup's guiding principles were to focus the research agenda on areas where women in the developing world have a disproportionate burden of disease or disability, and on neglected topics where research to date has been limited. The subgroup unanimously agreed that the greatest disparities globally are in the areas of maternal morbidity and mortality. More than 500,000 women die from childbirth and pregnancy complications each year, 99 percent of whom are in developing countries. Millions more suffer debilitating conditions related to pregnancy, unsafe abortion, and postdelivery complications.[2,3]

To address maternal mortality and morbidity effectively, it is important that research address not just tertiary prevention, such as access to quality obstetrical care, but also primary and secondary prevention, including nutrition, effective use of fertility control measures, safe abortion, and maternal health education.[4,5,6] The subgroup noted that the *Eunice Kenney Shriver* National Institute of Child Health and Human Development (NICHD) Global Women's and Children's Health Network focuses mainly on the tertiary prevention of maternal mortality and on approaches to improve child outcomes. It gives insufficient attention to primary and secondary prevention as well as to the role of health systems strengthening.[7,8]

The subgroup also stated that the sexual and reproductive health of female children and adolescents in developing countries should be a research priority, since sexual and reproductive health is cumulative and has effects across the lifespan. Moreover, inadequate attention has been given to improving the health of girls and young women in developing countries, particularly those who are poor, marginalized, and unmarried. Sociocultural issues that can have profound effects on women's later health—female genital mutilation, child sexual abuse, sex trafficking, early marriage, unwanted pregnancies, sexually transmitted diseases, and gender violence (including teen dating violence)—have been under-researched in developing countries.[9-13] Little research exists on their etiology and epidemiology, as well as on effective interventions to mitigate these practices in children and young women. It is imperative that local researchers be included in these studies, and that the research be culturally sensitive and responsive.

The subgroup noted that renewed attention needs to be given to family planning and contraception, particularly in sub-Saharan Africa and South Asia. The AIDS epidemic had drawn attention away from ongoing needs in this area.[14,15] Specifically, a wider range of contraceptives needs to be developed that can be used by men, can be used postcoitally by people who have infrequent or unplanned sex, and that are entirely under the woman's control (without the need for a provider as intermediary). There also need to be easier and cheaper ways to assess fertile times of the month for women and to achieve menstrual regulation.

The subgroup concluded that the most pressing research priorities were to reduce maternal mortality and disability, improve children and adolescents' reproductive health, and develop more effective and wide-ranging contraception methods particularly suited to conditions in developing countries. In addition, there is a strong need to build global women's health-research-and-implementation capacity, especially in terms of female researchers, policymakers, and managers. The group lamented that funding is lacking in areas of health where global disparities are greatest. For example, no global fund exists for maternal health, although one exists for AIDS, malaria, and tuberculosis. Current research grant opportunities through the NIH Fogarty International Center programs do not address women's issues specifically, and the scope of the activities of the Global Network for Women's and Children's Health Research needs to be broadened to include barriers specific to maternal and reproductive health.

The subgroup also discussed the research process. They noted that researchers need to test interventions that take into account the values, beliefs, and traditions of communities with respect to maternal and reproductive health. Participation of religious, community, and youth leaders can help ensure that data gathering and interventions are designed and implemented in culturally sensitive ways. Not only will culturally appropriate research yield better results, but research can help suggest alternative modalities to traditional practices that may be harmful to women. For example, the implementation of low-emission stoves in Guatemala has improved infant and child health outcomes while preserving traditional indoor cooking practices.[16]

Participants agreed that interdisciplinary and interprofessional research can address the complexities of maternal, sexual, and reproductive health in developing countries by taking into account ethnicity, culture, and biology. New modalities of problem identification and service

delivery may need to be tested to better assist specific populations, such as displaced women, orphans, and disabled women in resource-constrained settings. NIH grants that foster this type of interdisciplinary research will facilitate innovation in cross-cultural biomedical and sociomedical research methods.

Because global women's health researchers often work in isolated regions or are testing interventions targeted to specific groups, it would be valuable to them to have a single repository of comparative effectiveness research—including validated instruments, recommended methodologies, and data. The NIH could play a central role in the development of such a repository that would be freely accessible.

Because of liability and ethical concerns, pregnant and lactating women have often been excluded from drug effectiveness research. However, the subgroup felt that creative approaches need to be developed to include these women in drug studies, such as using a registry or a postmarketing surveillance model. Drugs that are available in developed countries may not have the same applicability in developing countries because of differences in nutrition, availability of refrigeration, and acceptability of administration. Research that examines traditional healing practices in the context of currently available pharmacologic regimens can help identify the best approach to introducing medications in developing countries.

Lastly, the subgroup discussed how best to build research capacity and promote women's leadership in health care. More attention needs to be paid to creative approaches for increasing capacity in developing countries, such as ongoing support for women educated abroad who return to their home countries, opportunities for women leaders to share experiences with one another, and gender diversification in the workplace. Furthermore, translational research models need to be developed for diverse settings in order to accelerate the use of bench science to direct patient care. Currently, translational research often assumes that women's experiences are universal and that scientific investigation from industrialized countries will translate in similar ways, not recognizing that context and resources can matter greatly.

Chronic Diseases Subgroup

This subgroup expressed dissatisfaction with the universal neglect of research into chronic diseases and women globally, even though most chronic disease is found in the developing world. For middle-income countries, chronic diseases are rivaling infectious diseases in importance.[17] The subgroup noted that managing chronic conditions among women is particularly challenging because of their caregiver roles, the costs of chronic disease treatment, and women's natural longevity, which makes them more vulnerable to chronic disease.

Women are disproportionately affected by particular risk factors and chronic disease manifestations, such as stroke, blindness, depression, and exposure to household air pollutants and cooking fuels. The group noted that focusing on women was essential to improving the health of the entire population because of the central role that women play in family health.

The subgroup was large and diverse. Participants included individuals new to chronic disease; individuals who had worked on other women's health topics and who were aware of

the increasing burden of these illnesses among women; and others with expertise in specific common and neglected chronic illnesses globally, including diabetes, chronic obstructive pulmonary disease, and mental health. A brainstorming session allowed all participants to contribute ideas for the final report.

During the second half of the brainstorming session, participants identified major emerging themes and sought to frame these in the language and interests of NIH and ORWH. The subgroup noted that unhealthy diet, sedentary lifestyles, and tobacco use underlie most chronic diseases. However, much remains to be learned about the potentially differential impact of these risk factors on women, and whether there are certain risk factors that solely relate to women. Moreover, in developing countries, factors associated with poverty, the environment, and women's unequal status may also be influential. The determinants of chronic depression among women in developing countries have been particularly neglected.

Participants identified the following as essential components of research in women's chronic disease.

1. Understand environmental factors and physical factors contributing to chronic disease burden in women: (1) early events and exposures (including *in utero*), (2) gender-based factors, (3) family events, and (4) mechanisms of action. Such studies would have a longer time horizon (e.g., 10 years) and would include novel designs (e.g., intergenerational, multilevel). Ideally, such studies would also attempt to understand the bidirectional impact of factors on developing countries and recognize the effects of immigration and multinational global influences.

2. Identify and measure social and cultural factors that influence chronic disease uniquely in women: (1) women's role or status, (2) the impact of men on women's health, (3) the impact of the family, (4) cultural or societal expectations, (5) the work or domestic environment, (6) norms and behavioral expectations, (7) aging, and (8) social determinants of health/social class. Such studies would also have a longer time horizon and be focused on mechanisms of action. Because these studies are focused uniquely on women, the potential exists in this area to use existing infrastructures to study and deliver care in areas of maternal and reproductive health to expand and collect data of relevance regarding mechanisms of chronic disease in women.

3. Assess, transfer, and develop interventions to prevent and treat chronic disease globally. The focus in this area would include evaluating interventions known to work in developed countries and translating them to other settings, as well as developing appropriate interventions in less developed settings. The focus is on comparative effectiveness and translation of appropriate interventions, but the timeline is much shorter, recognizing the need to get appropriate interventions to appropriate settings quickly and in an effective manner. Such work should be bilateral and focus on the implementation of global successes in the United States and in developing countries, with bilateral exchanges of ideas and innovation. Such work would also integrate organizations and institutions outside of the traditional health care sector (e.g., schools).

4. Expand chronic disease research capacities in developing countries: (1) increase personnel (clinical researchers and health workers in residency) and funding oppor-

tunities (the Fogarty International Center or the Building Interdisciplinary Research Careers in Women's Health [BIRCWH] program); (2) institutions; and (3) patient advocacy. Such work recognizes that a major threat to effectively addressing chronic disease in developing countries is the lack of infrastructure to deal with the long-term impact of such illness. Research capacity should address local solutions, improve the ability for bilateral exchange of ideas, and ideally be integrated into the public health and health care delivery infrastructures as well.

The major barrier to achieving these research goals is a failure to recognize chronic disease as the primary contributor to morbidity and mortality globally, particularly among women. A focus on chronic disease is central to improving the health of women globally, and the issues raised by chronic disease will only continue to grow over time. ORWH can play a major role in overcoming these issues by (1) continuing to emphasize this area as a focus in addition to the more traditional areas of maternal and reproductive health, and (2) creating opportunities to use the existing infrastructure for the study of issues in maternal and reproductive health to expand research into chronic disease and associated risk factors in women.

Infectious Diseases Subgroup

This subgroup considered the main infectious diseases that cause excess disease and mortality burden in developing countries, specifically the "gang of four": malaria, tuberculosis, neglected tropical diseases, and HIV/AIDS. The group noted that women bear a disproportionate burden regarding these diseases. Women, children, and individuals living in remote areas and urban slums are most vulnerable to the consequences of neglected tropical diseases.[18] The cochairs led a discussion about the need for biomedical research focused on the roles of sex and gender in health and disease. Many felt that this area of research had only been recognized in the past few decades as the differences between the biochemistry and physiology of men and women became more fully appreciated.[19] The group agreed that recent efforts to fill the gap in women's health research are starting to mobilize the scientific community in new directions but that more research in this area is urgently needed.

Within the discussion, priorities were set by assessing various infectious diseases and gauging their selective impact on women's health. Prioritization emerged as a result of consensual decision making within the group. The group felt that since malaria in pregnancy is a major risk factor for maternal mortality, particularly in Africa, it should be a priority research area. In addition, tuberculosis is responsible for approximately 9 percent of all deaths in women ages 15 to 44 years, and deserves more examination. Finally, more than half of HIV infections in sub-Saharan Africa occur in women, because of physiological, economic, and sociocultural factors. HIV in women in developing countries is another important and essential area of emphasis, particularly due to its contribution to the global burden of disease.[1]

Current barriers discussed include a relative lack of funding for gender-specific studies, particularly of infectious processes occurring in the developing world. Additional barriers include diminished access to health care by women in many developing countries.

Discussion then turned to possible avenues of innovation for research in infectious disease, including the biological, behavioral, and hormonal causes of disease and disease susceptibility; and the need to explore women's particular susceptibility to other diseases beyond HIV. Participants agreed that a transdisciplinary and translational approach would be needed to fully understand and treat these often intractable infections.[19] It was suggested that it would be valuable for NIH to develop Requests for Applications (RFAs) to fund research in different disciplines, such as genomics, where new technologies and sciences are generating important perspectives and new evidence for gender studies. In addition, more efforts to identify the institutions necessary for the implementation of interventions specific to women would create sustainable and long-term benefits for women's health.

In considering critical research gaps, the subgroup focused on three main areas: (1) understanding the dynamics of disease transmission, and why women are more susceptible to certain infectious diseases; (2) considering the special case of breast milk, and developing approaches to mitigate diseases passing from mother to infant; and (3) researching effective strategies to prevent infectious diseases, particularly when women are pregnant and most vulnerable.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Implementation science. Support is needed for innovative, translational research to facilitate the application of evidence-based and sustainable interventions in developing countries to improve women's health (particularly reducing maternal morbidity and mortality) and reduce barriers to care. Research should focus on the following:

- Preventive strategies that aim to reduce risk for reproductive, chronic, and infectious disease
- The development of standards of practice for how to conduct culturally sensitive research

Recommendation 2: Sexual/Reproductive health. Research is needed on the determinants, long-term consequences, and effective strategies for eliminating or reducing the following understudied issues that affect female children and adolescents in developing countries: early sexual trauma, female genital mutilation, exploitation and trafficking, coerced sex, gender-based violence, and early marriage. Longitudinal studies to determine cumulative effects on women across the lifespan should be instituted. Another area in need of increased research is unwanted pregnancy, particularly among the young, marginalized, and poor. Support is needed for the following:

- The development and evaluation of new and improved contraceptives—particularly male, postcoital, and female self-administered contraceptives—that are appropriate and sustainable for developing countries
- Behavioral research required to understand the factors underlying the expanded use of contraceptives in developing countries

Recommendation 3: Mechanisms of chronic disease risk across the life course. Research on the biological, environmental, behavioral, and physical factors that contribute to or protect

against chronic diseases (including mental illness) in women, as well as research that explores their mechanisms of action, is needed. Recognizing the effects of poverty, the environment, and women's unequal status, it is recommended that research focus on the following:

- Early events and exposures (including *in utero*)
- Family and intergenerational causes
- Lifestyle factors that uniquely affect women

Because chronic depression among women in developing countries has been particularly neglected, we recommend research that identifies both protective and risk factors for depression among these women. Best practices for prevention and treatment within various cultural, political, and economic contexts need to be determined.

Recommendation 4: Infectious diseases. Research is needed to understand the increased susceptibility of women in the developing world to various infections, including malaria, HIV, HPV, and sexually transmitted infections (STIs). The following research should be funded:

- The pathways (basic science) of behavioral and hormonal changes across the menstrual cycle and lifespan that can influence infectious diseases. This will lead to a better understanding of how women are affected differently, thereby contributing to better prevention and treatment.
- Pregnant women and/or women with compromised nutritional status. (These two conditions affect millions of women and place them at increased risk.)
- The physiologic mechanisms of transmission of HIV and other infectious diseases through breast milk, since breastfeeding is so important for children's health and well-being in resource-constrained environments.

Recommendation 5: Capacity building in developing countries. The brain drain of health researchers, medical practitioners, and program managers is a serious problem in most developing countries. To help slow or reverse this trend, we recommend enhancing research capacity in developing countries through the following:

- Mentorship programs
- Research training programs
- Leadership development of women
- Building supportive institutional environments (including those in nonhealth sectors)

Using models of female capacity building and career development in the United States, we recommend that similar efforts be undertaken in developing countries.

In addition, we recommend the development of a repository of information technology, standardized definitions, recommended methodologies, and data on women's health, which can be easily accessed and shared. This would enhance research among many disparate areas and populations around the globe.

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STEM CELLS

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Introduction

The working group conducted a roundtable discussion led by the cochairs, with input from participants representing industry, the basic science community, clinician-scientists, and medical practitioners. By exploring the exciting potential of using stem cells in groundbreaking basic science research and clinical applications, the group defined key research priorities with direct relevance to women's health, keeping racial and ethnic considerations at the fore:

- Sex-related differences in stem cell functions
- Role of stem cells in cancer biology
- Regenerative medicine approaches for targeting female-specific diseases
- Public education, advocacy, and science policy

These topic areas reflect the cutting edge in stem cell research and put at the forefront the areas in which investigations into the sex of a stem cell is becoming an essential component for combating disease. Sex differences in stem cell function and the impact of these differences on recipients may have important implications for understanding the way disease works in the body. Recent reports of the presence of estrogen and testosterone receptors on stem cells suggest that hormones may modify the function of cells. For example, researchers have found that muscle-derived stem cells transplanted into dystrophic mice efficiently regenerate skeletal muscle, but they could not obtain a male subfraction with a regeneration capacity similar to that of their female counterparts.[1] These and other findings have persuaded researchers to identify cell sex, a largely unexplored variable, and to consider the implications of relying on cells of one sex.

Achieving a more in-depth understanding of the molecular, biochemical, and functional characteristics of cancer stem cells and their sex differences may lead to the development of more effective and precisely targeted treatments. Stem cell research is also making groundbreaking advances in cancer research. Researchers have already been able to identify the molecular mechanisms that control self-renewal of cancer stem cells, which could ultimately lead to the prevention of tumor formation.[2] Furthermore, some scientists suspect that cancer stem cells may be the cells most responsible for resistance to the drugs currently used to treat cancer, and that sex differences in these stem cells influence outcomes. The development of drugs that target the tiny proportion of cancer cells with self-renewing properties is likely to have long-term benefit for many women's cancers, such as breast and ovarian cancer.

Finally, researchers are discovering aspects of stem cells that may allow scientists to create pluripotent cells (stem cells that have the potential to differentiate into any of the three germ layers), and this achievement could serve as a critical tool in cell replacement therapies and regenerative medicine.[3] The ability to manufacture pluripotent cells holds the promise of developing patient-specific therapies for many degenerative diseases and for designing new tools with which to study human development and disease progression for many diseases, including those that are specific to women.

All of these developments need to be translated into science policy through partnerships with academic and research institutions and leaders in research, business, advocacy, finance, law, and ethics. These parties must come together to create an influential advocacy strategy in order to chart the future of sex-related differences in stem cell investigations, stem cell cancer research, and regenerative medicine.

Summary of the Discussion

The group began by discussing important core concepts regarding possible sex-related differences in stem cells. This neglected variable may partly underlie the varying degrees of pluripotency observed in stem cells from different sources (e.g., embryonic or adult). Another important consideration is the potential for genetic/epigenetic differences between male and female stem cells—differences that could become amplified as a function of time in culture and/or donor age. For example, compared to other gender combinations, female donor/male recipient transplants are associated with increased graft-versus-host disease and transplant-related mortality for patients treated with allogeneic hematopoietic stem cell transplantation.[4] The group emphasized that the sex of stem cell transplants and recipients is not given appropriate consideration in current research or clinical applications, and that this omission could have serious repercussions for the future success of stem cell therapies.

In general, it was noted that a sophisticated and detailed characterization of existing stem cell lines is lacking, which is one reason why information about sex-related functional differences is as yet somewhat obscure. As a remedy to this problem, high-throughput technologies (e.g., proteomics, transcriptomics, metabolomics) could be used immediately to establish and document quality control measures for assessing phenotypic drift due to interlaboratory differences in culture conditions and other standard practices. It was also stressed that the data obtained from "-omics" technologies should be correlated with findings from functional assays of self-renewal, pluripotency, differentiation potential, tumorigenicity, and other stem cell properties.

In relation to cancer biology, sex differences have received very little attention given the potential importance of this variable. Researchers should explore how the physiology of the two sexes (in particular, the hormonal milieu) affects all stages of the disease process. For example, investigators need to know if there are sex-related differences in tumor-initiating cells that affect their stem cell-like properties; such differences could influence the response to therapy and, thus, remission and recurrence rates. Other unanswered questions concern the role of environmental agents and endocrine disruptors in the biology of sex-specific cancers (e.g., breast and prostate). Research on tumor-initiating or cancer stem cells will require robust standard laboratory practices to derive, propagate, and characterize these cells. Understanding the nature of tumor-initiating cells may improve the safety of stem cell therapies by preventing the development of tumors that may result from these therapies.

The working group agreed that regenerative medicine approaches offer great potential for treating diseases, including those that are specific to women, but that these approaches also raise important questions. For example, is there a difference in transplant success attributable to sex match or mismatch of grafts? Existing studies could be reviewed, and the scientific community, together with the FDA, could consider the possible effects of sex-related differences on the success of regenerative medicine approaches in terms of both the transplant and the recipient. The question of sex differences of donors and recipients in regenerative medicine could also be addressed through another approach, which could be readily implemented with current technologies. Male and female stem cells could be systematically studied in the high-throughput screening of potential pharmaceutical compounds.

Working group participants envisioned many exciting stem cell approaches to the treatment of female-specific diseases and conditions. In the future, regenerative medicine applications using stem cell science may improve the outcomes of assisted reproductive procedures. Candidate female-specific diseases include Asherman's syndrome (scarring of the uterine lining), which may be amenable to therapies involving mesenchymal stem cells. Because the female reproductive organs contain tissues that are highly malleable (as illustrated by pregnancy), with a high rate of turnover (as illustrated by menstruation), a stem cell-focused perspective may be key to understanding the biology of diseases in which these processes go awry. Endometriosis is only one example.

Working group participants noted that resident stem cells may be important therapeutic targets that could be exploited in regenerative medicine approaches. Potential treatments include fertility preservation and restoration. To this end, stem cell reconstitution of ovarian function in mice has been successful. Given the profound variations in the hormonal milieu of women over time, the group reiterated how difficult it is to approximate human sex-specific differences using animal models. Mice lack these variations, and the ethics and cost of using nonhuman primates create significant barriers. Thus, the development of cost-effective animal models that mimic the impact of female sex hormones on stem cell-based therapies should be a priority.

Finally, the group also underscored the importance of education, advocacy, and science policy in creating realistic expectations regarding regenerative medicine therapies and setting the national agenda for stem cell research. As a relatively new area that has basic science, translational, and clinical components, the stem cell field needs dedicated campaigns and advocacy groups that focus on education of the public. Communication with the lay public and the media via town hall meetings and at the national level will be crucial for increasing patients' willingness to participate in clinical trials (which is currently low) and for supporting nationwide funding for stem cell research that will deliver on the promises of regenerative medicine approaches.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Explore sex-related differences in stem cell functions. Use multidisciplinary "-omics" technologies and systems biology approaches to fully explore sex-related differences in stem cell biology and transplant success (historically and prospectively).

Recommendation 2: Explore the role of stem cells in cancer biology. Determine if there are sex-related differences in tumor initiation/progression/recurrence that involve tumor-initiating or cancer stem cells and that could, in turn, be exploited for therapeutic purposes.

Recommendation 3: Examine regenerative medicine approaches for targeting female-specific diseases. Consider the XX chromosome complement as a variable in all stages of the pipeline that leads to regenerative medicine therapies and other stem cell applications, such as high-throughput screening to identify pharmaceutical compounds with harmful or therapeutic effects.

Recommendation 4: Conduct public education, advocacy, and science policy. Educate the public, policymakers, and the media about stem cell-related issues, which will help create realistic expectations of the national research agenda and improve patients' willingness to participate in clinical trials.

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WOMEN'S HEALTH AND THE ENVIRONMENT

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Introduction

The cochairs began the session by presenting current insights on trends regarding adverse women's health outcomes, such as reduced fecundity, decreasing age at puberty, and the relatively high prevalence of certain female reproductive conditions, such as uterine fibroids and endometriosis.[1,2] It was also noted that there are racial and ethnic disparities in the distribution of a number of these conditions.[3,4] Environmental influences, defined as chemicals present in the environment, can affect women's health during development and various stages of life (e.g., impact of environmental chemicals on early onset of puberty, endometriosis).[5,6] They also noted that people in the United States are exposed to a large number of environmental chemicals, some of which have been measured in women.[7] Finally, it was noted that environmental chemicals are one of multiple environmental factors, which also include nutrition, stress, and local environments that influence women's health independently or in interaction with each other.[4] The importance of further understanding the disproportionate burden of these environmental factors on certain racial and ethnic groups and low-income communities was emphasized.[4]

A brainstorming session followed, with participants being encouraged to list their main areas of concerns and recommendations for the women's environmental health research agenda. Participants identified the following five areas for further exploration and discussion in smaller groups:

1. Influence of chemical exposures on disease etiology and healthy human development
2. Tools needed for assessment and research
3. Sources of exposure
4. Research translation and intervention, including health policies
5. Community-based participatory research

At the conclusion of the session, the small groups were charged with brainstorming research recommendations in their area, identifying emerging themes, and prioritizing the top three to five areas. The cochairs, science writers, and a member of the community-based participatory research subgroup synthesized the recommendations, identifying overlap among groups and broader recommendation themes. The synthesis process, resulting working group recommendations, and justification for the recommendations were then shared with the larger group for comment. Finally, it should be noted that extensive effort was made to reflect participant comments and concerns, and participants were actively included in the development of the final five recommendations.

Summary of the Discussion

The working group discussed the definition of "environment." Materials distributed to the working group suggested that the scope of the discussion regarding the environment be focused primarily on "environmental toxicants," defined as "chemicals, metals, and physical agents, such as ultraviolet radiation, that women may be exposed to in their daily environment, their work

place, and throughout their lives that may affect their health."[6] However, many participants expressed concern that "environment" was too narrowly defined, and that the working group should also address broader social and institutional factors (e.g., built environment, stress, violence, racism, unemployment, and social inequities) that are also aspects of the environment in which women live, and that may have important health effects.[8]

Several of the working group discussions emphasized the centrality of environmental exposures, however defined, in determining health status and disease outcomes. Although much recent biomedical research has focused on the promise of genomic and other technologies and their potential application to health, working group members felt strongly that environmental factors must remain a central focus of NIH research. While genetic factors may influence disease susceptibility, environmental factors play a critical role in determining whether a disease may manifest. Understanding the role of environmental factors, therefore, is key to developing personal, clinical, and public health strategies to improve health.

The working group agreed that the new frontier for research is the role of the environment in propelling our understanding of, and ultimately improving, the health of women. As such, the group agreed that research efforts should focus on the role of environmental chemicals in influencing women's health, particularly during critical windows of susceptibility (e.g., periconception, prenatal, early childhood, puberty, perimenopausal), and include additional environmental concerns that impact women's health, such as the built environment, stress, violence, racism, unemployment, and social inequities.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

1. Understand the effects of chemical and other environmental exposures on disease etiology in women, including a major focus on developmental programming of adult diseases and syndromes.
2. Expand the capacity and invest in the development and application of new technological tools to revolutionize our ability to measure efficiently, cheaply, and accurately environmental sources and exposures, chemical toxicity (particularly early markers of disease), and the human/environment interaction; and to allow us to conduct research in human populations.
3. Pioneer research efforts that will identify and eliminate the negative effects of environmental factors and sources of exposures on women's health.
4. In partnership with the communities most impacted, dramatically enhance women's health by strategically undertaking the synthesis, dissemination, and translation of evidence to better use environmental health science to improve clinical care, policy, and community health.
5. Develop innovative partnerships that include interdisciplinary approaches and community participation.

These five main areas are described in greater detail below, along with additional suggestions for research directions.

Recommendation 1: Explore the influence of chemical exposure on disease etiology and healthy human development. The working group agreed that the effects of chemicals and other environmental exposures on disease etiology in women is generally not well understood, and that research efforts should focus on the influence of chemical and other environmental exposures on disease etiology and healthy human development. A comprehensive research agenda that would better explore these effects would include the following:

- Developing appropriate animal and cell culture models for studying and understanding developmental programming of adult disease and the etiologies of diseases over the lifespan of women, including epigenetic causes; acute, chronic and multiple exposures; genetic susceptibility; chemical doses; and biomarkers predictive of disease outcomes.
- Translating these animal models and identifying crucial windows of susceptibility, beginning prenatally and continuing throughout all life stages in women, which increase the risk of disease through direct and/or transgenerational mechanisms and are affected by ethnic and other disparities. (The identification of human studies that may have stored biospecimens from longitudinal studies where health outcomes have been assessed many years later would complement the animal studies, and availability of such studies should be promoted.)
- Understanding the biological and pathophysiological mechanisms by which such epigenetic, genetic, cellular, molecular, metabolic, nutritional, immunologic, and environmental factors interact in women to increase the risk of disease through direct and/or transgenerational mechanisms, including investigation of disease syndromes.
- Understanding the complex interaction between reproductive and metabolic functions and how this is influenced by environmental exposures (e.g., reactions of insulin and how it affects female reproduction, especially during critical periods).
- Understanding the impact of the environment on the disease itself, including the whole trajectory of the disease.
- Developing better indicators of diseases and life stages (e.g., biomarkers and non-invasive tools) to study the impact of chemical exposures on disease etiology and developmental programming of adult disease syndromes, as well as on normal development.
- Developing innovative methodologies that consider lifecourse events and periconception/preconception in studying environmental impacts.
- Maximally utilizing genomics, proteomics, metabolomics, and genome-wide association study (GWAS) databases to study environ-“ome” and disease-“ome” interactions.
- Developing experimental models that will address interventions and the prevention of diseases attributable to environmental exposures.

- Understanding the role of the microenvironment in the context of diseases and treatment, e.g., nutrition and menopause in the U.S. population. (For example, in Africa, women do not report experiencing hot flashes and mood swings. It has been theorized that diet makes a difference, especially white yams.)
- Expanding the design of existing or soon to be initiated studies to incorporate environmental factors as confounders or modifiers.
- Identifying occupational exposures, especially among poor women, and identifying interactions of multiple factors that impact health (e.g., nutrition, SES).

Recommendation 2: Support the development of tools needed for assessment and research. To maximize researchers' ability to accurately measure environmental sources and exposures, understand how they interact with women's health, and conduct research with women, expanded capacity and new technological tools are needed for assessment and research, focusing on the following:

- Enhancing our ability to leverage epidemiologic studies by using existing longer term cohorts to add an environmental dimension (e.g., Women's Health Initiative, Framingham Heart Study, Study of Women's Health Across the Nation, National Children's Study), such as linking through geographic information systems (GIS) or evaluating stored biological specimens for environmental chemicals.
- Using GIS and personal sensors of exposure to improve exposure assessment.
- Enhancing the collection and banking of biological samples in ongoing studies to facilitate studies of environmental exposures and genetic susceptibility. (Repositories must be easily identified and proper cataloging of samples must be available to fully maximize tissue sharing and coordination across various research groups.)
- Developing new methods to measure chemicals, such as noninvasive biological samples (e.g., saliva) and lower concentrations in biological tissue and exposure sources (e.g., products, plants, animals, air), more efficiently and cost-effectively.
- Developing high-throughput methods and expanding capacity to conduct these assays to facilitate application of exposure measurement tools for population studies.
- Developing new rapid screening tools to identify chemical toxicity, identifying those that can be used now (e.g., hormones) and those that are still needed (e.g., stem cells), focusing on the most effective tools for identifying early indicators of disease.
- Revolutionizing the recruitment and followup of study participants using new technologies (e.g., text messaging, social networking). (However, privacy/HIPAA infrastructure issues would need to be addressed, and NIH-approved guidelines for collection and storage of samples would need to be developed.)
- Improving registry of data and tracking of health trends.

Recommendation 3: Identify and eliminate sources of exposure. The working group emphasized that research efforts were especially needed to identify and eliminate the negative

effects of environmental factors and sources of exposures on women's health, focusing on the following:

- Identifying a broad spectrum of underexplored environmental factors that impact women's health across the lifespan (e.g., chemical exposures, stress, violence, unemployment, lack of health care, built environment, racism), with particular attention being paid to key windows of susceptibility (e.g., *in utero*, placental influences, breast milk, infancy, prepubescent, postmenopausal).
- Better understanding disproportionately exposed subpopulations, for example, occupational groups, geographically-based groups (e.g., residents near hazardous waste sites or industrial zones) and how environmental factors might interact with one another and genetics in exposed populations.
- Identifying leading sources of exposure commonly found in women.
- Improving the understanding of personal susceptibility factors, such as the influence of body characteristics, behaviors, and interventions (e.g., obesity, alcoholism) on the behavior of a chemical in the body, and the potential health impacts of exposure.
- Understanding the impact of hazardous waste and pharmaceuticals throughout the lifespan, especially in regard to women's cognitive functioning and aging.

Recommendation 4: Support research translation and intervention, including health policies. The working group discussed the critical role of information synthesis and the translation of scientific evidence to dramatically improve clinical care, policy, and community health. The following strategies were suggested:

- Developing strategies and conducting evidence synthesis in partnership with communities to determine whether and what action is warranted (i.e., what strategies are most appropriate for different arenas, such as general education, clinical care, special populations, community groups, public health policy); identify exposures, windows of susceptibility, outcomes, modifiers of effect; and establish environmental health proficiency among clinicians and policy decisionmakers.
- Conducting comparative effectiveness research to identify best strategies to prevent or mitigate the negative effects of the environment on women's health.
- Developing best practices to empower stakeholders to act on this knowledge (e.g., social marketing).
- Funding health policy related research that evaluates how public policies can address environmental influences on women's health. This could include examining how the implementation of health policies (local vs. State vs. national) influences health, and evaluating which are most effective in preserving/improving public health. Comparisons with international policies also could be useful.
- Funding research that identifies gaps in knowledge, training, and critical assessment skills across health care disciplines, in women's health and the environment. This should include research on the development of educational programs and materials to address these gaps.

- Funding research to develop the most effective tools and methods for assessing chemical toxicity and more effectively evaluating the data, and reviewing the scientific literature to inform decisionmaking for clinical practice and policy development.
- Funding basic and applied research that identifies safer alternatives to widely recognized harmful exposures. Green chemistry, basic and applied research that identifies harmful exposures, should be prioritized.
- Funding new studies and supplements on occupational exposures.
- Creating a bioinformatics grid for health outcomes related to environmental exposures, and incorporating information relevant for clinical decisionmaking.
- Utilizing Web-based technologies for multidisciplinary collaborations.
- Incorporating clinical and community impact in research projects (as part of the original project or as a supplement).
- Identifying gaps in training and knowledge regarding environmental issues, research, etc.
- Developing effective training models for providers (e.g., CMEs). To the extent possible, training should be open source and Web-based.
- Evaluating methods for training physicians, nurses, and others in women's health and the environment, identifying clinical knowledge and practice gaps that inhibit incorporating reproductive health science into practice. (For example, what clinicians need to know both from content and critical appraisal perspective and how clinicians can understand science derived from animal data and apply it to humans).
- Including social marketing and communication research on messaging that is most effective in the environmental arena.
- Evaluating fast track research to inform chemical policy reform and develop interagency collaboration to lead to implantation of chemical policy reform.
- Researching appropriate criteria for women's health related information to be collected in large public health registries, similar to Surveillance Epidemiology and End Results (SEER).
- Synthesizing complex scientific information and bringing it to various groups (e.g., clinicians, public, decisionmakers).

Recommendation 5: Support community-based research. The working group concluded that three elements are necessary to conduct the innovative and revolutionary women's health research described above. This research advances the state of knowledge and makes the findings useful to clinicians, policymakers, and the community. The group said it was essential for researchers to take an interdisciplinary approach, develop innovative partnerships, and actively include local communities. The following were specifically recommended:

- Increasing NIH resources and support for community-based participatory research as a fundamental component of women's environmental health research, as it identifies new environmental factors, increases the quality and usability of research, and builds capacity

among researchers and members of the community that will result in effective solutions that prevent and mitigate negative environmental impacts on women's health.

- Increasing NIH resources and support for a range of interdisciplinary approaches that are critical to conducting research that addresses the multidimensional interactions between women's health and the environment. These approaches include examining complex interactions (e.g., between disease and race/SES or between genetic susceptibility to exposures and disease), creating multi-disciplinary partnerships (e.g., between biology and social studies), and forging unrealized relationships (e.g., partnering with technology innovators, such as Google, to adapt new tools to address environmental issues).
- Increasing patient education to avoid remorse from underinformed patients (e.g., women who missed their window of receptivity, awareness of environmental hazards).
- Enlisting other nontraditional partners in the conduct and dissemination of research, such as community colleges, which are less intimidating and more intimate learning environments, are able to engage impacted communities, and are good places to disseminate research.
- Evaluating ecological and geographical approaches where accumulated risk could be established (e.g., communities near freeways, homes with elevated lead), and tracking accumulated risk factors in affected communities.
- Encouraging community participation in research (e.g. developing questions, implementing research, systemic change), to create unique opportunities for community contributions.
- Enlarging the interdisciplinary approach spectrum that goes from basic science to clinical to community and back.
- Identifying differences between women's reproductive health and women's health and the environment, and the need to research broader environmental health factors that impact women's health.
- Stressing the quintessential importance of community participation in developing research questions, implementing research, disseminating findings, and moving towards systemic change.
- Increasing the range of community involvement.
- Encouraging the use of The California Endowment's "Places" initiative as a model for engaging and focusing on community needs (defined by them), realizing that this requires a long-term investment (e.g., 10 years).
- Promoting compensation, recognition, and additional resources. For example, anti-tobacco was successful because of additional resources for social marketing in the community.

- Encouraging the community to provide data and new knowledge, expanding dialogue about community involvement, expanding funding incentives (e.g., publication in community media is critical), increasing resources and NIH support for incentives (e.g., money, time), and recognizing that community-based research can take a longer time.
- Identifying the most critical women's environmental health factors, such as stress, violence, unemployment, racism, lack of childcare, substandard housing, access to healthy foods and food insecurity, access to parks and natural environments, transportation, work environment (no living wage, no health care), lack of social capital, lack of quality educational institutions, access to health care, and chronic disease (e.g., caregiving, community impact). This includes identifying the most critical environmental factors and stressors that impact women's health across the lifespan.

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HIV/AIDS AND WOMEN

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Introduction

Almost three decades after HIV/AIDS was first identified, the disease has spread throughout the United States and the world to become a significant health issue. The Centers for Disease Control and Prevention (CDC) estimates that someone in the United States becomes infected with HIV every 9.5 minutes.[1] Approximately 1 million people in the United States are currently living with HIV/AIDS, and more than 15,000 women were newly infected in 2007, mainly through sexual contact and injection drug use.[2] Women currently account for approximately 27 percent of cases of HIV/AIDS in the United States and more than half of these women are African-American.[2] Worldwide, the United Nations Program on HIV/AIDS reports that in 2007, 33.2 million people were living with HIV, and almost half (15.4 million) were women. Over the past decades, HIV/AIDS has shifted from a disease that affected mainly gay men and injection drug users in the United States to one that currently affects all groups of people and all countries of the world.

The HIV/AIDS epidemic has changed substantially from the time it was first identified. In the United States, the disease was originally associated with white men who have sex with men and with intravenous drug users, and the disease was fatal. HIV/AIDS now reaches into all segments of the U.S. population, and increasingly affects women, particularly women of color. Furthermore, since the advent of antiretroviral (ARV) medications, HIV/AIDS has been transformed from an acute into a chronic illness.[3] For both women and men, highly active antiretroviral therapy (HAART) allows them to live longer and healthier lives after an HIV diagnosis.

Despite the advances in treatment for people living with HIV, the demographic shifts require new thinking on the part of researchers and program managers. The prevention and treatment paradigms that for so long focused on gay men and drug users may not be appropriate and/or effective among women. In the context of HIV/AIDS, women may differ substantially from men in all areas, from basic biological factors affecting transmission to behavior and sociological and structural factors that place them at risk and influence their ability to access prevention, treatment, and care services.

The vast majority of basic science and other HIV research has been conducted on men, but because of shifts in the demographics of those affected by the disease, researchers and policymakers must pay much greater attention to issues faced by women. Scientists in the field have already identified a number of gaps, including, for example, the need for research on the basic science on biological differences between women and men, as well as on biological differences across a woman's lifespan; interdisciplinary research; the examination of assisted reproduction in serodiscordant couples; and research on specific populations (e.g., girls and women across the lifespan, women of color, transgender individuals, immigrants).

The working group discussed these known issues, as well as other issues that affect women in the United States and worldwide.

Summary of the Discussion

Working group participants represented the spectrum of those working in the area of HIV/AIDS, as did the information and comments they presented. In addition, a number of people living with HIV/AIDS actively participated in the working group. Four overarching themes emerged from the discussions: the need for female-specific care, the need to address gaps in the current research process, the need to take into account the entire lifespan of women, and the need for innovative funding mechanisms.

Prevention, treatment, and care in the United States have been based largely on models for and research on white men who have sex with men. These models often do not sufficiently take into consideration women's specific contexts and biology or ethnicity. As more women become infected, there is a need to conduct a wide spectrum of research focused specifically on women and HIV/AIDS, from basic science to comparative effectiveness research. For example, HIV/AIDS studies should ensure the adequate enrollment of women and minorities in order to have enough power to analyze data by these groups.

Beyond the topics of specific studies, changes are needed in the research process itself. Research should be more interdisciplinary and integrated, linking behavioral with biological aspects, and employing mixed methods (quantitative and qualitative) to explore new hypotheses and to develop a deeper understanding of social context and other factors. In addition, research models need to be more dynamic so that results quickly reach those who need the information, and so that they are understandable not only to scientists and researchers, but also to program managers, policymakers, people living with the disease, and their family and friends.

Innovative funding mechanisms are needed to support a broader spectrum of research, including mechanisms to support more resource-intensive and comprehensive studies, and to encourage better use of existing data (e.g., funding for secondary analyses, which may be more cost-effective than collecting new data). As an example, women and girls are affected by HIV throughout the lifespan, and they have very different issues, needs, and concerns from one phase of the lifespan to another. In particular, longitudinal and long-term followup research is needed to address emerging issues among females infected in the perinatal period, as they develop, and, in particular, as they enter their reproductive years. There is a need to facilitate the establishment of healthy behaviors in HIV-positive children, rather than waiting to intervene later. Included in this group are individuals who are aging out of pediatric care into adult care. Likewise, specific lifespan considerations need to enter into research on HIV/AIDS infections in reproductive age and post-reproductive-age women. What are the behavioral issues among older women that place them at risk? Long-term research is needed to study the cumulative effects of chronic HIV medications on women. These studies need to be complemented by lifespan research to understand more clearly biological differences between girls, women of reproductive age, and older women, as these relate to the treatment, course, and outcome of HIV infection.

Research is needed to examine a range of specific populations. Research involving people living with HIV ("prevention with positives") should examine reasons for nonadherence, whether these reasons vary by gender, and whether gender-tailored interventions improve adherence. In this same way, research is essential to understand how adherence and quality of care vary among women of color. In the transgender community there are many people with HIV/AIDS who are not currently being studied in the context of men. These patients should be studied in the context of women. For serodiscordant couples, research and care should address prevention as well as childbearing issues. For undocumented immigrants, who are often disenfranchised and experience social stigma, research on how to maximize access to services is necessary.

The working group's major recommendations address women and HIV, as related to behavioral and biologic prevention, health services and policy, reproductive health, pathogenesis and genetics, total disease burden, clinical trials, and pharmacology.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Research should develop new methods for understanding the concept of women's HIV/AIDS "risk," both behavioral and biologic. Current models often rely on research with white men who have sex with men, and may not apply to women.

- Research should look broadly at structural factors that differentially affect women and men, such as social and economic inequalities, homelessness, and violence.
- Studies should examine the contexts of women's lives and relationships, for example, stable relationships versus other types of relationships in which sex occurs. This would

include addressing the issue of women's autonomy and ability to make decisions about relationships, as well as the impact of drug and alcohol use in those relationships.

- A greater understanding of risk will require research on the best strategies for testing women for HIV, and on women-controlled protective methods other than the female condom.
- More in-depth research is needed on the changes in risk—both behavioral and biologic—across a woman's lifespan.
- Research must also examine issues of gender, race and ethnicity, culture, and stigma.

Recommendation 2: There is a need to develop new models of HIV/AIDS prevention, both behavioral and biologic, specifically for women. This may include both primary prevention and prevention efforts targeting HIV-positive women.

- The existing harm and risk reduction models were developed for white men who have sex with men, and may not be appropriate for women, considering the context of their risks and vulnerabilities. Therefore, new models need to be developed and tested.
- Researchers must also evaluate the extent to which preventive interventions and models are working.

Recommendation 3: New and integrated ways of conducting research on women and HIV/AIDS should be explored, looking at issues such as the relationship between behavioral and biomedical prevention, use of both qualitative and quantitative methodologies, and new ways to effectively disseminate research findings.

- Innovative research linking behavioral and biologic issues, such as the effect of medications on emotions and subsequent risk behaviors, can further our understanding of HIV/AIDS among women.
- The use of mixed methods (qualitative and quantitative) either simultaneously or sequentially, to research the link between the behavioral and the biologic should be encouraged. Use of mixed methods can deepen our understanding of HIV/AIDS issues among women.
- Investigators should include more definitive outcome measures (e.g., HIV incidence, biomarkers), which may require research on a much larger scale than has been conducted to date.
- Efforts to develop a more dynamic research model for more rapid turnaround in science—getting results to researchers, clinicians, and the public as quickly as possible, and in ways that are understandable to all—should be intensified. This may include encouraging collaborations and interdisciplinary research, as well as developing and continually updating annotated literature reviews of results.

Recommendation 4: Communities of interest to researchers should collaborate as full partners in the research process. Such participation can increase buy-in and mutual respect, improve research questions and techniques, enhance dissemination of results, and improve use of results in program development.

- Effective research must involve community-based organizations, not only as volunteers, but also as paid partners and experts. These groups already work closely with women at

risk and women living with HIV, and have a better understanding of what is happening in their communities to place women at risk. They may also be more effective at disseminating information and at using that information to implement prevention, treatment, and care programs.

Recommendation 5: Methodological studies of biologic markers for women should be strongly encouraged. Such studies will create a more nuanced understanding of women's physical risk and resilience, and of changes and differences across their lifespan.

- Biologic research should examine such issues as how women's upper and lower reproductive tracts are affected differently throughout the lifespan and in the various stages of HIV/AIDS; the effects of mucosal immunology, virology, pharmacology, and hormones on HIV/AIDS; sex differences in the efficacy and safety of existing ARV drugs (given that an effective HIV vaccine is not likely to be available within the next decade); the gap between reproductive endocrinology and HIV research; and potential sex differences in treatment adherence.
- Investigators should also consider the specific needs of special populations including presexual adolescents, HIV-positive adolescents, women over 50, transgendered persons, drug addicts, and the chronically ill.

Recommendation 6: There should be a collaborative effort to encourage health services and policy research to identify and address barriers to women's participation in research; access to health care services, including mental health care services; and continued presence in the health care system.

- Research should examine issues specific to women of various ethnicities and socioeconomic status regarding the types of service delivery that provide the best quality care at the least expense.
- Operations research may increase our understanding of the relationship between HIV prevention and referral services and reproductive health services, leading to improvements in prevention, treatment, and care. This may include a review of contraceptive counseling practices, referrals for care, cross-training of internists and obstetricians/gynecologists, best practices for testing for women, and the capacity of women's organizations to provide health services and to use science to improve their programs.
- ORWH should encourage analysis of the effectiveness of outcome trials across various populations, including women of various ethnicities and/or races.
- Investigators should be encouraged to conduct secondary data analyses across disciplines in order to use resources more effectively. These may include, for example, using the HIV Cost and Services Utilization Study data, or updating the study by adding questions looking specifically at gender and race and ethnic disparities.
- The methodology and design in implementation science must be strengthened, rather than simply applying previously effective programs across disparate populations.

Recommendation 7: Research is needed into the extent of childbearing among HIV-positive women, reproductive intentions, and methodologies for safe reproduction.

- Many people living with HIV want and do bear children. Research is needed regarding reproductive intentions and behaviors among HIV-positive women and their partners, and across race/ethnicity.
- Comparative effectiveness research may also look at various reproductive technologies that allow for pregnancy but may reduce the risk of HIV transmission (e.g., IVF, timed coitus, postexposure prophylaxis, preexposure prophylaxis, uterine insemination).
- Cost-effectiveness research is also needed.

Recommendation 8: Research on genetics and pathogenesis should use heterogeneous populations and employ better definitions of gender, race, and ethnicity.

- Pathogenesis and genetic research studies so far have primarily been conducted in white homosexual men. There is a need either to test and validate these findings in women, or to conduct new studies using heterogeneous populations.
- Because phenotypic sex is an inadequate proxy for biologic sex in the majority of clinical research studies, new studies must include women in order to examine evidence for sex differences in areas such as viremia, inflammatory response, and the immune system.
- Sex and gender differences can be biochemical, physiological, XY-chromosome related, or hormonal (sex steroids), and thus may affect genetic risk factors by sex on several levels. Study of such differences could lead to novel treatments.
- Race and ethnicity definitions should be reviewed. Genetic markers of heritage are important, but current categories do not adequately address this.

Recommendation 9: New clinical research on women and HIV is needed, as prior research on men may not be applicable.

- There is an overarching need to develop and validate research methodologies for different population groups by gender, race and ethnicity, nationality, etc. Such methodologies need to be disseminated to researchers.
- Research is needed to evaluate strategies to prevent long-term complications specific to women (e.g., cumulative effect of medications). For example, studies of underlying genetic markers may be done on a small scale, which is more cost effective than large-scale studies.
- Clinical research is needed to examine the intersection of HIV with other chronic illnesses, mental health, and other areas.

Recommendation 10: Research on biomarkers for precancer screening, therapy, and therapeutic vaccines needs to be encouraged. Such research should also examine lower cost options for low-resource countries.

- There are fundamental differences in the immune systems of women and men. Hence, research is needed to understand the differential effects of comorbidities that may accelerate or increase vulnerability to HIV (e.g., cancers and coinfections, inflammation due to HIV infection, mucosal immunology, reproductive aging, the menstrual cycle, expression of receptors, neuropathogenesis, dementia, liver damage, cardiovascular disease, obesity, autoimmune diseases, and migraines).

- Additional nondisease factors may also accelerate or increase vulnerability to HIV, and thus should be studied. For example, smoking and nutrition may interact in significant ways with HIV and vulnerability.
- New therapies are needed to prevent and treat HIV and comorbidities in order to address the increasing disease burden around the world.

Recommendation 11: HIV clinical trials research needs to address the growing population of HIV-infected women, ensuring that sufficient numbers are included in research to allow for analysis by sex and designing research that addresses the specific needs of women.

- Most research proposals include plans for recruiting women and minorities but, in many cases, not enough are recruited to allow analytical power for subgroup comparisons. Researchers should be encouraged to fulfill their targeted enrollment plans.
- Pregnant women must be included in HIV clinical trials in order to gain a better understanding of risks and benefits.
- Operations research is needed for the development of improved informed consent language for HIV research studies. Much of the language currently used in consent documents is not comprehensible to participants, implying that true informed consent does not always occur.
- Research is also needed regarding biomarkers of reproductive aging in chronically ill women. Studies should also examine the full reproductive tract for prevention of pathogenesis and coinfections.

Recommendation 12: Research is needed in the area of pharmacology to inform new treatments, address medication adherence, and focus on issues specific to women.

- There is no gold standard measure of treatment adherence. Research is needed to examine the determinants of adherence, the relationship of adherence to age, sex, autonomy, and other variables.
- Dosage studies are needed to understand whether dosing and toxicity to ARVs are related to body mass, gender, age, or pharmacogenomics (e.g., slow metabolizers). Such research will inform optimal treatment regimens.
- There is a need for methodologies for predicting drug interactions in early phase screening in pilot studies, so that not all drugs need to be studied individually.
- Research is needed in the area of novel methods for administration of drugs. HIV researchers can learn from other areas, such as contraception (e.g., patch, implant, IUD).
- Little is known about drug interactions and cumulative toxicity in combination therapy in women (e.g., preexposure prophylaxis with microbicides, hormone replacement therapy and ARVs, or different types of progesterone in combined contraceptives).
- Population diversity, especially in early phase clinical trials, is necessary in order to determine how sex differences affect a drug's efficacy.
- Research on new HIV drug treatment must address issues specific to women, such as drug metabolism, pharmacodynamics, pregnancy, breastfeeding (exposure to breast-fed

infants), drug interaction with contraceptives, aging (adolescence, premenopausal, postmenopausal), toxicities to drugs, penetration of target tissue, and comorbidities.

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INFORMATION TECHNOLOGY

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Introduction

Current information technology (IT) can contribute substantively to the clinical research process, and future advances in IT promise to further accelerate progress in women's health research. For example, novel IT can improve women's participation in clinical research by facilitating early and rapid screening of eligible participants to improve recruitment and retention, automating reminders and scheduling to facilitate study compliance, and providing immediate

reporting of events and increasing access to this information, among other benefits. The ability to share information across the health care system and between health care organizations, the community, and the research enterprise will enhance collaborative decisionmaking. Advances in IT have the potential to affect all stages of the clinical research process, ultimately improving outcomes in women's health.[1,2]

The Working Group on Information Technology started its meeting with a discussion of the great promise of advances in biologic and information science for improving women's health outcomes. In order to take full advantage of these advances, the group felt that the health community must radically alter its system of care delivery. The Institute of Medicine (IOM) has repeatedly reported the need to address systemic issues, such as quality of care, coordination of information and services, safety, and quality improvement.[3] However, the current system of care is fragmented and relies on inaccessible, nonstandard, noncomputable, and nonportable information about patients. In addition, there is no mechanism to facilitate and improve care across providers and institutions—resulting in a disconnection in delivery of care, clinical outcomes, and research for women's health.

The group based its discussion on the understanding that single, isolated advances do not achieve change, and that any new technology must be connected to larger systems of care and research. For example, electronic medical record (EMR) systems have not provided the panacea that some hoped—they simply make medical charts available in the form of electronic text files. These records do not allow for the storage and reuse of data for the multiple purposes of care and research. In addition, the information from these records is not available across institutions, or even within most systems of care delivery. In order to merge research with care, we must develop and implement systems that enable us to collect critical data automatically as a byproduct of care in order to improve quality.[4,5] This approach would dramatically improve research efficiency and leapfrog the challenges of getting more women into trials. It would also serve to reduce the redundancy created by repeated manual entry of clinical information by research coordinators and then again by third parties for each clinical trial. Finally, the integration of common electronic data at intake and along the care continuum would significantly reduce cost, labor, and inefficiency. A virtual cycle of improvement results when standards are adopted, high volumes of information are exchanged, and proprietary software and equipment are eliminated.

In addition to systems improvements, using IT to access medical information and education is an important area that deserves more emphasis. Women of all income levels are increasingly interested in using the Internet to research their treatment options and manage their care.[6,7,8] According to the Pew Internet and American Life Project, about 8 million Americans search the Internet daily for health information.[9] In addition to addressing the disconnect between research and care delivery, the failure to heavily invest in surrogate markers (biomarkers), and the failure to adopt standards, improvements in IT can harness the unprecedented power of the Internet for the benefit of women and the personal management of their health.[10,11]

The working group acknowledged that some progress has already been made. Access to high-quality health information by the lay public has been achieved through the Internet as well as

through electronic educational modalities. Telemedicine (distance learning for clinicians and consultations for patients far from medical care) has been used with success in some areas of women's health. For clinicians, continuing medical education and calendars of educational opportunities regarding women's health have been made available online. Creative new uses of IT have been developed by the Centers of Excellence in Women's Health. These modalities are only the beginning, and building on early success as well as facilitating innovation is crucial to creating real and sustainable improvements in women's health outcomes through IT.

Summary of the Discussion

The working group agreed on a basic understanding of IT, which includes software, hardware, and user behavior as it relates to software and hardware. Health IT includes infrastructure—tools and applications that are integral to the wide range of activities associated with research and clinical care. IT plays an important role in analysis, management, exchange, and integration of information across a wide range of disciplines, including clinical research, clinical care, molecular biology, genomics, proteomics, imaging, pathology, and epidemiology, among others.

Invaluable Role of IT in the Health Care System

The working group discussed the types of IT that have specific applications to health. Discussion points included the topic of informatics, an overarching term that applies to the gathering, manipulating, storing, retrieving, and classifying of recorded information. Within informatics, specialized areas include clinical or medical informatics, translational informatics (the application of both informatics theory and methods to translational research), bioinformatics, biomedical text informatics (e.g., natural language processing), imaging informatics (e.g., content-based image retrieval), computational biology (e.g., models), and information dissemination.

The working group agreed that the fundamental value driving health IT decisions was the creation of an evidence base for the continuous improvement of clinical care. As mentioned in Barack Obama's Plan for a Healthy America, "Comparative effectiveness [research] studies provide crucial information about which drugs, devices and procedures are the best diagnostic and treatment options for individual patients."[12] IT improvements should be aimed at the development of personalized and evidence-based medicine, individualized treatment, and quality care.

The group stated that health IT systems need to be interoperable, exchangeable, and mineable for information. There is a need to transform the process of clinical care and integrate data across settings and clinicians. Notions of where data come from (e.g., cell phone-based biophysical monitoring; patient-generated content online) need to be broadened. Population data should be used in a shared, interoperable way, not through a traditional "owned" registry model.

Defining the Data Needs of Women, Clinicians, and Researchers

The group agreed that the data gathered by new and improved systems must be interoperable across systems and platforms to be meaningful, useful, interpretable, exchangeable, and accessible. One issue that came up in the discussion was that ownership of data must be resolved, and that a commitment to sharing will improve knowledge and options for care and prevention.

Participants agreed that IT has immense value to health care because it provides an interconnected web of tools and applications that link participants in the health care ecosystem, including patients, providers, and researchers. Patient data are a valuable but currently underutilized resource. There is a need for rapid access to clinical effectiveness information as well as interdisciplinary data access across diverse communities of providers. Information dissemination is already challenging, as evidenced by the 4.2 billion Web pages indexed by Google. Thus, patients and clinicians need help to evaluate and distill accurate information through easy-to-use, portable, and integrated systems.

Investment in novel uses of IT to promote women's health and wellness is needed. New applications specific to women's needs for managing illness will change the way women engage with their health and health care. To improve health outcomes, research should focus on the range of information needed for clinical decisionmaking, managing and monitoring chronic conditions, motivating behavior change, empowering women, and enabling health and wellness-promoting activities such as coaching and self-care decision support.

Improvements in IT can result in increased collection and use of women's health data and, therefore, improved outcomes. There is a need to use clinical care data from systems of care for data mining and research applications. Clinical care databases can be used and adapted for research, which will serve to enhance the inclusion of women in research designs and processes by allowing their health information to be used in research without requiring their participation in a clinical trial. In that way, personal health records represent an opportunity both to integrate information into research and to educate patients about their own health. Patients can efficiently provide the critical followup information to enable evaluation of clinical care outcomes. Data must move quickly within a real-time adaptive design to effect changes in clinical care, rather than lag by 3 years as is common today.

Finally, an essential aspect of any new system is to create processes that provide for diversity. The wide variety of needs of women from different backgrounds must be factored into the ways science is communicated to consumers, and patients/consumers need to be educated about their roles in health care decisionmaking. Women from every background need to be able to build trust and have a level of comfort with online systems, and providers and researchers need to be aware that a "digital divide" still places the poor, older consumers, and immigrants at a disadvantage.

A Vision for the Future of Health Informatics

The goal of the second half of the discussion was "to define a research agenda that will facilitate the creation of systems that provide the right information, in the right format, to the right person, at the right place, and at the right time to improve health care decisions and outcomes." The cochairs established that priority research aims were to increase connectivity, productivity, and learning by use of technology. Expanding on this idea, group members agreed that there was an absolute need to rectify current inadequacies by engineering new data processes to help create a 21st century "knowledge economy" and a vision to frame clinical practice as a learning system.

The group acknowledged the need to identify existing barriers that may hinder improvements in IT for health care and research, and to address them. Although an integrated system is the ideal way to collect patient information, current academic researchers face disincentives to sharing information and data. One incentive for researchers and academics would be to examine data sharing through a lens of comparative effectiveness. This could demonstrate how improved information sharing allows learning from patient information—a currently underutilized resource that potentially holds answers to questions of health and disease.

Other barriers include privacy issues and the need to protect patient information and confidentiality. New systems must instill confidence in individual patients that all personal information will be kept safe and anonymous. The promise of a more personalized medical experience may reduce patients' fears—by allowing broader use of their personal data, patients can receive superior health care that is tailored to their individual health profile. In the evolving realm of personalized medicine, the unwillingness of systems and organizations to change presents another barrier. To overcome it, clinicians will need to adopt a model of continuous learning and change. In order to tailor treatment to individual biology, preferences, and consequences, such barriers must be overcome to ensure that research can be integrated into clinical care through IT-enabled processes.

Women's Input into Health IT

Group discussion led to the elaboration of IT issues specific to women's health. First, researchers and health informatics specialists must base their research on a broader definition of health that comes from women themselves, including aspects such as the environmental, sensory (visual and hearing), dental, and psychosocial domains. In addition, the group stressed the importance of educating women about the value of participating in clinical research and their central role in the success of trials. Despite sobering statistics about the low level of clinical trial participation, the tone of the discussion was optimistic—in some cases, passionate—that the process of clinical care can be reengineered to simultaneously generate the information required to improve care and conduct research. By doing this, the health care system can enhance the inclusion of women in research designs and processes, with the end goal of improving health outcomes for all women.

Next Steps: The Future

The cochairs then asked the group, "What do we need to do in terms of research and funding to facilitate the next step?" The group determined that demonstration projects were the best way of studying the multifaceted aspects of ways IT should transform the processes of clinical care and research. Through demonstration projects, stakeholders (e.g., female patients, clinicians, and researchers) can work collaboratively to contribute to and create an IT infrastructure that supports interoperable data exchange for clinical and research use. The output from such demonstration projects can be an understanding of best practices and research methods in order to create a learning culture (evidence-based management), while also identifying missing components and spurring development. This will best move us forward together towards meeting the vision and goals identified earlier.

Demonstration projects can show how to use IT connectivity to advance learning and care. There should be an explicit policy to encourage experimentation that encompasses care delivery, wellness, and research. In the end, demonstration projects can facilitate the beginning of changes in the culture of health care organizations, research organizations, and funders, including the Federal government.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Ensure that scientific findings from research inform best practices that are linked to data collection at other points of care, such as codes of patient conditions, clinician treatments, and reimbursements.

- Women's health variables and issues should be brought into data modeling and collection.
- Informatics initiatives should be encouraged to produce research-ready, standards-based clinical data at the point of care. These efforts should be IT-enabled with a focus on engineering new data collection processes. IT has to be designed and deployed to support quality improvements, including risk assessment and detailed feedback on the characteristics of care processes. These initiatives should also use IT to integrate evidence into care processes, continuously monitor and collect relevant data, and produce performance feedback. This information will help researchers and clinicians determine which women have a high risk of developing certain serious diseases and learn how to reduce their morbidity and mortality.
- A strong commitment should be made to common data standards, vocabularies, and terminologies, so that data and information can be easily shared and understood across disciplines. There is a need to collaborate with other public and private initiatives aimed at gaining consensus and harmonization of standards for the benefit of research on women's health.
- Research and evaluation on the nature and value of clinical and quality-of-care indicators should be funded. The option of including a requirement for clinical answers as well as scientific answers in all funded Phase III trials should be explored.
- Clinician and researcher collaborations should be encouraged to design products that model data elements essential for providing good care, effective clinical research, and evaluation of care processes and outcomes.

Recommendation 2: Invest in research on transforming information into knowledge.

- Focus research agendas on producing, distributing, and presenting useful information to different groups of stakeholders.
- Match new technology to specific contexts and conditions—e.g., distributing effective and appropriate data and tools to patients with basic literacy to help them manage their chronic diseases.

- Invest in research on building integrated processes that will fully link complex but relevant data. For example, various databases in external and internal contexts could be integrated with pollution control and environmental data to inform population health and clinical care beyond antiquated models of linear knowledge development. Considerations here include modeling necessary data and improving the capacity of EMR products to collect and report research-ready, standards-based data.

Recommendation 3: Support and lead the extension of data standards in therapeutic areas of special interest to women (e.g., STIs, female cancers, pregnancy, aging).

- Data standards should be developed through demonstration projects that will serve as a strategy for improving health care IT adoption and applications. For example, one can study and test the reengineering of processes for data collection and integration, the transformation of data into knowledge, and the impact on effecting change in care.
- Researchers need to model novel systems for IT-integrated women's health care delivery using demonstration projects to evaluate models.

Recommendation 4: Invest in the education of women on the importance of creating and sharing their information for research and using their information to promote health and wellness.

- Encourage women to participate in clinical trials (women have the lowest enrollment in such trials) and to permit the use of their personal health records.
- Address how individuals can benefit from participation in large-scale clinical research trials. For example, there are now millions of cancer survivors whose quality of life is impacted by pain and depression. Many of these patients can be helped—how do we collect this information from patients and treatment systems?
- Empower patients to act as critical data providers in the 21st century knowledge economy. For example, there is a need to merge data on tumor biology, treatment, quality of life, complications, and followup. Much of this information can be provided by the patients themselves.

Recommendation 5: Promote policies and capabilities that ensure patient information is safe and de-identified, yet accessible for research purposes.

- A critical question is, "Who owns data?" Ownership "silos" can impede access to patient information. Health information "banking" is one option, with patients controlling access.
- Data efficacy and safety should be top priorities in developing the best health IT.

Recommendation 6: Support initiatives that enable integration and sharing of clinical, molecular, imaging, and other information (e.g., population, environmental), and promote collaboration across multiple disciplines.

- Research is needed on how best to engineer information so that it can be communicated and actionable to a range of different stakeholders.
- There is a need to integrate data from literature and resources; there is a large body of knowledge that can be accessed and applied.

- Education and training are needed to promote information sharing and knowledge transfer among health care systems. This includes education and training for patients, providers, and researchers. There is a need to change the way information is acquired, transformed, and used to deliver care. Patients need training to learn to provide information and access information sources that they help generate. Providers need training to learn to use patient-generated information, and participate in transforming and improving care by integrating information and feedback at the point of care.
- Borrowing methods and strategies from other industries can help speed information access and use, as well as modeling and development of applications. Examples include online access to services and information (e.g., financial industry products, online reading, and music product markets).

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WOMEN IN SCIENCE AND HEALTH CAREERS

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Introduction

To achieve goals in women's health research, it is critical to champion the interests and support the career advancement of women in science, technology, engineering, and math, across all disciplines and sectors of the health professions. This working group was charged with defining strategies and approaches that will break down barriers and create opportunities to ensure that women in these fields can achieve their full potential. The group examined the ideas and recommendations of the Working Group on Women in Science and Health Careers convened in March 2009, at the conference at Washington University in St. Louis, and extended and prioritized them.

As part of this effort, the working group also addressed the particular career advancement issues facing women of color and women in nonmedical disciplines, including, but not limited to, women with Ph.D.s and with degrees in pharmacy, dentistry, nursing, psychology, engineering, and mathematics.

Summary of the Discussion

The working group included women and men from a wide range of disciplines and ethnicities. All participants identified important topics for future programmatic development and research, particularly research to address the multiple factors that influence the advancement of women in science careers.

The discussion began with each participant sharing personal perspectives on future directions to address barriers to recruitment, retention, reentry, and advancement of women in science at all stages of their careers. Specific attention was given to the many types of diversity within the realm of women scientists, including differences in sexual orientation, disabilities, race/ethnicity, and urban or rural residence. Participants addressed the need for increased funding for women scientists, and underscored the importance of changes in the institutional and organizational culture within academia to address specific barriers to the advancement of women in biomedical professions. Among the working group participants was Dr. Virginia Valian, who referenced the "gender schema," she had discussed in her keynote address at this meeting (see page 72).

Before breaking into two subgroups, the NIH cochairs provided the participants with a progress report on a variety of programs and policies that are in place or being addressed at the NIH. The working group endorsed five themes and recommendations from the St. Louis meeting:

- Institutional transformation
- Family-friendly policies
- Mentoring programs and evaluation
- Leveling the playing field and promotion
- "What is good for women is good for everyone"

While family-friendly policies and mentoring programs were identified as important topics, these types of issues were not included in the final report of this working group since these issues were highlighted in the recommendations from the St. Louis report.

The remaining three themes and recommendations from the St. Louis meeting—institutional transformation, leveling the playing field and promotion, and "what is good for women is good for everyone"—served as conceptual building blocks that allowed the San Francisco group to advance similar thoughts but not duplicate work already accomplished. The larger group then separated into subgroups to discuss and develop recommendations addressing two specific areas: cross-disciplinary issues and women of color. Subsequently, the cochairs refined the list of issues and recommendations into five categories that served as the focus of the final recommendations. These areas were:

- Pipeline
- Representation/leadership
- Research topics
- Training and education
- Transparency

The full working group reconvened and finalized the list of recommendations.

Pipeline

The working group discussed a number of concepts that evolved from individual concerns regarding the "pipeline" to a larger context involving institutional concerns and "transparency." It was noted that over a decade ago and under similar circumstances, Dr. Pamela Marino, Ph.D., National Institute of General Medical Sciences, developed a pathways model for career progression of women in science[1] as a frame for discussion of pipeline and career progression issues (see Figure 1). The model addresses the dynamics of the rates of career progression, exit, and reentry to the career path from high school to independent investigator. The model includes the potential for assessing dynamic rates of progression, as well as points to leverage and/or recover losses.

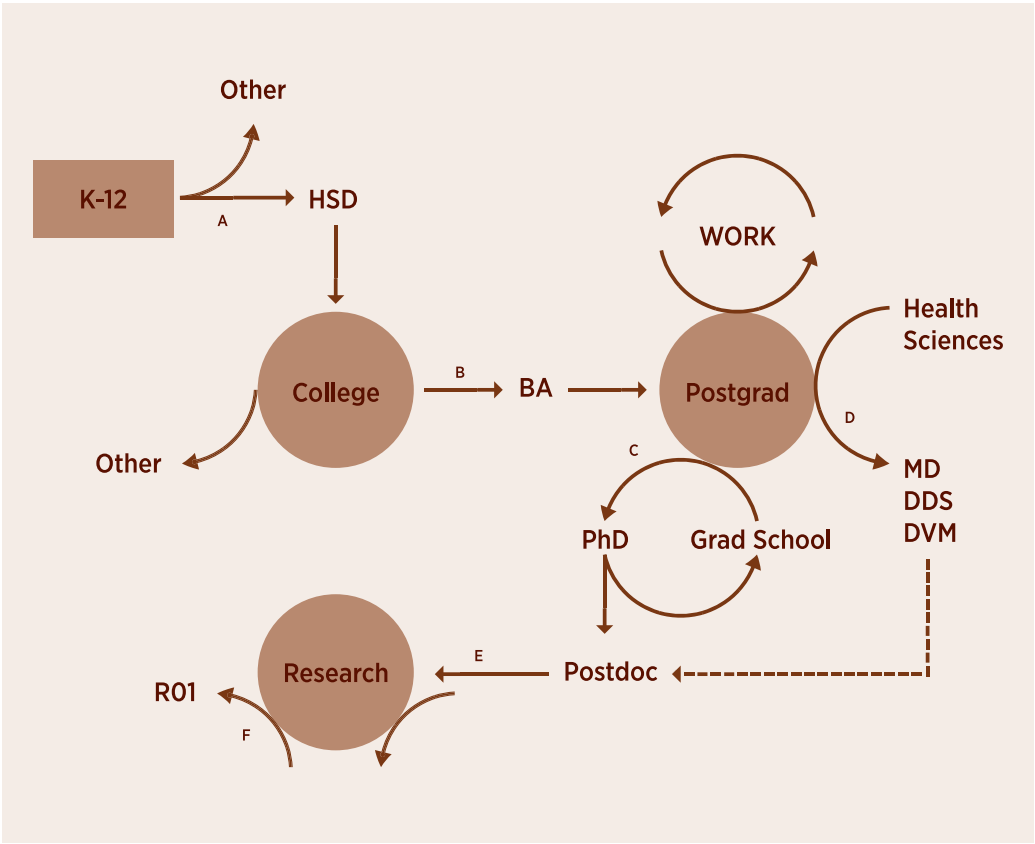

Figure 1. Pathways Model
SOURCE: Office of Research on Women's Health. (2000). AXXS '99. *Achieving XXcellence in science: Advancing women's contributions to science through professional societies* (NIH Publication No. 00-4777). Bethesda, MD: National Institutes of Health.

Within this model, one can situate issues related to the need to engage elementary school and college level students early in the science and research enterprise. One specific need is to develop better ways of communicating opportunities and support mechanisms, such as programs like Building Interdisciplinary Research Careers in Women's Health (BIRCWH) and NIH

reentry opportunities, to postdoctoral fellows and junior faculty members, who become discouraged and/or change career plans, resulting in leaks from the pipeline pathway. Within this context, clear information is needed on causal factors contributing to the leakage, such as family and maternity leave concerns, lack of insurance, difficulty in securing Federal funding, and effects of current NIH policies on institutional policies. Additionally, and throughout the pathways, there is both the challenge and the opportunity to address the role of mentors, particularly in providing advice on how to effectively achieve work-life balance. In terms of career maintenance, the group felt that there could be more support for the opportunity to go back and forth between academia and industry.

At all points in the pathways model, women of color are lost at a disproportionate rate relative to majority women. The sense of the group was that the number of minority women funded by the NIH is small. Critical issues include the need to enhance their entrance into the pipeline, and to determine at which steps in the pathways model women of color in biomedical sciences leave and how to ensure that they reach the academic track, successfully compete for NIH funding, and achieve leadership positions in science. The administrative supplements for providing summer research experiences for students and science educators, which was funded by the American Recovery and Reinvestment Act (NOT-OD-09-060) in 2009 and 2010, should be continued with emphasis on youth from disadvantaged backgrounds and on ethnic and racial groups underrepresented in the sciences. Greater use of the NIH Research Supplements to Promote Diversity in Health Related Research (PA-08-190) at all career levels may be a means to provide science experiences for youth of color, as well as among junior and more experienced academicians.

The discussion on the pipeline concluded with an emphasis on encouraging professional students to enter the pipeline by reducing the barriers that women, particularly women of color and lesbian women, face. Many gay youth and youth of color cannot imagine a future in the sciences because their mentors are few and not always in decisionmaking positions. Lesbian and minority women should be provided opportunities to do research on issues that affect them specifically. Factors that help women of all backgrounds to take on leadership and decisionmaking positions include formal mentoring programs, a strong linked pipeline from university to graduate or health professional school, and programs such as evidence-based parenting (education programs that have been studied in both controlled, clinical trials and community settings, and have demonstrated specific, expected outcomes) for pregnant or parenting faculty and postdoctoral fellows. In addition, women should be encouraged to become interested in conducting research in women's health at an earlier age, which will require new mechanisms and pathways starting in elementary school.

Transparency

Working group participants felt that there was opportunity for broader institutional change and enhanced transparency based on gender schema and issues related to women of color, disabled women, and lesbian women. One model to follow is the LCME/ACGME accreditation, which requires a report card on diversity from each specific program. One way to enhance this model would be to include consequences for failing to create a comprehensive diversity policy and results.

Participants felt that the current organizational culture does not do enough to encourage gender and racial diversity. There is a need to ensure that NIH-funded institutions put in place family-friendly policies, such as policies addressing spousal hiring, maternity and paternity leave (including leave for adoption), parents of children with disabilities, and families with ill partners or aging parents. Institutions should identify mechanisms that enable better visibility of the institutional contributions of women. Finally, universities should ensure clarity about on-ramps for academic careers, especially for those in their childbearing years and those caring for aging parents.

Training and Education

In the area of training and education, participants agreed that curricula in health professional schools currently lack material on sex and gender issues relevant to human physiology and human disease across the lifespan. Faculty are not sufficiently trained to address these questions and the national curricula do not require health care professions to examine sex and gender issues related to health across the lifespan. In addition to curriculum changes, mentor-development programs should be established that would provide mentoring, not only to students but also to midcareer to early senior career-level academics. The NIH could fund programs to develop tools that would enable faculty to mentor across gender lines.

Programs are also needed to address retention of those who have a support role in grant submission by providing training and education, tuition assistance and loan forgiveness, and competitive salaries. The Midcareer Investigator Award in Patient-Oriented Research (Parent K24), which provides protected time, training, and mentoring in clinical research, could be expanded to include Ph.D.s, particularly in fields such as the pharmaceutical sciences.

Research Topics

The discussion included development of a list of research topics not yet prioritized but important to advancing women's health. The following topics were discussed:

- Sex differences
- Physiology of menopause
- Interdisciplinary research on women's physiology
- Women's neurology
- Work and family issues, including families with older children and adolescents
- Organizational culture and change

Representation/Leadership

Discussion of concerns related to representation and leadership centered on developing an understanding of how some women gain prominent leadership roles in biomedical sciences while others reach a ceiling at lower level positions. The group was very supportive of the recent Request for Applications (RFA) for Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (RFA-GM-09-012). The aims of the initiative were to support: 1) research on causal factors explaining the current patterns observed in the careers of women in biomedical and

behavioral science and engineering, and 2) evaluation of the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these fields. Areas of interest included, but were not limited to, the following:

- Individual characteristics, including family and economic circumstances
- Institutional/departmental environment
- Organizational structure
- Disciplinary cultures or practices
- Special populations, such as women of color
- Features of the broader social and cultural context

The group supports reissuing this RFA.

The challenge of getting women into senior leadership positions and ensuring visibility of their accomplishments in science can, in part, be addressed by implementing significant award programs at local and national levels. The group felt strongly that institutions should be held accountable for any underrepresentation of women in leadership positions. Tools can be developed to address everyday issues such as how to discuss gender disparities, and funding for research in this area would be useful.

Based on the above rationale, the working group developed recommendations through an iterative process of discussion and refinement. The group identified four overarching themes.

- Include women of color in all deliberations regarding training, career development, research, and leadership representation.
- Address the organizational, institutional, and system factors that influence/limit the advancement of women in science (e.g., evaluation biases).
- Develop new and enhance existing communication strategies to inform constituencies about opportunities and research findings.
- Evaluate the effectiveness and implications of specific programs or policies prior to expansion.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Pipeline/Pathway

- Focus on pipeline/pathway issues along the career continuum and address issues of entry, transition, advancement, and retention, including issues that affect women at the senior level, particularly women of color.
- Identify, assess, and communicate best practices that address pipeline/pathway issues.

Recommendation 2: Transparency

- Increase environmental capacity. Funding agencies should ask for data on race/ethnicity and gender of faculty and leadership, as well as faculty development efforts at the institutional level.
- The NIH should amend the research grant application to add an "impact statement" that will address the benefit of the proposed work to the applicant's institution (science, education, training enterprise, particularly as it relates to women and people of color).
- Any NIH career development or training grant should include a section describing activities that will be undertaken to enhance the talent and career development of trainees on the grant.
- Institutions should be made aware that they may negotiate funding for faculty development efforts and work-life balance programs into their indirect funding rates.

Recommendation 3: Training and Education

- Advocate for the requirement of a Collaborative Institutional Training Initiative (CITI)-like training module that addresses gender and racial schemas for PIs.
- Ensure that salaries are comparable across K training awards.
- Advocate for the development of an equivalent K24 mechanism for midcareer basic scientists, including research on gender/sex and health disparities.
- Expand communication strategies related to transition and reentry awards.

Recommendation 4: Research Topics

- Increase emphasis/priority of research topics that address sex/gender, LBTI, and health disparities in women, as well as biomarkers for diseases that differentially affect women.
- Work with other professions and disciplines to identify best practices and research findings that foster organizational change and determine their applicability, synthesis, and translation to the biomedical community.
- Extend research on work-life factors that impact women scientists/clinicians' career success and advancement (e.g., elder parents, adolescents, disabled family members, etc.).

Recommendation 5: Representation and Leadership

- Professional organizations and funding agencies should develop ways to recognize institutions' achievement in the advancement of women and minorities in science.
- Consider the development of a MERIT* -like program in women's health that would recognize leadership activities in promoting women and minorities in science.
- Develop an extramural mentoring award for extraordinary accomplishments in mentoring.
- Initiate a community dialogue on "losing" senior-level women and minority faculty.

** The MERIT (Method to Extend Research in Time) Award provides principal investigators up to 10 years of research support in two 5-year segments without the need to renew the application after 5 years.*

References

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A Vision for 2020 for Women's Health Research: Moving into the Future with New Dimensions and Strategies
The Warren Alpert Medical School of Brown University
Women & Infants Hospital of Rhode Island
Providence, Rhode Island
September 21–23, 2009

DAY 1—PUBLIC HEARING

Location: Women & Infants Hospital of Rhode Island Conference Center

11:00 a.m.–12:00 p.m. — **Registration**

12:00–12:30 p.m. — **Welcome**

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Edward Wing, M.D.
Dean of Medicine and Biological Sciences, Frank L. Day Professor of Biology, Brown University

Constance A. Howes, J.D.
President, Women & Infants Hospital

12:30–2:00 p.m. — **Women's Health Research and Researchers: Setting the Stage for the Nation's Health through the Lifespan**

Perspectives from Policymakers/Legislators

The Honorable Jim Langevin
Congressman, Second District, Rhode Island

Governor Donald L. Carcieri

First Lady Suzanne "Sue" Carcieri

Lieutenant Governor Elizabeth Roberts

David Gifford, M.D., M.P.H.
Director, Rhode Island Department of Health

Frank T. Caprio
State Treasurer

Translational Research in Women's Health, from Basic Science to Bedside to Community

Maureen G. Phipps, M.D., M.P.H.
Associate Professor of Ob/Gyn and Community Health, The Warren Alpert Medical School of Brown University, Division Director of Research, Women & Infants Hospital

Translational Research in Public Health

Terrie Fox Wetle, Ph.D.
Associate Dean of Medicine for Public Health and Public Policy, Brown University

2:00–5:00 p.m. — **PUBLIC HEARING**

Moderator: Joanna M. Cain, M.D.
Chace/Joukowsky Professor and Chair, Ob/Gyn, Assistant Dean for Women's Health, Brown University

Receiving Public Testimony: Members of the ORWH Advisory Committee and Conference Committee

DAY 2 —SCIENTIFIC WORKSHOPS

Location: Women & Infants Hospital of Rhode Island Conference Center

7:30–8:30 a.m. — **Registration**

Moderator: Agnes B. Kane, M.D., Ph.D.
Professor and Chair of the Department of Pathology and Laboratory Medicine, Brown University

8:30–9:00 a.m. — **Welcome and Opening Remarks**

Vivian W. Pinn, M.D.

Clyde Briant, Ph.D.
Vice President for Research, Brown University

9:00–9:45 a.m. — **Keynote Address: Policy Gaps that Identify Research Gaps in Women's Health**

JudyAnn Bigby, M.D.
Secretary of Health and Human Services, Commonwealth of Massachusetts

9:45–10:30 a.m. — **PANEL: Lifespan Implications of Maternal Adaptation to Pregnancy**

Moderator: Joanna M. Cain, M.D.

Michelle Hladunewich, M.D., M.Sc.
Assistant Professor, Divisions of Nephrology and Critical Care, University of Toronto

Margaret Miller, M.D.
Assistant Professor of Medicine and Obstetrics and Gynecology, Department of Medicine, The Warren Alpert Medical School of Brown University

Caron Zlotnick, Ph.D.
Director of Behavioral Medicine Research, Women & Infants Hospital, The Warren Alpert Medical School of Brown University

10:30–10:45 a.m. — **Working Group Charge**

Vivian W. Pinn, M.D.

10:45–11:00 a.m. — **BREAK**

11:00 a.m.–3:15 p.m. — **Concurrent Working Groups: Drafting of Recommendations by Area**

Across the Lifespan

- **Prenatal, Infancy, and Childhood Years**
- **Adolescent Years**
- **Reproductive and Middle Years**
- **Pregnancy**
- **Menopausal Transition**
- **Elderly, Frail Elderly, and Healthy Aging**
- **Oral Health and Systemic Conditions**
- **Careers in Dentistry, Bioengineering, and Other Non-M.D. Disciplines**

3:15–3:30 p.m. — **BREAK**

3:30–5:00 p.m. — **Special Populations**

Moderator: Susan Cu-Uvin, M.D.
Professor of Medicine and Ob/Gyn, Director of the Women & AIDS Core, Center for AIDS Research, The Warren Alpert Medical School of Brown University

Disparities in Women's Health Research: Oncology Examples Across the Lifespan

Wendy R. Brewster, M.D., Ph.D.
Professor, Gynecologic Oncology, University of North Carolina

Addiction to Nicotine: A Lifespan and Diversity Perspective on Women's Health

Bess H. Marcus, Ph.D.
Professor, Department of Community Health and Department of Psychiatry and Human Behavior, Brown University

Beyond the Barker Hypothesis: Lifespan Implications of Intrauterine Environment

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Carmen Marsit, Ph.D.
Assistant Professor of Medical Science, Department of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University

5:30 p.m. — **Taking Research to the Environment/ Building Level**

Tours and Discussion of Environmental Design to Impact Neurodevelopment

6:00–7:30 p.m. — **Conference Reception**

DAY 3—SCIENTIFIC WORKSHOPS

Location: Women & Infants Hospital of Rhode Island Conference Center

8:00–8:15 a.m. — **Welcome and Opening Remarks**

Janine Austin Clayton, M.D.
Deputy Director, Office of Research on Women's Health, NIH

8:15–9:00 a.m.	**Creating the Future—Careers in Research in Biomedicine** **Shirley M. Malcom, Ph.D.** *Head, Education and Human Resources, American Association for the Advancement of Science*
9:00–10:45 a.m.	**Concurrent Working Groups: Finalization of Reports by Area**
10:45–11:00 a.m.	**BREAK**
11:00 a.m.–12:30 p.m.	**Working Group Results and Discussion**
12:30–1:00 p.m.	**Audience Feedback**
1:00–1:15 p.m.	**Closing Remarks** **Vivian W. Pinn, M.D.**

The Warren Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island
Providence, Rhode Island
September 22–23, 2009

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INTRODUCTION

This report covers the third strategic planning meeting, held September 21–23, 2009 at Brown University's Women & Infants Hospital of Rhode Island. The meeting format included welcoming remarks from the ORWH Director, University sponsors, the Governor of Rhode Island and several other legislators and policy makers; 19 public testimony presentations; 10 scientific presentations during the plenary session, including a keynote address from the Massachusetts Secretary of Health and Human Services; a charge to participants from the ORWH Director; and 8 breakout working groups. The value of developmental lifespan research on women's health provided the primary scientific organizing principle of the meeting; a major crosscutting perspective was the need for more rapid translation of biomedical research findings into information, community interventions, organizational changes, and policies to improve the public health of diverse populations of women. Plenary presentations that provided public health perspectives were complemented by presentations on special populations of women and on the lifespan health implications of maternal adaptations to pregnancy and of the fetal intrauterine environment. Below are highlights from the plenary presentations.

TRANSLATIONAL RESEARCH IN WOMEN'S HEALTH

Maureen G. Phipps, M.D., M.P.H.

Associate Professor of Ob/Gyn and Community Health, The Warren Alpert Medical School of Brown University, Division Director of Research, Women & Infants Hospital

Dr. Phipps gave an overview of the goals of translational research, identifying gaps and opportunities for interdisciplinary translational research to improve women's health. NIH research has provided a wealth of biomedical scientific knowledge about women's health across the lifespan, placing strong emphasis in recent years on the importance of speeding the translation of basic research into clinical applications. But efforts to translate clinical knowledge into interventions, services, and policies with measurable public health impact have had mixed success. To truly make an impact on women's health, translational research must go beyond "bench to bedside" by pursuing opportunities for dissemination, community uptake and involvement, including advocacy and policy development. Achieving this goal will require interdisciplinary collaboration and feedback between basic science researchers, clinical researchers, behavioral scientists, public health researchers, clinicians, the community, and policymakers.

Terrie Fox Wetle, Ph.D.

Associate Dean of Medicine for Public Health and Public Policy, Brown University

Dr. Wetle continued the discussion of translational research from the perspective of public health, describing the potential of using public health strategies in translational research to improve women's health. To effectively move newly discovered clinical interventions into the community, *translational public health research* is needed to provide the evidence base from which to design effective community intervention and dissemination strategies. Opportunities include applying public health expertise to designing clinical and behavioral research that will develop and test new interventions; assessing and monitoring the health of communities and at-risk populations to identify health problems and set priorities; designing community and population-based interventions to prevent disease and promote health; formulating new policies and practices to address local and national health problems; and assuring that

all have access to appropriate and cost-effective care, including health promotion and disease prevention services. Scientists, whose research has created the knowledge base for these activities, need to become key participants. To accomplish this, dissemination and communication skills should be elevated to the status of core competencies in women's health scientific career and leadership development programs. Individuals planning a career in translational public health research will need scientific preparation that not only provides a broad interdisciplinary perspective, but also helps them to develop highly technical competencies in areas such as the analysis of large linked population databases as well as model building that integrates genomic, epidemiological, and exposure data.

KEYNOTE ADDRESS: POLICY GAPS THAT IDENTIFY RESEARCH GAPS IN WOMEN'S HEALTH

JudyAnn Bigby, M.D.

Secretary of Health and Human Services, Commonwealth of Massachusetts

Dr. Bigby reviewed the current status of women's health based on key public health indicators. She noted that women have greater disability associated with chronic disease than do men. This pattern is due in part to women's greater longevity, but it also stems from gender differences in income levels and patterns of health care coverage. Furthermore, among different populations of women, disparities exist in health care coverage, use of services, and health outcomes. Since 2006, when health care reform was enacted in Massachusetts, coverage in the State has increased for previously underinsured groups. In the next few years, this expanded coverage should permit determination of the impact of removing financial barriers to access on women's public health indicators, such as disparities in receipt of adequate care during pregnancy and rates of preterm birth.

Nonetheless, even universal access will not solve problems posed by fragmentation of women's health care. Gestational diabetes mellitus (GDM) and its followup demonstrate this fragmentation. GDM increases risk for type 2 diabetes, with 35 to 60 percent of women who have GDM developing type 2 diabetes within 10 years. Despite a need for continuity in monitoring, postpartum glucose screening is still not routinely done for GDM women, nor is information about their GDM status routinely provided to their primary care physicians. New integrative models of services delivery for women should recognize lifespan health risks and concerns.

LIFESPAN IMPLICATIONS OF MATERNAL ADAPTATION TO PREGNANCY

Michelle Hladunewich, M.D., M.Sc.

Assistant Professor, Divisions of Nephrology and Critical Care, University of Toronto

Severe preeclampsia leading to preterm birth is a major cause of maternal and fetal morbidity and mortality. Recent epidemiological findings have challenged a long-held view that preeclampsia is inconsequential for later health. Now it is recognized as an early indicator of a woman's risk for later vascular disease—hypertension, myocardial infarction, stroke, and renal disease.

Animal models of preeclampsia provide insights into its pathogenesis as well as the shared mechanisms that underlie its association with later vascular disease. COMT

(catechol-O-methyltransferase) is the principal enzyme in the conjugation pathway for estradiol. Both COMT and 2-methoxyoestradiol (2-ME) are significantly lower in women with preeclampsia. A mouse model of the preeclamptic phenotype, produced in COMT knockout (-/-) pregnant mice, was rescued by administration of 2-ME. 2-ME also suppressed placental hypoxia and antiangiogenic factors that have been linked to placental pathology and pregnancy-related hypertension. Clinical applications of this research may include the use of 2-ME as a diagnostic risk marker for preeclampsia or as a therapeutic supplement to prevent or treat the condition. Translational research should continue to increase fundamental understanding of the mechanisms linking pathological syndromes of pregnancy to later disease and to provide new therapeutic and preventive targets.

Margaret Miller, M.D.
Assistant Professor of Medicine and Obstetrics & Gynecology, Department of Medicine, The Warren Alpert Medical School of Brown University
Dr. Miller described the move away from viewing women's health primarily in terms of its importance for pregnancy outcomes, citing an emerging paradigm that views pregnancy as having important lifespan implications for women's health. Pregnancy may unmask chronic disease, pregnancy outcomes may predict future disease, and pregnancy may provide an opportunity to identify health risks and disease. Normal changes in pregnancy present a picture of a "metabolic syndrome," with insulin resistance, hyperlipidemia, increased coagulation factors, upregulation of the inflammatory cascade, and increased white blood cells. Most women tolerate these changes with no problems, but others develop diseases such as GDM and venous thromboembolism.

Caron Zlotnick, Ph.D.
Director of Behavioral Medicine Research, Women &Infants Hospital, The Warren Alpert Medical School of Brown University
Dr. Zlotnick discussed what is currently known about perinatal depression and future research directions. Depression is a lifelong recurrent disorder, and females have twice the risk of being diagnosed with depression as do males. Depression during the perinatal period, defined as pregnancy and postpartum, raises a number of special issues. Some women have increased vulnerability to new-onset or recurrent depression at this time. Perinatal depression also raises unique treatment issues. Studies of antidepressant exposure in pregnancy have suggested increased risk for poorer infant outcomes, but medication discontinuation is also associated with higher rates of maternal depression relapse. Maternal perinatal stress has been associated with poorer offspring outcomes, impaired mother-infant bonding, and later child behavioral problems. Many women indicate a preference for psychosocial interventions for perinatal depression, but few such interventions, tailored to their special issues, are currently available.

SPECIAL POPULATIONS

Wendy R. Brewster, M.D., Ph.D.
Professor, Gynecologic Oncology, University of North Carolina
Dr. Brewster's presentation focused on health disparities in cancer. As the population ages, cancer rates are expected to increase proportionately. Because women on average live longer than men, cancer will increasingly become a woman's health issue. The elderly are

underrepresented in cancer clinical trials due to the presence of complicating medical comorbidities. To more adequately address geriatric cancer and its treatment, geriatric and cancer clinical researchers need to develop strong interdisciplinary, collaborative models of training, research, and care. Health disparities in cancer exist among different populations of women, as is the case for breast cancer. This type of cancer is more prevalent in White women, but causes higher mortality in Black women. Recent research indicates that the mortality disparity may persist even when screening and treatment are comparable for both groups of women. New research aimed at understanding this disparity is currently also examining the role of factors related to tumor biology in the disproportionate occurrence of an aggressive, early-onset form of breast cancer in Black women.

Bess H. Marcus, Ph.D.
Professor, Department of Community Health and Department of Psychiatry and Human Behavior, Brown University

Dr. Marcus discussed the numerous gender differences that have been identified in addiction prevalence, course, relapse risk, and treatment. Males are more likely to smoke, drink, and use drugs than are females, but trends indicate that the gender gap may be closing. Dependence on a substance, once use has started, is greater for females than males. "Telescoping" of the course of addiction occurs in females, who begin regularly self-administering substances at lower doses than males, become addicted faster, and enter treatment after fewer years of use. Females are at greater risk for relapse following abstinence, and their risk factors are different than those of males. For example, concern over weight gain is a major cause of relapse from smoking cessation in women. In a *Commit to Quit* smoking cessation trial specifically tailored to women smokers, participants were randomized either to an intervention of cognitive behavior therapy (CBT) to address weight gain concerns along with vigorous exercise or to CBT with control staff time. Those in the CBT and exercise arm had twice the quit rate as the CBT group alone. Those who exercised gained 6 pounds versus 12 pounds in the other group. Attention to gender differences in risk factors and concerns can affect substance abuse treatment outcomes.

LIFESPAN IMPLICATIONS OF THE IN UTERO ENVIRONMENT: BEYOND THE BARKER HYPOTHESIS

James Padbury, M.D.
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Carmen Marsit, Ph.D.
Assistant Professor, Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University

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Professor of Psychiatry and Pediatrics
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The Barker hypothesis is a theory that links disturbed intrauterine growth to the later development of cardiovascular disease. The original hypothesis was based on epidemiological findings that low-birth-weight offspring, whose mothers were severely malnourished during

the third trimester, had increased risk as adults for cardiovascular disease. This nutritional-adaptation hypothesis has been expanded to explain increased risk in adult life for a range of cardiovascular system outcomes such as diabetes, hypertension, and hypercholesterolemia. A more general extension of the hypothesis—to include other environmental stresses *in utero*—has also gained scientific currency. A plenary presentation provided evidence to support the conceptualization of maternal cocaine use during a critical period in fetal development as a stressor that downregulates the placental norepinephrine transporter system (NET). In this model, cocaine exposure *in utero* triggers a chain of events, leading from increased fetal exposure to catecholamines and altered fetal neuroendocrine activity to changes in the epigenetic expression of key genes. Changes in epigenetic programming provide the developmental link between prenatal risk exposure and later behavioral outcomes: activity rhythm dysregulation in infancy; poor inhibitory control and emotion regulation in childhood; and behavioral phenotypes that confer vulnerability to substance use in adolescence.

CHARGE TO THE WORKING GROUPS

Dr. Vivian M. Pinn delivered the charge to the working groups. Women's health research, she emphasized, must be comprehensive and must include the entire spectrum of research activities, from basic science to community dissemination. She noted that women's health research is an inherently interdisciplinary endeavor; those who would undertake it must bring to bear perspectives such as lifespan, sex/gender determinants, and health disparities and diversity. In her concluding remarks, she urged participants to think outside their disciplinary silos and to move beyond their current research or advocacy agendas to anticipate and envision the next generation of women's health research.

SCIENTIFIC WORKING AND DISCUSSION GROUPS

PRENATAL, INFANCY, AND CHILDHOOD YEARS

Cochairs:

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Introduction

The Working Group on Prenatal, Infancy, and Childhood Years identified four main topics for forward-looking research. Obstetric care represents a critical window of health care during the reproductive lifespan of women. Four topics were chosen because they represented situations or conditions occurring during pregnancy that have far-reaching effects on the developing child. The four topics chosen were 1) the molecular basis for developmental origins of health and disease—childhood onset; 2) the placenta as a functional endocrine and transport organ; 3) prenatal exposures to environmental toxins, inflammatory cytokines, drugs, and socioeconomic stressors; and 4) fetal therapy.

Summary of the Discussion

Molecular Basis for Developmental Origins of Health and Disease—Childhood Onset

The important concept known as fetal programming emphasizes that the intrauterine environment and the mother's prenatal exposures and experiences can have long-term effects on the health of the offspring. For example, epidemiologic studies show that aberrant fetal growth rate is a major risk factor for later development of chronic diseases such as coronary artery disease, stroke, type 2 diabetes mellitus, and hypertension. However, the etiologic factors for these relationships are not known.[1] In addition, these and other chronic diseases are more prevalent among minority races than Whites and among males than females.

Further analyses are needed of a broad range of prenatal conditions and stresses that could have long-term consequences on health and disease. Existing examples include the following:

- Gender differences in susceptibility to low birthweight as well as myocardial infarction.
- Impaired thyroid hormone function and brain development.

- Prenatal caffeine exposure, growth rates in preterm infants, and increased body fat later in life.

The underlying mechanisms are likely to be multifactorial and will require interdisciplinary approaches, including molecular studies to identify biomarkers. The identification of the developmental and molecular bases of sexual dimorphism should be included in this research.

Specific Examples of Fetal Programming Research

Roles of Insulin Resistance in the Pathogenesis of Obesity. One working hypothesis for fetal programming is that stressors and environmental toxins promote insulin resistance, which changes gene expression due to DNA methylation and alters protein expression in the brain. For unknown reasons, these factors contribute to chronic diseases during adulthood and likely contribute to disorders of childhood, including obesity. Research is needed to examine how the prenatal brain is influenced by differential gene expression. Equally important is an assessment of how differential gene expression occurs and is triggered. Molecular and biochemical approaches should be used. Novel methods are needed to detect early exposures and to track their later effects and identify individuals at risk. For example, the cause of the childhood obesity epidemic may be multifactorial, and consideration should be given to the pathogenic roles of maternal hyperglycemia, maternal weight gain, alcohol misuse, infant feeding practices (breastfeeding), and the effect of prematurity on the infant's weight gain early in the postnatal period. This approach could lead to the development of public health measures to prevent exposures in the future and has global relevance.

One study has shown strong associations between maternal plasma glucose levels (at lower levels than the standard criteria for a diagnosis of diabetes) and increased birthweight and increased cord blood serum C-peptide levels.[2] These findings indicate that research is needed to better identify mothers and fetuses at risk of becoming overweight newborns and the factors contributing to these problems.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Overdrive. Fetal adaptation to stress *in utero* is an important concept. The cause of intrauterine stress is probably multifactorial and cumulative. Stress pushes the HPA axis into overdrive, causing excess production and release of cortisol by the adrenal glands. Then, in the context of later exposure to obesogenic diets, the primed individuals gain weight rapidly and develop insulin resistance and type 2 diabetes mellitus in their teenage years or early 20s.[3] Importantly, rapid weight gain during the first 2 years of life increases the rates of myocardial infarction many years later. However, the specific role of the adrenal glands was put in doubt by the finding that loss of both adrenal glands does not modify mortality from cardiovascular disease. Remaining to be investigated, however, is the common thread of altered fetal programming with obesity and chronic disease risk as a result.

Innovative methods are needed for assessing allostatic load and critical window exposures and stressors that go beyond the HPA axis in relation to effects on childhood, adult, and gender-biased diseases. Attention should be focused on growth and sexual dimorphisms, mood disorders, depression and appetite regulators, and addictive disorders. Racial disparities are quite critical because, controlling for socioeconomic status and education, race remains a key

risk factor for low birthweight and infant mortality. In this regard, it could be postulated that allostatic load more effectively activates the HPA axis, leading to stress responses that are more sustained in Blacks than in Whites. This would constitute a greater degree of preterm stress and could contribute to preterm delivery and low birthweight.

Finally, other conditions and exposures during pregnancy likely will be found to influence fetal programming with effects on childhood neurodevelopmental disorders, autoimmune diseases, inflammatory disorders, addictive disorders, and precocious puberty. Research should be directed toward basic science approaches as well as mechanisms for translating research into clinical practice. This effort will require services beyond those provided by physicians, particularly given the prevalence of diabetes and obesity. Health care extenders such as nurse practitioners and physician's assistants could provide care, management, and followup of patients with obesity, type 2 diabetes, and related or secondary diseases during pregnancy and the interconception windows.

Placenta as a Functional Endocrine and Transport Organ

The vital role the placenta plays in the health of the fetus, and how impairments in its structure and function may facilitate fetal exposure to drugs, stressors, toxins, etc., are largely unknown, despite clear evidence that significant abnormalities in placental structure and function are associated with intrauterine growth restriction. An overarching concept for enabling studies of placental functions is the establishment of a placental biobank. It would make possible a systematic collection of data and sharing of reagents and data among multiple investigators, including globally. Besides placentas, biobanked specimens should include umbilical cord blood, amniotic fluid, meconium, DNA, and RNA. In terms of extending the investigations to clinical outcomes in children, adolescents, and adults, breast milk could serve as a vehicle for perinatal exposure to drugs, toxins, inflammatory mediators, and other substances.

Establishing a placental biobank would facilitate large-scale investigations that could perform the following:

- Lead to the identification of novel biomarkers of individuals at risk for becoming obese and developing significant and life-threatening cardiovascular, cerebrovascular, hypertensive, arteriosclerotic small-vessel disease, and type 2 diabetes mellitus later in life.
- Examine the effects of toxin, microbial, and drug exposures on development, behavior, and diseases, including obesity and type 2 diabetes.
- Investigate the mechanisms of placental transport of nutrients and drugs on molecular, biochemical, and functional levels.
- Track the effects of early prenatal exposures leading to epigenetic changes that have long-term consequences for health and disease.
- Determine drug (licit and illicit) effects on the fetus, child, and mother, and for examining transporter physiology or pathophysiology.
- Create models for studying multiple drug/toxin exposures on the fetus, newborn, mother, and child, as well as gender effects.

New technologies are needed to access placental function from maternal circulation. Free fetal nucleic acids circulating in maternal blood could be used to track health status, detect disease, and monitor effects of treatment. We already know that more than 100 genes are turned on or off based on their parent of origin, the imprinted genes; however, we have not yet constructed profiles of gene expression that correlate with healthy and disease states. Future studies should include the development and analyses of biomarkers, substrate and drug transport studies, and epigenetics and imprinting during critical windows. Apart from gene expression studies, proteomics should be used as complementary approaches, particularly because proteins are the ultimate mediators of cell signaling and function.

A very exciting and strategically important area of research will be to understand how shifts in gene expression early in life have lifelong consequences on health and disease. Mechanistically, a process known as "gene imprinting" occurs when genomic DNA gets methylated, resulting in lifelong silencing of gene expression. Examining patterns of DNA methylation in placenta, fetus, and offspring during different stages of development or critical windows could advance the understanding of molecular mechanisms of disease proneness, and thereby explain unexpected correlations such as the overlapping prevalence rates of low birthweight/small for gestational age and subsequent increased risk for cardiovascular death. This concept could be relevant to many adult diseases that have familial, but no apparent genetic, linkages. Factors influencing DNA methylation *in utero* most likely include stresses from various sources, including nutrient deficiencies, insulin resistance, poverty, violence, drug exposures, poor living conditions, and numerous unknowns. Consideration must also be given to modifiers that serve as "second" or "third" hits in propagating disease proneness. For example, prenatal stress combined with obesogenic and nutrient-deficient diets may play a large role in the growing pandemic of insulin-resistance diseases, including obesity, type 2 diabetes, and secondary effects that include cardiovascular disease. Therefore, this concept has global relevance.

Other concepts were raised. Dynamic models are needed to study placental function and drug/toxin transport. Rodent models have limited use, and subhuman primate models are generally unacceptable. Instead, the working group proposed that safe and well-controlled obstetrical-pharmacological centers be established for studying drug delivery, nutrients, and toxins across the placenta. Perhaps an artificial placenta could be developed and used for similar investigations, or perhaps to help sustain normal growth and development of at-risk fetuses.

Prenatal Exposures

Environmental toxins, inflammatory cytokines, drugs, and socioeconomic stressors influence fetal neurodevelopment and can adversely affect later-life function and biobehavioral diseases, as in the following examples.

Toxins

- Maternal, fetal, and early childhood exposures to toxins such as Bisphenol A and phthalates, which contaminate plastics, may lead to obesity because of their endocrine-disrupting effects.

- DDT exposure affects girls under age 13 by predisposing them to develop aggressive forms of breast cancer later in life. Because this relationship does not occur in older girls, understanding exposures within and outside of critical windows of development is important.
- Puberty is occurring earlier, particularly in girls; this trend began 20 to 30 years ago, along with the obesity/type 2 diabetes/insulin resistance epidemic. Is this phenomenon related to gene imprinting or differential silencing/activation of certain genes during prenatal development? We know that more than 500 genes are differentially expressed by gender. The effects of environmental toxins that could influence the estrogen-receptor activity or cause endocrine disruption have not been investigated. How do early exposures to toxins and endocrine disruptions result in changes in gene expression and function that predispose girls to undergo early puberty?

Inflammation

- Inflammation and cytokine activation mediate or contribute to many diseases, including intrauterine growth restriction, preeclampsia, and preterm delivery.
- Placental inflammation during the first trimester of pregnancy has been reported to increase the rate of schizophrenia, and IL6 has been implicated.
- An important avenue of research is to understand how inflammatory mediators influence *in utero* brain development and function, and predispose the offspring to develop neurobiological and behavioral diseases during adolescence and early adulthood. Do *in utero* inflammatory mediators alter critical genes responsible for neuropsychiatric function?

Drugs

- Development of novel biomarkers that detect drug exposures and the effects on the placenta, fetus, and child would lead to an understanding of how drugs change the developing organism.
- Tools are needed to identify mothers at risk for using addictive drugs during pregnancy that could result in physical, neurological, psychiatric, developmental, or behavioral abnormalities in the offspring. In addition, tools should be developed for assessing morbidity associated with addictive drug exposure and withdrawal in both mother and child.
- Many policies associated with detecting addictive drugs have punitive consequences with respect to maternal-child relationships. The policies across different States should be examined and the data used to restructure the paradigms for managing and treating mothers at risk.
- An additional line of investigation would be to examine the long-term effects of perinatal addiction, and to identify social determinants, access to treatment, and methods of translating the results into clinical practice. For example, assessing the effects of exposure to addictive drugs on patterns of child abuse, maternal stress, parenting difficulties, depression, smoking, and differential gender responses in the children are important goals.

Socioeconomic Stressors

- Antenatal and postpartum stress can also adversely affect childhood development, and persistent maternal stress interferes with and adversely affects parenting. Ample animal research shows that poor parenting has epigenetic effects on development. Maternal stress from the antenatal period to childhood results in significant development of childhood stress, thereby creating a closed circuit. Biomarkers and psychosocial markers of different types of stress are needed to detect and intervene in this cycle.

- Stress caused by racism, depression, and social determinants, such as poor housing, food insecurity, and family status, could represent chronic exposures that influence pregnancy outcomes and the health and welfare of the offspring. In the Adverse Childhood Experiences Study, which included 19,000 self-report questionnaires, it was found that long-term outcomes from chronic exposure to stressors were dose dependent and had stepped effects.[4] This retrospective study demonstrated relationships between long-term health effects and a series of adverse events, including smoking, substance abuse, obesity, chronic obstructive pulmonary disease, liver problems, mental health, suicide, sexually transmitted diseases, and teenage pregnancy. Higher proportions of heart disease and other conditions could be explained by cumulative adverse events that primarily center on violence.

No one factor or exposure could be responsible for the subsequent development of complex syndromes. For example, the pathogenesis of neurodevelopmental diseases, such as autism, should be considered in relation to adverse event stress, as well as stress caused by agent exposures, including toxins, environmental substances (e.g., mold, bugs, lead, licit and illicit drugs), addictive drugs, herbals, nutrients, and supplements. Autism has a large sex dimorphism that may correlate with high testosterone levels, raising the question as to whether hyperandrogenized brains or congenital adrenal hyperplasia predispose infants to become autistic. The potential role of endocrine-mediated neurobiobehavioral syndromes is reinforced by the fact that individuals with Cushing's disease have increased rates of neuropsychiatric disorders.

Thus, a systems approach to data analysis with consideration of multiple potential causes of stress in pregnant women and their fetuses will be required. Research should address the impact of cumulative adverse events, timing (critical window), thresholds, and interactions with addictive drug exposures on pregnancy and later life health, and track their effects with respect to age, gender, and race. Due to its complexity, the research will likely have to be interdisciplinary and use mathematical models such as the Granger causality analysis to pinpoint causality. It is unlikely that we will ever be able to isolate independent variables to determine how each one impacts pregnancy, fetal development, and later life disease profiles.

Another consideration for research is to design approaches for therapeutic intervention and prevention. Longitudinal studies should examine outcomes with respect to interconception reduction of allostatic stress load, and through improved monitoring and detection of at-risk individuals. The expectation is that these measures will help prevent generational drug and other substance abuse that stem from maternal and/or fetal stress. Design of preventive and therapeutic intervention measures should use collaborative efforts across various centers, such as medical, obstetric, psychiatric, and public health. Use of teams and community health workers to

improve outcomes will be important for overall outcomes. The study designs should be interdisciplinary and include agendas that cross various disciplines (e.g., medical obstetric, psychiatric, and public health) to promote the health of communities beyond hospitals and health centers. In addition, public-private partnerships need to be developed to encourage communities to remain committed to the overall goals.

Fetal Therapy

Today, fetal therapy is considered niche medicine and is not a public health priority. However, as the approaches are increasingly less invasive and with fewer maternal and fetal complications, the concept is growing in importance. Moreover, *in utero* repair of a few congenital defects has become a clinical reality.

One disease that can be successfully treated is fetal aortic stenosis, which in severe cases leads to hypoplastic left heart syndrome. Alleviating aortic stenosis early in gestation can prevent the subsequent development of hypoplastic left heart syndrome in some, but not all, fetuses. The pathogenesis of fetal aortic stenosis is not understood, but the 90 percent male occurrence rate may provide a clue.

Advancing the field of fetal therapy requires a better understanding of the pathophysiological basis of the conditions that potentially could be treated, for example, twin-twin transfusion syndrome. Currently, fetal surgery is used to treat this condition. However, little is understood about the mechanism of the condition, though it is known that virtually the same vascular connections exist between identical twins who do not develop the syndrome.

The explosion in the past decade in the number of treatment centers providing fetal surgical approaches around the world is worrisome because guidelines for treatment have not been established; there is no credentialing of practitioners and no oversight. Efforts should be made to address these issues and help elevate these procedures to evidence-based therapies. Considerations for clinical trials include whether control and sham procedures should be performed in determining the effectiveness of various fetal surgical approaches. The rationale for conducting controlled trials is the need to prioritize which procedures are effective and therefore worthwhile, and which, based on outcomes, should not continue.

The ever-growing access to fetuses via imaging, analysis of amniotic fluid, cells, fetal tissues, blood, and physiology has begun to inform the science about abnormal development and how to deal with diseases prior to birth. The changing field of ultrasound lends itself to earlier diagnosis and potential for early intervention. Major benefits from the improved access to fetuses for diagnostics include disease prevention by treating a condition that has secondary consequences on later organ development and function. In addition, better imaging and tissue analysis of fetuses will provide the opportunity to gain a better understanding about sex differences in fetal diseases requiring surgical or nonsurgical therapy.

To take advantage of these recent technologies in research applications, establishing a fetal therapy network is critical. This network, if modeled similar to the MFMU (Maternal Fetal Medicine Unit Network funded by the *Eunice Kennedy Shriver* National Institute of Child Health and

Human Development), would enable sharing of resources (materials, tissues, ideas) and provide much-needed guidelines, criteria, and benchmarks, and stimulate collaborative research about disease mechanisms. A fetal therapy network would make it feasible to study dysmorphologies that are rare in any one institution or setting. Both surgical and nonsurgical treatments could be used to treat otherwise fatal or debilitating conditions such as diaphragmatic hernia, hemaglobinopathies, cystic fibrosis, and possibly TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus) infections. Gene or stem cell therapeutic approaches could lead to prenatal prevention of sickle cell disease or thalassemia.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Investigate the molecular basis for developmental origins of child-onset health and disease. Research should focus on the molecular alterations during pregnancy that underlie the fetal programming that informs childhood development and growth. Because childhood obesity is epidemic and global, it should be a priority for research.

- Advance research at a molecular level starting with existing avenues of epidemiologic research, which include maternal hyperglycemia, insulin resistance, maternal weight gain, maternal obesity, infant feeding practices, and infant weight gain, especially in premature infants.
- Further expand the research of fetal programming and the molecular mechanisms of disease by supporting investigation of neurodevelopmental disorders, autoimmune diseases, inflammatory disorders, addictive disorders, precocious puberty, and diseases that have a sexually dimorphic phenotype.

Recommendation 2: Support research of the placenta as a functional endocrine and transport organ. Establish an interdisciplinary placental biospecimen banking mechanism to enhance research on antenatal antecedents to childhood health with a focus on the following:

- Functional studies
- Biomarker development
- Substrate and drug transport
- Epigenetics and imprinting during critical windows
- Development of technologies to access placental function from the maternal circulation, for example, free fetal nucleic acid
- Innovations toward development of an artificial placenta

Recommendation 3: Examine a range of prenatal exposures (addictive drugs, environmental toxins, stressors, nutrient intake) and their relationship to preterm delivery/low birthweight. Multidisciplinary approaches in clinical and translational research are needed to address the wide range of agents that could affect birth outcomes. The following is a brief, and not conclusive, list of potential exposures to be evaluated:

- Appraise the birth outcomes of licit or illicit addictive drugs.

- Develop innovative approaches/biomarkers for identifying exposures and effects.
- Expand screening efforts to move from research to practice.
- Evaluate the effect of multiple drugs and toxins (polydrug exposure) during critical windows of development.
- Propose and evaluate the effects of interconception substance abuse interventions.
- Perform comprehensive research on effects and measurements of antenatal and postpartum stressors and their impacts on parenting and child development by gender.
- Evaluate other prenatal exposures (e.g., environmental toxins, prescription drugs, over-the-counter drugs, herbs, and nutrients) and their relationship to birth outcomes.

Recommendation 4: Create and support a national multicenter network for fetal therapy and for translational research that brings together the basic science and clinical disciplines. Incorporate stem cell and gene therapy into the network's areas of study and treatment. Minimally invasive fetal therapies that will allow for antenatal treatment have become a reality and there is a need to share limited resources and expertise, minimize duplication, and use scientific approaches.

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ADOLESCENT YEARS

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Introduction

The Working Group on Adolescent Years addressed research priorities among adolescents and young adults, ages 10 to 24 years. Following an overview of the demographic characteristics of the U.S. adolescent population and the major causes of morbidity and mortality in this age group, each working group participant contributed ideas about the status of current research and innovative ideas for the future. After a discussion of these ideas, the working group generated a list of recommendations for future research.

Summary of the Discussion

Current data about health characteristics of adolescents and young adults in the United States include the following:[1]

- In 2006, there were 63.3 million adolescents and young adults, with 55.2 percent White, 16.5 percent Hispanic, 13.6 percent Black, 3.9 percent Asian/Pacific Islander, 0.9 percent American Indian/Alaskan Native, and 9.9 percent other. Ten percent were immigrants or foreign born.
- Much of the morbidity in adolescence and young adulthood stems from behaviors rather than intrinsic disease.
- Nearly 5 percent of young adults have a disabling chronic condition.
- In 2005, about 7 in 10 deaths among persons ages 10 to 24 were caused by motor vehicle accidents, homicide, and suicide.
- Unintentional deaths and violence impact non-White males disproportionately. Depression is the highest reported psychiatric disorder among teens, with the highest rates among Hispanic females, and suicide attempts are higher for girls than for boys.
- Rates of substance use are decreasing for binge drinking and daily cigarette use, including smoking half a pack; however, small increases in marijuana use and changes in "drugs of choice" have occurred, with more use of prescription drugs.
- Recently, adolescent and young adult birth rates have slightly increased.
- Sexually transmitted infections continue to increase and disproportionately affect Black females.

- Rates of overweight and obese adolescents nearly doubled from the mid-1990s to the mid-2000s. Rates of exercise and rates of fruit and vegetable consumption have not changed, however.
- Most females enter the health care system for reproductive health services. Males are seen more often in the emergency department.
- Although most adolescents and young adults saw a clinician and dentist in the past year, only 40 percent of adolescents have time alone with a provider.

More knowledge is needed about adolescent development in normal, healthy teenagers. Despite disadvantaged circumstances, some adolescents in every community are successful, but others fall into risk-taking behaviors. The working group discussed the following topics as candidates for research in order to elucidate protective factors that contribute to healthy behaviors and improve asset building* among adolescents:

- Breastfeeding by adolescent mothers
- First and repeat teen pregnancy
- Access to contraception and family planning
- Postpartum depression
- Eating disorders
- Substance abuse, particularly tobacco and alcohol use
- Inadequate physical activity
- Adequate nutrition
- Intimate partner violence

Participants said they believed little is understood about how culture and community influence the psychosocial development of adolescents in areas that include the following:

- Gender identity, roles, and formation
- Trends in sexuality among adolescents and young adults, including members of the lesbian, gay, bisexual, and transgender communities
- Early puberty transition and its role in risk-taking behaviors
- The changing structure of immigrant families and its role in gender formation
- International differences in gender formation and roles

Further understanding is needed on how the transition into and out of adolescence affects existing chronic disease, onset of new disease, and treatment. Areas of research might include the following:

- Adaptation of adolescents with chronic diseases across key life transitions, including changes in the clinical manifestations and treatment of asthma, allergies, and diabetes
- How the transition into adolescence will affect individuals with genetic and congenital disorders, such as children with autism

** Developmental assets are the positive relationships, opportunities, values, and skills.*

- Chronic diseases that first appear in adolescence, including autoimmune diseases, vulvar diseases, and chronic pain disorders
- Identification of diseases that are at a crucial period for intervention in adolescence, including obesity and mental health disorders
- Additionally, research on the effects of pharmaceuticals and of biological states on adolescents is important, including the following:
- Comparative analysis of the long-term effects of different contraceptive methods used by adolescents
- The long-term effects of teen pregnancy on health and disease
- The impact of adolescent breastfeeding on future health outcomes
- The effect of environmental stressors on the adolescent's biological and psychological health and well-being

Emerging genetic tools and other diagnostic tools may also be useful for studying adolescents' health. For example, adolescents' heightened addiction to tobacco has been documented through magnetic resonance imaging.

The working group acknowledged the need for translational research that will affect the community in a significant way. To reach adolescents, new strategies must be used to foster bi-directional communication between adolescents and their communities. One approach might be to incorporate adolescents in participatory research and peer education, including possibly forming a "Teen Advisory Board" that would keep up with the most current health trends. Adolescents could also play a role in identifying research questions that reflect emerging issues of concern to them and their peers, and, with appropriate training, supervision, and support, adolescents could have a role in data collection, data analyses, and presentation of results to community stakeholders, including policymakers and peers.

Research to improve the delivery of health care services to adolescents and young adults is a priority. Current delivery models have substantial gaps in terms of prevention, screening, referral, and early intervention with behaviors. These gaps often place these populations at increased risk for current and future negative outcomes. Research could determine the best methods to improve the adoption of new guidelines and provider adherence to guidelines, especially concerning cervical cancer screening, colposcopy, and human papilloma virus (HPV) vaccine distribution. Academic detailing, or face-to-face education of providers by providers using evidence-based information, is one method that needs further research.

Uninsured adolescents and young adults probably do not receive the care they need. They, as well as the insured, might best be served through access to a stable "medical home" that would have a multidisciplinary team of providers and could be in an ideal setting, such as school-based or community-based clinics. The medical home should offer strong counseling and education components, especially teaching that is aimed at reducing the stigma surrounding reproductive health.

A potentially important tool for influencing adolescent behavior is social marketing through new media technologies, including Twitter, Facebook, text messaging, video games, etc. These technologies could be used to generate educational programs and support for healthy behaviors, such as adolescent male involvement in family planning and parenting, as well as new campaigns for smoking cessation and increased compliance with medications.

The following overarching themes should be incorporated into all future research projects:

- Inclusion of all groups that are underserved and impacted by health disparities, including different ethnic and cultural groups; immigrants; individuals with special needs; members of the lesbian, bisexual, gay, and transgender communities; and parenting teens
- Consideration of the impact of health policies on adolescents and young adults
- Use of a variety of research methodologies, including community-based participatory research and comparative effectiveness research
- Interrelationships of the adolescent with family, school, community, and social environments and the bidirectional impact of each on adolescent health, safety, and well-being

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: As a basis for developing interventions to empower adolescents to engage in health-promoting behaviors that make them resilient, 1) identify protective factors in individuals and the environment that promote and sustain healthy behaviors across cultural groups; 2) describe gender formation, identity, and roles from cultural, societal, and biological viewpoints; and 3) identify factors that improve asset building among adolescents.

Recommendation 2: To understand how the transitions from childhood to adolescence and adolescence to young adulthood affect normal function, disease, and treatment, 1) conduct comparative research on a variety of issues, including the long-term health effects of pregnancy, different contraceptive methods, various models designed to reduce body mass index and increase physical activity, various HIV and sexually transmitted infection prevention models, etc.; and 2) increase the use of mixed methodologies, including community-based participatory research, when conducting research among adolescents.

Recommendation 3: To improve diffusion and uptake of new knowledge by adolescents and their health care providers, 1) involve adolescents and groups of interdisciplinary providers (e.g., primary care providers in the "medical home," other providers in other community-based settings) in not only conducting research/peer education, but also in developing communication channels for distributing new knowledge in ways that are more readily adopted by adolescents, their families, and providers; 2) examine the effectiveness of social marketing to influence adolescent behavior, including use of new technologies; and (3) conduct research on the uptake of new technologies, guidelines, and provider adherence, such as in the case of cervical cancer screening.

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REPRODUCTIVE AND MIDDLE YEARS

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Introduction

The Working Group on Reproductive and Middle Years focused on three topics related to reproduction—infertility, fibroids, and endometriosis—because of their serious impact on women's health during the reproductive years and the paucity of peer-reviewed research in these areas. Each cochair provided background information for the discussion and the development of recommendations by the group participants.

Summary of the Discussion

Infertility

Infertility is defined as the inability to conceive a child after 1 year of trying (or 6 months for women over 35) or, in some cases, the inability to remain pregnant. According to the Centers for Disease Control and Prevention, about 10 percent of women ages 15–44 have difficulty becoming or remaining pregnant.[1] Causes of infertility in females include ovulation disorders, fallopian tube damage or blockage, uterine abnormalities, and hormonal or genetic factors. Other disorders, such as fibroids and obesity, may also contribute to infertility. Causes of infertility in males are impaired sperm count or motility, or impaired ability of the sperm to fertilize the egg. In some cases, a combination of factors may play a role.

State of the Current Basic and Clinical Sciences on Infertility

Most infertility research studies focus on ovulatory disorders and on male factors. Major current NIH funding for infertility research is focused on fertility preservation research (in patients with cancer undergoing chemotherapy) and the role of adipose tissue. Significant gaps exist in current knowledge about the role of hormonal, genetic, and environmental factors, and of ovulatory dysfunction. For Black women, the high incidence of obesity and reproductive disorders, such as fibroids, might affect their ability to become pregnant. Many of these potential research areas have not yet been peer-reviewed or funded by the NIH.

Regarding medical assistance for individuals with conditions of infertility and impaired fecundity, there are significant racial, financial, health, and social disparities. The literature shows that little demographic difference exists among those who seek medical care for infertility, but there are large differences among those who use care and receive treatment, and in the outcomes of pregnancies. For example, the racial disparities in outcomes for *in vitro* fertilization are unexplained.

Opportunities for Advancing Basic and Clinical Sciences on Infertility

The issue of prevention is key to the future of infertility research and includes primary, secondary, and tertiary strategies.

Primary prevention should emphasize health education and promotion. Chlamydia affects 3 to 5 percent of reproductive-age women and can result in infertility.[2] Because the disease is often asymptomatic, funds to increase community-based screening are important. Developing rapid "point of care" to test for sexually transmitted diseases (STDs) in high-risk populations (e.g., male and female prisoners) may be an important approach to increasing screening rates. Other areas for study include the following:

- Brief interventions to modify and decrease risk-taking behavior
- Determining the efficacy and feasibility of partner-notification programs
- Development of a chlamydia vaccine
- Identification and remedy of social and cultural barriers to primary prevention

Communities should have access to education programs that are culturally specific in addressing preconception care. One goal of such programs would be to ensure that culturally sensitive information would be disseminated broadly enough to have an effect on behavior change. These education programs may help reduce infertility by providing health materials to educate women before they even consider having children (preconception counseling). These materials would include medical, psychological, and behavioral information about screening and interventions related to intimate partner violence.

The foundation for these education programs should be community-based research that addresses how to most effectively influence behaviors related to modifiable causes of infertility (e.g., STDs, tobacco use, nutrition, and physical activity). In addition, further studies are needed on epigenetics and the impact of the environment and various exposures on fertility.

Secondary prevention strategies are interventions for the early detection and prevention of disease progression. Development of these approaches requires additional knowledge and new technology to study the mechanistic pathophysiology of infertility. Multiple processes may be related to reproductive endocrinopathy, including infectious, immunologic, and psychiatric elements. Research focused on vaginal physiology (the only female-specific mucosal site) is also important.

Tertiary prevention involves reducing the negative impact of a disease. Research is needed to better identify biochemical and morphologic characteristics of oocytes and embryos that predict successful implantation and birth of a healthy child. Improving options for special populations (e.g., people with HIV, cancer survivors, those with genetic disorders) who seek assisted reproductive technology should be the focus of continued clinical research. Other areas for tertiary prevention research are as follows:

- Chronic pelvic pain, which is common and has a major impact on fertility[3]
- The mechanisms of chronic pelvic pain and improved therapies
- The impact of infertility treatment on the future health of the mother and infant
- Long-term sequelae of infertility treatment
- Social and psychological issues related to infertility treatment, such as multiple births, adoption, and barriers to care

Overall, treating the woman as a whole being is important, and such research should focus on evidence-based gender topics covering biological, environmental, psychological, behavioral, spiritual, and economic aspects of women's health.

Fibroids

Uterine fibroids are the most common gynecologic neoplasm. Though benign, fibroids often result in symptoms such as pelvic pressure and pain, abnormal uterine bleeding, urinary difficulties, constipation, or infertility. Fibroids result in a decreased quality of life for women and are the leading diagnostic indication for hysterectomy in the United States. Currently, $2.1 billion is spent annually in the United States for treatment of uterine fibroids.[4] Black women are at particular risk for symptomatic fibroid disease, with a three- to nine-fold increase in frequency and severity compared with non-Blacks. Effective alternatives to invasive treatment are few.

State of the Current Basic and Clinical Sciences on Fibroids

The pathogenesis of uterine fibroids is unknown. Prevalence data, twin studies, and familial aggregation studies indicate a genetic basis. Hormonal factors are also clearly involved; estrogen has long been known to stimulate growth of fibroids. How these hormonal factors result in the phenotype is unclear. Studies have shown that the growth rate of tumors is variable with variable response to gonadotropin-releasing hormone (GnRH) therapy. Genomewide association studies (GWAS) have provided a method to identify risk variants, and the future use of these risk variants in personalizing medical treatment, though unproven, is viewed with great optimism. Furthermore, although there are management steps to take now based on family history,

obtaining an accurate and complete family history of fibroids to optimize patient care is still not widely used in medical practice.

Fibroids have traditionally been classified by location (intramural, submucosal, subserosal, cervical), though this method may not be optimal for predicting tumor behavior. A standardized classification system for fibroids (similar to the Bethesda system for reporting cervical or vaginal cytologic diagnoses) is being developed and should improve the biological basis for classifying uterine fibroids. This evidence-based system includes pathology, magnetic resonance imaging (MRI), and genetics.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development, in collaboration with ORWH, has established a national fibroid tissue bank.[5] Tissue samples are collected from women during fibroid surgery, including samples from patients with unusual variants of fibroid disease such as hereditary leiomyomatosis, renal cell carcinoma, and benign metastasizing leiomyomatosis. This repository of well-characterized, well-preserved leiomyoma tissues will provide investigators in basic and translational research on fibroids with the opportunity to study the condition. The tissue bank is anticipated to strengthen the science base, improve the understanding of how uterine fibroids develop and grow, and provide clues to more effective conservative management of fibroids.

Though rare, malignant transformation of fibroids can occur. Mutations in the fumarate hydratase gene predispose to multiple cutaneous and uterine leiomyomatosis and renal cell carcinoma. Different histologic subtypes appear to predict different biological characteristics (e.g., size, growth rate, benign vs. malignant, perhaps bleeding, impact on fertility, etc.), but it is not known how often these various subtypes may progress to malignant counterparts. Disseminated peritoneal leiomyomatosis is a rare condition that has been reported after minimally invasive surgical treatment of fibroid disease. Though preference is increasing for these minimally invasive treatments, the frequency of these severe sequelae has not yet been determined.

Opportunities for Advancing Basic and Clinical Sciences on Fibroids

One hypothesis is that while most women develop uterine fibroids, a smaller number have symptoms or complications from them. There have been no long-term studies to follow women with fibroids from an early or asymptomatic stage to determine the frequency of various outcomes. A large cohort study of a high-risk population, ideally using MRI or ultrasound, would be useful in describing the natural history of this disease. Such a study would also help determine whether earlier intervention or treatment would improve outcomes. Early intervention and increasing access to health care are important issues in the current movement for health care reform.

Large cohort studies are needed to assess environmental factors and to provide large datasets with phenotype and genotype information that would help identify risk alleles. Creation of a database would enable researchers to collect a large amount of patient information over time. These data would include family medical history and could incorporate biomarkers from urine or serum, which would be valuable in the search for a target to inhibit the growth of fibroids.

Widespread public participation in a fibroid database is crucial. Enrolling women in the database will require their trust. Contacting potential participants through primary care physicians and patient advocacy groups is one way to reach large numbers of women with fibroid disease. The Internet is another vehicle that could be used to contact large numbers of potential participants. A possible model is the "Army of Women," an online resource for recruiting women to participate in breast cancer research. In this model, women interested in participating as research subjects may voluntarily enroll in a database. They may then be notified about clinical studies in which they are eligible to participate. Innovative incentives should be developed for women for participating in a national health database.

The 1,000 Genomes Project is an international effort to produce a publicly available catalog of human genetic variation.[6] The catalog can be used for association studies relating genetic variation to disease and could ultimately lead to use of a patient's genome analysis for prediction of risk, diagnosis, and drug and dosage selections.

Women with fibroid disease often experience symptoms, such as severe menorrhagia, which can be socially embarrassing and can limit their quality of life. The stigma of such medical conditions should be reversed through public education so that those afflicted will seek treatment. Increasing public health literacy about fibroids is important. The Internet can be a source of valid health data, and most patients would benefit from being directed to the best sources of online health information. NIH is in a unique position to be the "public face" of medicine. In that role, NIH could develop "information prescriptions" for health care providers to give to patients. The "prescriptions" would specify sources of trusted health care information (e.g., Medline Plus) to help patients better understand their conditions. Informing the public about the results of research funded by the NIH through materials written for the lay public (e.g., NIH Medline Plus magazine) would improve the public's scientific literacy.

Endometriosis

Endometriosis is a condition in which endometrial-like cells appear and flourish outside of the uterine cavity. Endometriosis may cause significant dysmenorrhea, chronic pelvic pain, dyspareunia, and gastrointestinal and urinary symptoms, and may contribute to infertility. It is estrogen dependent and thus typically occurs during the reproductive years in 5 to 10 percent of women.[7] While the exact cause of endometriosis is unknown, proposed theories for its development implicate multiple factors, including anatomic, genetic, and hormonal factors; the immune system; and the environment.

State of the Current Basic and Clinical Sciences on Endometriosis

Current understanding of the pathophysiology of endometriosis is limited. Twin and family studies suggest a genetic basis for endometriosis. Many more studies have looked at the role of the environment. In one animal model, stress exacerbated the development of endometriosis activity. Dioxins have been shown to disrupt the action of estrogen in reproductive tissues, resulting in progesterone resistance and the disruption of progesterone-mediated regulation of matrix metalloproteinase (MMP). Environmental phytoestrogens and xenoestrogens (e.g., genistein, bisphenol A) exhibit hormonal activity and may contribute to the development

of endometriosis. Nuclear antioxidants can regulate the growth of endometrial cells and may have clinical potential in the medical management of endometriosis.

Immunologic mechanisms and factors related to inflammation are also likely to be important to the pathophysiology of the disease. Current studies are examining loss of complement protective CD55 expression, which may contribute to increased MMP expression and promote the ability of endometrial fragments to rapidly invade the peritoneal surface, acquire vasculature, and establish the disease. An NIH-funded translational study is looking at the effect of the immunomodulator rosiglitazone on concentrations of peritoneal fluid cytokines in women with endometriosis; concurrent laboratory experiments to explore fetal DNA microchimerism as a cause for the chronic immune response seen with endometriosis may provide a novel pathophysiologic mechanism for the disease.

Recently published studies of the *in vivo* analysis of the impact of the adoptive transfer of human immune cells into immunocompromised mice receiving autologous human endometrium suggests that a robust immune system is protective against development of the disease.[8] Ongoing studies of inflammatory factors such as CRP, IL-12, IL-6, sTNFR1, sTNFR2, and IR are also looking at mechanisms and potential diagnostic biomarkers and treatments. Another recent study showed that the inflammatory environment that occurs in the endometrium of patients with disease results in high tissue factor (TF) expression, which, in turn, signals via PAR-2 to further produce inflammatory cytokine or chemokine production and macrophage recruitment, suggesting that TF might be a target for therapeutic intervention.[9] Inflammatory factors related to endometriosis may increase risk for some types of ovarian cancer.

Complex hormonal factors play a role and are the focus of ongoing research. Aromatase, an estrogen-synthesizing enzyme, produced by the implants themselves, have provided evidence on why and how the disease persists after menopause. This research indicates that the endometriosis lesions can produce estrogen, creating a microenvironment conducive to their continued growth. Endometriosis has also been associated with reduced responsiveness to progesterone, which may be a factor contributing to endometriosis-associated infertility. The influence of exercise, obesity, and lactation on endogenous estrogen biosynthesis is another area of intense research.

Improved technology and tools for noninvasive diagnosis are another focus of research: circulating biomarkers (CA-125, circulating antibodies), menstrual fluid biomarkers, advanced imaging techniques (such as ultrasound or MRI technology), and biologic probes. Treatment studies have recently examined norethindrone acetate as well as oral contraceptives vs. leuprolide. An oral GnRH antagonist is in Phase III trials. Also, hysterectomy is a potential treatment.

Little is known about how to prevent endometriosis. Lactation may be protective, but the precise biologic mechanism for this is not known; therefore, additional studies are necessary.

Opportunities for Advancing Basic and Clinical Sciences on Endometriosis

Prevention of endometriosis should be an important goal for future research. Preventing the disease, however, depends on more knowledge about earlier detection. Epidemiologic studies of

adolescents are needed in order to understand the natural history of the disease, identify risk factors, and determine optimal treatment approaches to clinical practice. Currently, the only way to reliably diagnose endometriosis is by laparoscopy. Identification of biomarkers (e.g., CA-125, genetic markers, or circulating antibodies) in the serum or menstrual fluid would make noninvasive diagnosis easier and potentially enable earlier detection.

To facilitate basic research, repositories are needed that contain tissue specimens from women with endometriosis. A complete GWAS with a significant number of subjects to detect associations might reveal a unique target for the pathogenesis of endometriosis. Continued efforts to develop good animal models for endometriosis are also important.

Not all endometriosis is symptomatic. Additionally, the amount of pain a woman feels is not necessarily related to the stage of endometriosis; there may be several disease processes involved in chronic pelvic pain. Continued efforts to investigate the mind-body link between pain syndromes are important. Studies that are designed to look specifically at the natural history of primary dysmenorrhea might also be valuable in this regard. There is significant overlap among chronic pain syndromes (e.g., pelvic pain, fibromyalgia, irritable bowel syndrome). Elucidating the connection of depression and a history of victimization or traumatic events with functional pain syndromes is an important issue to consider for basic and clinical research.

Current antiprogestins have side effects and can cause endometrial growth. GnRH analogs are expensive, and long-term treatment has been shown to cause significant decreases in bone mineral density. Continued effort should be directed at developing other options for medical treatment.

Many women with endometriosis suffer from autoimmune inflammatory diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies, and asthma. Further efforts should be directed toward finding a common underlying mechanism that influences the development of these conditions.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Create a prospective, longitudinal cohort study of adolescents and women to study factors that affect reproduction and wellness. The study should be designed with access to genetic, environmental, and psychosocial information and linkage to longitudinal medical records, including the following:

- Physical exam
- Family/medical/social history
- History of victimization/traumatic events
- Initial blood and urine samples
- Tissue samples and baseline imaging

- Validated questionnaires of quality-of-life/psychological status

The outcomes might include incidence and progression of benign gynecologic disease, biomarkers for disease, and tissue signature.

Recommendation 2: Coordinate data from past and current cohort studies that have involved adolescents and women. Coordination of cohort data would enable researchers to add focused questions that might not have been relevant at the time the earlier studies were designed. Researchers could also request additional material from study participants for genetic and molecular analyses. Additional analyses of previously collected material would also be possible.

Recommendation 3: Similar to the model of the Gynecologic Oncology Group, establish a national registry in which practitioners can enroll patients with specific diseases so that data can be more readily shared among researchers who might also collaborate on future randomized trials. This multidisciplinary, multi-institutional, prospective approach would facilitate state-of-the-art research in diseases that affect reproduction and wellness in women.

Recommendation 4: Coordinate large mechanistic studies around a disease. In a multicenter effort focused on prediction of risk, disease prevention, and identification of targets for personalized therapies, study diseases that affect the reproductive health and wellness of women, including fibroids, endometriosis, chronic pelvic pain, infertility, autoimmune diseases, and pelvic floor relaxation. GWAS offers the potential for understanding basic biological processes and for identifying further targets for molecular (including epigenetic) analysis.

Recommendation 5: Expand existing tissue banks and develop a National Tissue Repository. Expand existing tissue banks to include tissues from the gynecologic system and urinary tract of normal women by establishing a national registry (partnering with trauma centers and the National Disease Research Interchange).[10] Enhance the current repositories to encourage more widespread participation from practitioners, patient advocacy groups, and members of the community. These repositories would provide the essential materials for studies to develop new technologies and therapies for diseases that affect women.

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Introduction

As an introduction to their discussion about potential research avenues on pregnancy, the participants of the Working Group on Pregnancy acknowledged a number of underlying issues. In many ways, pregnant women are an underserved population, in part because major clinical and research areas pertaining to pregnancy have been neglected or deliberately avoided, possibly because of discomfort with pregnancy in general or the disadvantage of pregnant women and nonobstetric health care providers. The following examples illustrate neglected research areas:

- Little pharmacologic data exist on drug metabolism and safety in pregnancy, with the result that many practitioners discontinue their patients' needed medications during pregnancy, and many women do not receive optimal drug therapy because they are pregnant.
- The available data on the normal physiology of pregnancy are dated, having been obtained from small numbers of patients with now-obsolete technology, before accurate monitoring techniques became available. Importantly, existing physiologic data may not be relevant to the third (or more) of pregnant women who are obese or morbidly obese.
- A wide range of providers care for pregnant women in the United States and worldwide, representing a wide range of knowledge, skill, and experience. Some of these providers may not provide optimal care for pregnant women. The fact that no system currently exists to effectively provide continuing obstetric education to such providers may contribute to the well-recognized racial and socioeconomic disparities in obstetric outcomes observed in this country.
- Unlike other clinical groups, obstetric patients themselves are often uninformed and unable to advocate for themselves.

Summary of the Discussion

The working group discussed the following five potential areas of obstetric research:

- Development of an obstetric research infrastructure.
- High-impact pregnancy complications.
- Preventive care to optimize pregnancy outcomes and maternal and child health.
- Optimal prenatal, intrapartum, and postpartum-interpregnancy care.
- Patient and provider education.

These five areas were discussed in the context of the following four themes:

- Pregnancy complications with important implications for public health, and factors increasing risk for complications.
- Pregnancy's effect on preexisting maternal medical conditions and provision of appropriate care.
- Pregnancy as a "stress test" revealing vulnerability to the future development of chronic disease, and ways to interrupt disease progression.
- Fetal "programming," or pregnancy's influence on the health of the adult that the fetus will become.

Development of an Obstetric Research Infrastructure

The working group participants concurred that research on pregnancy complications ideally should be coordinated to target basic, translational, and clinical aspects of each disease and its treatment, and that this kind of comprehensive research endeavor cannot be accomplished without an informatics infrastructure. A national pregnancy database and tissue bank is needed, containing blood samples from the child and both parents as well as amniotic fluid and placental samples when available, along with detailed family and personal medical histories, social and economic data, environmental exposures, and infant/child outcomes. Banking specimens from pregnancies with common complications (e.g., preterm labor or preeclampsia), as well as more rare disorders (e.g., acute fatty liver), would accomplish the following goals:

- Enable researchers to perform a variety of investigations ranging from detailed genetic or proteomic studies to epidemiologic analyses.
- Support studies that are more statistically powerful than can currently be done.
- Enable the development of new genetic tests and the discovery of new biomarkers.
- Facilitate collaboration among research groups.
- Facilitate the collection of powerful intergenerational data, enabling study of the vertical transmission of risk factors as well as providing a better understanding of the concept of fetal programming. This kind of complete prospective data collection would support both hypothesis-driven and observational research, and would make retrospective studies more valuable by ensuring complete, unbiased, and prospective data collection.

The working group participants strongly recommended that the database be attached to the infrastructure being developed for the National Children's Study (NCS), a congressionally mandated interagency study designed to examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21.[1] Because the NCS already plans to collect a great deal of information about the parents and prenatal course of each enrolled child, a fairly complete pregnancy database could be created by adding more specific pregnancy-related data fields and ensuring the collection of tissue samples. This would allow a valuable informatics infrastructure to be created at a reduced cost, compared to creating such an infrastructure de novo. The database should be kept flexible at the beginning and reviewed regularly, and more data fields could be added as necessary with regular review. Ideally, women consenting to participate in

the database should be followed for several years after pregnancy, both to enable the study of recurrent risk and to facilitate research on the development of chronic adult-onset diseases that are heralded during pregnancy, an association proposed by the Barker hypothesis.[2]

The working group also believed that new, valuable obstetric research databases could be created inexpensively by providing funding to obtain followup information from subjects who have already participated in a study that created an obstetric research database. Ideal databases would be those that collected metabolic data during pregnancy because obtaining followup of those women and their infants would enable studies of fetal programming as well as pregnancy determinants of adult-onset disease. An example of such a database was created for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network randomized trial of treatment for mild gestational diabetes. This study enrolled nearly 1,000 women and collected detailed dietary information in addition to standard prenatal data, but was not funded to permit followup of the children born to study mothers.[3]

High-Impact Pregnancy Complications

The United States has a high perinatal mortality—6.9 per 1,000 live births—compared to industrialized European countries. The United States currently ranks 30th, behind Singapore, Poland, the Czech Republic, and other countries with far fewer resources. Although this rate is largely attributable to the high rate of preterm births in this country, the U.S. mortality for infants born at 37 weeks of gestation or more is also higher than in most European countries.[4] In the United States, perinatal deaths result in large part from common pregnancy complications, such as spontaneous preterm birth, indicated preterm birth for complications such as preeclampsia, and other hypertensive complications at term. Although many preterm infants now survive because of advances in neonatal care, many survivors suffer neurologic and other organ system damage and require considerable medical support for the rest of their lives. These pregnancy complications seriously affect not only the offspring of such pregnancies, but also society. Examples of high-impact pregnancy complications with the highest personal and societal effects and their relevant research questions include the five below. Each of these five major complications should be studied from the following four key perspectives:

- Implications for public health, and factors that increase risk for the complication.
- Effect on preexisting maternal medical conditions and practitioners' ability to provide appropriate care.
- Maternal vulnerability to the future development of chronic disease as revealed by the complication, and ways to interrupt disease progression.
- Effect on fetal "programming," or pregnancy's influence on the health of the adult that the fetus will become.[2]

Preterm Birth

What are the maternal and fetal factors that contribute to preterm birth, and how can these factors be modified? Current data suggest that oral health, genetics, environmental exposures, and stress all play roles, but none of these factors has been fully evaluated. Importantly, these factors have not been evaluated in an integrated way, which is essential because preterm birth is a multifactorial disease.

Preeclampsia

What causes preeclampsia and how can it be prevented? If it is a marker for susceptibility to the later development of maternal cardiovascular disease, by what mechanism does this occur and how can this progression of disease be averted?

Infection

What factors increase susceptibility to maternal and fetal infections? How does infection contribute to other complications such as preterm birth, and can susceptibility be altered or decreased?

Obesity

What factors predispose women to obesity? How does obesity cause or predispose women to have pregnancy complications such as stillbirth, preterm birth, and hypertension? What is the relationship between obesity-related sleep apnea and adverse pregnancy outcomes? How do obesity-related pregnancy complications influence the later development of adult-onset disease?

Mental Health/Depression

Does pregnancy increase a woman's susceptibility to psychiatric disease? How does maternal psychiatric disease affect the course of pregnancy and fetal development? How does this disease concurrent with pregnancy influence long-term outcomes for both the child and the mother?

In addition, a process should be developed to provide expedited funding to study unexpected health care crises affecting pregnant women and pregnancy outcomes. For example, the H1N1 influenza pandemic is expected to cause disproportionate morbidity and mortality among pregnant women. It would provide a unique opportunity to study immune changes and function during pregnancy to determine the physiologic changes of pregnancy that put women most at risk, and to study the effects of this virus on both the mother and the developing fetus. The effects of hurricane Katrina on the Gulf region afforded a missed opportunity to study the effects of different kinds of stress on the course and outcomes of pregnancy. Unfortunately, current protocols for obtaining research funding are too cumbersome to allow for the rapid funding that would be required to support such research.

Preventive Care to Optimize Pregnancy Outcomes and Maternal and Child Health

Studies of Maternal Physiology

For various reasons, many women receive substandard care during pregnancy. Existing data on normal pregnancy physiology was obtained years ago with obsolete techniques and equipment, and are therefore incomplete or even inaccurate. Some aspects of maternal physiology have never been studied, with the result that high-risk pregnancy management—especially critical care, intraoperative, and anesthetic management—cannot always be evidence based. Importantly, despite the epidemic of morbid obesity in this country, particularly among women of reproductive age, knowledge of how obesity affects maternal physiology is so limited that it

cannot be used to make informed management decisions. Decisions regarding anesthesia and surgical options for such women are particularly fraught because they must be based on data extrapolated from nonpregnant obese patients and pregnant women of normal weight—neither of which is likely to be completely relevant. Because maternal obesity is also an important factor contributing to the development of a variety of pregnancy complications as well as fetal and neonatal morbidity, understanding the physiology of obesity during pregnancy is vital to research in these other areas. A comprehensive study of maternal physiology, and especially of obesity during pregnancy, is needed.

Drug Metabolism in Pregnancy

The most egregious pregnancy-related information gap concerns drug metabolism and safety in pregnancy. Few pharmacologic studies have included pregnant women, and even fewer have been designed specifically to investigate drug metabolism and safety in pregnancy. As a result, many women discontinue or are told to discontinue their medications when pregnancy is diagnosed, often with disastrous results. Furthermore, many women who ordinarily would be treated pharmacologically for diseases that become apparent during pregnancy do not receive such therapy because many physicians are reluctant to initiate drug treatment in the absence of data. Consequently, if pregnant women receive drug treatment at all, many of them are treated with drugs that have been on the market for a long enough time that experience with their performance during pregnancy has been acquired over many years. This results in pregnant women being treated with medications that have been on the market for 20 years or more rather than newer, more effective agents, and many receive the wrong medicine or the wrong dose. Thus, the lack of pregnancy-related pharmacologic data results in suboptimal obstetric care. A small, four-center Obstetric-Fetal Pharmacology Research Units Network,[5] funded by NICHD, has recently been established to study drugs in pregnancy—a good, but insufficient, start. Nevertheless, experience gained from this research network could be used to design and fund additional networks so that more drugs can be studied efficiently and effectively during pregnancy.

Nutrition

The current unprecedented epidemic of obesity in this country disproportionately affects women of reproductive age. Previously unknown factors that contribute to obesity have recently been recognized, but have not been adequately studied. Fetal programming appears to be one of the most important factors contributing to overweight, and appears to affect disadvantaged women disproportionately. For example, impoverished women are at increased risk for growth-restricted infants as a result of suboptimal diet, coexistent medical conditions such as hypertension and diabetes, unhealthful habits such as smoking or drug abuse, and living in a high-stress environment. Available data suggest that the growth-restricted infants of such women are at a significantly increased risk of becoming morbidly obese adults.[2] Adult obesity predisposes an individual to hypertension and diabetes, thus putting the next generation at risk and perpetuating the cycle of adverse obstetric outcomes leading to adverse adult health.[6] This situation is believed to be a major contributor to the disparity in adverse obstetric outcomes currently evident in this country, and has tremendous personal and societal consequences.

Psychological Stressors

Large racial and socioeconomic disparities exist in pregnancy outcomes, particularly with regard to common, but serious, pregnancy complications, such as preterm birth and hypertension. Evidence is now accumulating to show that many adverse pregnancy outcomes have multifactorial etiologies, with environmental factors and maternal stress playing important, but largely unspecified, roles. Focused research is needed to identify important psychological stressors during pregnancy, including social issues, violence, and mental health problems; to define the physiologic effects of these stressors on both mother and fetus; and to identify ways to lessen or nullify the effects of such stressors on pregnancy.

Optimal Prenatal, Intrapartum, and Postpartum-Interpregnancy Care

Current standards for prenatal, intrapartum, and postpartum-interpregnancy care are based largely on tradition rather than sound scientific evidence. For example, the optimal number and content of antenatal visits, the best strategies for monitoring the fetus during labor and delivery, and the most appropriate method for postpartum-interpregnancy screening for and treatment of chronic diseases are all largely unknown. Simultaneously, obstetricians across the country are facing a professional liability crisis, with the result that every aspect of the care they provide during pregnancy has the potential to be scrutinized, criticized, or blamed for an adverse outcome. Thus, research is needed to investigate basic aspects of pregnancy care as well as to develop creative new ways to provide prenatal care more efficiently and cost effectively.

Patient and Health Care Provider Education

Another factor contributing to the large disparity in pregnancy outcomes is the disparity in the quality of the health care and patient information provided by different practitioners during pregnancy. Effective strategies for educating and updating health care providers and their patients are desperately needed. Some of the most important research topics in this area include developing optimal strategies for pregnancy planning; screening for a variety of maternal and fetal abnormalities; and counseling and pre-, intra-, and postpartum management of patients with gestational diabetes, hypertension, and other chronic conditions, such as thyroid disease or seizure disorder. The most effective strategies for patient education must also be developed.

For educating both the provider and the patient, projects that use information technology are needed. Centralized electronic medical records, which will be in place nationwide in the near future, could provide support for providers through a variety of mechanisms—such as providing prompts for the optimal schedule and content of prenatal visits, information for maternal counseling, standards for prenatal testing, and strategies for fetal evaluation. Informational Web sites could also be commissioned to provide up-to-date information to the general public.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Develop an effective obstetric research infrastructure that includes a national pregnancy database and a tissue bank. Serious consideration should be given to attaching the database to the infrastructure being developed for the National Children's Study.

Also, the value of obstetric databases that have already been established can be enhanced by additional funding to collect followup information from database participants.

Recommendation 2: Identify and study the top five high-impact pregnancy complications that account for the major portion of perinatal mortality, and study those in the context of the following four perspectives:

- Implications for public health, and the factors increasing risk for the complication.
- Effect on preexisting maternal medical conditions and the practitioners' ability to provide appropriate care.
- Maternal vulnerability to the future development of chronic disease as revealed by the complication, and ways to interrupt disease progression.
- Effect on fetal "programming," or pregnancy's influence on the health of the adult that the fetus will become.[2]

Potential complications include preterm birth, preeclampsia, infection, obesity, and mental health, including depression. In addition, a funding mechanism should be established to enable rapid funding for the study of crisis-related acute health issues in pregnant women.

Recommendation 3: Support research to develop preventive care that optimizes pregnancy outcomes and maternal and child health, especially with the following approaches:

- Funding for the comprehensive study of maternal physiology, and especially for the study of obesity during pregnancy.
- Use of experience gained from the Obstetric Pharmacology Research Units Network to design and fund additional networks so more drugs can be studied efficiently and effectively during pregnancy.
- Research on nutrition during pregnancy and its effect on the intrauterine environment and fetal programming.
- A focused research effort to identify important psychological stressors during pregnancy—including social issues, violence, and mental health problems— to define the physiologic effects of these stressors on both mother and fetus, and to identify ways to lessen or nullify the effects of such stressors on pregnancy.

Recommendation 4: Determine standards for optimal prenatal, intrapartum, and postpartum-interpregnancy care and management, as well as new and creative ways to provide prenatal care more efficiently and cost effectively.

Recommendation 5: Fund demonstration projects using electronic medical records, the Internet, and other venues for provider education and support, and for patient information transfer.

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MENOPAUSAL TRANSITION

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Introduction

The Working Group on Menopausal Transition agreed to distinguish the effects of aging that both women and men experience through the "middle years" from those unique to the menopausal transition. The timespan of the menopausal transition is defined as ages 40–59, and postmenopausal as ages 60–69, with further recognition that aging follows a continuum from the decades before and after this 30-year range. The menopausal transition is that period in life beginning with variation in menstrual-cycle length in a woman who has elevated follicle-stimulating hormone (FSH) levels and ending with the final menstrual period. The transition lasts approximately 4–5 years.[1,2]

Summary of the Discussion

To begin the discussion, the three cochairs highlighted current research findings on the physiology of the menopausal transition; on current recommendations for the use of menopausal hormones; and on health issues and causes of death for women in their middle years, with a focus on cardiovascular and bone health, and cancer. The normal menstrual cycle of young reproductive-age women was compared with that of older middle-age women, whose cycles are more likely to be anovulatory and/or characterized by higher FSH levels, variable estradiol levels, lower progestin, and lower dehydroepiandrosterone sulfate (DHEAS) levels.[3] The DHEAS levels vary by ethnic/racial group, with decreases being particularly apparent in African-American women.[4] Androgen levels, however, decrease only slightly, with substantial amounts continuing to be secreted by the postmenopausal ovary. Nearly all common menopausal symptoms are believed to result from decreasing estrogen and reports have included hot flashes, paresthesias, palpitations, cold hands and feet, headache, vertigo, irritability, anxiety, nervousness, depression, fatigue, weight gain, insomnia, night sweats, and forgetfulness. The majority of women complain of mild and moderate symptoms; however, a small percentage experience severe symptoms, with hot flashes and vaginal discomfort generally appearing before the final menstrual period, whereas bladder symptoms appear later. Chronic diseases appear more than a decade later.

The concept that women are protected from heart disease until menopause, after which they lose this protection as estrogen levels decline, has been challenged by an analysis of British data (which closely resembles U.S. data) of sex differences in coronary heart disease (CHD) by age. In the study, there was no suggestion of a change in rates associated with menopause.[5] Furthermore, death rates for adults hospitalized for myocardial infarction were higher for middle-age women than men, whereas they were similar from age 70 onward.[6] This difference arises in part because of gender-related bias in medical practice, including differences in the recognition and treatment of CHD. There are also physiological differences between women who experience CHD in the middle years compared with those who are much older and constitute the majority of CHD patients.

In contrast to what appears to be a steady age-related increase in heart disease death rates for women, breast cancer death rates decrease at menopause.[7] Bone mineral density, which shows a similar, steady decline in both men and women starting at about age 30, shows an accelerated decrease during the 3- to 5-year menopausal transition, after which the rate of decline again resembles the rate of loss in men.[8]

Other health status observations from studies include the following:

- Body weight and waist circumference appeared to increase at a greater rate after the final menstrual period over a 6-year period of observation, whereas skeletal muscle mass was unchanged.[9]
- Total body weight increased in early postmenopausal women ages 50–59 over 7 years; however, weight was relatively stable in those 60–69 and decreased in those 70 and older.[10]
- The percentage of men and women who have suboptimal levels of sleep was the same during the middle or later years, though the percentage increased in all age groups of both sexes from 1985 to 2004.[11]

Lung cancer deaths have increased dramatically in women over the past decade, whereas breast and colorectal cancers have decreased.[12] Breast cancer incidence is higher in White versus Black women, particularly from age 50 and over, whereas death rates from breast cancer are higher in Black versus White women across the age spectrum.[13]

The group discussion emphasized two key points: 1) knowledge is lacking about the fundamental biological processes underlying and associated with menopause, despite its impact on the quality of life of many women; and 2) during midlife, women may begin to experience major chronic illnesses that affect their health in later years. Therefore, it is important to determine how and why risk factor profiles change during midlife and to identify prevention strategies that may effectively reduce morbidity prior to, during, and after the menopausal transition.

The working group participants discussed different types of menopause and were interested in the range and variation of the experience, differences in rate of changes, and associations with health outcomes. Research on specific symptoms and temperature physiology in women was considered to be too limited. There was considerable interest in utilizing new technologies to study the physiology of menopause, as well as mathematical modeling in distinguishing between aging and the menopausal transition. Research on sex differences in chronic diseases and aging, in general, was strongly endorsed. Specific stressors affecting women in their middle years include the "sandwich generation" burden of having to care for both children and older parents. The middle-year period also includes an increasing number of women who have delayed first pregnancies. There was considerable enthusiasm for studying women from *in utero* through their lifespan, ideally as a long-term cohort study, but more practically as a set of current cohorts combined with some new cohorts recruited to fill in the gaps. It was acknowledged that age cohorts vary substantially across generations and that the health issues of women in the current and future population differ from those of the past generations for a large number of reasons.

The discussion also addressed how to take advantage of electronic medical charts to improve health care of women and reduce costs. Participants noted that some available databases can already be linked; for example, the Surveillance, Epidemiology, and End Results (SEER) Cancer Registry[14] can be linked to the Centers for Medicare and Medicaid Services (CMS) database. Other health concerns included improving CMS screening modalities, promoting prevention,

and improving access to care, particularly in medically underserved women. Research on specific biomarkers for detecting tumors, targeted therapies, and new strategies for treating cancer was encouraged. There was interest in the physiologic impact of microchimerism, that is, the presence of embryonic stem cells from a woman's offspring that have been found to be circulating in the mother three to four decades later. Epigenetics was considered an important emerging concept that should be utilized to study the remaining questions about menopause.

Recommendations

The overall goal of the recommendations is to distinguish the physiologic changes and chronic disease risks associated with the changes occurring at the menopausal transition from those arising as a result of aging—and place them in proper perspective. In this regard, comparison with the changes occurring in men, in oophorectomized women, and in women with premature ovarian failure should be instructive. It is still true that the causes of menopause are unknown in women, and safe and effective therapy for signs and symptoms of menopause remains to be established.

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Conduct research toward distinguishing changes related to aging from those related to the patterns associated with the menopausal transition (e.g., early/late onset, prolonged/short symptoms, biochemical/cellular/genetic profiles). This research could answer the following types of questions:

- Are there genetic and epigenetic differences and/or influences?
- Are there physiologic differences between symptomatic and asymptomatic women?
- Do women in whom symptoms persist differ from those in whom symptoms quickly disappear?
- Does the menopausal transition have distinct and separate patterns?
- Are there differences in women in whom menopause begins early compared with those in whom it begins late?
- Is quality of life affected by patterns, symptoms, and treatment?
- Does cellular aging play a significant role?

Recommendation 2: Enhance research on the basic physiology of changes associated with menopause, emphasizing a systems biology approach and translation into safe and effective management. This research would clarify the roles of the central and autonomic nervous systems and the neuroendocrine system in the changes observed (e.g., temperature regulation; pulse rate and blood pressure; sleep, mood changes, weight changes, and distribution of fat; urogenital, dermatologic, and bone changes), and strategies for short- and long-term safe and effective management of signs and symptoms.

Recommendation 3: Develop and assess new technologies and communication tools (e.g., portable devices, imaging, biological profiling on microchips) for their impact on individual and public health outcomes during the years of the menopausal transition. It should be possible to identify and/or develop the following:

- Innovations in bioengineering and materials science that can be used to manage symptoms of the menopausal transition (e.g., vasomotor symptoms by heat dissipation via engineered clothing).
- New analytic models, using statistical and mathematical tools and simulations, to interpret the complex interactions among aging, the menopausal transition, multiple biological systems, and chronic disease.
- Large databases to study comparative effectiveness and outcomes in midlife services and treatments (e.g., SEER, Kaiser, Intermountain Health).
- New tools (e.g., portable digital devices, imaging, biological profiling) to facilitate diagnosis and personalize health care.
- New information technology (e.g., social networking) that can be used to educate the public to change behavior and improve health outcomes via validated sources.
- Information about changes during the middle years that can be used to reduce health care costs by developing accurate risk assessment tools.

Recommendation 4: Promote research that uses and follows cohorts of women from different generations over time to determine what chronic diseases develop in the context of their reproductive lives, patterns of menopausal transition, culture, environment, and genomes. Investigators should be encouraged to take the following actions:

- Use (existing and/or new) cohorts of women for whom expression profiles (e.g., genome, proteome, and environmental factors) are characterized to document the development of chronic disease and influence on the patterns of the menopausal transition.
- Examine how past reproductive function and history (e.g., menarche, use of oral contraceptives, and parity) affect menopause and subsequent chronic disease.
- Identify how interactions among comorbidities (e.g., obesity, diabetes, hypertension, cardiovascular disease) influence the menopausal transition.
- Study the effects of environment and culture.
- Determine if epigenetic changes in one generation influence the menopausal transition, aging, and chronic disease in subsequent generations.

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ELDERLY, FRAIL ELDERLY, AND HEALTHY AGING

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Introduction

The Working Group on Elderly, Frail Elderly, and Healthy Aging was given the task of identifying the most promising and important avenues for research on the health and health care of older women. Both the absolute number of women 65 and older and the percentage of elderly women in the population are projected to increase substantially during the first half of the 21st century. These population trends are attributable to the aging of the Baby Boomer Generation and to the longer life expectancy for women than for men.[1] Furthermore, unlike men, the majority of women will live their later years and die without their life partner as a caregiver. For example, an NIH-funded 2005–06 study of social relationships and aging, using a nationally representative probability sample of community-residing adults ages 57–85, found that 49.8 percent of women ages 75–85, but only 18.3 percent of men, were widowed. Fewer than 40 percent of women, but 72 percent of men, in that age group were married or living with a partner.[2] The demographic shift outlined above has critical implications for women—for their health, quality of life, and the experiences of late-life illness and dying.[3]

The working group posited four principles that should be used in evaluating and recommending potential research strategies aimed at improving the health of elderly women: a broader

scope of the research approach, effectiveness studies in the approach, focus on the whole person in health care delivery, and comprehensive use of existing information sources.

For the purposes of this report, we have defined the elderly as 65 and older. Human development continues until the end of the life course, and there are differences within the age group after 65; thus, it is no longer acceptable to designate this as one analytic group.

Scope of the Research Approach

- Much of the research on the health of elderly individuals has been notable for a focus on single-disease processes commonly found in the elderly. In contrast, the working group considered a new approach to research strategies for women's health aimed at the following:
- Understanding the effect of multiple concurrent morbidities on the health of elderly women
- Fostering the promotion of wellness (biological, psychological, and social) in elderly women, recognizing that vitality in old age has important antecedent predictors that operate throughout the lifespan
- Selecting research germane to the needs of women of different characteristics, including diverse ethnicity and race, physical conditions and abilities, cognitive and mental conditions and abilities, sexual orientations, and gender perspectives
- Addressing the health not only of individual women, but also of communities

Effectiveness Studies in the Research Approach

The working group decided that the most important criterion for recommending a research strategy to the ORWH is that the strategy should have the potential to lead to meaningful improvements in health, health care, or health outcomes. The group emphasized the importance of translational research at the levels of bench-bedside and population-patient. The group articulated the belief that the next decade of interventional research on elderly women's health should move from efficacy to effectiveness. This shift (i.e., to an emphasis on effectiveness) will require expansion of therapeutic trials and public health interventions to include older women, many of whom have multiple medical conditions and are using multiple medications (i.e., prescription, over-the-counter, and vitamins/nutritional supplements).[4]

A Focus on the Whole Person in Health Care Delivery

The working group expressed the opinion that the current quality of care of elderly women is diminished by a health care delivery system that is fragmented, focused on disease processes, and reactive. In contrast, the working group placed a high value on research focused on health care delivery models with the potential to shift the focus of care from organ systems to the whole person. A version of the advanced medical home tailored to needs of elderly women (and men) may be a model worthy of further exploration.[5] Implicit in the focus on the whole person is the need to provide elderly women with skills, support, and tools to evaluate the advantages and disadvantages of screening options, therapies, diagnostic tests, and the boundaries of care as decisionmakers for themselves and in the role of caregiver.

Comprehensive Use of Existing Information Sources

A recurrent concern of the group was that, in designing future-oriented research strategies, the value of existing resources not be overlooked. The group emphasized that 1) existing data resources funded by NIH should be made more widely available to the research community, 2) ongoing cohort studies of aging should be evaluated for and leveraged to expand relevance for older women's health issues, and 3) research should have the potential to culminate in studies of effectiveness (see section 2 above). The group pointed out that large NIH investments in population-based research on aging (e.g., the Health and Retirement Survey[6] and several international comparative studies), if expanded to incorporate issues salient to older women (either through new data analysis or supplemental data collection), could serve as useful tools for investigating important questions that are currently unanswered. In addition, although some research questions have been explored in a robust fashion, large gaps remain regarding the implementation of the results of these studies. As an illustration, members of the group expressed the opinion that pelvic floor exercises (Kegel exercises) are efficacious for some women in treating and preventing urinary incontinence. Women can do such exercises at virtually no cost in their homes, yet most women who could benefit do the exercises improperly, or not at all. In view of the disconnect between theory and practice, the group expressed the opinion that further research on pelvic floor strengthening exercises and similar low-cost interventions should be directed at designing and evaluating the effectiveness of home-based and public health strategies for helping elderly women to incorporate Kegel exercises into their daily lives, rather than in reestablishing the efficacy of these exercises under highly controlled, experimental conditions.

Summary of the Discussion

The working group highlighted the following seven issues.

The Impact and Relevance of Early and Midlife Events on the Health of Elderly Women

In keeping with one of the themes of the conference, namely that pregnancy can be viewed as a window into a woman's health throughout her lifespan, the group discussed methods for linking early and midlife events to the health of older women. For example, calcium intake by young girls is a key determinant of peak bone mass,[7] which in turn determines whether osteoporosis occurs in older women. A clearer understanding of the connections between early and midlife events could result in improved strategies for preventing illness; promoting health (biological, psychological, and social); and empowering women to make more informed choices regarding their health.

Given the barriers to performing the ideal study for elucidating the connections between early and midlife events and the health of elderly women (e.g., longitudinal studies with 90-year followup periods), new kinds of interdisciplinary research teams and new analytic methods are needed that could exploit existing data sources to elucidate these connections. New study designs could combine minimally invasive biological and physiological measurements (many can be done in the home) with gold-standard survey research methods for population-based research on aging and elderly women's health.[8]

The Challenge of Meaningful Inclusion of Individuals With Multiple Medical Conditions and Complex Medication Regimens in Research Studies

Elderly women are likely to have multiple concurrent medical conditions and to use a large number of medications. Recent population-based data indicate that among people ages 57–65, women are more likely than men to be taking multiple medications.[9] Many research studies are designed to exclude individuals with complex medical profiles. Alternatively, model adjustment is done with overly simple methods that count the number of multiple morbidities or medications. As a result, many research studies disproportionately exclude elderly women from participation or use analytic strategies that diminish the relevance of study findings for these older women. Furthermore, the traditional focus on single-disease processes leaves unexplored the effect that multiple concurrent morbidities have on the health of the individual.

Multidisciplinary efforts are needed that aim at (1) creating a uniform approach to multiple concurrent morbidities in order to include elderly women in research studies, (2) designing studies that are relevant to the health of elderly women, and (3) ensuring that study findings are relevant to elderly women.

Defining the Usual Aging Process

Although much is known about certain aspects of the aging process (e.g., bone density, cerebral morphology, memory), there are biological, psychological, and social aspects of aging that remain unexplored. Although a third of the life span, on average, is spent post menopause, research on older women typically groups together all those 60 or 65 and older. For example, more research is needed on age-related tissue degeneration that occurs in women. It is notable that a Medline literature search combining "vulva" with "aging" or "elderly" resulted in only a single reference that was germane to the topic.[10] However, that reference described vulvar changes, but did not differentiate between changes found in "menopausal" women and those found in elderly women. There are also major gaps in knowledge about the social and relational contexts of women's aging and the gender differences in these contexts, including sexual and intimate relationships, social networks, and ideal living arrangements.[11]

Roles of Aging Women

Older women's lives often follow a different trajectory from those of older men.[12–14] Women's lives are often marked by intense periods of caregiving responsibilities for parents and partners. In particular, the fact that women spend their final years without the support of their life partners has economic, health, psychological, and sociological consequences.[15–17] Women are more likely to spend their final years in health care facilities (rather than in their homes), often with economic constraints, and often without a caregiver who can serve as an advocate and companion.

Personalized Medicine

The working group explored personalized medicine through an age/gender lens and stated that it is important to provide women with information and tools, including technology literacy that would enable women to make informed choices throughout their lives and would ensure that their choices would be respected by caregivers. Given the importance of computers as a

health information resource, the lack of computer literacy among many older women is an important barrier to their health care decisionmaking processes and should be addressed.

End-of-Life Care

The working group identified end-of-life care as an area in particular need of attention, especially the following concerns:

- End-of-life care and palliative care are often accessed far too late to be optimally beneficial.
- Staff in long-term care facilities often lack the ability to identify persons for whom palliative care might be appropriate.
- Women's wishes regarding end-of-life care are often ignored because they have no one to represent them or advocate for their preferences.
- Large disparities exist and remain insufficiently addressed regarding end-of-life care, for example, monetary resources, access to a caregiver/partner, driving/mobility, partner in decisions about advance directives, and ability and supportive resources to stay in one's own home vs. being institutionalized.[18–20]

Critical Needs

Given the changing demographics in the United States and the impending surge of elderly patients, the working group endorsed the opinions expressed by a number of prominent groups, such as the International Longevity Society and the MacArthur Foundation. For example, the Institute of Medicine report on Work Force Needs for an Aging Society states that the existing geriatric expertise within the current health care workforce is inadequate for the projected needs of the changing U.S. population and that the current health care delivery system is poorly designed to meet the needs of the oncoming wave of elderly people.[21]

Recommendations

Based on the principles selected by the working group and the subsequent discussion, the working group identified the following recommendations to provide guidance to health administrators, clinicians, scientists and the public as to areas of investigation that merit greater research.

Recommendation 1: As a basis for developing and evaluating the effectiveness of strategies to promote physical and cognitive resilience in the elderly, support research designed to identify early and midlife factors that are determinants of later life resilience and disease, both at the individual and at the community/population level. These predictive factors could be biological, psychological, or social/environmental.

Recommendation 2: To make research more relevant and applicable to broader populations of older women, develop new strategies designed to enable the integration of information on multiple morbidities and medications into research design and analysis.

Recommendation 3: To provide reference points for identifying opportunities for research, establish normative data and its variation in insufficiently explored areas of aging women's bodies and functions, such as female genitalia and genital tract, balance, musculoskeletal integrity, and sexual function of older women.

Recommendation 4: To empower elderly women to make optimal health decisions—for themselves and others—when faced with decisions involving screening programs, diagnostic tests, options for treatment, and end-of-life care; conduct research aimed at understanding how elderly women access, process, and act on health and health care-related information and needs for themselves and others. Conduct research designed to assist elderly women in accessing reliable health-related information, including technology-based resources.

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ORAL HEALTH AND SYSTEMIC CONDITIONS

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Introduction

Prior to the discussion by the Working Group on Oral Health and Systemic Conditions, several speakers presented information addressing how to identify gaps in the current state of knowledge, the specific impact of oral health on women's health, and future research needs. The presentation topics were as follows:

- Oral health and systemic disease in women, with an emphasis on the oral–systemic links during the perinatal period
- Early childhood caries
- Sjögren's syndrome
- Temporomandibular disorders and chronic pain
- Salivary diagnostics
- Bisphosphonate-associated osteonecrosis of the jaw
- Oral cancer

To facilitate discussion about the lifespan, the group created a chart and divided it into five components representing the lifespan. An additional category was used for areas cross-cutting the lifespan. As the discussion progressed, topic areas and research ideas were recorded on the chart.

** The cochairs gratefully acknowledge the premeeting assistance of the following individuals in providing concepts and preparing material on key topics in oral health: Kim Boggess, Christopher Engeland, Mark Heft, Linda Kaste, Stefanie Russell, Jeanne Sinkford, David Wong, and Athanasios Zavras. Their affiliations are included in the participant list.*

The focus of the working group was the connection between oral health and systemic disease; therefore, discussions emphasized that the mouth is a window to a person's general health status.[1] Two main themes emerged: 1) oral health is integral to general health, and the two should not be evaluated in isolation; and 2) oral–systemic relationships are bidirectional and extremely complex.

Summary of the Discussion

Oral Health and Pregnancy

The working group elaborated on a theme that had been presented in the plenary session of the ORWH conference: Conditions unmasked during pregnancy, such as diabetes, could predict future chronic disease, such as cardiovascular disease. The group discussed the potential for oral conditions during pregnancy to also serve as a window to future oral conditions, such as periodontal disease. Additional discussion highlighted the following concepts:

- The biology of pregnancy, including hormonal alterations, salivary changes, immunological changes, and changes in microbial community structure, have a demonstrated negative effect on oral health, including gingival health and periodontal disease, the effects of which may be clinically significant.
- Sociological factors, such as gender roles, socioeconomic status, and psychological factors, likely contribute to oral health outcomes during pregnancy.
- Pregnant women are less likely to visit the dentist than nonpregnant women, and evidence is lacking about the safety of treating women during pregnancy.
- Despite the null results found in two randomized trials evaluating the effect of dental treatment in the second trimester on the prevention of adverse birth outcomes among women with periodontal disease, the trials resulted in several significant findings and implications for future research.[2,3] Of particular importance was the finding that it was safe to provide standard periodontal therapy to pregnant women at that point. This finding alone will significantly contribute to the paucity of evidence regarding possible risks associated with treating women during pregnancy.

Remaining unanswered questions regarding periodontal disease, its therapy during pregnancy, and its effect on improving birth outcomes include 1) whether the inflammatory response associated with periodontal disease is responsible for the observed adverse birth outcomes and, if so, 2) whether there is an ideal time in which periodontal therapy can be done at the lowest risk possible.

During the discussions, additional areas of needed research were identified. These areas included the following:

- Development of health policy based on empirical findings to improve access to and use of oral health care by women across their lifespan
- Additional understanding of whether pregnancy promotes or accelerates dental disease, including periodontitis and dental caries
- Exploring how oral health status during pregnancy might be a window to future disease

- Promoting positive health behaviors during the perinatal period that will improve the long-term health and oral health of women and their offspring

Early Childhood Caries

Early childhood caries (ECC) is the most common chronic disease in children, particularly those living in poverty who have limited access to dental care.[4] ECC is increasing significantly in children ages 2 to 5, resulting in a larger number of fillings and increased overall cost for care, with large disparities of incidence in minority and poor populations. The mother is considered to be the "gatekeeper" to a child's propensity to develop the disease in both biological and social contexts.

To date, research has focused on the causes of ECC as the interactions among the oral microflora, the host dentition, and the substrate. Future research should also explore 1) the effects of family and social life, 2) maternal-child transmission, 3) understanding the determinants of ECC, 4) multimodal and curative interventions, and 5) comparative effectiveness research on ECC prevention. Furthermore, the development of salivary diagnostics may enhance detection of early risk for ECC and increase the understanding of bacterial colonization and virulence.

Sjögren's Syndrome

As many as 3.1 million people suffer from Sjögren's syndrome, and an estimated 90 percent are women. The risk of developing the disease increases significantly around the time of menopause.[5] Currently, there are no accepted criteria or tools for diagnosing Sjögren's syndrome, and no outcome criteria for trials testing the biological agents for treatment. The understanding of Sjögren's syndrome is severely limited, with the following gaps commonly cited in the research literature:

- Absence of universally accepted classification criteria resulting in a lack of good prevalence or incidence data in any population
- Insufficient understanding of etiology and pathogenesis
- Lack of clarification of differences in genetic predisposition for primary versus secondary cases
- Scarcity of studies establishing optimal dental treatment for those with salivary dysfunction as a result of Sjögren's syndrome
- The role of sex hormones and their mechanism of action in the development of the disease
- The impact on quality of life

Temporomandibular Disorders and Chronic Pain

Temporomandibular disorders (TMDs) share common symptoms with other chronic autoimmune disorders, such as chronic fatigue syndrome and fibromyalgia. However, whether and how these diseases share common etiologies are not understood. Recent studies show that medical management is as effective as surgical intervention. Future research should center on the genetics of TMD, chronic pain, and autoimmune disorders and should explore the potential presence of common pathophysiologies between them.

Salivary Diagnostics

Studies are underway to validate the ability of salivary diagnostics to identify biomarkers in the saliva for a few diseases (e.g., Sjögren's syndrome, oral cancer). If embraced by practitioners, this technology may improve access to care, decrease health disparities, accelerate the diagnosis and treatment of a disease, and significantly affect global health.[6] Research is still needed to understand the biological mechanism of the presence of biomarkers in the saliva for diseases affecting distant diseased organs, such as breast cancer.[7]

Bisphosphonate-Associated Osteonecrosis of the Jaw

Bisphosphonates (BPs) are drugs that prevent or treat bone resorption through selective inhibition of osteoclastic activity. More than 3 million American women receive oral BPs to control or prevent osteoporosis, and a smaller fraction receives intravenous BPs during cancer therapy to control bone metastases, bone pain, or hypercalcemia. Use of high doses of intravenous BPs, and on rare occasion low doses of oral BPs, has been associated with the development of osteonecrosis of the jaw (ONJ), a serious condition.[8] Because the pathophysiology of bisphosphonate-induced ONJ is unclear, research is needed to understand the details about its etiology, prevention, and treatment. Similarly, methods are needed to predict who is susceptible to developing ONJ in order to allow population screening prior to BP initiation. Research is also needed on the oral health outcomes of long-term use of oral BPs, such as osteopetrosis of the jaw, especially as they relate to dental procedures such as surgical extractions, dental implant placement, and orthodontics.

Oral Cancer

Although oral cancer in the United States is typically thought of as a man's disease, the annual incidence among women is substantial—similar to that of cervical cancer. The American Cancer Society estimates indicate that 11,270 new U.S. cases of cervical cancer and 10,480 new U.S. cases of oral cavity and pharynx cancer will be diagnosed in women in 2009.[9] Several regional studies have shown that awareness of oral cancer and its risk factors among the general population and the medical community is consistently low. The literature also indicates that although men and women with oral cancer share risk factors, their risk profiles are not identical. Similarly, for reasons not adequately understood, equal exposures to tobacco alone and tobacco combined with alcohol have been shown to lead to different risk levels for men and women, with the risk for women being greater. An understanding is needed of how hormones, nutrition, tissue wound response, and health behaviors of women affect oral cancer incidence because this area is largely understudied. In particular, future research should investigate a possible relationship between human papilloma virus (HPV) exposure, HPV oral infection, and oral cancer in women, and should monitor the impact of the HPV vaccine on rates of oral cancer in women. Equally interesting would be studies that explain the disparity in oral cancer rates among men (estimates for 2009 indicate 25,240 new cases) and women seen in the United States, but not as seen in the homelands of major immigrant groups to this country,[10] and to investigate whether interventions that decrease the incidence of oropharyngeal cancer in men are appropriate for or adaptable to women.

Recommendations

The following research recommendations may help to provide guidance to health administrators, the health professions, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Salivary Diagnostics

- Research the underlying biology of salivary diagnostics and its translation into research, clinical care, and population applications for diseases particularly affecting women's health (Sjögren's syndrome, breast cancer, ovarian cancer, diabetes mellitus type II).
- Encourage genomic studies of oral diseases such as caries, periodontal diseases, and Sjögren's syndrome using salivary diagnostics and evaluating the effectiveness of salivary biomarkers to predict diseases throughout the woman's lifespan.

Recommendation 2: Pregnancy and Oral Health

- Continue research to clarify the relationship between periodontal disease and adverse birth outcomes.
- Conduct longitudinal studies that would lead to an understanding of whether changes unmasked during pregnancy predict future oral diseases (e.g., periodontal disease).
- Promote behavioral interventions that would serve to increase access to and use of dental care for women during pregnancy. Explore whether women are more amenable to oral health behavioral change interventions during pregnancy in an effort to improve oral health for themselves or their offspring.
- Encourage genetic and behavioral studies to evaluate maternal risk factors for offspring with craniofacial abnormalities.

Recommendation 3: Chronic Disease and Oral Health

- Encourage additional research on pathophysiology, genetics, systemic treatments, and evidenced-based treatments for chronic diseases with oral health sequelae, such as
  - Sjögren's syndrome;
  - chronic facial pain syndromes such as temporomandibular disorders;
  - cancers of the oral cavity and pharynx;
  - eating disorders, depression, and HIV; and
  - diabetes.

Recommendation 4: Impact of Systemic Disease Treatments on Oral Health

- Research oral health outcomes of commonly used medications to treat systemic diseases, including the development of serious adverse effects.
- Evaluate the pathophysiology of oral adverse effects, prevention, and optimal therapies of women receiving the following:
  - Cancer chemotherapy (associated with mucositis and other conditions that might compromise the patient's survivorship and well-being).

- Bisphosphonates, either intravenous therapies to control cancer or oral medications to control or prevent osteoporosis (associated with osteonecrosis of the jaw and/or osteopetrosis).
- Stem cell transplantation (associated with a number of serious oral complications).
- Radiation damage to head and neck tissue (associated with soft-tissue lesions and osteoradionecrosis).
- Drug-induced xerostomia (associated with increased dental caries rates and reductions in quality of life).
- Highly active antiretroviral therapy (suspected to be associated with effects on the oral health of offspring of HIV-positive mothers).

Recommendation 5: Oral Cancer

- Research the complex interactions among hormones, nutrition, tissue wound response, and behaviors of women across the lifespan, and how they affect oral cancer development.
- Evaluate the potential link between HPV and oral cancer in women and include monitoring of oral cancer rates in women as HPV vaccine use increases.
- Research behavioral change interventions to evaluate strategies for decreasing oral and pharyngeal cancer risk factors in women.

Recommendation 6: Caries Prevention across the Lifespan

- Encourage research to identify the maternal role in transmission and management of caries.
- Support multimodal interventions that reflect the complex nature of the caries process in order to increase the effectiveness of prevention strategies.
- Establish best practices for interventions that address the oral health needs of the elderly.

Recommendation 7: Pain

- Conduct basic and clinical research to understand where, when, and why oral/facial/cranial pain occurs.
- Research the relationship between hormonal changes and increased incidence of temporomandibular disorders and other chronic pain syndromes.
- Evaluate current and new treatment options for the management of chronic pain.

Recommendation 8: Hormones across the Lifespan

Encourage research to better understand the role of hormonal changes on oral health outcomes throughout a woman's life, particularly the changes that accompany menopause and the menopausal transition.

Recommendation 9: Longitudinal Studies

- Continue and expand oral health measures in national population-based studies, including the Behavioral Risk Factor Surveillance System, National Health Interview Survey, and

National Health and Nutrition Examination Survey; and integrate them into large, ongoing cross-sectional and prospective studies.

- Communicate the value of women's oral health and the need to include women in all clinical trials for data collection, interpretation, and outcomes.
- Ensure that the "new science" (e.g., genomics, proteomics) includes oral components as major contributors to the understanding of general health and health treatment outcomes in the future.

Recommendation 10: Update women's health in medical and dental curriculum and other health profession studies as the foundation of knowledge required for the understanding of women's health across a lifespan and for the training of future health professionals.

Recommendation 11: Provide leadership training at the executive level so that global collaborations can be arranged that relate to women's health initiatives across disciplines and populations.

Recommendation 12: Provide mentored training programs such as Building Interdisciplinary Research Careers in Women's Health that target health issues affecting women and girls.

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CAREERS IN DENTISTRY, BIOENGINEERING, AND OTHER NON-M.D. DISCIPLINES

Cochairs:

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Henry M. Goldman School of Dental Medicine, Boston University

Valerie Wilson, Ph.D.
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The Warren Alpert Medical School of Brown University

Introduction

The charge to the Working Group on Careers in Dentistry, Bioengineering, and Other Non-M.D. Disciplines was to develop recommendations for advancing women in those disciplines over the next 10 years. Participants developed a list of topics for discussion: mentoring, reentry, retention, interdisciplinary research, part-time work, leadership, minorities, tenure and promotion, and unique obstacles to women's careers.

Group participants noted that many barriers for women in the workforce that exist today were there 30 years ago, and that the recommendations from the 1991 ORWH workshop on careers reflect some of the same issues that are of concern today, such as the lack of productive networking opportunities, mentoring, and reentry programs. Underlying the barriers to effective participation in advancing women's health may be the apparent lack of prestige of the field of women's health as a professional enterprise.

Summary of the Discussion

The discussion centered on several key issues that led to the group's recommendations: career tactics and paths, training opportunities, and mentoring.

Career Tactics and Paths

The group observed that although men and women may end up at the same point in their careers, the career path may take different trajectories. Whereas a man's career path typically might be linear, this is less likely to be the case for women. Women face several challenges, including meeting societal expectations and balancing family and work. Women in science and engineering positions continue to face unique pressures associated with stereotypes and social norms about women's competence and ability to succeed in these fields. Such pressures often impact the career choices and opportunities of women.

Women are more likely than men to make measured, calculated career decisions and to consider many factors in a three-dimensional matrix paradigm (e.g., family, childcare, and profession) when making career choices and considering promotion or leadership opportunities. The delicate and challenging balance between work and family is always a consideration and often creates unique workforce models that may include part-time work, lateral moves, career shifts, or extended leaves of absence for childcare or other family responsibilities. Research careers nearly always extend beyond an 8-hour workday, and women with children need resources to meet their family obligations. The option of part-time work is often rebutted by colleagues and supervisors, with the assumption that part-time workers are not successful; however, research has not been conducted to examine whether this assumption is accurate. One approach to addressing this part-time question might be to reconceptualize K awards (which provide support and "protected time" [3–5 years] for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence) or create new awards to support part-time workers and evaluate their outcomes.

To attract women to biomedical careers, more female representation and diversity within leadership positions is necessary. Female students often believe the stereotype that females are not competent in math and science, which leads them to choose other career paths. Female role models in these fields are needed to assure young girls that they can succeed in these fields. However, women are not offered leadership opportunities as often as men; thus, women risk failure more than men once women reach these positions. Women need to be given the opportunity for leadership positions and then must be trained and willing to take the risk once the opportunity arises. As women age, they are usually liberated from principal family obligations (children are out of the home) and are able to focus more on their career. Policymakers and researchers should consider how to reset the image of women so that they are considered for leadership positions and opportunities at every age, including when they are older.

In discussion of models where women have achieved success and stature, the military was raised as an example of meritocracy. In seeking to identify what characteristics were unique to the military environment that might be modeled in other areas, participants honed in on what was necessary for advancement. Participants concluded that the rules for promotion in any

work environment need to be clear, as they are in the military. However, this is not the case in some other sectors. In addition, the academy generally imposes unique time constraints and frameworks for advancement to award of tenure, meaning that if tenure is not achieved within a designated period, the opportunity is lost. In academia, this translates to the maxim "publish or perish." But consideration should be given to stopping or adjusting tenure clocks to accommodate the unique characteristics of women's career paths.

The differences between industry and academic positions should be made clear to women. In industry, the corporate, and therefore common, goal is to increase the bottom line, which leads to more collaboration and teamwork. In turn, this tends to accommodate and provide resources for helping with family obligations (e.g., childcare). This is not the case in academia, where the environment is more one of individual competition. Childcare options and resources for faculty as well as postdoctoral fellows and graduate students are needed in many universities.

What are the risks and myths associated with changing career paths? Women are often told that moving from one sector to another may ruin their careers (e.g., that they may be unable to reenter a research career once they leave). How can we change the stigma associated with changing career paths? How can we liberate women to feel free to pursue alternative career paths without fear of professional recriminations? Do we need to change the model of what constitutes a successful career? Women with Ph.D.s are often told that having a position at an R1 research university is the only way to be successful (R1 research universities offer a full range of baccalaureate programs, are committed to graduate education through the doctorate, give high priority to research, award 50 or more doctoral degrees each year, and receive annually $40 million or more in Federal support). Success is measured by publications and grants, but this may not be the best measure. Research is needed to address the best way to measure success. These measures will have clear implications for promotion and tenure decisions that are crucial for women's advancement in academic and nonacademic careers.

Training Opportunities

Training opportunities, such as reentry and retraining, should be available to women throughout their careers. Refresher courses might be valuable for women trying to get back into a field after a break (e.g., taking time out to have children). Today, because of a lack of available academic positions (among other reasons), more women are choosing careers in smaller universities, which often makes them less viable candidates for R1 university positions or other career advancement opportunities. Yet, small liberal arts schools might provide a nurturing, supportive environment for women scholars, both in training and as faculty, an environment that could overcome barriers to career advancement if the colleges were given the resources to assist women researchers through mentoring and collaboration.

Research is needed to examine the success of current training programs. For example, are the postdoctoral reentry programs and similar programs at NIH successful? Is better dissemination of these programs needed to increase applications? Do historically all-female colleges and universities provide an operational model that fosters collaboration and risk taking more than coeducational institutions? Do they provide more supportive entry and retraining points?

Mentoring

A central, nationwide mentoring network would benefit women throughout their careers as a central location to ask for advice and obtain deeper resources than those available at any individual institution. Women often need multiple mentors to address a wide range of issues, including current workplace expectations, family situations, research direction, and future career opportunities. A professional needs an adviser in her field to advise her about meeting career goals and finding career opportunities. In addition, some women could benefit from a coaching relationship (support, encouragement, and problem solving to help with life skills and family situations). A central mentoring network Web site would accommodate various types of mentoring and coaching on all facets of a woman's career. It would also be a place to find opportunities for collaborations and interdisciplinary research, career positions, and advice. Women may need anonymous advice on how best to handle delicate work-related issues. Having a mentor outside of one's institution offers the benefit, at least in theory, of a "politically safe" environment in which one may share information or ask candid questions without fear of local repercussions. A network would also broaden the professional expertise available to all junior faculty members, researchers, and trainees.

Not everyone is suited to be a mentor or a mentee. Mentoring requires mutual trust and respect. Assigned mentors are generally not as effective as mentors chosen by the mentees. Effective mentorship generally requires training. Mentors should be trained in leadership skills (e.g., active listening, giving and receiving feedback, effective networking, constructive criticism, time management, budget skills). They should be informed about career options in all employment realms. Senior women in high-ranking positions might receive focused training on how to recruit junior women into a position and train them as replacements (succession planning). Such developmental opportunities for women are much more likely to be offered from other women than from men.

A compilation of best mentoring practices is needed, as is timely dissemination of such information. A meta-analysis is needed to determine the effectiveness of various programs, such as child care centers; loan repayment programs; banks of donated leave time from which colleagues could draw, without need of repayment, for emergency personal leave needs; and principal investigator (PI) replacement programs for daily laboratory functioning (e.g., a lab manager to take over PI responsibilities in a PI's absence). All of these programs affect women's career paths. Having a central location where women can access information about such programs would assist them when making career choices. Having a compendium of research on these policies and programs also would be beneficial to institutions and organizations interested in establishing similar programs.

Recommendations

To meet current and future needs of women in biomedical careers, the working group identified the following recommendations to provide guidance to academic institutions and administrators, the health professions, clinicians, and scientists.

Recommendation 1: Further Research

- Evaluate the risk-taking behaviors and choices involved for girls and women to enter, remain in, and advance along the career continuum.
- Fund pilot studies to learn more about part-time workers; specifically, the success of part-time workers and the challenges they face.

Recommendation 2: Resource Development

- Establish effective collaboration and networking nationwide by developing an Internet-based network of mentorship for all levels of careers that would provide connections for collaborations, career development, and job opportunities across disciplines.
- Develop a compendium of best practices of factors that affect and support careers.
- Develop new ways to measure success in academia, moving away from a focus primarily on publications.

Recommendation 3: Training Needs

- Develop flexible reentry/retraining programs for various careers across the professional lifespan beyond biomedical and behavioral research.
- Encourage leadership training in all ORWH- and NIH-funded grants, with the goal of teaching mentors about multiple career pathway options, creating more diversity in leadership structures, and providing incentives for leadership training for women.

A Vision for 2020 for Women's Health Research: Moving into the Future with New Dimensions and Strategies
Northwestern University Feinberg School of Medicine
Northwestern Memorial Hospital
Chicago, Illinois
October 14–16, 2009

DAY 1—PUBLIC HEARING

Location: Feinberg School of Medicine, Robert H. Lurie Medical Research Center

12:00–1:00 p.m. — **Registration**

1:00–1:15 p.m. — **Welcome**

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Andrea Dunaif, M.D.
Charles F. Kettering Professor of Medicine, Chief, Division of Endocrinology, Metabolism, and Molecular Medicine, Feinberg School of Medicine, Northwestern University

1:15–2:30 p.m. — **OPENING PANEL: Diverse Populations and Disparities**

Moderator: Barbara (Bobby) W. K. Yee, Ph.D.
Professor and Chair of the Department of Family and Consumer Sciences, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa

Eleanor Hinton Hoytt, M.S., M.A.
President and CEO, Black Women's Health Imperative

Nancy Woods, Ph.D., R.N.
Dean, School of Nursing, University of Washington

Francisco A. R. Garcia, M.D., M.P.H.
Professor of Obstetrics & Gynecology and Public Health, Director, Center of Excellence in Women's Health, University of Arizona

Carolyn Stern, M.D.
Physician and Partner, DeafDOC.org, Unity Health System

2:30–2:45 p.m.	**Video Tribute by Tavis Smiley on Women's Health Research** **Tavis Smiley** *PBS Broadcaster, Author, Advocate, and Philanthropist* **Introduced by: Vickie M. Mays, Ph.D., M.S.P.H.** *University of California, Los Angeles*
2:45–5:30 p.m.	**PUBLIC HEARING** **Moderator: Andrea Dunaif, M.D.** **Receiving Public Testimony: Members of the ORWH Advisory Committee, NIH Coordinating Committee, and host scientists**

DAY 2—SCIENTIFIC WORKSHOPS

Location: Thorne Auditorium, Arthur Rubloff Building, Northwestern University, Chicago, IL

7:30–8:30 a.m.	**Registration**
8:30–8:45 a.m.	**Welcome and Opening Remarks** **Vivian W. Pinn, M.D.** **Daniel I. Linzer, Ph.D.** *Provost, Northwestern University*
8:45–8:55 a.m.	**Welcoming Remarks** **Maggie Daley** *First Lady of the City of Chicago*
8:55–9:30 a.m.	**Keynote Address: 2009 H1N1 Influenza: Research Activities and Potential Impact on the Nation and its Women** **Carole Heilman, Ph.D.** *Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases*

9:30–10:15 a.m.

PANEL: New Technologies—Overview and State of the Science

Moderator: Colleen M. Fitzgerald, M.D.
Assistant Professor, Feinberg School of Medicine, Northwestern University, Director, Women's Health Rehabilitation Program, Rehabilitation Institute of Chicago

Todd Kuiken, M.D., Ph.D.
Associate Dean of Academic Affairs, Feinberg School of Medicine, Northwestern University

Teresa K. Woodruff, Ph.D.
Professor of Obstetrics & Gynecology, Feinberg School of Medicine, Professor of Biochemistry, Molecular Biology and Cell Biology, Weinberg College of Arts and Sciences, Northwestern University

10:15–10:30 a.m.

Working Group Charge

Vivian W. Pinn, M.D.

10:30 a.m.–3:15 p.m.

Lunch and Concurrent Working Groups

- **Understudied and Underrepresented Populations: Minorities, Urban, Rural, Disabilities, and Issues of Poverty**
- **Understudied and Underrepresented Populations: Lesbian, Bisexual, Transgender, and Intersex Issues**
- **Clinical and Translational Research**
- **New Technologies/Bioengineering/Imaging**
- **Genetics and Epigenetics**
- **Sex Hormones and Disease**
- **Neuroscience**
- **Women in Science Careers**

3:15–3:30 p.m.

BREAK

3:30–5:00 p.m.

PANEL: Team Science at Northwestern University

Moderator: Holly Falk-Krzesinski, Ph.D.
Director of the Office of Research Team Support, NUCATS Institute and Office for Research Development, Office for Research

Noshir Contractor, Ph.D.
Director, Science of Networks in Communities (SONIC) and Professor, McCormick School of Engineering & Applied Sciences-Industrial Engineering and Management Sciences, School of Communication-Communication Studies, and Kellogg School of Management-Management and Organizations

Brian Uzzi, Ph.D.
Co-Director, Northwestern Institute on Complex Systems and Professor, Kellogg School of Management—Management and Organizations; Weinberg College of Arts & Sciences—Sociology; McCormick School of Engineering & Applied Sciences—Industrial Engineering and Management Sciences

5:00–6:00 p.m. **Conference Reception**

DAY 3—SCIENTIFIC WORKSHOPS

Location: Plenary Session, Thorne Auditorium; Breakouts, Wieboldt Hall

8:30–8:40 a.m. **Opening Remarks**

Janine Austin Clayton, M.D.
Deputy Director, Office of Research on Women's Health

8:40–9:15 a.m. **Keynote Address: Retaining Women in Academic Careers**

Phoebe S. Leboy, Ph.D.
President, National Association for Women in Science

9:15–10:45 a.m. **Concurrent Work Groups: Finalization of Recommendations**

10:45–11:00 a.m. **BREAK**

11:00 a.m.–12:30 p.m. **Working Group Presentations by Cochairs and Discussion of Working Group Results**

Moderator: Andrea Dunaif, M.D

12:30–12:45 p.m. **Closing Remarks**

Andrea Dunaif, M.D.

Vivian W. Pinn, M.D.

Northwestern University Feinberg School of Medicine
Northwestern Memorial Hospital
Chicago, Illinois
October 15–16, 2009

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INTRODUCTION

This report covers the fourth strategic planning meeting, held October 14–16, 2009 at Northwestern University's Feinberg School of Medicine. Participants were welcomed by the Office of Research on Women's Health and Northwestern cosponsors as well as by Maggie Daley, wife of Chicago Mayor Richard M. Daley. The format of the meeting included public testimony, a plenary session, and eight breakout groups. The plenary session included three panel presentations, two keynote addresses, and a charge from the ORWH director to meeting participants. Major themes of the plenary presentations were health disparities in understudied populations of women, the application of new technologies to women's health, and multidisciplinary science teams of the future. Below are highlights from the plenary presentations.

SUMMARIES OF PLENARY PRESENTATIONS

OPENING PANEL: DIVERSE POPULATIONS AND DISPARITIES

An opening panel of the plenary session called attention to health disparities in five special populations of women—urban women; those living on the U.S.-Mexico border, Deaf and Hard-of-Hearing women; Black women; and Asian/Pacific Islander women. Below is brief synopsis of major points raised concerning each group.

Nancy Woods, Ph.D., R.N.
Dean, School of Nursing, University of Washington

As of 2008, Dr. Woods explained, more than one-half of the world's population was living in urban areas. For the foreseeable future, trends toward global urbanization will continue to shape urban environments as hubs of economic growth, particularly in emerging economies. Little scholarly literature, however, has addressed the needs of urban women. What is known about their health status? They are generally found to be healthier than rural women, but this statistic holds primarily for higher income women. It also masks subpopulation differences and is not sensitive to changing population dynamics. Urban environments are multidimensional and best broken down into dimensions for purposes of study. The benefits of this approach can be seen from a study of urban social environments and health. The study, carried out in several Philadelphia urban communities, found that higher Black racial composition and higher community social capital were both independently associated with lower all-causes Black mortality. The built environment also influences health behaviors. The Black Women's Health Study found that high housing density was positively associated with utilitarian and exercise walking.

Francisco A. R. Garcia, M.D., M.P.H.
Professor of Obstetrics & Gynecology and Public Health, Director, Center of Excellence in Women's Health, University of Arizona

Dr. Garcia began by defining the U.S.-Mexico border as a 2,000-mile long strip extending inward about 62 miles on either side of the border. In 2009, more than 12 million people were living in the area, including, on the U.S. side, large numbers of Mexicans—both those with long ties to the area as well as recent immigrants—and members of American Indian tribes. These groups have lower educational levels and incomes than non-Hispanic whites. Higher rates of cervical cancer and obesity are two of the health disparities characterizing the groups. Addressing health disparities will require multidisciplinary approaches that consider

the disparities in income, education, and culture and acculturation, as well as disparities in access to health care and in health behaviors. Not only should research attempt to identify risk factors, but also to determine those protective factors that confer resilience on some individuals in the community.

Carolyn Stern, M.D.
Physician and Partner, DeafDOC.org, Unity Health System
Dr. Stern said that Deaf/Hard-of-Hearing (D/HH) status is the most common disability recognized by the Americans with Disabilities Act. It affects 1 in 10 Americans, with 1 in 100 profoundly affected. Women born D/HH have profiles similar to English-language minorities, including limited socialization with the spoken-language community, lower educational attainment and socioeconomic status, lower health literacy, and less access to health services. Those who become D/HH later in life have poorer health and less frequent screenings and doctors' visits. Communication is the major barrier to successful access to health care in the D/HH community. It limits not only women's access to their own health care and information, but also family members' health care because D/HH women serve as portals for their family's entry into the health care system. Furthermore, there is not enough baseline information to characterize the health needs of D/HH women and their families. Community-based participatory research and recruitment are necessary to increase research pipelines needed to help D/HH women.

Eleanor Hinton Hoytt, M.S., M.A.
President and CEO, Black Women's Health Imperative
Ms. Hoytt said that, by most health measures, Black women have poorer outcomes than majority White women. Black women have the highest or near highest rates of most major chronic conditions (hypertension, diabetes, stroke, most cancers, glaucoma, arthritis, and lupus) and risk factors for poor health (obesity, sedentary lifestyles, drug dependence, tobacco use, depression, sexually transmitted diseases, low immunization rates, and partner violence). Health disparities largely reflect disparities in the social determinants of health, in access to therapies and prevention and differences in health behaviors. This complexity of risk factors calls for a shift from a strictly biomedical model to an interdisciplinary model.

Barbara (Bobby) W. K. Yee, Ph.D.
Professor and Chair of the Department of Family and Consumer Sciences, College of Tropical Agriculture and Human Resources, University of Hawaii at Manoa
Dr. Yee noted that a widely held perception of Asian and Pacific Islanders is that they are a "model minority," with Asian women having the longest life expectancy of any group in the United States. Nonetheless, subpopulations show health disparities, and disaggregated analysis is required to address these fully. For instance, in Hawaii, Pacific Islanders have diabetes twice as often as Whites. Hepatitis disproportionately affects some Asian subpopulations. Data disaggregation and analysis are needed to refine the identification of risk factors contributing to health disparities among subpopulations of Asians.

KEYNOTE ADDRESS: 2009 H1N1 INFLUENZA: RESEARCH ACTIVITIES AND POTENTIAL IMPACT ON THE NATION AND ITS WOMEN

Carole Heilman, Ph.D.

Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH

Dr. Heilman addressed special issues of the H1N1 epidemic for women. A 2009 New England Journal of Medicine report on H1N1 hospitalizations found that 73 percent of those hospitalized had at least one underlying medical condition. These conditions included asthma; diabetes; heart, lung, and neurologic diseases; and pregnancy. Because women have more asthma and chronic pulmonary diseases than men, this risk profile, in combination with obesity, raises special concerns for severe H1N1 complications in women. Pregnant women appear to be at increased risk for severe H1N1 complications. This increased vulnerability stems in part from pregnancy-related physiological changes in lung function and circulation. However, pregnancy is also a period of immune suppression, and hormones are critical factors in changes in maternal immunity. This is an area of translational and clinical importance that is also ripe for collaboration.

PANEL: NEW TECHNOLOGIES—OVERVIEW AND STATE OF THE SCIENCE

The panel on new technologies, moderated by Colleen M. Fitzgerald, M.D., Assistant Professor, Feinberg School of Medicine, Northwestern University and Director, Women's Health Rehabilitation Institute of Chicago, discussed the potential of technological advances to improve health outcomes and quality of life, spur further innovations, and facilitate translation.

Todd Kuiken, M.D., Ph.D.

Associate Dean of Academic Affairs, Feinberg School of Medicine, Northwestern University

Dr. Kuiken described a breakthrough innovation in neural-machine engineering that allowed an amputee to more precisely direct the movement of a prosthetic limb by his own thoughts. Noting that technology "should enable the human," the presenter showed a video of Jesse, who has been called the first "bionic man." A double amputee, Jesse can now use a prosthetic arm to shave, open bottles, and perform many other activities essential to independent living. The pioneering technique that made this possible is a muscle reinnervation, which takes an amputee's own nerves and connects them to a healthy muscle. A myoelectric limb uses electrical signals from the muscle, activated by the user's own thought-generated nerve impulses, to move. Such an example of a neural machine interface holds future hope that the brain can be harnessed to machines in other applications. In the future, perhaps paralyzed people will be able to use their thoughts to operate computers, wheelchairs, robots, and other mechanical devices.

Teresa K. Woodruff, Ph.D.

Professor of Obstetrics & Gynecology, Feinberg School of Medicine, Professor of Biochemistry, Molecular Biology and Cell Biology, Weinberg College of Arts and Sciences, Northwestern University

Dr. Woodruff began with the hypothesis that the innovation of new technologies will drive the next generation of discovery research and lead to major health advances. Because technologies should drive innovation, but not create or increase health disparities, in a time of limited resources it is important to insist on the inclusion of women early in the process of device

development and technology design. Considering sex differences in basic research is important because science is on a continuum, with basic science providing the source of clinically relevant hypotheses. Such consideration has not always happened in the past—but sex differences are important, whether they are identified at the cellular or system levels, or in an animal model. As an example, recent research has shown that coronary artery plaque forms differently in women than in men, but most existing diagnostic technologies, designed on the male model, are better at detecting risk in men.

Translational technologies have the potential to bridge basic science and clinical research translation. Among the top innovations that serve the greatest unmet needs to which an investment of resources is most likely to yield major benefits are the imaging technologies, biomaterials design, nanodiagnostic applications, self-assembling materials and regenerative medicine, and the assessment technologies—high throughput analytic methods, microscopy, proteomics, and bioinformatics. Encouraging translational scientists using these technologies to focus more on sex differences requires highlighting the scientific issue in unexplored areas and providing examples of scientific successes.

PANEL: TEAM SCIENCE AT NORTHWESTERN

The presentations in the team science panel provided an introduction to the field of social networking science and provided examples of the application of its methods to questions about the scientific impact of teams.

Holly Falk-Krzesinski, Ph.D.
Director of the Office of Research Team Support, NUCATS Institute and Office for Research Development, Office for Research

Dr. Falk-Krzesinski, the panel moderator, noted the increased demand for collaboration in science and medicine, and a trend toward the multidisciplinary and interdisciplinary approach of team science. The Northwestern University Clinical & Translational Sciences (NUCATS) Institute aims to advance team-based, cross-disciplinary translational biomedical research and to focus on the empirical field of "the science of team science." The Oncofertility Consortium, a program that has 10 linked grants at 6 institutions, provided an example of team science and its empirical evaluation.

Brian Uzzi, Ph.D.
Co-Director, Northwestern Institute on Complex Systems and Professor, Kellogg School of Management—Management and Organizations; Weinberg College of Arts & Sciences—Sociology; McCormick School of Engineering & Applied Sciences—Industrial Engineering and Management Sciences

Dr. Uzzi assembled evidence that scientific breakthroughs are the result of individuals embedded in collaborative networks rather than solitary endeavors. Since the 1950s, teams have predominated in the physical sciences, with the biomedical sciences more recently also adapting that model. Team science, which has grown to include vast cross-university networks, has had a greater impact, as shown by citations in the published literature, than solo science. Furthermore, cross-organization teams tend to perform better in terms of impact than within-institution teams, despite claims that proximity and easier communication should be decisive benefits for the latter group. More impactful publications, as measured by journal citations, also result

from networks that periodically introduce new members into coauthorship, indicating that the infusion of new ideas by such members or the additional synergy they add to the existing publications networks may benefit scientific innovation.

Noshir Contractor, Ph.D.
Director, Science of Networks in Communities (SONIC) and Professor, McCormick School of Engineering & Applied Sciences—Industrial Engineering and Management Sciences, School of Communication—Communication Studies, and Kellogg School of Management—Management and Organizations

Dr. Contractor continued by introducing the methods of social networking science and demonstrating how they can be applied to the design, diagnosis, and evaluation of social knowledge networks, using the Oncofertility Consortium as an example. The coevolution of knowledge networks science and methods along with advances in 21st-century cyberinfrastructure that better capture relational data has facilitated modeling of social knowledge networks and analysis of the effects of different network forms. The multidisciplinary field of oncofertility was the subject of a four-site social network clustering analysis, which showed dramatic increases from before to after the consortium's establishment, both in intersite and interprofessional collaborations. Similar methodologies can be applied to evaluations of other multidisciplinary team science efforts.

KEYNOTE ADDRESS: RETAINING WOMEN IN ACADEMIC CAREERS

Phoebe S. Leboy, Ph.D.
President, National Association for Women in Science

Dr. Leboy discussed the problem of the underrepresentation of women M.D. and Ph.D. scientists in medical schools at progressive rungs of the career ladder. Although women M.D.s and Ph.D.s are at parity with men in the initial stages of careers, they show marked attrition from academic medicine at the associate and full professor levels. This attrition has been attributed to a number of causes, including family demands; the competitive academic environment of a 7-day workweek, which is incompatible with childrearing; and institutional bias in evaluation and reward. In addition to continued vigilance by institutions to the elimination of institutional barriers and bias within their own ranks, the NIH may also be able to make policy changes, such as changing the time commitment for mentoring on training and senior career grants or encouraging NIH-funded institutions to put family-friendly policies in place.

CHARGE TO THE WORKING GROUPS

Before the full group reconvened in smaller working groups, the ORWH Director provided them with their charge for their work efforts. Noting how exciting the plenary presentations had been, she asked the working groups to help the NIH chart the future direction of women's health research. Specifically, she asked them to address a number of questions. What value does the ORWH add in the coming era of technological advances? What is the more for the women's health research and career development enterprise that will not be done if the ORWH does not take the lead? What science and technologies are particularly innovative as well as addressed to critical women's health needs? What science-based initiatives, falling within the mission of the NIH, are high priority? Is there a new scientific paradigm to be added to the Office's approaches to women's health to facilitate these initiatives? The working groups, she noted, are essential in shaping the product of the year-long planning process. She ended by underscoring what she hoped would emerge from the process: recommendations that anticipate new science rather than ones that merely recapitulate the status quo.

SCIENTIFIC WORKING AND DISCUSSION GROUPS

UNDERSTUDIED POPULATIONS SUBGROUP 1: MINORITIES, URBAN, RURAL, DISABILITIES, AND ISSUES OF POVERTY

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Introduction

Women and girls in vulnerable societal statuses—minority women, immigrant women, women in urban and rural areas, disabled women, girls in the foster care system, women prisoners, veterans, and women living in poverty—experience special and sometimes unique health concerns in terms of disease risk, incidence, course, access to care, and disease-related disability. They are likely to fall below the national mean on general health and mental health status indices. Although the impact of disease-related disability is disproportionate in these women relative to the general population, they are often underrepresented in biomedical research, clinical trials, and natural history studies. Explanations for this underrepresentation are multifactorial and include lack of effective outreach, perceived difficulties in sustaining participation, mistrust of research, or lack of perceived benefit to others like them, language and communication barriers, or time demands as workers and caregivers. Women from these populations

may also have limited access to and knowledge of health resources and they often receive a different level of care when they do contact health care providers. The goals of the Understudied Populations Subgroup 1: Minorities, Urban, Rural, Disabilities, and Issues of Poverty Working Group were to identify the most significant health issues facing these women (hereafter referred to in this report as "understudied") and the most promising research strategies to remedy the issues. The diversity of understudied groups and the unique configuration of risk and protective factors found in a particular population of women were acknowledged by the working group. However, their deliberations focused primarily on identification of crosscutting research issues and overarching themes that would be applicable to most—if not all—groups of understudied women.

Summary of the Discussion

The discussion of the working group began with a brief introduction by each member and a statement concerning a topic of interest to be considered when structuring research studies about women's health. It quickly became apparent that the five initially identified understudied groups of women, based on the charge reflected in the title of this report, were not sufficiently comprehensive of those whose statuses result in vulnerability to their health. Other groups of women such as Asian Americans, Native Hawaiians, Native Americans or American Indians, foreign born, refugees/immigrants (particularly those without legal status), women veterans, incarcerated women, and girls in foster care were noted by the group as understudied. Despite this diversity, certain common cross-cutting concerns were identified.

The first and most significant cross-cutting concern identified by the group was the role of trauma in the health of the understudied groups of women. The definition of trauma is complex, and it can include both institutional and relational experiences; acute and chronic trauma; and ongoing and remote trauma. Some questions that arise are whether there is a gendered nature to trauma; how trauma affects women's health over the lifespan; and how it impacts the intergenerational health of women's children and grandchildren. Trauma can be viewed as a continuum, from sustained stresses to acute insults/injuries. For example, poverty constitutes a chronic stress rather than acute stress. Trauma can also be classified as historical (institutional) or relational. Instances of historical traumas include those experienced by such groups as American Indians, African-American slave descendants, and other groups who have experienced longstanding institutional discrimination. The legacy of eugenics policies and institutionalization of the disabled presents another example of historical trauma. The effects of such histories can impact group members' motivation to participate in clinical trials. Women from underrepresented and understudied populations are at greater risk of relational traumas throughout their lives. These traumas can include intimate partner violence, elder mistreatment, homelessness, unintended pregnancy, involvement in sex work, sex trafficking (especially of young girls), hostile work environments, and natural disasters. Relational traumas can not only affect current and long-term health outcomes of the individual, but they also can have intergenerational impact. Multidisciplinary approaches, including the collaboration of medical practitioners, basic researchers, and historians, are well suited to addressing the impacts of trauma(s) on understudied populations of women. The group saw trauma as a paradigm approach to thinking about its role in women's health in general and, in particular, for those most vulnerable understudied women.

A second cross-cutting concern was the dearth of health studies based on an integrative model of health, such as a biopsychosocial model. The biopsychosocial model attempts to be integrative in its scope. It has as its goal the inclusion of contextual as well as individual factors, and the bridging of disciplines such as medicine, public health, economics, and social and behavioral sciences. In the past, research has tended either to address biomedical issues or social/behavioral issues, but not integrate these issues in a research protocol, with resultant limitations in understanding the complex contextual influences and social interactions that contribute to disease, disorders, and syndromes. Biomedical research, the major activity of the NIH, could benefit from increased conceptualization of health issues in terms of a biopsychosocial model, with attention not just to the individual, but also to family, neighborhood, community, and larger societal contributions to negative health outcomes in vulnerable women. As an example, disability versus independence in elderly women can be discussed in terms of the model. Independence in old age is the end result of numerous physical, social, and environmental factors over the lifespan. All too often, in later years of a woman's life, she may suffer significant physical disability that impacts independent aging in place. As a biomedical issue, disability in aging can be considered in terms of sarcopenia or the infiltration of muscle by fat. From a biopsychosocial perspective, sarcopenia can be seen as leading to loss of mobility, self-care, social functions, and overall health; these consequences in turn are associated with increased hospitalization, falls, hip fracture, and shortened lifespan. Addressing these issues may also require addressing emotional and mental health issues in order to promote increased activity and self-care behaviors.

Following discussion of crosscutting concerns for women in understudied populations, working group participants identified five overarching themes. They are: (1) access to/inclusion in biomedical research; (2) disaggregation of data; (3) the importance of place, space, and context in biomedical research; (4) developmental lifespan and intergenerational perspectives; and (5) communications. Within the framework of the special concerns and overarching themes identified, participants were asked to address future needs for research, and new methodologies, technologies, and approaches to identify and include previously understudied groups in biomedical research. Discussion is summarized below for each theme.

1. Access to/inclusion in biomedical research. Women from understudied populations often have limited participation in health research, particularly when it is outside of the primary care setting. This is frequently a result of such factors as lack of effective recruitment/outreach to the women; lack of effective communication on how the research can benefit others like them; or research that poses a major time burden or lacks culturally tailored methods. Modes of research that continue to rely significantly on face-to-face interaction, landline telephones, or significant reading requirements result in lack of participation for large segments of underserved women because of geographic isolation, time commitments, or inability to fully participate because of lack of comprehension accommodations. Communication barriers include the use of recruitment and participation strategies that do not accommodate limited literacy, translation for non-English speakers, or effective communication methods for the sensory impaired. Physical barriers are also a problem in particular for women in isolated geographical locations, those with limited transportation access, and those who are physically

disabled and lack mobility. Several important points were made by working group participants concerning access/inclusion issues; bulleted highlights are given below:

- **The development of new data collection methods could address research issues for understudied populations of women**. Data collection and reduction strategies need to be improved to capture data on the populations and to reduce the burden on participants. Use of emerging technologies (personal digital assistants, cell phones, electronic transmitters, Skype, etc.) would benefit outreach to underrepresented women. Research using telelinks should be explored to reach the populations. Use of telecommunications to interact with patients on reservations, in isolated locations, and the disabled could improve recruitment, participation, and maintenance in study cohorts. Electronic medical records would enable more effective work with populations that frequent emergency rooms rather than relying mainly on clinic populations.

- **New methods and devices are needed to enable noninvasive approaches to biospecimen/biomedical data collection**. Development of new technologies is needed to monitor physiological health processes and psychological responses to trauma, so that early detection of indicators for poor or good physical, emotional, and functional outcomes is possible. These technologies should be able to distinguish biomarkers of both chronic and acute stress, and they should be able to capture data in real time. The development and implementation of noninvasive specimen collection (e.g., saliva collection, sweat patches, ankle bracelets, etc.) could improve data gathering of understudied women in remote locations or who do not frequent the health care system. For elderly women, the ability, for example, to measure fatty infiltration of muscle (sarcopenia), inexpensively and at low risk, will help identify those at risk for hospitalization, fall, and shortened lifespan. Muscle mass can be quantified using computerized tomography and skeletal attenuation models, but such approaches are expensive and have fairly high radiation exposure. There is a need to develop newer, less expensive imaging techniques that would help advance this area of investigation. For example, the use of ultrasound could be explored for such application. Metabolic studies about what promotes sarcopenia and studies of mechanisms for mobilizing fat from muscle and maintaining muscle function are needed for elderly women. The use of robotic and haptic technologies for providing interventions for the disabled, frail, and relatively immobile homebound and for rural women would provide newly accessible treatment options.

- **Efficiencies of scale may facilitate the participation of understudied populations of women in clinical research**. Because the number of visits required for a study can be an impediment to women's participation, there must be new efficiency as to what is brought into the community. Researchers from several institutions should consider collaborations so that a community is approached in a collaborative manner by researchers. This would potentially reduce research burden on participants as well as facilitate enrollment. Collaboration among health centers that serve smaller populations and larger universities would be beneficial in this regard. Again, the use of technologies such as specially designed cell phones and PDAs to capture needed ongoing biological measures should be explored to reduce travel and the burden of participation.

- **Improvements are needed in the training of the research and biomedical workforce as well as in the diversity of researchers and health care providers**. Individuals from understudied groups may be more likely to participate in research and to seek access to care if they are able to interface more frequently with doctors and researchers who offer culturally appropriate interventions and approaches.

2. **Disaggregation of data**. Much currently available information on women's health comes from data sources that are aggregated in larger racial/ethnic/socioeconomic status/geographic groups; average tendencies for the overall sample are often reported rather than for specific subpopulation groups. Even if results are presented in terms of gender, ethnic, racial, age, and socioeconomic categories, findings may lack the level of specificity needed to characterize problems in special populations of understudied women by allowing for several statuses simultaneously to be considered (e.g., age, race/ethnicity, socioeconomic status [SES], place). Current registries could be mined for analysis of disaggregated data; future registries and datasets should aim to include a fuller range of racial/ethnic, SES, sexual orientation, and age subpopulation groups and data points that allow for better contextual analyses (geographic information, e.g., neighborhood, region, census tract, the primary language spoken, and health services in regions). Consideration in planning analyses should be given to contextual and demographic factors, some of which are outlined in the first bullet below:

- **Current Office of Management and Budget definitions do not fully capture information needed for disaggregatio**n. Study participants are often grouped together without full consideration of the impact of social, racial/ethnic, or legal status. Many characteristics of women play important roles in health over the lifespan. Among these are immigration and refugee status; age and generational status; disabilities; rural or urban location; education, income, occupation, and wealth; religion; veteran status; homelessness and incarceration history; self-identified race and ethnicity; and sexual orientation and gender identity.

- **Qualitative work is an important methodological task needed for appropriate measurement and disaggregation**. Qualitative work may be done during interviews to allow participants to self-identify to the researchers and make known any barriers to access. Qualitative research may be particularly important for understudied groups of women because they are less likely to volunteer contextual information and because their culture may otherwise be defined by someone other than themselves, such as a husband or father.

- **Mental health status information should be studied in disaggregate groups**. Acute, chronic, and chronic relapsing mental illnesses are important causes of functional disability; they also have significant impact on the course of general health conditions. Prevalence of mental disorders and risk and protective/resilience factors need to be identified in understudied populations as well as psychological distress and well-being.

- **A methodological development is needed to deal with statistical, reliability, and validity and interpretation issues that disaggregation poses**. Methods for nonburdensome, reliable collection and the development of statistics for small samples are critical needs. Special consideration needs to be given to statistical significance and multiple testing in small-sample disaggregated groups because these issues may negatively impact the

validity and reliability of findings from small groups. To further address reliability and validity issues and to enhance interpretation, more robust statistical methods are needed for analyzing and modeling disaggregated data.

- **To facilitate comparison across datasets and subgroups, a core set of standard measures needs to be identified and implemented across studies**. Because it may not be feasible to power all studies to address statistical significance in all subgroups of potential interest, meta-analysis based on a core set of measures may be an option. Where appropriate, existing well-validated population measures can be evaluated with regard to their psychometric performance in new populations and, as needed, they may be modified. New measurement instruments should also be developed for use in small groups with large variance and skewed distributions.
- **In designing new large-scale studies, sampling frames should enable study of the role of culture, race, and language on health outcomes**. Plans for appropriate data disaggregation should be incorporated into a study's framework, with sample size and sampling techniques considered a priori rather than left to post hoc analyses. Sampling considerations should include those of the stability and isolation of a population because these factors may create certain unique health implications. For example, the human papilloma virus, the major risk factor for cervical cancer, may have a distinctive transmission and oncologic potential in Appalachian women because of the long-term stability of that population.

3. The importance of place, space, and context in biopsychosocial and biomedical research. Social context influences health and illness. The biopsychosocial model is needed to understand the causation of many conditions where biological (genetic and biochemical), sociological (stressors), and psychological (development and life experiences) factors interact to produce a health outcome. Women are often responsible for family cohesion and childcare. Research on their roles must be contextualized to the environments in which they are living and working. Therefore, their multiple roles in family and community should be studied with regard to setting (e.g., rural and urban) or family structure (e.g., single-parent or paired relationships). Transportation and isolation issues are also important to consider when addressing health research in these communities. Women in rural areas as well as urban areas are often affected by the time and distance to a clinical trial. Below are some bulleted issues that were specifically discussed with regard to this overarching theme:

- **Local study conditions must be conducive to participation of women in understudied groups**. A study's location must be achievable and nonthreatening. It must be welcoming and provide a sense of personal safety. Some examples might include community spaces such as schools, houses of worship, or community centers. There should be no fear of being turned away. Onsite child care should be provided if possible. Research should, when possible, be seamless in assessing health issues, but it should also provide women with information about access to health care and health tools that exist to intervene in their health problems. Space in which research is conducted must be accessible for the disabled. There should always be accessible entrances, readily available alternatives to stairs, and methods for participation that accommodate the differently abled whether their impairments are sensory, physical, or emotional.

- **Geography might not always define a community, and this should be considered when choosing a clinical trial location**. For example, a house of worship might be in a community, but not part of it. Furthermore, people may use health centers closer to work than to home. Place, although important, is often impacted by economic resources, and, therefore, definitions of place as community or neighborhood should be consistent with women's self-defined context of place.

- **The physical context of a study is particularly important when conducting research involving underrepresented women**. Vigilance about who else is in the room is important when conducting studies and interviewing. This may affect responses. Furthermore, research needs to embed people within their family or relational context and with regard to with whom they live and for whom they are responsible in their lives.

4. Developmental lifespan and intergenerational perspective. A developmental lifespan perspective includes not only longitudinal considerations, but also consideration of the complex interplay of family factors on the health outcomes of women. The health of a young woman needs to be studied as an important issue in its own right, but also as an important influence on that woman's health as she ages. Furthermore, due to their care giving and central family and social roles, the health of women across the lifespan has impact on families across generations. The following bulleted points received special emphasis with regard to developmental and intergenerational issues.

- **Caregiving has complex effects on women's health and the health of families**. Caregiving may provide caregivers with certain health benefits as well as health risks, and these benefits and risks need to be more fully understood in terms of context and the lifespan. Caregiving has potential intergenerational impact as well.

- **Aging and aging with disabilities have a significant impact on the individual and the family**. This is true for children, nondisabled siblings, and other relatives. Conversely, the impact that chronic diseases most frequently affecting women have on independence is also poorly understood.

5. Communication. Cultural sensitivity and awareness are core competencies for health researchers and health care providers seeking to work in communities of understudied women. Cultural competence means being aware of the needs of a specific population and training to approach the population in a way that enhances health outcomes. Further research is needed to determine relationships between cultural competence skills in the researcher/health care provider and health outcomes in the community. Such research is critical to the further development of policy on cultural competence training, for instance in curriculums for medical students and researchers. The following bulleted points were discussed specifically by working group members:

- **Community members should be fully involved in the design of studies**. For clinical research to proceed and succeed, those with the disease or those at high risk of the disease—i.e., the community involved—should be taken into account in the design and conduct of studies and the reporting of results. Many clinical studies fail to reach any conclusions due to poor accrual, which suggests a disconnect between the research plan and that community. Research plan review at all levels, including local Institutional Review Boards, should assess the plan from the perspective of that community. The research

results should be conveyed back to the community to acknowledge their contribution and to disseminate the information derived. One example is the dissemination of the Diabetes Prevention Program (DPP) presentations back to the participants enrolled in DPP.[1]

- **Communication must be increased within study design**. Simplification of consent forms will help communication between researcher and participant. Consent forms are currently designed mainly to protect the institution, not the individual. Consent forms that meet Federal standards for the protection of subjects, but also are comprehensible and acceptable to communities, are much needed. Translation services have increased the numbers of languages in which research materials and tools can be made available and should be incorporated into study designs to broaden participation of subpopulation groups.
- **Cultural sensitivity and subpopulation group knowledge must be increased in researchers through education and training**. Because context is so important to all aspects of the research process, from recruitment of women in community-based participatory research to the design of meaningful research and the interpretation of findings, researchers and biomedical participants in the research process need to have professional acuity and cultural sensitivity to enhance their ability to interact and intervene effectively with members of the community. This training could be part of graduate education attached to NIH training grant participation, and other training can occur as a part of postdoctoral or continuing education efforts, which can be done in partnership with communities. Particularly for interactions with women research participants, competency training may include increased awareness of the role of mental health conditions, trauma, and resilience in general health outcomes.
- **In communicating with members of understudied groups, the definition of health should be expanded**. It should be more expansive than pathology and medicine; it should include levels of functionality, well-being, and satisfaction.
- **New technologies are needed to address communication with the developmentally disabled, the elderly, and stroke victims**. Film clips and interactive technologies can help low-literacy groups. Consideration needs to be given to technologies to enhance communication with low-vision groups and those with cognitive, hearing, sensory motor, or other disabilities and impairments that may affect ability to participate or provide research data in traditional ways.

Recommendations

The Working Group on Understudied Minorities, Urban, Rural, Disabilities, and Issues of Poverty offered the following recommendations for research, technology development and training. The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Increase participation and inclusion of understudied groups of women in biopsychosocial, biomedical, and other research designs. Examples of approaches and research needed to improve participation and inclusion are given below.

- Develop new technologies and methodologies for remote data collection.

- Develop new measures, statistical approaches, and sampling methods in small samples to include understudied subpopulation groups of women.
- Develop strategies to overcome time/distance/literacy/differently abled/ social role barriers in order to enhance and increase participation of understudied groups of women in various research designs.

Recommendation 2: Studies of women's health need to incorporate considerations of place space, and context. Effective research that is broadly translatable to diverse groups of women requires the conceptualization of women's health issues in terms of a biopsychosocial model that attends to and integrates biological, social, mental health, societal and developmental factors as influences on health, disease, and well-being.

- Increase measurement of specificity and detail in order to identify culturally contextual factors that distinguish the influential factors and risk details within groups (disaggregation).
- Develop methods and data sources that provide attention to meaningful aspects of the cultural context of women's lives, from the woman's perspective.
- Include studies throughout the lifespan, from girls to frail elderly women and across generations.

Recommendation 3: Integrate a focus on the role of trauma in health outcomes of understudied groups of women. A biopsychosocial research agenda for understudied women needs to encompass the role of trauma on health outcomes:

- Identify commonalities in the experience of trauma and its consequences across diverse groups of women as well as special issues in particular groups (e.g., women with disabilities; women from immigrant groups).
- Enhance focus on the "gendered" nature of trauma and the ways that women's experiences of trauma influence lifespan and intergenerational outcomes.
- Enhance the linkages of trauma intervention research findings to intervention systems in place so that there is sustainability after the studies are over.
- Support the development of technologies to monitor real-time stress and trauma that can be used for research and for early interventions for stress.

Recommendation 4: Improve health communication and literacy. Relatively little evidence is available to inform "best practices" for improving the health literacy levels of women from understudied subpopulation groups.

- Identify how women access health and well-being information as a function of their different statuses (SES, geography, age, sexual orientation, differently abled).
- To enhance participation in future NIH research designs, identify the reasons why participants have not been included in past or current research activities (e.g., lack of literacy in research designs in the areas of language, communication and/or cognitive barriers).
- Examine and identify effective ways to use women's existing social networks to disseminate health information and translational findings from NIH research.

- Determine and investigate methods for the improvement of women's and girls' health literacy through use of public campaigns and activities, much the way that campaigns have been engaged to teach women about appropriate ages for screening and vaccination activities. Ensuring that women increase their health literacy will also improve health literacy for their children and other family members.
- Design research to determine best practices for communication styles at both the patient and provider levels that enhance women's experiences in health care interactions for the purposes of screening, treatment, and development of sustained health prevention-based health habits.
- Determine and investigate best practice strategies for increasing: the level of knowledge of understudied subpopulation groups of women about health and health-habit behaviors; participation in health research and accessing research findings; and careers in health research.

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UNDERSTUDIED AND UNDERREPRESENTED POPULATIONS SUBGROUP 2: LESBIAN, BISEXUAL, TRANSGENDER, AND INTERSEX ISSUES

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Introduction

Lesbian health and health-related disparities were clearly documented in the 1999 Institute of Medicine (IOM) report on lesbian health.[1] In the decade following the IOM report, a number of significant advances were made: improved methodological rigor and quality of research; expanded understanding of the health and health-related concerns of lesbian women; and a broadening of the scholarship to address the needs not just of lesbians, but also of bisexual, transgender, and intersex (LBTI) people.

Stigma and discrimination, and accompanying stress, influence the health of sexual minorities, their families and friends, and may have greater impact on the most vulnerable sexual and gender minority groups. Two-thirds of lesbian, gay, bisexual, and transgender (LGBT) students report feeling unsafe at school because of their sexual orientation. Traumatic injury and death is a constant in transgender communities. In the first national survey of transgender people, more than two-thirds reported verbal harassment and nearly half reported having been victims of assault with a weapon, sexual assault or rape. Population-based data have demonstrated that lesbians and bisexual women have higher rates of alcohol use, mental disorders, and smoking. Data from prominent studies including the Massachusetts Behavioral Risk Factor Surveillance System and the Growing Up Today Study show that lesbians are more likely than heterosexual women to be obese or to have higher body mass index relative to heterosexual peers.[2,3] Definitive data on cancer disparities are still unavailable, although community research has shown that lesbians with cancer have different needs and sources of support, findings of importance for tailoring interventions.

Against this backdrop, working group cochairs and participants discussed the directions for research on the health of sexual and gender minority populations in the coming decade.

Description of the Working Group Process

Members of the Working Group on Understudied and Underrepresented Populations Subgroup: Lesbian, Bisexual, Transgender, and Intersex Issues included working group cochairs, invited investigators, clinicians, and community advocates. Collectively they engaged in a democratic and collaborative process and developed a set of research recommendations. To enhance discussion, an agenda was devised to assure incorporation of the diverse perspectives of the members. A preliminary set of recommendations was created following the public testimony and subgroup discussions. These recommendations were refined and finalized following extensive review from working group cochairs and participants.

Summary of the Discussion

Members of the working group identified several issues as central to advancing research during the next decade on the health of sexual and gender minority women. These include the need to accumulate appropriate data, to expand support for research and training, and to develop the breadth of research to advance the health of sexual and gender minority women.

Need for Appropriate Data

Research on the health status and needs of the sexual and gender minority women is greatly constrained by limitations in available data. Participants identified the failure to include sexual and gender minority identification in data systems of the U.S. Census Bureau and other Federal statistical agencies as a major impediment to research progress; another is the absence of routine measurement of sexual and gender identity in NIH-funded research. Working group members noted that while significant progress has been made in developing state-of-the-art measures appropriate to identifying and characterizing sexual and gender minority populations, these measures have not been widely disseminated or adopted.

Participants also noted that further development and dissemination of research methodologies is needed to improve data on the health of sexual and gender minority women. For example, the identification of best practices for sampling, recruitment, and assessment of sexual and gender minority populations would help to inform the design of new studies. Methods research on dissemination would help increase access to data and develop a shared knowledge base. Participants noted research gaps and the unique challenges to studying these populations, including specific dissemination issues regarding protection of confidentiality when data are shared.

Expanding Support for Research and Training

Many existing NIH funding programs provide opportunities for researchers interested in studying sexual and gender minority women, but few initiatives actively draw attention to research gaps and opportunities in this area. There was some discussion about the IOM Panel on LGBT Health, which represents an important occasion to update and extend the findings of the 1999 IOM report on lesbian health. Such a panel would review the state of the science and identify research gaps as well as best methodological practices from qualitative research to population-based research in representative samples. Participants emphasized the need for inclusion of each of the LBTI subpopulations in the IOM and other major research initiatives.

Participants were concerned about the lack of inclusion of sexual and gender minority populations in discussions about health disparities. The current NIH definition of health disparities does not recognize LGBT and intersex populations. Inclusion of sexual and gender minority populations could greatly advance research on LBTI women.

Expanded opportunities for training will be needed to complement new opportunities for research. There is a need not only to better equip researchers to address issues in the health of sexual and gender minority women, but also to institutionalize cultural competency training related to sexual and gender minorities for all health care practitioners.

Comprehensive Models for Research

Research on the health of sexual and gender minority women builds on knowledge gained in stages, beginning with descriptive evidence on relative risks for health and disease outcomes in different populations, and progressing to research on mechanisms producing disproportionate risks and then to "best practices of intervention." Participants noted that research is well advanced along this continuum for some outcomes, such as mental health and alcohol abuse, but for others even basic descriptive research is highly limited. Expanding the range of research on conditions and diseases that disproportionately affect sexual and gender minority women is an essential step in advancing the health of this population.

Participants also believed an overemphasis on disease outcomes had served to limit potential advances. They noted that positive health is an important outcome in and of itself; that positive health is a continuum; and that understanding the sources of resilience and strength that contribute to positive health provides essential knowledge for understanding the development of adverse health outcomes. They agreed that only a "change in framework" that includes attention to wellness as well as disease will adequately advance research.

Beyond the Individual: Need for a Holistic Perspective

Health risks and health resiliency among sexual minority women are influenced by the interplay of sexual and gender identity, behavior, and feelings of attraction—that are in turn influenced by age, race, ethnicity, religion, geographical region, class, and disability status. Noting the broad span of influences that contribute to health and disease, working group participants stressed the importance of engaging interdisciplinary teams in research. Relevant expertise must be drawn from the biological sciences (e.g., on genetics and hormonal pathways), the psychological sciences (e.g., understanding personality and attitudinal factors), and the social sciences (e.g., research on the impact of stigma and discrimination, cultural meanings of gender, and the effects of public policies). The need to develop research strategies that can integrate methods and insights across scientific boundaries applies to all health research. Participants emphasized its particular importance in the case of research on the health of sexual and gender minorities, population groups for whom social and cultural stigma plays a large role in health-related processes.

Intervention Research and Beyond

Advancing basic research on the health of sexual and gender minority women is useful only if it contributes to improved health. Increased effectiveness may be achieved by broadening the scope of research. The working group strongly agreed that adequate attention be given to intervention research. Interventions can take multiple forms, from improving medical practice, to developing interventions to change risky behaviors, to changing policies that affect the health of sexual and gender minority populations. The development of interventions should be grounded in research on the multiple factors that affect health and disease outcomes in these populations. Targeted intervention research in these populations is needed to assess efficacy. Once effective interventions have been identified, mechanisms to disseminate them and ensure successful implementation will be another important target for research.

Concepts of Gender in Women's Health Research

Finally, the group identified a shared concern relating to the concepts of gender used in research on sexual and gender minority women's health. Participants noted that the categories of gender identity and sexual orientation are complex and fluid; this complexity needs to be more clearly acknowledged as does the importance of distinguishing among diverse groups within this larger population. Research on the meanings and enactment of gender and sexual orientation, including the biological, psychological, and sociocultural processes that influence these, could significantly advance the understanding of the role that gender plays in all health research.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Sexual orientation and gender identity should be measured as core demographic variables in all federally funded national surveys. To achieve this goal, we recommend the development of a toolkit to assist researchers with the following: measurement of sexual orientation (identity, behavior, attraction) and gender identity (female, male, transgender, intersex); strategies to enhance the methodological rigor of research (e.g., sampling and recruitment); and assessment of the unique determinants of health outcomes (e.g., discrimination and minority stress).

Recommendation 2: Expand support for interdisciplinary research and training related to the health of sexual- and gender-minority women. Research and training opportunities should be incorporated into existing research and training programs focused on women and gender (e.g., Building Interdisciplinary Research Careers in Women's Health K–12) as well as those aimed at reducing health disparities among minority group populations (e.g., Minority Research Infrastructure Support Program).

Recommendation 3: Support a comprehensive program of research on the health of sexual and gender minority women across the lifespan. Research programs focusing on sexual and gender minority women should include a continuum of research goals and methodologies including qualitative, community participatory, basic discovery, translational, and epidemiological research.

Recommendation 4: Expand research on the determinants of health beyond the level of the individual (e.g., personality, risk behaviors). Encourage the use of multi-level theoretical and analytic models that examine biological, psychological, social and structural (e.g., public policy and institutionalized discrimination) determinants of health.

Recommendation 5: Prioritize the development and evaluation of effective, culturally appropriate and methodologically rigorous clinical and community-based health promotion and prevention interventions. Best practices and findings of these intervention trials should be disseminated widely to funding organizations, to policymakers, and to the scientific, clinical and general communities.

Recommendation 6: Reframe the study of women's health to include broad based multi-faceted definitions of gender that go beyond male–female dichotomies or considerations of "social influences" on (biological) sex. Fund research that examines gender as a social construct that may or may not be tied to biological sex, thereby assisting the sciences to expand research on gender beyond current dualistic conceptualizations (i.e., many claim an understanding of the difference between sex and gender, but still use them synonymously in research practice). Future research on gender should include, but not be limited to, definitions and measurement of gender as a continuum rather than a binary concept among women and men; biological influences on gender identity and expression; cultural influences on interpretation of biological anatomy and gender expression; the social and psychological consequences of gender nonconformity; and the processes through which gender-based norms and beliefs affect all people's health.

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CLINICAL AND TRANSLATIONAL RESEARCH

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Introduction

Clinical and translational research can play a critical role in advancing women's health. The reporting of clinical research, investigating potential sex/gender differences at every opportunity, can begin to address research questions where prior studies are equivocal. The translation of clinical research studies into practice and policy is also critical so that scientific findings can be used to fully benefit human health. Confirmatory studies in diverse populations would enhance the impact of clinical research on clinical practice. Women's health, through clinical research, will improve as the following are optimized: augmenting investigators' toolboxes for recruiting women and girls into both non-sex–specific and sex-specific research studies; more fully analyzing potential sex and gender differences in the available research data; using technological advances to disseminate results; and investing in future hypothesis generation and reanalysis by creating accessible data repositories. Participants in the Clinical and Translational Research Working Group were challenged to address how clinical and translational research can be enhanced and how the health of women and diverse populations will be advanced as a result of redefining the parameters within which research is conducted, and to identify far-reaching priorities with the greatest potential to advance women's health.

Summary of the Discussion

The working group discussion was lively and varied across a number of topics. The group was well represented across institutions, professions, academics, NIH staff, community providers, and health consumers. A number of overarching issues related to clinical translational research in women's health took priority in setting the working group's agenda. Highlights of discussion of these issues are organized below under five major headings.

Innovative Research Study Designs To Enhance the Conduct of Clinical Studies and the Translation of Findings

In discussing the state of current clinical research, the working group highlighted several areas in which clinical study design could be improved to enhance both the conduct of the research as well as the translation of findings into the community. Participants discussed the importance of understanding the population of individuals who might directly benefit from a study. This can not only enhance recruitment of subjects into clinical studies, but also allow for straightforward dissemination and translation of findings into clinical practice. It was noted that new models for the conduct of research should include understudied populations such as the "older old" (defined as greater than 75 years of age); groups of women not normally studied (e.g., pregnant women and women in the military); underrepresented minorities (URMs); the lesbian, gay, bisexual, and transgender (LGBT) people; and underserved populations (e.g., remote and rural areas; inner city areas with poor transportation).

Questions related to different designs for clinical studies and the need to model "real- world" environments were raised. More real-world designs might translate better to actual clinical practice and adaptation to the community. Women, for example, report symptoms differently from men and their reported levels are interpreted differently by clinical investigators. Women may also use additional products to improve their well-being (i.e., holistic medicines) in addition to traditional medicines. The impact of these additional products may be independent, synergistic, or detrimental in the presence of traditional medicines.

Working group participants discussed the importance of conducting more lifespan and intergenerational studies, such as the Study of Women Across the Nation (SWAN)*. SWAN focused on menopause but, in general, longitudinal designs could be very informative if done across the lifespan (e.g., Study of Adolescents Across the Nation). Such studies can help to evaluate the many facets of an individual's lifestyle to understand better the onset of disease within various populations as well as the prevention of disease. These facets include diet, environmental factors, physical activity, and social environment, to name a few.

New study designs may require scientists to think beyond the "gold standard" of the traditional randomized, placebo-controlled clinical trial. As appropriate, longitudinal observational studies can be considered to capture more "real-life" conditions of study participants. Studies such as these may be readily translated into practice.

Lower Risk for Conducting Clinical Studies

Working group participants discussed possible ways for the NIH to foster conversations with a diverse group of scientists, such as basic, clinical, bioethics, translational, and community-based researchers, on how to conduct research studies in vulnerable populations such as pregnant women, "older old" individuals, or those with comorbidities. These should involve discussions of how to address these issues with research Institutional Review Boards (IRBs) and ethics committees. Additionally, it was noted that the NIH should work to strengthen the policies and guidelines that address inclusion, analysis, and reporting on women involved in clinical studies. Discussions of these policies with other federal agencies, such as the Food and Drug Administration, Health Resources and Services Administration, and Centers for Disease Control and Prevention as well as with other non-Federal agencies and professional societies, are particularly important to ensuring that women and underrepresented minorities can be included in of clinical research studies and trials when it is appropriate.

Clinical Studies/Trial Recruitment Strategies

Working group participants discussed current clinical study/trial recruitment practices and several strategies for recruiting women and girls into both non-sex–specific and sex-specific research studies as well as ways to have broader, more inclusive recruitment of participants for clinical trials. Trial locations should be accessible to more potential participants. This will involve providing transportation, conducting studies using a mobile facility, conducting studies in clinics or hospitals outside the investigator's primary facility, offering clinic visits at times outside the usual clinic days and hours, and providing childcare onsite. Understudied populations, such as individuals who live in rural areas, may have limited access to large hospitals

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** Study of Women Across the Nation (SWAN). More information is available online at http://www.nia.nih.gov/researchinformation/scientificresources/SWANdescription.htm.*

or universities where studies are generally held. Academic and community organizations as well as groups and networks should be encouraged to work together to increase participant engagement and recruitment. Several existing groups within most universities (e.g., women's groups, underrepresented groups) could be enlisted in an effort to inform the public of past and ongoing studies and encourage individuals to participate in studies.

Building Trust in Clinical Research

Trust is a crucial element in subject participation in clinical trials, especially among underrepresented minorities. Educational efforts are needed to inform women and URMs about the process of research studies. Many women are unaware that medical research traditionally has been conducted in men, primarily white men, and the differences between sexes and genders and among races may lead to use of drugs, treatment, procedures, and practices that may be inappropriate for other groups (women and URMs). Additionally, much of the population is uninformed about how Federal funding goes into medical research, and the safeguards that exist for clinical trial participation such as IRBs, Health Insurance Portability and Accountability Act rules, and other ethical and privacy guidelines. Enhancing community awareness of the benefits of increased participation of women and underrepresented minorities in clinical research, along with providing information on the safeguards in place to ensure subject safety, will help to increase recruitment of these groups.

New Strategies and Tools for Data Collection, Analysis, and Dissemination

The working group discussed a number of strategies that could be applied to the collection, analysis, and dissemination of data obtained through clinical studies and clinical trials. The discussion of these tools focused on ways to improve access to new knowledge obtained through clinical studies to the scientific community to augment efficacy and effectiveness of future trials, as well as to the populace in general to improve their understanding of women's health issues. For example, for studies that terminate due to unsuccessful recruitment or negative findings, information could be recorded detailing the conditions that may have contributed to lack of subject participation. This information would be valuable to future investigators who may encounter similar obstacles and who could benefit from understanding methods that have failed in the past. NIH programs and study sections could also benefit from this information. Negative findings offer valuable scientific information on the efficacy and safety of pharmaceuticals, therapies, and other interventions.

New database technologies could be used for storing medical research information accessible to other researchers and enhance data exchanges across institutions and agencies. Database registries of this type would offer a number of potential uses, such as enabling investigators to find more subjects with a specific disease type and providing information on study techniques that are successful so that investigators do not have to reinvent their methodologies from scratch.

The group also discussed the importance of analyzing sex and gender differences in research studies as well as retrospectively analyzing data from previous clinical trials where such analysis was neglected. The dissemination of these results is an important issue, and new and creative ways to translate findings to the provider and health consumer should be studied.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: To engage women and girls more fully in clinical studies, especially underrepresented communities, it is important to create the next generation of recruitment strategies and tools to assist researchers in reaching the maximum number of potential subjects. These include:

- Research on new methodological techniques and tools, including creative approaches to research designs that address the needs of the participants (e.g., alternatives to standard RCTs);
- Broader inclusion criteria that reflect the real-world population (e.g., diverse enrollment);
- Culturally based communication, social networking, and social media to foster connections; and
- Research on informatics approaches to expand use of registries/shared databases for recruitment strategies.

Recommendation 2: It is important to expand the value of NIH research and incorporate knowledge obtained from clinical studies into the community by moving beyond the "bench-to-bedside" research model to one that emphasizes the next step of translating evidence-based science to community stakeholders, including providers, participants, insurance companies, and users of research findings. Ways to accomplish this include the following:
Incorporate stakeholders in the development of the study design as well as the dissemination and translation of the findings.

- Provide training and incentives for community-based clinicians and other stakeholders to engage in research.
- Disseminate knowledge obtained from clinical studies into the community and incorporate knowledge into community practice.
- Develop and use new tools and technologies (e.g., tracking use of new practice guidelines through electronic medical record).
- Encourage greater use of common measures among researchers.
- Measure impact of dissemination and translation of study findings.

Recommendation 3: The NIH should maximize the value and impact of current and future studies. This will promote research connectedness and allow for further dissemination of research results to the community as well as to other researchers. Among ways to accomplish this are the following:

- Add substudies into larger studies, and encourage sharing of specimen collection.
- Learn from all "nonsuccessful" studies (e.g., futility studies and negative findings).

- Develop and maintain large database registries of research methodologies, data, and research findings, and make them accessible to a variety of academic institutions as well as other research agencies.
- Develop data repositories for sharing of data among researchers that can lead to future hypothesis generation and reanalysis.
- Fund studies that are "real-world studies" with broad inclusion criteria that engage hard-to-study populations (e.g., pregnant women, "older old") and understudied groups (e.g., racial/ethnic minorities, LGBT).

Recommendation 4: Investigators and clinical centers can be uniquely positioned to address several barriers to lowering the risk for conducting future studies on higher risk or more vulnerable populations, such as studies on pregnant women. Approaches to reducing barriers include the following:

- Build trust and research "connectedness" to the community.
- Test new designs in research to involve hard-to-reach populations in underserved areas (e.g., rural "teleresearch").
- Engage and train community-based health care providers to participate in clinical research.
- Build on the global health research community engagement model.

NEW TECHNOLOGIES/BIOENGINEERING/IMAGING

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Introduction

The development and application of new technologies has transformed the way diseases are diagnosed and treated in many fields. During the past decade, progress in basic science research, such as the development of *in vitro* tissue models and high-resolution imaging methods, has shown promise for a better outlook for understanding pathogenesis and treatment of numerous diseases prominent in women. In clinical medicine, advances in imaging and diagnostics have revolutionized disease diagnosis and management. Such benefits brought by existing technologies, unfortunately, have not reached women of all ages or social classes as intended. The working group discussed factors that prevent application of existing technologies and generation of new technologies for improvement of women's health. Particularly important are the existing technologies that may be underexploited due to a lack of sex- and gender-based standardization, which limits their research and clinical use. Moreover, as new technologies are developed, we must ensure that potential sex differences in their application or output are considered. Furthermore, women are interested in affordable and accessible technology; thus, thinking about these issues at all stages is important, particularly in regards to design and manufacturing.

Underexploited technologies are not applicable to all women because their development and standardization have been based primarily on studies conducted in male subjects and animals. The effect of sex on biological responses to drugs and disease treatment regimens is now clearer than ever. Many routinely performed medical technologies and procedures (e.g., cardiovascular disease imaging and joint replacements) were originally designed, tested, executed, and standardized using male models; this has become an issue demanding improvement due to increased awareness of physiological differences between the sexes.

In light of current fragmentary knowledge of disease prevention and treatment in women and insufficient exploitation of existing technologies in sex-based research, discussion of the working group focused on several emerging technologies with great potential to impact women's health. What ensued from the discussion was the identification of urgent and unique problems that present barriers to the improvement of women's health as well as knowledge gaps and resource needs. The issues were discussed taking into consideration the powerful influences of society and communities on women and on sex-based research, and, as a correlated outcome, on women's health. A synthesis of recommendations to address these issues followed. Among the recommendations was a call for change in the way that scientific research and clinical trials are carried out, and support for the dissemination of information about promising new technologies to improve women's health. The synthesis of discussion in the following section describes the relevant technologies with emphasis given to the development of sex- and gender-based diagnosis and treatment for diseases, and improvement of access to and the affordability of these technologies.

Summary of the Discussion

Shortcomings in sex-based scientific research and medical applications were identified and became recurring themes in the working group's discussion of new technologies as they impact women's health. Several ways to address the shortcomings were discussed, as follows:

1. Strongly promote interdisciplinary and cross-professional collaborations involving advanced technologies that aim to specifically address aspects of women's health and sex-based studies. Such collaborations gather expertise, knowledge, and findings from various fields, which is essential considering the multifaceted nature of current issues on women's health. Implementation of such collaborations should be encouraged and rewarded.

2. Research should be conducted in both male and female animal models and human subjects. Inherent physiological differences between the sexes are rarely considered in research and development except in the obvious case of the reproductive system. There was consensus within the working group that most tissues display sex-dependent differences, but existing references and simulations are derived from male models and are therefore improperly applied to the understanding of female physiology. It was agreed that sex-based differences should be necessary considerations in the initial design of new models and prototypes, and that technologies should be exploited without hesitation to study these inherent differences.

3. Disease diagnosis and treatment should be tailored to sex-specific needs and should evolve not only in design, but also in affordability. The newest, most powerful technologies often carry a high price tag and are therefore accessible only to institutions (and patients) with large budgets. Making an existing product or method affordable without sacrificing quality is a challenge in technological innovation. Currently, affordability of new technologies for those in need is typically not a prioritized consideration as early designs are refined and improved.

4. Design and implementation of longitudinal studies are necessary on two fronts. First, there is an increasing need for all-in-one systems that can sustain the extended culture of cells or tissues *in vitro* while simultaneously allowing the researcher to observe these samples with minimal interference. Many long-term studies are currently done in "snapshot" style, wherein static images of a sample at a given time are acquired and threaded together to create a biological story with narrative gaps. Second, studies spanning the lifetime of an animal model or a human subject are difficult logistically and financially, though data on aging are absolutely necessary in a time where life expectancies continue to increase. Finally, data collection over the long-term requires new innovations in informatics for data storage, handling, and processing.

5. Research teams, including those working in the development and application of advanced technologies, should anticipate translation of their results toward the improvement of health and the treatment of human diseases. This has been a particular concern in the academic community, where much of the scientific innovation occurs. Taxpayers largely support basic research via government agencies such as the NIH. Therefore, government-funded institutions have the responsibility to conduct research that is translatable and with the intent of benefiting the tax-paying citizens.

6. Accessibility to technology should be enhanced for all women to include access to educational materials and health registries. From veteran scientists in academia to members of health-disparities communities, there is a common misperception that

males and females are essentially biologically identical. The origin of this erroneous belief may be in the lack of public education regarding sex-based biological differences. Initiatives for increased awareness should be created and supported.

Recommendations

To reach out to women of all ages and social classes for education and research purposes, as well as to stress sex and gender-based differences in conducting research, the working group proposes two sets of recommendations. The first set of recommendations calls for immediate action and provides guidance to academic institutions and administrators, the health professions, clinicians, scientists, and the public. The second set of recommendations represents priorities in research or the development of new technologies.

Agenda for New Technologies

Recommendation 1: Advocate for a mandate to use male and female animals and human subjects in all appropriate research. Currently, there is only the requirement of the inclusion of women in NIH-funded studies. The working group recommends that this become an issue of national concern for both government and private funding agencies.

Recommendation 2: Establish the new field of *genderomics* and national genderomics centers. No currently defined field of research is intentionally sex based. The working group recommends that the ORWH and NIH create the field of genderomics and delineate funding specifically for studies to identify critical differences in normal and diseased cells and tissues between males and females. Creating this field will not only bring attention to the necessity of sex-based studies, but also expressly encourage them via funding mechanisms.

Recommendation 3: Develop a position statement on the application of new technologies for sex-appropriate research and clinical care. The working group recommends that the ORWH and NIH officially support the application of emerging technologies to sex-differences research studies and, as appropriate, to clinical care settings.

Recommendation 4: Support a national repository for all clinical registries. Perhaps one of the most difficult aspects of clinical trials and surveys is the recruitment of participants who meet a given set of criteria. The working group recommends the creation of a central repository of existing local clinical registries that is accessible to all researchers. We anticipate that this will improve the pace and quality of studies that rely on patient information and participation. Computational and data management issues can be centralized and take advantage of the rapidly expanding information technology opportunities.

Priorities in the Research and Development of New Technologies

Recommendation 5: Specificity. A lingering biological challenge has been the identification and effective exploitation of molecular markers that unequivocally set one cell type apart from another. The working group recommends that the next generation of technological innovations be exploited to define sex-specific characteristics at multiple levels, from atoms to entire populations. Such knowledge will facilitate the development of new technologies for targeting and delivery of drugs and probes in a sex-appropriate manner. Finally, existing

references and simulations in the laboratory and the clinic (e.g., phantoms) are largely derived from male models and generalized to both sexes. These should be updated to reflect the physiology of both sexes.

Recommendation 6: Efficiency and efficacy. Point-of-care diagnostic tools have been instrumental in expanding health care management opportunities out of academic centers and into underserved areas. The working group recommends that fast, reliable, inexpensive, operator-independent, and portable diagnostic methods continue to be developed. Additionally, many symptoms are common among multiple diseases, therefore requiring time and sometimes invasive procedures for a proper diagnosis, and perhaps even leading to misdiagnosis. Along with the identification of specific molecular markers, diagnostic tools should evolve to provide accurate differential diagnoses in an efficient and efficacious manner.

Recommendation 7: Affordability and accessibility of research tools. The next generation of engineering innovations should make low-cost adaptations of existing, high-cost technologies that capture comparable levels of resolution and quality. The working group recommends that affordability and accessibility of new technologies be required as part of the development opportunity.

Recommendation 8: Integration. Data analysis and interpretation are critical aspects of research, but this process can vary significantly depending on the operator and/or the platform. This is particularly true in the case of emerging technologies, where novel algorithms must be developed for operation and data collection. The working group recommends that such algorithms and methodologies be made to provide objective outcomes as early in development as possible. This way, data become easily transferable and uniformly interpretable among research groups as new technologies become widespread. This will also facilitate the creation of a national directory of databases and registries housing sex-specific information.

Recommendation 9: Longitudinality. In a time where life expectancies steadily increase, there is scant knowledge about the process of aging, sex differences in aging, and how human physiology is inherently different at age 80 versus 20. The working group recommends that new technologies be able to accommodate long-term studies, not only of cells and tissues in a culture dish, but also of humans as they grow and age. This includes noninvasive imaging methods, development of reliable molecular markers as imaging probes and as biological targets, and computational innovations for data storage, handling, and manipulation. This may also include advances in the point-of-care devices that can track factors over time. In addition, new prototypes should be sensitive to and accommodate age-related changes in physiology.

GENETICS AND EPIGENETICS

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Introduction

The session began with a discussion of the current state of research in genetics and epigenetics. We defined epigenetics as heritable traits not encoded in the genome, including histone methylation and acetylation, DNA methylation, and small RNAs. All participants emphasized the significance and challenges of the new technologies available to researchers, including genomewide association studies, the increased affordability of sequencing, and the emerging "-omics" fields, such as proteomics. The increasing availability of these technologies provides new opportunities to study women's health issues and explore sex-based differences in biology and disease. Discussion focused on the importance of promoting awareness of sex differences in research models, enhancing communication and collaboration among women's health researchers, and increasing the availability and reliability of data from current and future studies in women's health.

Summary of the Discussion

The following major issues and areas of concern emerged from discussion within the working group.

Accessibility of Current and Future Data, Both Published and Unpublished

Researchers typically collect clinical samples with a focused purpose, based on their specific research interests. However, these samples potentially could be used for multiple studies if the origin of the tissue and its manner of collection were adequately documented and made available to other investigators. As epigenetics is an emerging field, it would be extremely useful to mine the data from previous experiments and publications, and perhaps reuse samples for epigenetic analysis. For genetics studies as well, the necessity of large cohorts makes it very useful to be able to use samples and/or data from previously collected datasets. For researchers to mine existing datasets, they need the following:

- Extensive information about how the samples were collected and processed;
- As much information as possible about the subjects from which they were collected;
- Standard procedures for tissue collection;
- A consistent metric for assessing subjective phenotypes; and
- A thorough checklist of biographical criteria.

Standardization in these areas, as well as the establishment of a bioinformatics platform that is able to record and present these data in an accessible and comprehensive format, would maximize the usefulness and cost effectiveness of clinical studies, while still protecting the rights of the subjects.

Necessity to Adjust Current Institutional Review Board (IRB) Procedures

This step is needed to broaden the use of samples collected, particularly as new genetic and epigenetic analysis tools are developed. Again, the ability to reuse samples from current and ongoing clinical studies is extremely important for maximizing the usefulness of patient samples. One major challenge to a collaborative effort of this sort is the highly laboratory- and project-specific nature of current IRB applications. An "umbrella" application or master form could be useful in streamlining the approval process for common or standard experimental designs. Further information required by a university or necessitated by an atypical experimental method could be added as supplementary forms. Most importantly, the working group suggests that an add-on consent form should be included for clinical studies, allowing patients to consent to the use of their samples for future IRB-approved research, even if that study is not specifically one for which they were recruited or sampled. This would lead to the development of an extensive database of well-annotated patient samples that could be used to explore genetics and epigenetics questions in women's health, without the necessity of recruiting new cohorts of female subjects to explore each question.

Need for Development of a Global Approach to Women's Health

This global approach should include an "-omics" approach and longitudinal studies.

One important feature that distinguishes women's health issues from men's health issues is the wide range of hormonal changes that a woman experiences over her lifetime, including puberty, pregnancy, and menopause. In addition, the lifespan of women is typically longer than that of men, leading to additional health issues. The effect of these changing physiological conditions on disease progression, treatment effectiveness, and risk factors is not well reflected by current animal models or human studies.

In female animal models of disease, it is important to account for a range of ages and different stages of development. Within human studies, it is important to sample multiple age groups, accounting for pre- and postmenopausal subjects. To obtain the most complete overview, it would be useful to develop multiple profiles whenever possible for female test subjects, including:

- Genetic and epigenetic analyses;
- Expression data; and
- Proteomics, metabolomics, etc.

Inclusion of Women in Clinical Trials and Female Animals in Experimental Models

A significant deficit in the current experimental climate is the lack of emphasis on including female animals in trials. This is often because researchers are unwilling to deal with special considerations such as accounting for the reproductive hormonal cycling status in experimental animals. Other barriers include the high cost and technical difficulties of using female experimental animals, that could more accurately reflect human female physiology.

In human studies, sex is still too often a factor that is "corrected for;" instead of analyzing the results separately for male and female subjects, the results are pooled, eliminating potentially valuable information. For women's health to be studied adequately and accurately, resources need to be devoted to developing new and promoting existing female animal models of disease, and emphasizing the requirement for female subjects in human studies.

Need for Education of Health Care Providers and Collaboration Between Clinicians and Researchers

Because genetics and epigenetics are relatively new fields, there is a gap between what researchers are able to discover and what health care professionals are able to implement. A specific lack of education exists in the medical school curriculum, which should prepare doctors to comprehend, communicate, and apply genetic data in their patients' interests. Clinicians and researchers should communicate routinely about what genetic and epigenetic findings are important and relevant to health, and which patients can benefit most from this information. Interdisciplinary cooperation between genetics and epigenetics researchers and traditional women's health researchers is essential in capitalizing on these new technologies to benefit women.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, and scientists as to areas of investigation that merit greater research.

Recommendation 1: Catalog and harmonize genetic and epigenetic data in women and experimental models.

- Standardize data collection.
- Optimize/expand current medical databases.
- Develop phenotype databases for experimental animal models (medical record surrogate).

Recommendation 2: Promote and facilitate collaborations among interdisciplinary scientists studying women's health.

- Improve the mechanisms for facilitating data collection and sharing; develop expeditious IRB processes among collaborating institutions and maximize use of existing data collections for future genetic and epigenetic studies while protecting subjects' rights.
- Broaden access to databases, including Government databases (e.g., Veterans Administration) and private insurance companies (e.g., Kaiser Permanente).
- Expand tissue and biobanks; improve and standardize annotations.

Recommendation 3: Develop new technologies to promote and facilitate analysis of "multiomic" datasets in women's health and sex-based biology.

- Determine which genetic and epigenetic information is critical.
- Develop inexpensive and rapid assays for genetic and epigenetic analysis.

- Develop co-analysis tools to study interactions with peptidomics, proteomics, metabolomics, etc.

Recommendation 4: Develop experimental models of disease.

- Exploit current and develop new animal models of disease to study the biology of sex differences.
- Improve models for studying sex chromosome effects and their interactions throughout the lifespan. These include models of the effects of X-inactivation, escape from X-inactivation, and mosaicism.
- Improve models for studying disorders of pregnancy (e.g., epilepsy).
- Develop mechanisms to increase basic comparative research between male and female animals.
- Improve education concerning the biology of sex differences, including Sex chromosome effects and developmental and activational effects of gonadal hormones.
- Develop methods to train investigators in how to conduct sex-based biology.

Recommendation 5: Promote new areas of research on genetics and epigenetics of women's health.

- Study pharmacogenetics in women across the lifespan and at transition points.
- Conduct research on the interactions of small RNAs on phenotypes in women across the lifespan and at transition points.
- Improve recruitment of women subjects.
- Explore ways to increase the number and percentage of women entering and thriving in the fields of genetics and epigenetics

SEX HORMONES AND DISEASE

Cochairs:

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Introduction

Sex hormones have broad effects on disease processes. They are major determinants of differences in the sex-specific prevalence of a number of disorders. The hormonal milieu differs in women across the lifespan and during pregnancy. Interested participants in the Working Group on Sex Hormones and Disease defined research priorities in basic studies and in translational and clinical studies of sex hormone actions in conditions such as cardiovascular disease, diabetes, and autoimmune disorders. Furthermore, innovative research possibilities with existing clinical datasets or new populations were suggested.

Summary of the Discussion

The discussion of the Working Group on Sex Hormones and Disease centered on identifying the gaps in research that have impeded advances in the diagnosis and treatment of major diseases affected by sex hormones. These diseases include cardiovascular disease, autoimmune disorders, type 2 diabetes, Alzheimer's disease, metabolic bone disease, sleep disorders, obesity, and cancer. The working group was composed of investigators and clinicians who discussed observations and key issues in their areas of expertise. This discussion was informed by an initial update on the state of current knowledge of specific sex-hormone-dependent disease states, which was provided by cochair Dr. Andrea Dunaif. In addition, the working group focused on identifying gender disparities in the diagnosis, physiology, and pathophysiology of disorders that were identified as requiring further research. The following major concepts emerged from the discussion:

1. In the field of sex hormones disease research, current gaps in knowledge need to be addressed. In addition, several emerging areas were discussed that have the potential to advance the frontiers of existing knowledge, improve diagnostic capabilities, and drive development of novel therapies.

2. New technologies need to be developed to advance the field of sex hormone research. These technologies would include metabolomics, proteomics, and improved assays that would allow further refinement and understanding of the role of sex hormones in normal and abnormal development.

3. Basic, clinical, and translational research ideally should be conducted with the purpose of resulting in improvements in direct patient care while at the same time considering the social context of the individual. The latter would include education, outreach/public involvement, and regulation of consumer safety through accessibility of information. A partnership among basic researchers, clinical scientists, and physicians needs to be fostered to promote an integrated "team science" approach as opposed to working in parallel.

4. With regard to specific disease categories involving sex hormones, many questions remain unanswered, including the following:

- Cardiovascular disease. Is administration of sex-steroid hormone therapy beneficial to the vasculature?
- Autoimmune disorders. Why are the majority of autoimmune disorders more common in women? How do sex-steroid hormones affect the progression of disease? Are gender differences present in the pathogenesis of diseases?
- Diabetes. Why is the cardiovascular disease protection commonly present in premenopausal women lost when diabetes is present? Could estrogen receptor modulators prevent or modulate the natural history of diabetes? Are lower survival rates after myocardial infarction in women with diabetes related to sex hormones?
- Metabolic bone disease. Are there sex differences in the action of hormones on bone?
- Obesity. How do sex hormones regulate food intake in humans? What are the mechanisms involved in different responses to hormones of fat cells located in different depots? How do sex hormones influence the sympathetic nervous system?
- Sleep disorders. Are the sex differences in the pathology of sleep disorders a consequence of differences in sex-steroid concentrations?
- Alzheimer's disease. Would early initiation of sex-steroid hormone therapy impact cognitive function?
- Musculoskeletal system. How is estrogen involved in proprioreception? What role do endogenous androgens play in muscle mass in women?
- Cancer. What role do sex hormones play in the pathology of hormone-dependent cancer and other forms of cancer?

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Use a systems biology and integrative physiology approach to (a) perform a comprehensive inventory of sex-steroid-dependent disease states; (b) create databases of normative sex-steroid concentrations across the lifespan; and (c) identify model pathways and biological networks relevant to sex-steroid-dependent disease processes. The paucity of centralized resources containing information on sex differences has had a negative impact on the advancement of sex hormone disease research. To address this deficiency, it is proposed to take a systems biology approach to creating and disseminating information:

- Catalog and create databases of structure, efficacy, and tissue specificity of endogenous sex steroids and pharmacological compounds and tissue expression patterns of receptors, coactivators, corepressors, and steroid metabolizers, with consideration of systems/connectivity.

- Model pathways and identify biological networks by identifying molecules shared between networks, integrating networks, including direct and indirect effects of sex steroids, and implementing computer modeling.

Recommendation 2: Focus on the impact of critical periods of development on health outcomes. It is becoming more apparent that physiologic/environmental influences at certain times during the lifespan have a significant impact on future health outcomes and disease. Therefore, it is of vital importance to decipher the role of sex hormones and other factors during critical windows of development and to understand how they affect future health outcomes. Important areas of potential for advancing these aims include the following:

- Research into the role of sex hormones during fetal programming, the perinatal period, "minipuberty," puberty, menarche, and menopause
- Studies of the epigenetic effects of sex steroids and environmental endocrine disruptors
- A focus on prevention and development of novel interventions to reduce disease burden
- The creation of new datasets and the use of existing datasets from clinical trials and registries to maximize the impact of this research

Recommendation 3: Investigate the chronobiological basis of sex-based disease. The fact that sleep architecture is different between men and women has been established.[1] Investigating the relationship between sex hormones and sleep architecture is important. Areas of consideration for future research should include the following:

- Causal relationships between sex steroids and circadian rhythms, and sleep/wake cycle differences
- Intracellular "clock" genes and their regulation

Recommendation 4: Examine the interaction between genetic sex and hormonal sex. Aside from the well-characterized differences in sex-steroid hormone levels between men and women, there are also inherent genetic differences. The following include topics for prospective research:

- The role of sex steroids in modulating genotype/phenotype interactions
- Differential effects of selective hormone receptor modulators (e.g., selective estrogen receptor modulators)

Recommendation 5: Focus on local tissue metabolism beyond aromatase. Endocrine secretion of sex hormones is not the sole factor in determining cellular response. Local biosynthesis, secretion, and metabolism of hormones and their precursors must also be considered, and this continues to be an understudied area. To bridge the gaps in knowledge in this field, future research should include research on the following:

- The influence of race and ethnicity on sex-steroid hormone biosynthesis, secretion, and metabolism as the basis for different disease prevalence rates and phenotypes
- The prereceptor effects of prohormones and pharmaceuticals
- The importance of nonclassical signaling pathways in the genesis of sex-steroid–based disease

Recommendation 6: Develop technological and pharmacological therapies tailored to sex hormone levels. The discovery and implementation of novel technologies could drive a more individualized approach to medicine. In addition, the development of new technologies could improve diagnostic capabilities and the ability to implement evidence-based medicine by overcoming current limitations on data acquisition. Focal points include the following:

- Develop new diagnostic and research tools to improve sensitivity and detection limits of hormone assays; improve the efficacy, delivery methods, and cost effectiveness of current sex hormone therapies; and facilitate implementation of nanoscale and other emerging technologies.
- Translate sex hormone research and pharmacogenomic studies into personalized patient care.

References

1. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. (2003). *National Sleep Disorders Plan* (NIH Publication No. 03–5209). Retrieved from http://www.nhlbi.nih.gov/health/prof/sleep/res_plan/index.html

NEUROSCIENCE WORKING GROUP

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Introduction

Sex differences in brain development, structure, and function are well recognized. The best characterized of these are related to sexually differentiated reproductive behavior and neurohormone secretions. It is increasingly clear, however, that neuronal development and function are sexually differentiated in many other ways, such as stress responsiveness, body weight regulation, nocioception, mood and affect, and aspects of social behaviors and cognition. Basic science studies of these processes, however, remain largely focused on male animal subjects, and do not address adequately the specific neurobiological principles that govern the processes in females. In addition to sex differences in normal physiological and behavioral processes, there are differences in prevalence of and/or other aspects of many human neural disorders.

Differences in prevalence are striking for some conditions (e.g., depression and eating disorders are more prevalent in women than men). For other conditions, such as epilepsy, drug abuse, and sleep disturbances, males and females have distinctive features. Basic studies show the female brain receives sex-specific endocrine signals from the ovaries that are quantitatively and qualitatively different from those conveyed by testicular hormones; sex differences arise in both the development and operations of a variety of neuronal circuitries. The mechanisms by which estrogens and progestins act in the brain and the peripheral nervous system are also thought to be key to understanding other female-biased pathophysiological conditions in humans such as multiple sclerosis and other neuroimmunological diseases. Conversely, the potential protective effects of ovarian hormones in the female brain are increasingly recognized, including the protective actions of estrogens in neurological injury and disease.

Summary of the Discussion

Participants in the Neuroscience Working Group were charged with helping to define priorities for basic science research on sexually differentiated brain function that could advance progress in understanding sex/gender differences in human psychiatric, neurological, neuroendocrine, neuroimmunological, and injury- and trauma-related neural disorders. A number of overarching general issues were raised by group participants. First, they noted that despite the substantial sex/gender differences in the prevalence, presentation, and response to treatment of a variety of diseases and disorders related to the brain, basic neuroscience research seldom focuses on sex differences and often ignores their relevance.† Second, they noted that lack of awareness of the pervasiveness of sex differences in the brain exists not only in the field of basic and clinical neuroscience research, but it also extends to the general public. The tendency of popular culture to sensationalize sex differences obscures the importance of their implications for understanding brain function and disease. When the public views the existence of sex differences in the brain as indicating inequality of the sexes and therefore as "politically incorrect," researchers are often cautious about pursuing sex differences research and hence may minimize the consideration of the effects of sex differences on neurobehavioral health and disease. Third, working group participants noted that, even when sex differences of the brain are considered, a remaining impediment is the gap between basic research and clinical relevance. The nervous system is difficult to study experimentally, often requiring the use of invasive procedures. Although in-depth studies have been done in animal models, whether such basic information generalizes to humans remains unknown. Although neuroscience has shifted toward understanding how the interplay among genes, hormones, and experience influences behavior, animal models usually fail to incorporate sex as a variable, and it is more typical for researchers to ignore sex or dismiss it as too complicated to incorporate into experimental designs. Rather than continue to ignore sex differences, participants agreed that the culture of neuroscience research must change to acknowledge that sex differences in nervous system structure and function are normal and can be important. To better understand sex differences in the brain, both a shift in paradigm and a shift in methodology are needed.

Basic Research Issues

A major focus of the discussion was why sex differences are so often ignored in basic neuroscience research. Given the gender disparities that exist for human neurological and other brain

† *The 2003 Institute of Medicine report* Exploring the Biological Contributions to Human Health: Does Sex Matter*? notes the importance of distinguishing between sex and gender in order to sharpen research questions. Sex differences refer to biological based (e.g., genes, chromosomes, reproductive systems) differences between males and females and gender differences to a human being's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation..*

diseases, the avoidance of studying female phenotypes in animal models must be addressed. The group agreed that responsibility for this disparity lies with both the basic neuroscientist investigator and the study sections, who may provide discouraging or incomplete feedback. Factors relating to the investigator include the following:

- Researchers are not aware of the pervasiveness of sex differences, nor of the proper subtleties inherent in studying them.
- Investigators believe they must control all experimental factors, and accounting for variables such as cyclical differences in hormones creates an impossibly large experiment.
- Experimental standards and phenotypes have been defined using male animals, making it difficult to evaluate behavior that may differ in females depending on the cycle.
- There is a lack of emphasis on sex differences in the brain in graduate and medical school curriculums. When such differences are discussed, they are a short section at the end of the book rather than integrated into the rest of the curriculum.

The lack of recognition of the importance of sex differences in brain function and disease within the broader scientific community also influences grant reviews and funding decisions. The group agreed that an important issue to address was the way in which studies proposing to investigate sex differences are evaluated. Some issues include the following:

- When researchers interested in studying sex differences propose to include female animals, they are often criticized in study sections for not controlling for factors such as hormone fluctuation.
- Many members of study sections do not have the expertise on sex differences or on the proper ways to evaluate variables such as estrous or menstrual cycling.
- While clinical research now requires the inclusion of female subjects, a similar requirement has not been implemented in basic research. The working group believed that rather than mandating the inclusion of female animals in studies, the more important issue that must be addressed is changing the awareness of sex differences.

Translational Research Issues

Another major problem identified as part of the discussion was the lack of cross-talk between those doing basic neuroscience research and practicing clinicians working with human patients. This lack of bidirectionality has resulted in an uncertainty over the relevance of current basic neuroscience research to human health and brain disease, particularly with respect to sex differences. In particular, there was extensive discussion regarding the animal models currently being used in basic neuroscience research. Several issues identified include the following:

- There is a lack of knowledge regarding whether the animal models used in the lab accurately reflect what is happening in the human brain and the resultant clinical outcomes. Thus, it has been difficult to translate findings on sex differences from rodent models to make assumptions about human neurophysiology, and there is a great need to validate the animal models that are being used to study sex differences in brain function.
- There is a lack of understanding regarding which animal models are the best to use for the condition and/or disease state being studied. Often researchers use animal model systems that do not necessarily reflect the true physiological state being examined (e.g.,

using ovariectomized young female rats to study menopause), and there is a need to develop better models for behavioral and disease research.

- A major obstacle is the current inability to move beyond identifying correlations between structure and function in the brain to determining causes and effects; one example is determining the specific effect of signaling through a steroid receptor within a certain population of cells at a particular point in time on eventual disease outcome. This is partly because of the inherent complexity of the nervous system and partly because of the imperfect nature of the animal models of disease.
- Interpreting and drawing definitive conclusions is difficult from studies using currently available genetic tools to manipulate animal subjects (e.g., knock-out and knock-in mice) due to a lack of cell specificity and direct targeting approaches.
- There is a lack of understanding of fundamental questions such as the differential distribution between the sexes of steroid receptors within the human brain. There is also little knowledge as to whether the current information derived from rodent and primate models can be extrapolated to sex differences in human neurophysiology.

Need for a New Research Paradigm

A new paradigm is needed for basic and translational/clinical neuroscience studies of sex differences in brain and behavior. Over the years, the basic experimental paradigm in neuroscience has shifted from studying the effects of genes alone on the brain and/or behavior disorder, to studying the effects of both genes and hormones on the brain and/or behavior disorder. However, the effects of an individual's experiences can also influence both gene expression and hormone levels, and vice versa. Thus, to fully understand sexually differentiated brain function and brain disorders, the following effects of experience, in addition to genes and hormones, all acting throughout the course of an individual's lifespan, need to be integrated and considered:

- Genes that are differentially expressed or modified in females and in males need to be identified.
- The fact that males and females have different life experiences and exist in different social environments needs to be recognized, and feedback generated from these differences may alter gene expression or brain circuitry to ultimately affect their predisposition to certain disease states. For example, early onset of puberty results in different experiences for girls and boys, often being perceived as a negative experience for girls, but a positive experience for boys.
- Environment includes learning, experience, and psychosocial variables, which are all determinants of health and disease states in humans. Current research tries to control for these variables, in addition to controlling for sex differences that influence hormones and their effects on learning and experience, instead of modeling them.
- There is a lack of integration of dynamic events such as brain development, socialization, and brain plasticity that occur throughout the lifespan of an organism, and the ways in which they lead to the downstream expression of genes, which ultimately influence susceptibility to disease.

Recommendations

The following research recommendations may help to provide guidance to research and health administrators, clinicians, and scientists as to areas of investigation that merit greater research.

Recommendation 1: Promote the recognition and understanding among researchers of sex differences in brain function and brain disorders.

- Integrate the study of sex differences into neuroscience graduate and medical school training curriculums.
- Develop and disseminate didactic tools through professional organizations (e.g., Society for Neuroscience, Organization for the Study of Sex Differences).
- Sharpen and clarify sex/gender definitions as a heuristic/means for focusing research questions that seek to understand differences between male and female subjects.

Recommendation 2: Convene a panel of experts to make recommendations to NIH Peer Review administration on the inclusion of female animal subjects and/or the focus on sexually differentiated brain function and disease in basic neuroscience research.

- Ensure that study sections understand sex differences research.
- Ensure that the peer-review-process-intended plan for analysis by sex is honored in the final research design and tabulation of the analysis.

Recommendation 3: Develop new animal research paradigms to study the epigenetic influences impacting development of neurological and psychiatric disorders. What determines sex-specific or sex-biased brain disease vulnerability, course, and/or response to therapeutics?

- Develop experimental paradigms that model sex-specific or sex-biased experiential, hormonal, and psychosocial effects on gene expression, and intra- and intercellular signaling properties in the brain.
- Develop and use high-throughput epigenomic approaches to characterize the large-scale epigenetic alterations associated with experience and related to sexually differentiated brain function and disease.

Recommendation 4: Develop new molecular genetic approaches in animal models to study the impact of developmental stage, experience, hormones, and aging on sex-steroid hormone signaling *in vivo*, as well as new generations of transgenic and gene targeting approaches.

Recommendation 5: Develop and support new approaches to define similarities and differences in sexually differentiated brain function and disease in humans and animal models; for example, through the use of comparative imaging (i.e., functional magnetic resonance imaging, or fMRI) of sexually differentiated brain function in order to both validate current animal models and to establish systems that are better models for specific conditions and/or disease states.

Recommendation 6: Develop new methodologies in experimental animals for identification, targeted imaging of, and application of pharmacological agents to sexually differentiated cell populations in the brain.

WOMEN IN SCIENCE CAREERS

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Introduction

The goal of the Women in Science Careers working group was to generate innovative approaches for the Office of Research on Women's Health to take that would enhance the careers of women in basic, clinical, and other biomedical sciences. Working group participants were intimately familiar with the challenges faced by female clinicians and researchers at all stages of career development. They were a diverse group in various stages of their career, including graduate students, postdoctoral fellows, program directors, former presidents of national professional organizations, deans, and educators. This varied background helped focus discussion on not only retention of women in science careers, but also reentry of women into senior positions in the workforce, as well as what factors initially attract females to scientific professions. Given the charge of making short-term, achievable recommendations, the group discussed how several existing NIH career development mechanisms (e.g., Building Interdisciplinary Research Careers in Women's Health and other K awards) could be useful for supporting effective mentoring or reentry of female scientists.

The overarching theme identified by the group was that the biomedical enterprise has yet to address the paradox that, although significant economic, demographic, and social changes have occurred over the past several decades, there have not been parallel, significant adjustments made to the career paths and the workplace that optimize the ability of trainees to contribute to scientific excellence. Although these societal changes affect the entire workforce, given the known disparities between genders and among majority and underrepresented groups, the ORWH must continue to be an advocate and supporter of women and women's health research.

Summary of the Discussion

By asking the working group participants to explain why they were attending this particular session and what they hoped to achieve, the following common concerns about careers for women in science were identified:

- Women often seem more likely than men to choose or be relegated to alternative or nontenure-track positions.
- Talent is often not identified and therefore not nurtured.
- Women rarely advance to leadership positions.
- Focus needs to remain on attrition rates of women in science careers and productive interventions.
- Work-life balance and gender role collisions are of continuing concern, particularly regarding the absence of family-friendly environments at academic institutions (lack of lactation facilities, brief or unpaid maternity leave, overcrowded or inadequate child care availability, etc.).
- Women's health research is stigmatized as of lesser value or lower status than other areas of research.
- There is a perception of gender-based pay inequity, possibly due to unconscious gender bias in hiring or choice of research fields.
- There is greater potential for backlash against women leaders in the sciences.
- There is a prominent role of female mentorship, yet a lack of recognition for mentoring.
- Recognition of science careers outside of medicine (nursing, pharmacy, dentistry, etc.) is needed.

The cochairs posed four questions to identify new strategies and to identify where existing programs for career development could be extended or strengthened in the next decade:

1. How can the return on investment be optimized by identifying and developing all research talent?
2. How can full career development be supported through alternative pathways and time frames?
3. How can more women be advanced to top leadership and receive adequate support?
4. How can available opportunities be more effectively publicized?

The group noted that women now constitute more than 50 percent of college-aged students. To continue to attract the next generation, scientific curiosity needs to be identified and encouraged at a young age and developed throughout a woman's undergraduate career. Substantial resources are invested in training women scientists. The group discussed ways to optimize return on that investment by focusing on women in graduate school and beyond. Clearly the support of mentors is critical not only for transition stages in a scientist's career, but also for retention of women in academic careers and overall career development. The group was concerned that contributing time to mentoring could actually detract from associate or assistant professors' ability to pursue research, further hindering their advancement into a leadership role in the future. Institutions must recognize the value of these activities and factor them into tenure and promotion decisions. Training was also proposed to help mentors use their time more effectively. Participants referenced successful mentor training programs at Vanderbilt University; University of California, San Francisco; and Baylor University.

The next issue addressed was facilitating transitions of women in science careers, with an emphasis on understanding that publicizing alternative pathways and time frames may be effective in retaining and advancing women and preventing their dropping out. Implementing solutions to resolve the conflict between personal and professional goals is critical for supporting women who have taken time off from research or clinical practice for family responsibilities. The group identified two subsets of women who pursued alternative timeframes and/or pathways after having children: those who left early in their career and those who left senior positions. Several options were explored to provide ongoing career support for these women. The first is allowing women to "keep a thread" by maintaining a relationship with their laboratory or institution while on leave. This would aid in reentry because knowledge of current techniques and areas of study would remain up to date. In addition, extending eligibility of current funding options and providing support for mentors of late-career-stage women reentering the workforce would also be beneficial. Finally, encouraging institutions to foster a family-friendly environment for male and female staff is critical for retaining excellence in science. The group was aware that the NIH cannot mandate this, but suggested that it could incorporate questions into grant applications requesting that the institution describe its family-friendly policies.

Keeping women in leadership roles and providing support to them is also critical for maintaining scientific excellence. The group recommended development of programming to fund and train senior women in leadership roles in conjunction with existing programs such as those of the Executive Leadership in Academic Medicine and the Association of American Medical Colleges. The importance of institutional or systems change regarding gender equity has been a recurrent theme in the regional ORWH workshops. It was suggested that the ORWH consider investing in organizational knowledge diffusion as a strategy to build on the research findings that will emanate from the 14 recently awarded (2009) NIH research grants focusing on factors that influence the careers of women in biomedical and behavioral science and engineering.

Finally, the most easily remedied problem identified was the lack of publicity for funding opportunities, training, mentoring programs, and assistance with development of grant applications that have been pioneered by the ORWH. The group discussed ways to make information more accessible to women and women's health researchers, allowing more scientists to take advantage of these opportunities.

Recommendations

The Women in Science Careers working group sees a sustained role for the NIH in supporting and advancing women and women's health research agendas. The four recommendations provided below recognize the intrinsic value of existing NIH programs and suggest enhancements that promote their use in the future. These recommendations were developed to provide guidance to academic institutions and administrators, health professions, clinicians, and scientists as to areas of investigation that merit greater research.

Recommendation 1: Aid in developing research talent and increasing return on investment:

- Explicitly encourage awareness of unconscious bias in decisionmaking ("bias literacy") that may impact hiring, promotion, and attainment of leadership roles.
- Include financial support for mentors and Principal Investigators on training grants and career development awards, as was the case with Roadmap K12, and include a part in the application for a Mentor Development Plan.

- Use existing mechanisms (e.g., K24 or K07) to support midcareer investigators both to encourage them to be mentors and to potentially develop curriculums relevant to women's career advancement (e.g., mentor training).
- Invest in Organizational Knowledge Diffusion to capitalize on existing and forthcoming research on women's biomedical career development.
- Provide funds in training and career development grants for program evaluation so that the most effective techniques could be publicized for others to adopt.

Recommendation 2: Facilitate reentry of women into the scientific workforce:

- Expand the target group of K grants to support mentored reentry of senior independent researchers and Principal Investigators.
- Allow more flexibility of time distribution for research and nonresearch effort on K awards.
- As part of the description of the environment in a proposal for training and career development awards, ask for information about institutional family-friendly policies. This could be viewed as "Organizational Knowledge Diffusion" and is similar in some ways to the National Science Foundation-funded Institutional Transformation awards. However, the main difference is in the fact that the award is not given to the institution explicitly for transformation, but to encourage implementation of family-friendly programs and to provide information to trainees about these policies.
- Explore a "Keep a Thread" funding mechanism to allow part-time faculty to remain involved in their field of science or medicine to facilitate future reentry.

Recommendation 3: Help women attain leadership positions and support those in leadership roles:

- Explore providing funds for leadership training along with research training and/or career development (i.e., pre- or postdoctoral trainees) on R01 awards.
- Cosponsor leadership training programs with professional societies.
- Create a toolkit for leadership workshops.

Recommendation 4: Publicize opportunities for funding and support:

- Develop a central Career Advice platform that will provide the contact information of knowledge-rich people (e.g., an NIH Help Line) to assist with grant development and applications.
- Develop a user-friendly Web site that consolidates information on funding and career development available at the NIH for supporting women from all backgrounds (including underrepresented minorities, individuals with disabilities, and individuals from disadvantaged backgrounds). Update this site regularly.
- Highlight potential for partnerships between research-intensive and other institutions (e.g., nonresearch-intensive, teaching-focused, and minority-serving institutions).

A Vision for 2020 for Women's Health Research: Moving Into the Future with New Dimensions and Strategies
A Public Hearing and Scientific Workshop
Emory University School of Medicine
Atlanta, Georgia
February 16–17, 2010

DAY 1—SCIENTIFIC WORKSHOPS AND PUBLIC HEARING

Location: James B. Williams Medical Education Building

8:00–8:20 a.m.

Welcome and Opening Remarks

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, Director, Office of Research on Women's Health (ORWH), National Institutes of Health (NIH)

Nanette K. Wenger, M.D.
Conference Chair, Professor of Medicine (Cardiology), Emory University School of Medicine, Chief of Cardiology, Grady Memorial Hospital

Video Welcome
The Honorable Lisa Murkowski
U.S. Senator, Alaska

8:20–8:30 a.m.

Welcoming Remarks

The Honorable Kasim Reed
Mayor of Atlanta (Represented by Candace Byrd, Chief of Staff)

8:30–8:40 a.m.

Welcoming Address: The Role of the Medical School in Advancing Women's Cardiovascular Health Research

Thomas J. Lawley, M.D.
Dean, Emory University School of Medicine

8:40–9:45 a.m.

OPENING PANEL

Moderator: Jackson T. Wright, Jr., M.D., Ph.D.
Professor of Medicine, Nephrology & Hypertension/Medicine, Case Western Reserve University

Basic Science Vistas in Women's Cardiovascular Health Research

W. Robert Taylor, M.D., Ph.D.
Director, Division of Cardiology and Professor of Medicine and Bioengineering, Emory University School of Medicine

Pregnancy and Cardiovascular Health Research

Sarah Berga, M.D.
James Robert McCord Professor & Chairman, Reproductive Endocrinology & Infertility, Emory University School of Medicine

The Health of Latino Women: Perspectives from the Hispanic Community Health Study—Study of Latinos

Larissa Avilés-Santa, M.D., M.P.H.
Medical Officer, Epidemiology Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute (NHLBI)

Ethical Considerations in Advancing Women's Cardiovascular Health Research

Paul Root Wolpe, Ph.D.
Asa Griggs Candler Professor of Bioethics; Raymond F. Schinazi, Distinguished Research Chair in Jewish Bioethics; Professor, Departments of Medicine, Pediatrics, and Sociology; Director, Center for Ethics, Emory University

9:45–10:00 a.m. — **Audience Response**

10:00–10:15 a.m. — **BREAK**

10:15–10:30 a.m. — **Pregnancy History Predicts Cardiovascular Disease in Women: What More Do We Need To Know?**

Janet Rich-Edwards, Sc.D., M.P.H.
Director of Developmental Epidemiology, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

10:30–10:45 a.m. — **Welcoming Remarks**

James W. Wagner, Ph.D.
President, Emory University

10:45–11:00 a.m.	**NHLBI Perspective** **Patrice Desvigne-Nickens, M.D.** *Medical Officer, Heart Failure and Arrhythmias Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute*
11:00–11:30 a.m.	**Keynote Address: Women in Biomedical Careers—Implications for Advancing Women's Cardiovascular Health Research** **Kathy Griendling, Ph.D.** *Professor of Medicine, Vice Chair for Faculty Development, Emory University*
11:30–12:45 p.m.	**PUBLIC HEARING** **Nanette K. Wenger, M.D.** **Receiving Public Testimony: Members of the ORWH Advisory Committee and Host Scientists**
12:45–1:00 p.m.	**Working Group Charge** **Vivian W. Pinn, M.D.**
1:00–1:15 p.m.	**BREAK**
1:15–5:00 p.m.	**Lunch and Concurrent Working Groups** • **Pregnancy and Cardiovascular Disease Research and Ethical Considerations** • **Cardiovascular Disease in Elderly and Frail Elderly Women—Optimal Management and Research** • **Microvascular Disease, Biomechanics, and Application of New Technologies to Cardiovascular Research** • **Stem Cells, Progenitor Cells, and the Vista of Cardiovascular Regenerative Medicine** • **Unmet Needs in Diagnostic Testing for Women with Cardiovascular Disease** • **Issues of Cardiovascular Prevention Across the Lifespan with an Emphasis on Gender and Underserved Populations** • **Women's Careers in the Biomedical Sciences**
5:00–6:30 p.m.	**CONFERENCE RECEPTION**

DAY 2—KEYNOTE ADDRESSES AND WORKING GROUP PRESENTATIONS

Location: James B. Williams Medical Education Building

8:30–8:40 a.m.

Welcome and Opening Remarks

Janine Austin Clayton, M.D.
Deputy Director, Office of Research on Women's Health

8:40–8:45 a.m.

Perspective on Women's Cardiovascular Disease

Elizabeth Barrett-Connor, M.D.
Distinguished Professor and Chief, Division of Epidemiology, University of California, San Diego

8:45–8:50 a.m.

Introduction to Keynote Speakers

Nanette K. Wenger, M.D.

8:50–9:15 a.m.

Keynote: A View of the Legislative Role, Local and National, in Advancing Women's Cardiovascular Research

The Honorable John Lewis
Congressman, 5th District, Georgia

9:15–9:45 a.m.

Keynote: Role of Public/Private Partnerships in Addressing Indigent Care: Implications for Women's Cardiovascular Health Research

Michael A. Young, M.H.A., FACHE
President and Chief Executive Officer, Grady Memorial Hospital

9:45–11:15 a.m.

Concurrent Working Groups: Finalization of Recommendations

11:15 a.m.–12:45 p.m.

Working Group Presentations

Moderator: Nanette K. Wenger, M.D.

12:45–1:00 p.m.

Closing Remarks

Vivian W. Pinn, M.D.

Emory University School of Medicine
Atlanta, Georgia
February 16–17, 2010

WORKING GROUP COCHAIRS

PREGNANCY AND CARDIOVASCULAR DISEASE RESEARCH AND ETHICAL CONSIDERATIONS

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National Institutes of Health
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Robert N. Taylor, M.D., Ph.D.
Professor and Vice Chair for Research
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CARDIOVASCULAR DISEASE IN ELDERLY AND FRAIL ELDERLY WOMEN: OPTIMAL MANAGEMENT AND RESEARCH

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MICROVASCULAR DISEASE, BIOMECHANICS, AND APPLICATION OF NEW TECHNOLOGIES TO CARDIOVASCULAR RESEARCH

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STEM CELLS, PROGENITOR CELLS, AND THE VISTA OF CARDIOVASCULAR REGENERATIVE MEDICINE

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UNMET NEEDS IN DIAGNOSTIC TESTING FOR WOMEN WITH CARDIOVASCULAR DISEASE

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ISSUES OF CARDIOVASCULAR PREVENTION ACROSS THE LIFESPAN WITH AN EMPHASIS ON GENDER AND UNDERSERVED POPULATIONS

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WOMEN'S CAREERS IN THE BIOMEDICAL SCIENCES

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Judith G. Regensteiner, Ph.D.
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University of Colorado-Denver School of Medicine
Aurora, Colorado

INTRODUCTION

This report covers the fifth strategic planning meeting, held February 16–17, 2010 at the Emory University School of Medicine. The topic of the meeting was cardiovascular disease (CVD), the leading cause of mortality among women in the United States. The format of this meeting, the only one of the five regional meetings to have a disease-specific focus, included plenary presentations, public testimony, and seven breakout sessions of the scientific working and discussion groups. The breakout groups were charged with developing recommendations for pregnancy and CVD research; CVD research focused on the elderly; applying new technologies to CVD; cardiovascular regenerative medicine; diagnostic testing for women; CVD prevention across the lifespan for women and underserved populations; and women's careers in the biomedical sciences. The reports from the scientific working groups follow a brief summary of highlights of the plenary presentations.

SUMMARIES OF PLENARY PRESENTATIONS

The meeting opened with welcomes to participants. **Vivian W. Pinn, M.D.**, director of the Office of Research on Women's Health, noted that the establishment of a women's health office at the National Institutes of Health in 1990 was motivated in large part by public concern over the exclusion of women from CVD clinical trials. Since the establishment of ORWH, mortality in women from CVD has fallen somewhat, but less so than in men.

Nanette K. Wenger, M.D., the Emory meeting organizer, noted that symptoms of CVD in women continue to be underrecognized and undertreated by clinicians. Despite two decades of awareness of inequities in research on CVD in women, they continue to be underrepresented in clinical trials and incur greater mortality as a result of CVD than do men. **Kasim Reed**, Mayor of Atlanta, in a statement read by Candace Byrd, Chief of Staff, emphasized the link between improved public health and effective prevention and treatment of the number one killer of the nation's women. **Thomas L. Lawley, M.D.**, Dean of the Emory University School of Medicine, spoke of the need for medical schools both to partner with basic scientists to advance knowledge and to team with women's health advocates to more effectively communicate the importance of research to professionals and the public.

Senator Lisa Murkowski, Senate cosponsor, with Michigan Senator Debbie Stabenow, of the HEART for Women Act, welcomed participants in a video and commended them for undertaking such important work over the next two days. She spoke of the proposed legislation, which aims to raise awareness among women and their healthcare providers of heart disease and stroke and provide gender- and race-specific information about CVD to clinicians and researchers. The bill would also authorize the expansion to all 50 states of the Centers for Disease Control and Prevention (CDC)-funded WISEWOMAN program, which provides screening for low-income, uninsured women at risk for heart disease and stroke.

OPENING PANEL

The opening panel of the plenary session, moderated by Jackson T. Wright, Jr., M.D., Ph.D., Professor of Medicine at Case Western Reserve University, presented perspectives on basic

science research in CVD, pregnancy and cardiovascular health research, underserved populations, and ethical considerations.

W. Robert Taylor, M.D., Ph.D.
Director, Division of Cardiology and Professor of Medicine and Bioengineering, Emory University School of Medicine
Dr. Taylor began with an overview of sex differences in cardiovascular physiology and in biological risk factors. In men, the most common cause of a heart attack is a plaque rupture, resulting in coronary thrombosis. In premenopausal women, however, thrombosis is more likely to result from plaque erosion than rupture, and erosion is associated with higher mortality. Furthermore, women with myocardial infarction (MI) are less likely than men to have antecedent obstructions in their major coronary arteries. A significant portion of women suffer from another form of heart disease affecting the smaller arteries, the microvasculature, that delivers blood directly to heart muscle tissue. In addition to sex differences in initiating events, there are other sex differences in inflammatory processes, in the signaling pathways that mediate the responses of smooth muscle cells and endogenous vasoconstrictors, and in microvascular remodeling. Such differences contribute to the clinically manifest sex differences in MI, heart failure, atherosclerosis, and collateral vessel formation.

Sarah Berga, M.D.
James Robert McCord Professor and Chairman, Reproductive Endocrinology and Infertility, Emory University School of Medicine
Dr. Berga highlighted maternal pregnancy effects on offspring CVD risk and pregnancy as a biological stress test—revealing vulnerability to later CVD in women who experience pregnancy complications such as preeclampsia and gestational diabetes. A growing body of literature indicates that maternal stress during pregnancy can alter the epigenetic expression of genes in offspring. For example, maternal malnutrition during pregnancy has been linked to an increased risk of diabetes and CVD in offspring when they reach adulthood. Psychological and social stresses also may alter gene expression in offspring by exposing the fetus to increased levels of adrenocortical hormones in the placenta. Maternal nutritional and social stress may alter metabolic function in offspring.

Larissa Avilés-Santa, M.D., M.P.H.
Medical Officer, Hispanic Community Health Study—Study of Latinos, National Heart, Lung, and Blood Institute
Dr. Avilés-Santa described a recently initiated NHLBI study of risk and protective factors for CVD and pulmonary disease in Hispanic women. Collecting information on cohorts at multiple sites throughout the United States, the study will include data on ethnic and socioeconomic factors as well as measures of cognitive processing, emotional regulation, biological vulnerabilities, and health behaviors. The effort should provide a model of biopsychosocial vulnerabilities and resilience.

Paul Root Wolpe, Ph.D.
Director, Center for Ethics, Emory University
Are pregnant women a vulnerable population for research? Is there a gender bias in clinical research? Dr. Wolpe's presentation addressed these issues. In regulations promulgated in 1974,

pregnant women, along with prisoners, children, and those with reduced cognitive capacity, were characterized as vulnerable populations whose recruitment and consent to research required a higher level of scrutiny. However, a pregnant woman who has a serious health condition and needs more information about its treatment is, in fact, fully able to provide informed consent and decide whether to participate in clinical research. Current wording of regulations may inhibit such research.

Dr. Wolpe argued that devaluation of women's health can be seen in the relatively low number of research publications that report analysis by sex of participant and in the failure of clinical medicine guidelines to incorporate gender-based findings. Gender bias is most emphasized in clinical trials, but there is also evidence for bias in other kinds of clinical research, e.g., epidemiology and health services. To overcome bias, steps should be taken to include gender-related issues in terms that provide the framework for scientific research searches.

Janet Rich-Edwards, Sc.D., M.P.H.
Director of Developmental Epidemiology, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

Dr. Rich-Edwards discussed the role of preeclampsia and gestational diabetes as predictors of later risk for CVD, presenting some preliminary results from the Nurses' Health Study II. These pregnancy complications appear to fall within the range of other early indicators of risk for CVD and could be useful predictors. There are many unanswered questions about the association of pregnancy outcomes and complications with the health of both parent and offspring. Dr. Rich-Edwards proposed examining cardiovascular risk factors as they emerge in mothers, fathers, and offspring. A longitudinal family cohort, recruited during pregnancy and followed up for several years, could yield several new research leads. A family cohort would allow researchers to explore the emergence of sex differences in cardiovascular risk in early life and thereby plumb some of the earliest origins of sex differences in CVD risk. One possible finding might be that pregnancy characteristics predict future CVD risk in mothers and children because they reveal subclinical CVD risk factors, like proinflammatory states or high risk angiogenic profiles. Such a study would enable researchers to get a step closer to understanding whether preventing or treating pregnancy complications might actually change the trajectory of mother and child.

Patrice Desvigne-Nickens, M.D.
Medical Officer, Heart Failure and Arrhythmias Branch, Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute

Dr. Desvigne-Nickens highlighted NHLBI-funded resources and research priorities. Over the years, NHLBI has funded major cohort studies of CVD, from the Framingham Heart Study to the Women's Health Initiative. These laid the groundwork for clinical trials of prevention and treatment and the development of risk indices. NHLBI has greatly expanded its investment in research infrastructure, technology development and biorepositories. Looking forward, major health advances may accrue from studies of healthy lifestyles and behavior change. Fundamental sex differences research offers the potential for insights into regenerative repair mechanisms. Study of sexually dimorphic patterns, whether in symptoms, plaque morphology and rupture, or in microvascular disease and molecular signatures will benefit both women and men. The ultimate goal of all this research will be the fine tuning of personalized medicine and improved health outcomes.

KEYNOTE ADDRESS: WOMEN IN BIOMEDICAL CAREERS—IMPLICATIONS FOR ADVANCING WOMEN'S CARDIOVASCULAR HEALTH RESEARCH

Kathy Griendling, Ph.D.

Professor of Medicine and Vice Chair for Faculty Development, Emory University

Dr. Griendling addressed the value of women conducting biomedical research on CVD. Women researchers bring talent equal to men, unique perspective and empathy, greater understanding of and interest in women's health issues, and ownership of health issues. Women are entering academic medicine at rates comparable to men but their attrition is higher and they are underrepresented in leadership positions. To remedy this situation and to increase gender-focused CVD research, institutions need to address barriers to the retention of women, whether family-related or due to unrecognized bias. To address the dearth of women in leadership positions, more leadership training opportunities need to be made available to women. In addition, there should be gender-specific, high-quality mentoring and advising from the early stages of a woman's career.

KEYNOTE ADDRESS: A VIEW OF THE LEGISLATIVE ROLE, LOCAL AND NATIONAL, IN ADVANCING WOMEN'S CARDIOVASCULAR RESEARCH

The Honorable John Lewis

Congressman, 5th District, Georgia

Congressman Lewis, a Civil Rights leader, began by noting that he is a member of the Congressional Health and Stroke Coalition, which is committed to raising awareness of CVD. He emphasized that medical research should be a national budget priority. Research done at Emory and other major research universities on CVD has been remarkable for men but unacceptable disparities exist for women with CVD. We should not rest until they are more fully acknowledged and addressed through research and research dissemination activities.

KEYNOTE ADDRESS: ROLE OF PUBLIC/PRIVATE PARTNERSHIPS IN ADDRESSING INDIGENT CARE—IMPLICATIONS FOR WOMEN'S CARDIOVASCULAR HEALTH RESEARCH

Michael A. Young, M.H.A., FACHE

President and Chief Executive Officer, Grady Memorial Hospital

Mr. Young spoke about the role of public-private partnerships in addressing indigent care. Grady Memorial is a public hospital that treats a disproportionate number of uninsured women. Uninsured adults receive fewer and less timely preventive and screening services and do not consistently receive care for chronic diseases. A few years ago, Grady was losing money and was unable to upgrade its physical plant and clinical facilities. Through partnerships with the business community and philanthropic organizations, the hospital has turned around. It is now a major trauma and HIV/AIDS center and boasts new cardiovascular (CV) testing and imaging facilities. Grady Memorial has improved patient care by using new communication technology to track patients, provide transportation to appointments, and promote communication among treating physicians. As a result, ER admissions are down and the hospital is able to control costs while providing better coordinated care to patients.

CHARGE TO THE WORKING GROUPS

Dr. Pinn provided a charge to meeting participants before they broke into groups. She asked the working groups to help the NIH chart the future direction of women's health research. What science and technologies are most innovative? What are the highest priority issues in addressing women's health needs? What new initiatives within the NIH mission are needed? What can the Office do to facilitate these initiatives? She ended by expressing her hope that working group recommendations would not summarize the status quo but anticipate new science needed over the next decade to advance women's health.

SCIENTIFIC WORKING AND DISCUSSION GROUPS

PREGNANCY AND CARDIOVASCULAR DISEASE RESEARCH AND ETHICAL CONSIDERATIONS

Cochairs:

Janet W. Rich-Edwards, M.P.H., Sc.D.
Brigham and Women's Hospital

Robert N. Taylor, M.D., Ph.D.
Emory University School of Medicine

NIH Cochair:

Catherine Y. Spong, M.D.
Eunice Kennedy Shriver *National Institute of Child Health and Human Development*

Science Writers:

Neal Dickert, M.D., Ph.D.
Emory University School of Medicine

Erin Galbraith, M.D.
Emory University School of Medicine

Introduction

Any serious examination of women's health issues must consider the implications of pregnancy and fertility. Pregnancy produces a unique and dynamic physiologic state that has numerous implications, particularly regarding CVD. Pregnancy can complicate the management of preexisting CVD, such as congenital heart disease, cardiomyopathy, and hypertension. Pregnancy also is associated with specific and well-known health problems such as postpartum cardiomyopathy, spontaneous coronary artery dissection, and pregnancy-related hypertensive disorders. Management of preexisting CVD and pregnancy-associated cardiovascular conditions has important immediate and long-term impact on the health of mothers and fetuses. Because of the unique state of interdependence that exists during pregnancy (i.e., the "maternal-fetal unit"), both the clinical treatment of pregnant women and clinical research involving pregnant women raise important ethical challenges.

Mounting evidence suggests that some complications during pregnancy appear to be associated with long-term CVD. Data from large cohorts, including the Nurses' Health Study II (NHS II), suggest that the presence of preterm delivery, pregnancy-induced hypertension (PIH), and gestational diabetes mellitus (GDM) appear to have important associations with long-term CVD. Indeed, these novel risk factors appear to be as important as other well-known CVD risk factors such as hyperlipidemia, family history, and overweight/obesity. Furthermore, evidence indicative of long-term vascular remodeling in women with complicated pregnancies points to a causative role in the development of long-term CVD. It is estimated that 25 percent of women who have given birth experienced at least one complication of pregnancy that may have CVD implications, making the public health impact of pregnancy complication-related cardiovascular risk potentially very large.[1–4]

The focus of this working group's discussion was on the emerging science examining the relationships between pregnancy complications and CVD, and the ethical considerations raised by conducting clinical research in pregnant women. The principal goal was to identify priorities for future research that can further uncover the relationships between pregnancy complications and cardiovascular risk and identify potential avenues for assessment and prevention.

Summary of the Discussion

The discussion of the working group focused on the following major areas: (1) examination of associations between pregnancy history and CVD risk; (2) pathophysiologic evidence for causal relationships between pregnancy complications and CVD; (3) potential clinical implications of pregnancy-related CVD risk; (4) ethical considerations regarding the conduct of clinical cardiovascular research with pregnant women; and (5) identification of other potential priority areas for research related to pregnancy and CVD, such as preexisting CVD and primary cardiac complications of pregnancy.

1. Examining Associations between Pregnancy History and CVD Risk

How a woman "goes through pregnancy" appears associated with her cardiovascular status over time. An association between pregnancy complications and cardiovascular risk appears well-established. It may be that pregnancy functions as a "stress test" in that the cardiovascular and metabolic demands of pregnancy unmask clinically silent vascular dysfunction and disease. Pregnancy complications such as hypertension, GDM, and preterm delivery may be the manifestations of preexisting subclinical disease.[1] Similarly, it has been suggested that women who do not suffer pregnancy complications may have the physiologic ability to handle the cardiovascular demands of pregnancy and thus are at lower risk of future CVD.[2] Or, it may be that pregnancy complications actually cause cardiovascular injury and thus serve as an independent risk factor for CVD rather than a marker for potential CVD risk. Much of the subsequent discussion focused on potential ways to study these hypotheses and their potential clinical implications.

Particular complications appear to have important links to cardiovascular disease. Data from several large cohorts have provided evidence of associations between GDM, preterm birth (PTB), PIH, and future CVD. GDM, for example, predicts future type 2 diabetes mellitus, an established CVD risk factor.[3] NHS II findings indicate that PTB is associated with hazard ratios in the range of 1.6–2.3 for early CVD, with earlier delivery associated with greater risk. PIH has been associated with similarly increased risk. Furthermore, evidence suggests that the increased risk associated with these complications is additive; women with multiple complications have significantly greater long-term CVD risk.[4,5,6]

Low birth weight (LBW) is another complication that has been associated with maternal CVD, with a 25 percent decrease in maternal CVD outcomes with 500 g increases in neonate body weight.[7] However, recent data from the NHS II suggest that, when corrected for gestational length, LBW may not be as clearly associated with long-term CVD risk. Further studies should closely examine the long-term CVD implications for mothers who deliver offspring with evidence of fetal growth restriction at any gestational age, rather than relying on birth weight, which is a mixed outcome of both fetal growth and gestational length.

Available data sources are limited. Existing data sources are limited with regard to examination of the relationships between pregnancy complications and CVD risk. Much of the evidence to date has been drawn from European linked vital statistics registries. However, these data sources lack information on lifestyle risk factors such as smoking, activity, or diet, as well as intermediate risk factors such as body mass index, hypertension, and hyperlipidemia. Another limitation is that they do not capture the diverse demographics of the U.S. population. The NHS II is one of few large U.S. cohorts to collect pregnancy history data.

Another major limitation is that current CVD trials and cohorts do not adequately capture reproductive history, including details on pregnancy complications and outcomes and general fertility history. Conversely, most pregnancy-related cohorts, which typically end at delivery, do not capture CVD outcomes and data. A further limitation is the general inability of major records systems to link data from different clinical settings. As a result, data from delivery and other hospitalizations cannot be linked to primary care data. Such linkages are essential to understanding relationships between pregnancy and long-term CVD risk. Related, most existing records systems and research cohorts provide no way to link maternal and offspring data. As more is learned about the fetal and maternal genetic contributions to pregnancy complications, cohorts that collect biological samples from mother and child will be needed to determine the role of genes in the associations of pregnancy complications with maternal CVD.

2. Pathophysiologic Evidence for Causal Relationships between Pregnancy Complications and CVD

Cardiovascular alterations in pregnancy as potential causes of long-term CVD. In addition to the above-discussed epidemiologic evidence of associations between pregnancy complications and CVD risk, there are reasons to believe that complications of pregnancy may actually cause vascular changes that increase long term CVD risk. Working group participants noted that there are numerous cardiovascular changes found in pregnancy that may be associated with CVD risk. For example, there is evidence that placental microparticles and hormone/metabolic alterations significantly affect vascular cell function. In addition, pregnancy has been associated with resistance vessel remodeling and autoantigen production against angiotensin II receptors.

Data also indicate that pregnancy complications associated with later CVD risk are associated with particular cardiovascular changes that may be responsible for long-term risk, particularly in preeclampsia. There is pathologic evidence of significant glomerular change in the kidneys of preeclamptic women. Changes in endothelin levels have been associated with pregnancy and the preeclamptic state. Preeclampsia has also been associated with acidification of albumin and the apparent loss of the protective function of more basic albumin, the presence of antibodies to the angiotensin II receptor, and significant arterial changes on the maternal side of the placenta. These observations offer support to the hypothesis that pregnancy complications (particularly preeclampsia) may actually play a causal role in long-term vascular change, particularly remodeling of resistance vessels.

3. Potential Clinical Implications of the Links between Pregnancy Complications and CVD

Risk Assessment. The association between some pregnancy complications and long-term maternal CVD appears to be as significant as many more well-established CVD risk factors currently included in risk assessment tools such as the Framingham risk score. One potential application of these data would be the explicit inclusion of pregnancy history as part of such CVD risk assessment tools. Similarly, if genetic associations emerge, genetic assessments may aid in CVD risk stratification. Furthermore, pregnancy history may be used to craft more specific screening schedules for women with a history of pregnancy complications. For example, recommendations for glucose screening after pregnancies complicated with gestational diabetes exist; similar schedules may be developed for hypertensive disorders of pregnancy.

Clinical Interventions. In addition to risk stratification, pregnancy complication-related CVD risk may present a potential target for clinical intervention. Preventive education in postpartum weight management and lifestyle modification could be more precisely tailored and timed for women with pregnancy complications. Interventions might also include traditional therapy for CVD and CVD risk, such as statins, antihypertensive medications, etc. Alternatively, interventions might be directed at minimizing the complications during pregnancy, particularly if a causal relationship between such complications and long-term CVD risk can be established. Importantly, such interventions may be beneficial to pregnant women and to fetuses.

4. Ethical Considerations in the Conduct of Cardiovascular Research with Pregnant Women

Ethical implications of pregnancy for research vary. Working group participants noted that the maternal-fetal unit is conceptually complicated. As a result, research in pregnancy raises unique questions and challenges regarding risks and benefits, and pregnant women are often considered to be vulnerable subjects from a regulatory and ethical perspective. However, the extent to which pregnancy raises special considerations, and the extent to which pregnant women and their fetuses should be considered vulnerable, varies greatly based on the type of research conducted. Unlike many other sources of vulnerability, such as cognitive impairment, pregnancy does not necessarily have any implications with regard to decisionmaking. As a result, most observational studies that focus on risk prediction, genetic analysis, and other CVD outcomes raise few unique ethical issues.

Clinical trials of intervention pose unique ethical considerations. Interventions during pregnancy can raise the potential for both risk and benefit to pregnant women and to fetuses, and analysis of maternal and fetal interests can be complex. Of particular challenge are intervention trials that may pose significant risks to both mothers and fetuses, such as *in utero* surgery trials. Careful analysis is also warranted regarding trials of interventions such as statins, diabetes regimens, and diet that may be directed toward reduction of maternal CVD risk. Finally, the group discussed the importance of ensuring that pregnant women are not arbitrarily excluded from trials in conditions affecting pregnant women and, when included, that they are adequately represented so the results will be generalizable to pregnant women as a population.

5. Management of Other Pregnancy-related Cardiovascular Conditions and Preexisting CVD

Primary cardiac complications of pregnancy. Although not the working group members' area of expertise, the prevention and treatment of primary cardiac diseases emerging during and after pregnancy (e.g., postpartum cardiomyopathy, spontaneous coronary dissection, and myocardial infarction), was also discussed as an important issue warranting more in-depth evaluation and discussion by experts in management of these conditions.

Management of existing CVD during pregnancy. The paucity of data regarding pharmacologic treatment options for preexisting cardiovascular risk factors in pregnant patients reflects the low numbers of pregnant women included in the large clinical trials for treatment of traditional CVD risk factors or myocardial infarction. The increasing age of women who bear children will result in larger numbers of women with underlying CVD and cardiovascular risk factors. This expanding patient population further pushes the need for studies evaluating the efficacy of treatment options in these women. The working group also discussed ethical issues surrounding treatments for pregnant patients with preexisting CVD. Working group members believed that this critical issue required extensive consideration by a group of individuals with special expertise related to the area.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, ethicists, and the public as to areas of investigation that merit greater research.

Recommendation 1: Assess the utility of pregnancy data for CVD prediction and prevention.

- Longitudinally follow pregnant women for emerging cardiovascular risk factors in a systematic and detailed way. Necessary data will include regular blood glucose and blood pressure checks in the postpartum years. Studies will also need to follow patients across clinical settings (labor and delivery and primary care), over the lifespan (prenatal period, delivery, and postpartum), and capture both maternal and child outcomes.
    - Ideal approach—Establish a large-scale longitudinal cohort beginning before pregnancy (ideally at birth).
    - More pragmatic approaches—Selectively follow historical cohorts. Include data necessary for cardiovascular risk assessment in pregnancy cohorts and trials (such as the National Collaborative Perinatal Project or other observational pregnancy cohorts that collect high quality pregnancy phenotypes). Include pregnancy history data in ongoing longitudinal chronic disease cohorts (such as the Framingham Heart Study, Women's Health Initiative, and CARDIA). It is also critical to ensure that emerging records systems facilitate linkages of pregnancy history data with chronic disease data.
- Develop and evaluate clinical protocols to predict and prevent CVD in women with pregnancy complications to assess whether the screening and followup are effective and to establish guidelines for clinical practice.
- Develop educational materials for patients and clinicians regarding the risk of CVD after complex pregnancy.

Recommendation 2: Elucidate mechanisms linking complex pregnancy to CVD.

- Develop and validate noninvasive means of assessing vascular function and injury before, during, and after pregnancy. Assessment methods must be repeatable over time and ideally should be integrated into ongoing trials and observational studies. Critical to these studies will be the inclusion of preconception baseline data.
- Clarify the role of pre- and postpartum psychosocial determinants and gene-environment interactions in both the development of complications and the development of CVD.
- Use animal models to establish causal relationships. Animal models allow investigators to induce pregnancy complications, assess long-term maternal cardiovascular effects of complications, and assess the effects of treatment during and after pregnancy on maternal cardiovascular risk.

Recommendation 3: Assess the impact of potential interventions on pregnancy-related CV risk.

- Assess the effects of current treatments on maternal cardiovascular outcomes. Such assessments should include both traditional cardiovascular treatment (e.g., statins, beta blockers, and dietary modifications) as well as current clinical protocols for pregnancy complications such as GDM and preeclampsia.
- Identify potential novel interventions designed explicitly to minimize maternal CV risk associated with pregnancy complications. Animal models may be particularly useful.

Recommendation 4: Evaluate study-specific ethical implications of pregnancy for research.

- Recognize that vulnerability is a context-specific concept. Pregnant women often are not vulnerable subjects. Many studies related to pregnancy history and CVD risk prediction do not raise special ethical concerns simply because the woman is pregnant, and concerns about vulnerability should not hinder such research.
- Carefully evaluate the implications of intervention trials for mothers and children. Intervention trials to improve care are vitally important but can involve short and long-term risks to pregnant women and fetuses; thus, intervention trials raise particular challenges because of the ethical complexity of the maternal-fetal unit. Animal models may present valuable opportunities to minimize risks.

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CARDIOVASCULAR DISEASE IN ELDERLY AND FRAIL ELDERLY WOMEN

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Introduction

The U.S. Census Bureau projects that the population of U.S. residents aged 65 and older will increase from 39 million in 2008 to 88.5 million in 2050, representing growth from 13 percent to nearly 20 percent of the total U.S. population. The number of the oldest old (85 years and older) is expected to grow from 5.3 million in 2006 to nearly 21 million by 2050.[1] In 2008, it was estimated that there were 73 men for every 100 women in the 65 and older group and only 48 men per 100 women for the 85 and older group.[1]

Approximately 60 percent of all cardiovascular disease (CVD)-related deaths in the United States occur in individuals 75 years or older, and most of them are women.[2,3] Improved CVD prevention and management are therefore critical, not only to delay disease and mortality,

but also to extend optimal function and quality of life. Elderly women are a unique group in terms of comorbidities, risks, and ethical considerations related to the testing of new interventions. Age-related changes occur in cardiovascular physiology (for example, decreased arterial compliance, increased cardiac afterload, and left ventricular diastolic dysfunction) and in drug metabolism. These changes are likely to affect treatment response and the probability of adverse reactions. CVD manifestations that are particularly prevalent among elderly women—specifically, heart failure with preserved systolic function and atrial fibrillation—are understudied. Very little is currently known of the pathophysiology, risk factors, clinical outcomes, and appropriate management of these conditions as they apply to elderly women.

To date, most CVD trials exclude individuals older than 75 and those with comorbidities. Between 1991 and 2000, 25 percent of enrollees in U.S. acute coronary syndrome trials were women, despite the fact that they account for 43 percent of patients with myocardial infarction. CVD trial samples tend to be unrepresentative (i.e., healthier) of the population of affected individuals because those with comorbidities are excluded. Limited data from clinical trials, coupled with a perception of higher risk from treatments, can translate to suboptimal care for the elderly. Evidence-based recommendations that form the basis of clinical practice guidelines do not properly account for age-related differences in physiology, response to treatment, and susceptibility to adverse reactions. Outcome measures such as health-related quality of life and physical and mental functions are typically not captured in clinical practice or clinical trials.

Measurements of independence and frailty are often neglected. The expected dramatic increase in the number of frail female octogenarians over the next two decades warrants much more attention to this area. Frailty is a term used to characterize elderly individuals (typically the oldest old) who have decreased function and increased vulnerability due to impairment in multiple organ systems. The pathophysiology of frailty is incompletely understood and is likely to be heterogeneous. The concept of frailty captures a vitally important aspect of functioning but despite its importance, assessments useful in clinical medicine are lacking, and available research and clinical data are inadequate to effectively direct patient care. This is especially true for elderly women with CVD.

Summary of the Discussion

General Framework

Based on considerations summarized in the introduction and raised in the initial discussions, the working group identified the following general principles to inform future research on CVD in elderly and frail elderly women.

1. ***Populations***. There are two types of understudied populations that should be the focus of future research: a) elderly women (not necessarily frail), defined as those older than 80 years of age; and b) frail elderly women, those with generalized decrease in function and increased vulnerability due to impairment in multiple systems.

2. ***Context***. Important areas of research include: a) prevention, with consideration of a broader set of outcome measures that are relevant to elderly persons (CVD events, functional decline, frailty); and b) management (of CVD, risk factors, etc.), considering risk and benefits that are relevant to this group.

3. ***Methodology***. Future studies should include a) new longitudinal, observational studies of older women; b) new clinical trials focused on elderly women; and c) creative use of existing resources, such as rigorous analyses of large clinical databases, and collaborations across existing or ongoing trials or cohort studies in order to gather larger numbers of elderly patients (similar to the Cohorts for Heart and Aging Research in Genomic Epidemiology [CHARGE] consortium).

4. ***Themes***. General thematic areas discussed include:

- **Need to better understand CVD disease processes that burden elderly women**, such as atrial fibrillation and heart failure with normal systolic function. Many challenges are centered on diagnosis, prevention, and management of these conditions and understanding of sex differences.

- **Need to research effectiveness and safety in the prevention and management of CVD in elderly women**, especially those with comorbidities. Perhaps the largest barrier to studying the elderly and frail elderly female population has been a lack of inclusion or underrepresentation in most clinical trials. The pooling of major cohorts already in existence represents an efficient way of gathering data. Moving forward, elderly patients should be included in clinical trials of new drugs and devices, and the safety of current interventions should be examined in the elderly and frail elderly population. An underappreciated clinical outcome that is especially relevant for the elderly and frail elderly is quality of life. To improve quality of life indicators, it is important to design behavioral interventions applicable to the frail elderly female population.

- **Need to rigorously define and assess frailty and to study its determinants, mechanisms, and treatments**. Determinants and mechanisms include biological, socioeconomic, demographic, and genetic factors. Examples of proposed areas of study are: 1) urban versus rural environment and the differing social structures that are beneficial or detrimental in relation to frailty; 2) social support, family structure, and other cultural factors; 3) biological variables such as muscle mass, muscle and fat composition, nutritional intake, and energy expenditure; and 4) adoption of new technologies in the study of frailty, such as microarrays, telomeres assessment, genetics, epigenetics, and proteomics. Novel interventions are needed, including nutritional, physical, pharmacologic, and behavioral interventions to prevent or delay frailty and improve outcomes in frail elderly.

Recommendations

The working group summarized its deliberations into four major recommendations to advance research and management of CVD and CVD risk factors in elderly and frail elderly women. The recommendations may help to provide guidance to health administrators, clinicians, scientists and the public as to areas of investigation that merit greater research.

Recommendation 1: Support research on the prevention and management of common clinical manifestations of CVD in elderly women, such as heart failure with preserved systolic function and atrial fibrillation.

Specific areas of management in need of further study include: Identification and diagnosis; etiology and physiology; and prevention and treatment. Below are examples of needed research/approaches:

- Develop new cohorts and /or leverage populations and data from existing cohorts to obtain reasonably robust estimates.
- Promote collaborations across existing cohort studies of older adults within the United States and internationally.
- Design new clinical trials exclusively among older patients, or that include substantial numbers of older patients.
- Promote the use of ancillary studies to existing trials involving the evaluation of patients 80 years of age and older.
- Encourage rigorous use of existing clinical databases such as large HMOs or Medicare as additional means to address these questions.

Recommendation 2: Support research on the effectiveness and safety of prevention and management strategies for CVD in elderly women with comorbidities, including clinical trials and use of existing clinical databases to determine drug and/or device safety in the elderly. Specific examples include:

- Studies of the role of comorbidities in triggering CVD.
- Studies of the role of comorbidities in cardiovascular outcomes.
- Studies of cost effectiveness and safety of guideline-based preventive interventions in this population (e.g., cardiovascular risk modification, automatic implantable cardioverter defibrillator use).

Recommendation 3: Support research on the prevention and management of frailty among elderly women with CVD or CVD risk factors, and on the role of CVD as a determinant of frailty.
Specific areas include:

- Studies to formulate a universal and clinically applicable definition and assessment of frailty.
- Studies of etiology/physiology/mechanisms. Encourage and support research to determine the underlying mechanisms of frailty, especially in relation to CVD, including approaches that exploit new technologies (microarrays, telomeres, genetics, epigenetics, proteomics, etc.).
- Innovative clinical trials of the prevention and treatment of frailty.
- Longitudinal studies examining frailty and CVD in the elderly female population, focusing on social and biological determinants.

Recommendation 4: Support new measures and inclusion guidelines in order to obtain better data for the prevention and management of CVD in elderly and frail elderly women.

- Include measurements relevant to older people in new clinical trials (physical and cognitive function, quality of life, independence).

- Perform behavioral research to improve lifestyle and compliance using interventions relevant to elderly persons.
- Advocate or mandate the inclusion of elderly persons in clinical trials to evaluate the efficacy and the safety of new devices and therapies.
- Advocate or mandate safety assessment of new or existing interventions among elderly/frail elderly prior to including such treatments in clinical practice guidelines.

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MICROVASCULAR DISEASE, BIOMECHANICS, AND APPLICATION OF NEW TECHNOLOGIES TO CARDIOVASCULAR RESEARCH

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Introduction

Cardiovascular disease (CVD) is the leading killer of both women and men. Despite sex differences in CVD outcomes, relatively little is known about sex differences in the science of CVD, ranging from basic science inquiry to pathophysiological understanding, diagnostics, and therapeutics. The Institute of Medicine (IOM) published a monograph in 2001 exploring biological contributions to human health entitled *Does Sex Matter?*[1] The IOM report came up with three conclusions: 1) sex does matter and should be considered when designing and analyzing studies in all areas of health-related research; 2) the study of sex differences has been predominantly observational research, and the next step is study of mechanisms and therapies related to sex differences; and 3) barriers to the advancement of knowledge about sex differences in health and illness must be eliminated. For the purpose of the following discussions we define microvascular coronary heart disease as evidence of ischemia in the absence of macrovascular epicardial obstructions. The pathophysiology of microvascular ischemia continues to be better defined for targeting coronary reactivity, whether endothelium, or non–endothelium, dependent. The goal of this working group was to identify areas for future basic science research that will help understand the biological differences between sexes pertaining to CVD and frame the development of new, gender-targeted technologies.

Summary of the Discussion

The working group discussions centered on four broad issues: 1) understanding sex differences in vascular biology, pathophysiology, and biomechanics; 2) developing a bioinformatics network on "sexomics" in order to identify sex-related biomarkers in CVD; 3) developing new imaging techniques attuned to women's CVD pathophysiology; and 4) implementing new gender-specific therapeutics. Major issues within each of the areas are summarized below.

Focus Area 1: Sex Differences in the Vasculature

There is significant evidence that the vasculature of men and women reacts differently to injury. For instance, women appear to have more diffuse atherosclerosis, less luminal stenosis, higher incidence of endothelial dysfunction, and a higher prevalence of microvascular dysfunction compared to men.[2,3] The pathoanatomic substrate for coronary thrombosis also differs between men and women. In men, 80 percent of thrombi tend to occur due to plaque rupture, whereas in women, 20 to 40 percent of coronary thrombi occur on an intact atherosclerotic plaque with superficial athero-intimal erosion.[4,5] This plaque erosion is a common finding in sudden cardiac death (SCD) in younger women who were smokers and postmenopausal women who are taking estrogens. Conversely, plaque rupture leading to thrombosis is relatively more common in men and older women. Plaques that tend to rupture are composed of a large lipid-laden core, have increased intimal and adventitial inflammation, and exhibit increased neovascularity. Inflammatory cells trigger death of smooth muscle cells through apoptosis and produce matrix-degrading enzymes which can induce depletion of the collagen framework leading to loss of collagen, thinning of the fibrous cap, and, eventually, rupture. Importantly, lipid-filled plaques have inflammatory cell-derived tissue factor (TF) that is a prototypical trigger for activating the clotting cascade. When a lipid-rich plaque ruptures, TF is immediately exposed to circulating blood, which, with other factors, stimulates the production of thrombin, leading to platelet-fibrin thrombus formation.[6] Furthermore, it is unclear whether and when there is "a smooth transition"

from microvascular pathology to macrovascular epicardial disease expression or whether these are two distinct processes, which share many of the triggers and some of the pathways.

The mechanisms of sex differences in this process are not well understood. *Enhanced endothelial apoptosis* is associated with exposure of TF on the luminal side, and a higher prevalence of superficial endothelial erosions with increased sex-specific circulating coagulability.[7,8] Additionally, *systemic inflammatory processes* increase anticardiolipin antibodies, which are more prevalent in women; and TF, which may not be originating from the plaque but from the circulation, may also create a prothrombotic state. Normally, cell-derived tissue factor remains contained within circulating leukocytes and is not available to trigger thrombosis. However, under certain conditions, circulating leukocytes can shed membrane microparticles, which have been shown by electron microscopy to be laden with TF.[9] Accordingly, these microparticles can be delivered to platelets and to other circulating leukocytes and the transfer of TF from circulating cells can occur at the site of endothelial erosion. This can cause thrombosis even though the plaque does not contribute TF.

Spontaneous coronary artery dissection (SCD) is a rare clinical syndrome that is more prevalent in women than in men. In fact, 80 percent of cases occur in women, particularly in premenopausal women, often in the peripartum setting.[10] *Reproductive hormones* may contribute to this, in that matrix metalloproteinases may be induced by hormonal alterations and may promote intimal disruption and dissection. The clinical presentation frequently is SCD and less commonly unstable angina, acute MI, heart failure, or shock. Interestingly, the left anterior descending coronary artery is more commonly affected in women, the right coronary is more commonly affected in men, and simultaneous multiple vessel dissections can also occur.

Focus Area 2: Bioinformatics

Most methods of noninvasive evaluation have been obtained via research done on majority male populations. It is an accepted concept that women present differently than men in many pathological states, including CVD. In order to understand what evaluations are needed to accurately diagnose a pathologic state in a female patient, we must first understand how women differ from men in their biologic and physiologic profiles and responses. A better understanding of the various biomarkers in women to evaluate cardiovascular health and illness needs to be obtained. These data, once obtained, need to be banked and analyzed in a timely manner so the data can be used for patient care.

Focus Area 3: Improved Imaging Modalities

Imaging modalities provide noninvasive means of anatomic and pathophysiologic evaluation. Optimally, they could also provide means for initiating and directing alternate therapeutic option. Improved data on the biologic markers and how they differ in women should improve both imaging modalities and optimize management capitalizing on the biologic differences between men and women.

Focus Area 4: New Therapeutics

Current therapy for CVD is based on studies that provide a general improvement in the population as a whole, but benefit at the individual level is less clear and may involve overutilization of resources and expensive management modalities for some but underutilization for others. Biomaterials have been created to attempt enhanced tissue and vascular regeneration, but none has been completely successful, whether it is due to failure of the device or incompatibility with the patient. We need to provide treatment targeting individual patients allowing for individualized medical care for people at high risk for CVD. In order to accomplish such a tall order, we need to obtain information that will lead to an improved understanding of differences in vasculature between men and women, using bioinformatics to better understand these differences on a microbiological level; and translating this personalized information into the provision of personalized medicine. [11]

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendations for Focus Area 1: Sex differences in vasculature

A better understanding of the mechanisms underlying sex differences in the vasculature is necessary to develop sex-specific diagnostic and therapeutic modalities. Research is recommended in the following areas:

1. Biomechanics of the vasculature:
    - Analysis of extracellular matrix components in the vascular wall responsible for sex differences in vascular compliance and elasticity.
    - Sex differences in fluid dynamics and shear stress.
    - Cyclical differences in fluid and solid mechanics resulting from the menstrual cycle and gravid states.
    - The interplay of vascular biomechanics and the immune system.
    - The role of lymphatics and inflammatory mediators.
2. Effects of sex hormones on:
    - Vascular extracellular matrix composition and vascular biomechanics.
    - The immune system response.
    - Vascular expression of receptors for vasoactive molecules.
    - Long-term effects of cyclical changes across the lifespan on vascular physiology.
3. The role of sex differences in perivascular fat distribution as an influence on vascular function and structure.

4. Sex differences in angiogenesis and collateral vessel development:
    - Sex differences in the number of circulating progenitor cells and their potential for differentiation to endothelial cells.
    - Sex differences in vascular smooth muscle and endothelial cell migration and proliferation.
    - The role of neural network/neurons in adventitia.
5. Development of improved models to study the microvasculature.

Recommendations for Focus Area 2: Bioinformatics

1. Encourage the discovery of novel biomarkers to identify women at high risk for CVD in various areas of study:
    - Sexomics—Which biomarkers may be better for evaluating women, as opposed to men, and why
    - Genomics
    - Proteomics—Uncovering the protein differences that exist between women and men and using that data to improve the evaluation and treatment of women
    - Metabolomics
    - Epigenomics—Understanding the effects of epigenetic factors and the possible aberrant functions that can present in women so a better understanding of cardiovascular pathologic states can be obtained
2. Encourage the development of high-throughput methods for data collection so information can be used and distributed in a timely manner.
3. Encourage systematic data collection to allow for ease of organization and analysis.
4. Collect all data into an NIH databank or database for modeling.

Recommendations for Focus Area 3: Improved Imaging Modalities

1. Optimize imaging on several levels. This will require better methods to enhance visualization of both microvasculature and macrovasculature and the development of novel markers to allow for alternate methods of visualization. Such improvements in imaging should optimize the evaluation and treatment of women, which at this time is lacking. The working group identified the following needs in this area:
    - Novel nano-based markers to evaluate microvascular density.
    - A method by which to merge metabolic states and the imaging of vessels and myocardium to better understand functionality in states of health and disease.
    - New biomechanical assessments of myocardium and vasculature to help gain an understanding of the physics involved and how they differ in cardiovascular health and disease.
    - Direct and accurate *in vivo* measurement and imaging of microvascular flow dynamics.

- Imaging for sex specific disease characterization.
- Improved modalities to provide a means of evaluating differences between men and women over a lifecycle.
- Dynamic sex receptor modulation imaging to improve our understanding of the differences between men and women and how we may use these differences to enhance treatment.

Recommendations for Focus Area 4: New Therapeutics

1. Design tissue-engineered medical products to have an appropriate microvasculature and microenvironment with respect to sex. This microenvironment should consist of the extracellular matrix and its components (e.g., proteins), other vital cell types (e.g., inflammatory cells), intracellular and extracellular components, lymphatics, and innervations.
2. Further investigate cell-based therapeutics with an understanding of the contribution of sex and age to this concept.
3. Develop matrices that optimize regenerative processes to allow for biomaterials that are superior to those now available.

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STEM CELLS, PROGENITOR CELLS, AND THE VISTA OF CARDIOVASCULAR REGENERATIVE MEDICINE

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Introduction

Stem cells, regeneration, and repair are fundamental mediators of health and disease. These processes impact cellular structure and function in all organ systems. While many different types of stem and progenitor cells have been identified, each has positive and negative attributes in their potential for effecting myocardial and vascular repair. Which cell types will be most applicable to treatment of cardiovascular disease in humans is currently a subject of intense study. Very little is known on how (or if) sex-based differences will play a role in selection and preparation of cells, their ultimate potency, delivery methodology, and therapeutic effect. The goals for the Stem Cells, Progenitor Cells, and the Vista of Cardiovascular Regenerative Medicine Working Group were to assess the needs of the research community and to recommend scientific opportunities to further the understanding in this important field.

Summary of the Discussion

The working group identified five major areas for discussion. Each of these areas is also the subject of recommendations in the "Recommendations" section. Below is a summary of key points raised by participants for each of the areas.

1. **Burden of Cardiovascular Disease (CVD) in Women.** Working group members noted that CVD imposes a heavy burden on women's health and accounts for 25.6 percent of all deaths in U.S. women.[1] Current CVD management includes preventive therapies and lifestyle changes to ameliorate risk factors and secondary prevention for those with coronary artery disease, myocardial infarction, or heart failure. Revascularization approaches center on relief of ischemia and potentially on preservation of heart function. Since these treatments cannot repair or regenerate damaged myocardium and may not be feasible in the presence of unrevascularizable disease, ischemic cardiomyopathy may develop due to adverse remodeling. For the past 20 years, researchers have been exploring novel ways to restore and regenerate blood vessels and the myocardium.

   Until recently, however, research has often overlooked the crucial effect of sex on CVD and its related therapies. It is known that before menopause, women are better protected from coronary artery disease than age-matched male counterparts. However, by the age of 60, this cardiovascular protective effect is lost. Although some of the premenopausal protection is attributed to estrogens, estrogen replacement therapy does not abolish this increased risk in postmenopausal women. It has been hypothesized that this age-dependent susceptibility in women may be at least partly due to changes in regenerative capacity. Accelerated research into the specific mechanisms underlying sex differences in CVD risk and clinical manifestations is needed.

2. **Regenerative cells as biomarkers of cardiovascular health**. A second area of intensive discussion by working group participants was the utility of regenerative cells as biomarkers of cardiovascular health. Studies on circulating progenitor cells suggest that their numbers and function correlate with cardiovascular health. It is likely that these rare but essential cells perform necessary functions to maintain vascular health. The number of circulating endothelial progenitor cells (EPCs) inversely correlates with death from cardiovascular causes[2] and cardiovascular events.[3] However, this early evidence has largely been gathered in men. Diseases such as metabolic syndrome, hypertension, and diabetes reduce circulating progenitors, as do many medications.[4,5] The significance and mechanism of these effects on EPCs and other progenitor cell types are unknown.

   Clinical studies in relatively small numbers of subjects suggest that circulating progenitor cells also vary by age in women.[6] Premenopausal women have higher circulating levels of EPCs compared to men, but their numbers are lower after menopause, similar in number to age-matched males. The number of progenitors increases by approximately 25 percent after hormone replacement therapy in postmenopausal women.[7,8] EPC-enriched populations vary during the menstrual cycle, with higher numbers during the luteal phase, and there is evidence for cyclic bone marrow progenitor cell mobilization. These cyclic effects during the menstrual cycle appear to be mediated by estrogen, vascular endothelial growth factor, and nitric oxide. Working group participants identified a pressing need for more fundamental biological research on stem cells, especially in relation to biological sex and hormonal influences.

3. **Clinical trials for cardiovascular regeneration—the relevance of sex**. Various endogenous and transplanted cell types and bioengineered materials are under investigation for the treatment of heart diseases, but their value in men versus women remains largely undetermined. Progenitor and stem cells from various sources, including skeletal myoblasts, endogenous cardiac progenitor cells, and bone marrow mononuclear cells, are currently undergoing clinical evaluation.[9–11] A variety of delivery approaches, devices, and clinical syndromes is being studied. One interesting subpopulation of bone marrow and circulating cells, EPCs, has been studied most extensively, largely because of their availability, safety, and reputed ability to enhance angiogenesis in the border zones of infarcts and in unrevascularizable tissue. The beneficial effect of EPCs is most likely due to their paracrine effects.[12–14] The number of EPCs and their ability to form colonies and vessels *in vitro* and *in vivo* appear to be enhanced by estrogen.[8,15–17] Despite this, the majority of subjects enrolled in clinical trials to date have been men, so the value of these therapies in women is not yet known.

   Considering that cell source is a critical issue for any type of cell-based therapy, there is early evidence that potency and availability is influenced by sex. Also, therapy in postmenopausal women may be different from that of premenopausal women depending on cell source. For example, human cardiac progenitor cells (c-kit and Islet-1 progenitors) are more often available from the right atrium in women than in men.[18] However, mobilization capacity of bone marrow progenitors appears not to be sex dependent, although this has not been systematically studied. A recent report found that androgen receptors in female endothelial cells made them responsive to the angiogenic effects of testosterone. In male mice, castration impaired angiogenesis, an effect reversed by androgen treatment.[19]

4. **Pluripotent stem cells, gender, and estrogen**. Embryonic stem cells and induced pluripotent stem (iPS) cells are capable of proliferating and differentiating into several cell types. Embryonic stem cells have enormous regenerative potential but their clinical applicability is restrained by ethical and immunological barriers. By contrast, iPS cells, first described in 2006, can be autologously generated from terminally differentiated tissues (skin, blood, adipose tissue, or fibroblasts) and then induced into pluripotency by activation of embryonic genes by viral vectors, plasmids, and proteins.[20, 21] The basic biology as well as stringent definitions for iPS cells needs to be established in a sex-specific manner. This will allow for better comparison of data amongst research groups and the streamlining of cell advancement into clinical trials. How sex influences iPS cell generation efficiency, their dedifferentiation and redifferentiation, remains to be explored. For example, physiological concentrations of testosterone in men and premenopausal concentrations of estrogen in women have a positive effect on the chondrogenic potential of chondrocyte progenitor cells *in vitro*. Therefore, cell therapy approaches that may be potentially beneficial for the regenerative potential in late stages of human disease may be sex-specifically procured and expanded.[22]

   For example, estradiol accelerates reendothelialization and estrogen mobilizes bone marrow-derived EPCs.[23, 24] Estrogen, via specific receptors, modulates the proliferation and survival of progenitor cells. Additionally, studies using cultured human EPCs

from peripheral blood mononuclear cells disclosed consistent gene expression of the estrogen receptor. Under the physiologic concentrations of estrogen, proliferation and migration were stimulated, whereas apoptosis was inhibited in cultured EPCs.[25]

5. **Enabling Technologies**. The field of regenerative cardiovascular medicine is very new and the technology to achieve the goals outlined above is not developed. Fundamental tasks such as identifying cells, characterizing their pluripotency, sorting them, and expanding them are imprecise and rudimentary. Evaluation of the secretome of cells with *in vitro* analysis, which removes the cells from their physiologic environment, may alter their function and products. Fluorescence-activated cell sorting is the fastest way to separate cells, but it relies on superficial surface marker expression that may or may not correlate with cell function and potential. Because the use of EPCs in clinical application has been limited by varying definitions of cells as well as the lack of reproducibility of experiments, it will be essential to develop new technologies to fully exploit the potential of EPCs and to develop other cell types for clinical use.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

1. Accelerate discovery of sex-specific differences related to CVD. Examples of needed research include efforts to:
   - Investigate whether the known reduced risk of coronary heart disease in premenopausal women is merely due to the effects of estrogen and progesterone, or due to differences in stem cell function before and after menopause.
   - Determine whether different mechanisms of CVD progression between sexes (e.g., erosions vs. plaque rupture), are related to differences in stem cells.
   - Develop regenerative cell therapy approaches for CVD as a priority in older women.
   - Improve understanding of how special populations of women, e.g., pre- vs. postmenopausal women, athletic women with amenorrhea, and women with premature CVD events, may benefit from regenerative medicine therapies.
2. Develop new knowledge of the fundamental biologic mechanisms of stem and progenitor cells.
   - Improve understanding of how sex influences endogenous regenerative processes throughout the lifespan.
   - Determine sex-based mechanistic differences including genetic, epigenetic, molecular, proteomic, physiologic, and hormonal differences.
   - Investigate cell-associated “secretomes” at all stages of differentiation, including somatic, adult, embryonic, and iPS cells.
   - Evaluate how age and sex affect regenerative potential throughout the lifespan—*in utero*, infancy, childhood, puberty, adulthood, pregnancy, and after menopause.
   - Evaluate the effect of risk factors and disease on stem cell function.

3. Exploit emerging knowledge about how sex differences influence therapeutic efficacy and whether optimal regenerative strategy is similar in men and women.
    - Investigate whether cell sources vary between sexes (e.g., bone marrow, adipose, heart, and non-autologous cells).
    - Foster the study of procurement bias.
    - Explore the importance of extracellular matrix and microenvironment in transplanted sites.
    - Develop preimplantation cell strategies that utilize sex-based advantage.
    - Develop different delivery methods.
4. Integrate advances in the fundamentals of how sex differences influence iPS function.
    - Incorporate the relevance of sex and sex hormones in study of iPS cell dedifferentiation and redifferentiation.
    - Explore the feasibility of sex hormones as adjuncts to therapy with iPS cells (*ex vivo* treatment, dual delivery).
5. Establish the required resources to enable comprehensive laboratory, preclinical, and clinical methodologies.
    - Quantify fundamental biologic sex differences.
    - Facilitate procurement, process, and delivery.

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UNMET NEEDS IN DIAGNOSTIC TESTING FOR WOMEN WITH CARDIOVASCULAR DISEASE

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Introduction

This report synthesizes the discussions of the working group on unmet diagnostic testing needs for women with cardiovascular disease (CVD). Consistent with the principles of comparative effectiveness research,[1] the working group focused on those areas where a research agenda could address and influence the greatest number of female lives. Moreover, the charge for this working group was to set forth a research agenda for the future that identified critical gaps in knowledge. This report will highlight relevant background material for each of three critical areas that were deemed sufficiently important for the improvement of the quality of care of women undergoing CVD diagnostic testing or imaging-based risk assessment. Importantly, early and precise recognition of atherosclerosis and heart disease is essential for the objective of improving women's longevity and quality of life.

Summary of the Discussion

Topic 1: Pathogenesis of Myocardial Ischemia and Anatomic Correlates

Considerable epidemiologic evidence supports a delay in the onset of CVD whereby women become symptomatic and are diagnosed with obstructive coronary artery disease (CAD) approximately 10 years later than their male counterparts.[2] Gender differences have also been frequently reported in higher rates of nonobstructive CAD in symptomatic women versus men across all adult deciles of ages, with the exception of the very elderly.[3] This signal of a differential atherosclerotic disease process has largely been ignored, with limited focused research efforts detailing the development and progression of atherosclerosis culminating in obstructive CAD. There are disparate pieces of information that describe a unique female-specific process which not only is differentially time related but also may result in an acute coronary syndrome presentation of varying etiology.[4–6] Investigations led by Virmani and colleagues[7–9] detailed a greater frequency of plaque erosion in women (compared to plaque rupture occurring more often in men) with sudden cardiac death. This early evidence suggested a strong influence of gender and sex-related differences in plaque progression and notably may contribute to differential clinical presentation. Coupling this information with other sex differences in vascular biology, one starts to unfold an exploratory model on detecting the "vulnerable" female patient.

The NIH-NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) registry performed extensive testing on a sample of nearly 1,000 symptomatic women. This study forms the basis for much of our knowledge and thoughts on gender differences in CAD. An important focus of WISE was the delineation of at-risk women without obstructive CAD. Key findings in women with nonobstructive CAD include frequently documented nonobstructive atheroma by intravascular ultrasound as well as abnormal invasive coronary reactivity testing.[10]

A more recent report explored mortality differences by gender in obstructive CAD extent and severity as well as nonobstructive plaque by coronary computed tomographic angiography (CCTA).[11] Importantly, nonobstructive atherosclerosis was predictive of death in women but not men.[11] These data reveal an ever-increasing prevalence of nonobstructive plaque for women

as they age; a trend not seen for men. These data suggest that men may progress rapidly through stages of constrictive remodeling whereas women may linger within more extensive, expansive remodeling.

A recent review[12] has put forth a preliminary working model that the working group agreed could form the basis of a research agenda. That is, research is needed to understand gender-specific normative standards for plaque progression and composition and how they contribute to worsening clinical outcomes for women. The group prioritized this agenda as critical to formulating an understanding of a working hypothesis on plaque development and progression, including plaque composition, and the interplay between atherosclerosis with myocardial blood flow and vascular function as well as proatherogenic factors including traditional and novel CVD risk factors.

Topic 2: Subclinical, Asymptomatic Women

CVD remains the number one killer of women and men,[13] despite focused public policy and clinical practice guidelines efforts aimed at primary prevention of traditional risk factors. The most recent statistics from the American Heart Association note that 432,700 women and 398,600 men died from CVD in 2006.[13] Although considerable declines have been reported over the past few decades, a detection gap remains that may form the basis for novel approaches to detection of at-risk women. Importantly, a recent evaluation of the NIH-NHLBI Atherosclerotic Risk in the Community (ARIC) study revealed marked declines in sudden cardiac death for men with only marginal trends for women.[14]

For asymptomatic individuals, use of a global risk score (e.g., Framingham risk score [FRS]) is central to the initiation of preventive therapies and the designation of high risk status.[15] Yet, the FRS is a poor estimator of 10-year CVD risk in women less than 70 years of age and in ethnic minorities.[16,17] Efforts to improve the FRS have resulted in an adapted score that includes novel risk markers, such as high-sensitivity C-reactive protein and family history of CVD.[18] Lloyd-Jones also put forth the concept allowing for a differentially lower near-term (i.e., 10 year) risk but focusing on the high lifetime CVD risk in women.[19] More recent efforts have also examined improved classification of risk in women by employing direct atherosclerotic disease markers, such as coronary artery calcification (CAC).[20–22] These reports importantly note that atherosclerotic disease markers, such as CAC, play a unique and additive role in risk assessment of women.[23] Yet, none of these efforts have provided an exhaustive testing and validation of novel risk markers and how they result in net reclassification improvement in important CVD outcomes.[24]

This working group supports a research agenda that would result in improved detection of asymptomatic women at moderate to high risk who may be candidates for more intensive lifestyle or risk factor modification strategies.

Topic 3 - Symptomatic Women

Women present more often for evaluation of chest pain including more frequent atypical symptoms that often include non-specific factors such as fatigue or shortness of breath.[12, 25] Historically, the presence of atypical symptoms in women has often been ignored or treated

as non-cardiac in origin; more recent evidence supports an elevated CVD risk in symptomatic women regardless of its stated quality or characteristics.[26–28]

Diagnostic testing in women is fraught with challenges that include strategies that rely on exercise testing in females with prevalent functional disability.[29–31] The under-recognition on the part of clinicians of women who are functionally disabled and/or are unable to perform routine activities of daily living represents a significant and commonly missed opportunity to focus prevention efforts and identify women at risk for CVD.[32] A second major limitation with current imaging modalities is the high rate of technical limitations or artifact challenges that diminish the accuracy of testing in women.[33] For example, women who are often obese present major technical challenges in terms of imaging and for the morbidly obese, equipment weight limits may preclude testing.

An additional major challenge is that current diagnostic testing strategies seek to define the woman with obstructive CAD, with much of the published literature focusing on the most sensitive and specific test.[33] However, this type of strategy remains poorly optimized for women with non-obstructive CAD. Importantly, demonstration of ischemia in women is often categorized as a "false positive" test when co-occurring with non-obstructive CAD. Yet, evidence supports that the extent and severity of ischemia, as demonstrated on varied cardiac imaging modalities, is an effective risk stratifier of women.[33, 34] This latter point is important because it signifies that ischemia, regardless of the underlying burden of obstructive CAD, is prognostically important. Moreover, the development of gender-optimized, ischemia-guided strategies of care, such as the optimal medical therapy strategy trials (e.g., VA-sponsored Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation [COURAGE]) should aid in focusing anti-ischemic therapy to at-risk women.[35] Moreover, in a recent substudy within the COURAGE trial, a serial testing strategy was put forth that focused optimal medical management toward ischemia resolution as a guide to improving patient outcomes.[36] The development of serial medical management strategies may prove useful for women with chest pain and documented ischemia.

Despite the fact that nearly 10 million women undergo diagnostic testing each year in the US, current guidelines are not supported by randomized trial evidence identifying an accurate and efficient strategy for improved detection and guided treatment of symptomatic women. The development of uniquely female trials oriented toward guiding anti-ischemic treatment strategies based on evidence of demonstrable stress-induced ischemia should be aggressively undertaken.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the public as to areas of investigation that merit greater research.

Recommendations for Pathogenesis of Myocardial Ischemia and Anatomic Correlates

1. Elucidate the sex-specific pathobiology of development and progression of microvascular and epicardial obstructive CAD, including the interplay between vascular dysfunction, nonobstructive atherosclerosis, and plaque composition. To date, the tools available

to image and quantify microvascular abnormalities and plaque characteristics require further development for reliable, clinical (perhaps, noninvasive) application.

2. Research in this area should lead to the development of a model which incorporates anatomic and functional parameters as well as accelerating factors such as hormonal, metabolic, and inflammatory influences which ultimately leads to timely and accurate detection of the vulnerable, high risk, female patient. Current diagnostic testing strategies that focus on obstructive CAD may require a paradigm shift to detecting gender-specific risk markers, including abnormalities within the microcirculation.

Recommendations for Subclinical, Asymptomatic Women

1. Develop highly accurate risk-based algorithms tailored to young and older women and men of different ethnic and racial backgrounds that incorporate and comparatively evaluate the effectiveness of standard risk assessment compared to strategies that include novel (e.g., imaging, biochemical, and physiologic) markers or factors that improve classification of at-risk women. A critical component to gender-optimized, population screening is the accurate detection of moderate-high risk women, necessitating long term risk prediction models.

2. Incorporation of novel risk markers may require collaboration through biotechnology partnerships with the goal to provide clinically useful, inexpensive, reliable, and safe biomarkers.

Recommendations for Symptomatic Women

1. The development of "right test / right woman" diagnostic test strategies focusing on the development of novel, pretest risk scores incorporating symptoms and gender-focused risk factors and comorbidity, in clustering, that result in appropriate stratification of at-risk women.

2. This research agenda should also incorporate comparative effectiveness research employing randomized trials of strategies centered on pre-catheterization, noninvasive as compared to invasive testing approaches.

3. Central to these comparative effectiveness trials are the comparison of strategies incorporating functional, ischemia testing alone or in combination with anatomic approaches.

4. Trial-specific aims must focus on identifying diagnostic testing strategies resulting in improved clinical outcomes, safety, and cost efficiency.

5. Within this agenda is the focus on female-specific protocols (e.g., radial approaches to angiography, smaller catheters for diagnostic catheterizations, new radioisotopes for reduced breast tissue artifact in nuclear imaging) to improve quality imaging, reduce procedural risk, and employ radiation reduction strategies (whenever possible).

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ISSUES OF CARDIOVASCULAR PREVENTION ACROSS THE LIFESPAN WITH AN EMPHASIS ON GENDER AND UNDERSERVED POPULATIONS

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Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in adult women across the United States and approximately one third of women are expected to develop cardiovascular disease in their lifetime.[1] Underserved populations, especially African Americans, experience a disproportionate burden of cardiovascular disease; and a variety of reasons underlie these differences. "Underserved groups" include those with disabilities or disadvantages on the basis of their place of residence, geographic location, age, race, ethnicity, underlying chronic conditions, or social status.[2] These persons may also receive less healthcare because of economic, cultural, or linguistic factors.

Summary of the Discussion

The Working Group focused on differences between men and women in clinical aspects of cardiovascular disease development that deserve greater research attention.

The sections that follow summarize discussions related to several key areas including: 1) education and provider tools; 2) better CVD risk profiling in women from underserved populations; 3) clinical therapeutic gaps in knowledge; 4) basic science; and 5) clinical practice. In addition, the group encouraged further research related to medical records of insured minorities and investigation of the determinants of cardiovascular disease from such resources.

1. Education and Provider tools

Areas of research that merit special attention include: a) provider education; b) school-based interventions; c) workplace educational programs and interventions; and d) community-based interventions that could take place using community facilities and those provided directly to community members.

Measures and Methods. The risk factors for cardiovascular disease are reasonably well understood and current evidence suggests these risk factors apply to women and to underserved populations. Risk factor reduction and improved healthcare performance measures for underserved women are important goals, and further research is needed to specifically identify the methods that are effective in women, who are more likely to be underinsured, have limited resources, reduced access to primary care and subspecialty providers, and modern facilities.

Comparative Effectiveness Research. A variety of ways to improve care and access for women and underserved populations deserve research attention, and many of the opportunities would probably be characterized as comparative effectiveness research. Novel approaches could be compared to existing care models with either serial designs (before-after comparisons) or parallel designs (observations made at the same time and site specific interventions compared) designs.

Different ways to deliver education and care should be evaluated to carry out these types of programs. Research on models of delivery might include comparisons of traditional clinical office-based medical care, use of health providers such as nurses, dietitians, physical activity experts, and disease specific specialists. Newer methods of assessment include quick tools such as risk assessment with easy-to-understand interpretations, and use of techniques that are easily understandable and accessible by patients and clients. The efficacy/effectiveness of financial incentives should also be considered when developing and evaluating programs including the incentives for clients, providers, and employers.

2. Better Vascular Disease Risk profiling in women and underserved populations

Metabolic Syndrome in African Americans. The diagnosis of metabolic syndrome is common, highly linked to obesity, and associated with increased CVD risk. However, the utility and implications of the diagnosis are less clear for African Americans.[3] It is usually defined by the presence of three or more of the following: glucose intolerance, low HDL cholesterol, high triglycerides, elevated blood pressure, and increased abdominal adiposity. Despite higher rates of CVD, the tendency toward lower triglyceride levels and higher HDL cholesterol levels in African Americans may lead to a lower prevalence of this condition than would otherwise be expected. Further study on the determinants of metabolic syndrome risk in African Americans and the

development of effective strategies to prevent or treat obesity in African Americans are greatly needed.

Cardiovascular Disease Risk Profiling. Both Whites and African Americans are very likely to develop cardiovascular disease during adulthood. Most of the risk prediction algorithms were derived from White populations. Less is known concerning how well the risk algorithms can be applied to African American population groups and other underserved groups that were not well represented in the datasets that were used to develop the estimating equations.[4]

Research concerning the accuracy and precision of cardiovascular disease risk assessment in women and underserved groups should include: a) evaluation of traditional risk factors; b) an improved definition of left ventricular hypertrophy by echocardiogram in African Americans; c) consideration of the role of novel markers in blood specimens; d) inclusion of inflammation biomarkers such as C-reactive protein; e) consideration of vitamin D levels, which are well-recognized to be lower in persons with darker skin pigmentation; f) genetics; and g) subclinical CVD assessment. There is also a question of the utility of calcium scoring in African Americans because this population group experiences high risk for vascular disease events but appears less likely to have lesions that are calcified prior to the development of the clinical vascular event.[5, 6]

3. Clinical therapeutics gaps in knowledge

Preserved systolic function heart failure: how to treat it in women. Heart failure is currently one of the most common clinical diagnoses made in American adults and is responsible for a very large number of hospitalizations. Non-invasive methods have been developed to assess heart failure, and it is possible to categorize individuals as having heart failure that has systolic, diastolic, or both systolic and diastolic abnormalities. Women and persons with diabetes mellitus are more prone to develop heart failure with preserved systolic function; and further research is needed to understand the pathophysiology of heart failure and its different presentations in women.

Efficacy of defibrillator therapy in women with heart failure. Patients with heart failure and reduced cardiac output with diminished ejection fraction are candidates for defibrillator implantation. More research is needed about such placements in women.

Nitric oxide enhancing therapy for primary prevention of heart failure. The results of a heart failure clinical trial showed that long-term oral nitrate therapy combined with hydralazine reduced the risk for secondary events in African Americans, especially among African American women. Further research into the mechanisms of benefit is needed particularly concerning whether it extends to the prevention of initial heart failure events.

Are cardiovascular disease preventive therapies different in women vs. men? The efficacy of cardiovascular disease prevention strategies is often assumed to be the same for men and for women. Further sex-specific and minority-specific investigation into the role of cholesterol lowering, blood pressure therapy, antiplatelet therapy, minimally invasive interventions such as catheters, and cardiovascular surgery should be undertaken to improve understanding of

the efficacy and side effect profiles of such treatment strategies in women and underserved minority groups. Part of this research should specifically investigate the role of metabolic and genetic factors that might underlie the differences between men and women.

4. Basic Science

Adult men and women are both very likely to develop cardiovascular disease in their lifetimes. Women experience greater longevity, extremely low risk for vascular disease events prior to menopause, and greatly increased vascular disease risk after the menopause. Investigation of human subjects and animals that are especially susceptible to atherosclerosis is needed to provide further information related to these differences. To better understand the differences in vascular disease risk in humans, studying non-human primates may be especially productive.[7, 8]

A variety of reproductive health issues in women are of special interest related to vascular disease pathophysiology and risk, and would benefit from research, including studies of: (a) the link between CVD and age at menarche or age at menopause; (b) female animal models of CVD and the effects of estrogen preparations on the vascular system; (c) diastolic dysfunction and cardiac remodeling in women; (d) thrombosis risk in women; and (e) the pathophysiology of myocardial infarction and vascular function in women.

5. Clinical practice

Women who experience clinical cardiovascular disease are more likely to have worse outcomes than men.[9] Investigations into the significance of preceding levels of risk factors, gender-related differences in treatments at the time of the vascular events, rehabilitation and convalescent care, and long-term care after the event are important considerations to improve our understanding of these differences.

Specific areas of research that deserve attention include: a) women-centered cardiac rehabilitation; b) telemedicine for rural populations vs. usual care to manage patients; and c) ensuring adequate participation of women in secondary prevention studies.

Recommendations

The following research recommendations may help to provide guidance to health administrators, clinicians, scientists, and the population as to areas of investigation that merit greater research to identify women at increased risk for cardiovascular sequelae.

1. **New education and provider tools are needed, including:**

   - New assessments of the comparative effectiveness of various methods of behavior change and assessments of determinants of response in children, adolescents, and adults.
   - Potential vehicles for interventions include health provider education, school-based interventions, workplace and community-based interventions, and interventions during pregnancy.

- Methodological studies needed include comparisons of new versus traditional models of delivery and studies of the impact of financial incentives.

2. Better vascular risk profiling in minority women and those from underserved populations is needed, including:

- More research to provide better metabolic syndrome characterization in African American women and other minority groups.
- Better risk factor profiling of women from high risk groups, using
  - traditional risk factors;
  - blood pressure assessments and ECG-LVH;
  - novel markers in blood specimens, including inflammation and adiposity markers, vitamin D levels, and genetics;
  - subclinical CVD assessment; and
  - utility of calcium scoring in African Americans.

3. Studies are needed to address clinical therapeutics gaps in knowledge for women including:

- Treatment of diastolic heart failure.
- Efficacy of defibrillator therapy in women with heart failure.
- Nitric oxide enhancing therapy for primary prevention.
  - Shown in secondary prevention mostly in African-American women.
  - Determine whether this therapy is effective for primary prevention in African-American women and other groups.
- Determine whether there are pharmacologic differences between women and men for CV-preventive therapies.

4. Basic science research to address issues such as:

- How do characteristics of menarche, timing of menopause, and quality of ovarian function relate to CVD?
- Female animal models to study estrogens and their preparations' impact on CVD.
- What is the importance of diastolic dysfunction and heart remodeling in women?
- Why is risk of thrombosis/bleeding greater in women?
- Pathophysiology of MI and vascular function in women.

5. Clinical practice studies are needed, including:

- Women-centered cardiac rehabilitation
- Comparative effectiveness research for different medical strategies

- Rural populations
- Urban populations
- Ensuring adequate participation of women in secondary prevention studies

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WOMEN'S CAREERS IN THE BIOMEDICAL SCIENCES

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"For every bright mind that doesn't reach her or his full potential, biomedical research loses a new idea, a new approach, or a new perspective."[1]

Introduction

Over the past few decades, the number of women entering the field of biomedical research has steadily increased. However, the proportion of women in leadership positions has remained consistently low and women still lag behind their male counterparts in attaining positions of scientific leadership.[2,3]

This problem is not unique to women with careers in biomedical science. In 2006, the American Association of University Professors conducted a study evaluating the role of women in higher education. The study included 1,445 colleges and universities and revealed that while women earn more than half of all Ph.D. degrees in the United States they comprised only 45 percent of tenure-track faculty, 31 percent of tenured faculty and just 24 percent of full professorships in 2005-2006.[4]

This pattern also applies to the area of academic medicine where women represent a substantial proportion of faculty positions but the numbers of women serving in leadership positions such as department chairs remain disproportionately low.[3] In an effort to narrow the gender gap in science, medicine, and engineering, the National Institutes of Health (NIH) continues to explore the factors that interfere with the trajectory of women's career paths and to devise interventions to minimize obstacles. In addition, the NIH has well-established programs designed to promote women's careers in the biomedical sciences.

Summary of the Discussion

The working group, comprising clinicians, scientific investigators, engineers, pharmacists, and NIH representatives, discussed the current status of women in biomedical research and the factors that contribute to the gender gap in leadership positions. The majority of the discussion focused on methods whereby the NIH is involved in promoting career development of women in biomedical science to maximize their career potential and to enable their rise to higher positions in academia. The acronym "MILES (Mentoring, Institutional Transformation, Leadership, Educational Pipeline, and Support for Careers) Ahead" was chosen as representing the areas that needed focus to sustain and further the development of women's careers in biomedical research.

The following are the major concepts that emerged from the discussion:

Mentoring

The working group identified mentorship as a key component to a woman's success in biomedical research. There are issues pertaining to both mentors and mentees that must be considered. Group members felt that a large percentage of mentors would benefit from formal mentorship training. They suggested that the NIH could devise and offer methods of training mentors in the development of skills required for good mentorship. This could take the form of workshops at NIH on mentoring, short-term courses at the NIH, and/or even virtual mentorship online courses. Mentees could also benefit from courses developed by the NIH explaining the key ingredients of a successful mentorship relationship and the role of the mentee in accomplishing this goal. The type of mentoring that works best for mentors and mentees could also be explored in such courses. Many NIH K (career development) awards feature a team mentorship approach which may include content as well as career mentors.

Working group members also recognized that there needs to be a formal evaluation of mentors and the mentoring relationship. Mentors, mentees, and the leadership responsible for mentoring programs should take part in the formal evaluations. Mentees also need to receive appropriate and timely feedback. Appropriate multidimensional feedback for both mentors and mentees will optimize good practices and discourage practices that undermine the goals of mentorship. This may be fostered through the development of programs and other institutional methods evaluating the quality of mentoring at multiple career stages.

One of the major obstacles that limit the ability of experienced scientists and clinicians to undertake the mentorship of junior colleagues is lack of funded time for mentoring. This could be addressed by developing and offering grants which support protected time for both the mentor and mentee. One current grant model that could be replicated or extended to funding mentoring programs for women is the NHLBI's "Programs to Increase Diversity among Individuals Engaged in Health-Related Research" (PRIDE). This is a grant that funds research, education, and mentoring programs for minorities with a goal of increasing diversity in the biomedical sciences workforce. Another method that can potentially be used to assist with this effort involves expanding existing grant mechanisms such as the ORWH Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, which is designed to provide mentoring for junior faculty (http://orwh.od.nih.gov/interdisciplinary/bircwhmenu.html).

Additionally, participants discussed other mechanisms which would encourage or reward mentors. Including mentoring activities on biosketches would draw attention to their importance and would be another way of encouraging mentorship. These efforts to recognizing the value of mentoring could have long term benefits by encouraging and enabling scientists of the highest caliber to train and mentor the next generation of scientists.

In addition to mentorship at one's home institution or department, mentorship should also be encouraged across institutions and across disciplines. This would provide trainees at smaller institutions a more diverse and experienced pool of potential mentors and collaborators. Funding agencies and institutions could support programs utilizing novel mechanisms such as cross-institution, cross-disciplinary, or web-based mentorship opportunities that could pair mentees with mentors throughout the country. Such innovative forms of mentoring could

provide support to mentees, mentorship training to mentors, and even opportunities to leverage existing funded research programs as opportunities for mentorship. Social networking Web sites and emerging technologies could be utilized to facilitate connections between mentees and mentors.

Institutional Transformation

Institutions need to equip women in biomedical science with the tools that will enable them to maximize their full potential and rise to positions of leadership. Looking "MILES ahead," funding agencies and professional societies can play an exciting and key role in the development of women's careers in the biomedical sciences by encouraging and rewarding transformational changes within institutions. This would potentially bring about greater retention and job satisfaction of female scientists and faculty.

Institutional career development offices, which address the needs of postdoctoral fellows and faculty, as well as students, would aid in ensuring equal opportunities for career advancement across the sexes. Funding agencies may play a role in offering seed grants to such offices to develop and implement innovative programs and institutions should recognize and value their efforts.

Many NIH institutional career development and training grants provide opportunities and incentives for institutions to leverage the resources of multiple departments to create interdisciplinary or translational programs. The BIRCWH and Clinical Translational Science Awards are examples of such programs, which can foster women's careers by providing extensive mentoring, enhanced research infrastructure, and offering opportunities women to take on leadership roles.

The issue of encouraging women surgeons to go into research while carrying out their mandated clinical duties was raised. There continues to be a need to facilitate research training for those in higher paying specialties and professions; however this cannot be addressed by current grant mechanisms while maintaining equitable salary scales for researchers in all fields. In addition, ensuring that allied health professionals, such as nurses, pharmacists, and physical therapists, have access to research and career development grants would generate research in novel areas and further diversify the scientific workforce.

Leadership

Another overarching goal identified by the working group was increasing the number of women in leadership roles within the biomedical sciences. This requires effective training of women in leadership skills. Programs such as Executive Leadership in Academic Medicine provide extensive year-long training, but tend to be relatively small, costly, and focused on specific career stages. The Association of American Medical Colleges (AAMC) also offers excellent leadership seminars for early- and mid-career women but access to these is also limited and demand often exceeds supply. Professional organizations offer an important opportunity for career development and advancement through their meetings and should be encouraged to provide leadership short courses, which could focus on junior-, mid- or senior-level faculty needs with specific training in leadership appropriate to that level, at their meetings. Organizations could partner with

funding agencies on the planning, development, and execution of such programs which could be inexpensive, widely available, and would provide attendees with both the toolkit for leadership at their current level and a map for further advancement. People would likely be very drawn to such courses and the benefit could be widespread.

In order to narrow the gender gap that exists in leadership positions in the field of biomedical sciences, awareness needs to be raised at the highest levels in institutions. Current statistics on women in leadership roles should be presented to the institutional leaders and discussions held to determine key strategies that would result in more women having opportunities to attain leadership positions.

Leadership succession is also a major issue that must be addressed on an institutional level, and it provides opportunity for gender diversity in leadership as women are prepared and considered for these positions. Early planning regarding the transition of leadership of divisions, departments, laboratories, and major research projects with an attention to the distribution of women in such roles is needed. Funding agencies could require that leadership training be included in career development and training grants, such as NIH K awards. The group suggested that departments that have an active program for faculty development could potentially be recognized for their efforts by their institutions and professional societies.

Recognizing the benefits of inspirational narratives of the journeys travelled by accomplished female leaders in biomedical science, it was thought that a collection of abbreviated biographies of such individuals should be made available to more junior women. These stories would also be enlightening to young women in high school and college, and could result in some of these young women exploring careers in biomedical sciences by providing new role models. The publication *Women in Science at the National Institutes of Health, 2007–2008* could serve as a model.[5] Institutions and professional organizations should be encouraged to develop similar publications and to create exhibits, perhaps during Women's History Month, to recognize and highlight women at those institutions or in those professions.

Educational Pipeline

Educating and exciting girls and young women about science and medicine increases the likelihood that they will choose educational paths that make these careers possible. One such example is the Jackson Heart Study in Jackson, Mississippi, where middle-school children are engaged to participate as health advocates in their communities. Career fairs where biomedical professionals explain their fields and the work that they do to middle or high school students were suggested. In this type of direct interaction, young people can see the passion that these adults have for their work and can ask questions about the steps they need to take to reach these goals. It would be especially powerful to young women if many of these demonstrators were women—as proof that women can achieve in any career. It is important to encourage girls and young women to pursue these professions before they make important decisions about their high school and college curriculum—such as number and type of science and math courses they should take. Working group participants also noted that many career opportunities are not apparent to women entering the work force. The biomedical careers that tend to be emphasized

are physicians and researchers in academic practice. This ignores the vast number of positions in private industry and government, where valuable research and patient care are performed.

Support for Careers

For many women, their central role in the family results in career paths that do not follow the traditional timeline. Because some women choose to either leave their jobs temporarily or decrease their status to part time, programs and policies should be in place so that a woman's career is not limited or ended by the need to attend to family or other caregiving responsibilities. There are currently reentry grants awarded by the NIH for scientists (men or women) returning from providing care for a family (http://grants.nih.gov/grants/guide/pa-files/PA-08-191.html). Since many of the working group members were not aware of these grants, they recommended an effort to increase publicity. In addition, NIH grant applicants who have taken a hiatus from research may apply for an extension of their Early Stage Investigator status.

This alone is not enough, however. There are many women who continue to work while caring for a family member, which can result in gaps in productivity. These women need an extended timeline for career goals, whether that means research deadlines, tenure track mileposts, or other metrics by which researchers are judged. NIH currently provides no-cost extensions on research grants and allows career award grantees to reduce their efforts to part-time for one year. The American Heart Association grant applications ask if there are gaps in productivity and the reasons for them. The NIH is currently exploring mechanisms to offer a similar opportunity on its grant applications.

In addition to increased flexibility, working group participants also suggested that current NIH and professional society career development and mentoring programs be made available across career stages. This increased support will increase the number of women reaching more senior positions—positions of leadership where they in turn can effect change to increase the number of women who achieve research careers.

Recommendations

The following research recommendations may help to provide guidance to health academic institutions, administrators, clinicians, and scientists as to areas of investigation that merit greater research.

1. Mentorship

- Mentor training, in the form of short courses or workshops in conjunction with professional conferences or web-based courses, should be developed to help scientists learn and enhance the skills needed to be successful mentors.
- Training for mentees on how to be effectively mentored and how to mentor others should be provided as part of career development and training grants.
- Expand the availability of interinstitutional and interdisciplinary mentorship, using innovative mechanisms to increase the number and diversity of experienced individuals available to guide more junior women in science.

2. Institutional Transformation

- Academic and research institutions should be encouraged to have faculty development programs, which could be initiated with seed grants from funding agencies and professional societies.
- Expand existing funding opportunities (such as the BIRCWH) where NIH support is likely to be leveraged by institutions.

3. Leadership

- Professional societies and funding agencies should partner to design and conduct leadership courses that focus on junior, mid-level, and senior faculty with specific training in leadership appropriate to each level.
- Create a role for addressing leadership succession in grants. Suggestions include incorporating leadership training or faculty development into career development awards.
- Funding agencies and professional organizations should consider funding institutional faculty development offices which would promote women's careers.
- Develop "Story Corps"-type narratives for women's careers, which can serve as an inspiration for those more junior using the *Women in Science at the National Institutes of Health 2007-2008* as a model.

4. Educational Pipeline

- Institutions, professional societies, and funding agencies should sponsor career fairs encouraging girls and young women to pursue and remain in careers in the biomedical sciences, with an emphasis on having women professionals as presenters to serve as inspirational role models.
- Opportunities for partnership between public and private agencies to create a national curriculum on careers in the biomedical sciences for middle school and high school students should be developed.
- Highlight and share the experiences of accomplished women in biomedical research to provide more role models to young women and the future generation of scientists.

5. Support for Careers

- Flexibility is needed in timelines for research projects for tenure-track for women who are primary caregivers.
- The current reentry grant program should be continued and augmented with more publicity and funding.
- Gaps in productivity due to family responsibilities should be noted on grant applications and reviewers should be educated on how to appropriately weigh these gaps into funding decisions.
- A broader range of career development awards are needed throughout the spectrum of women's careers—early, mid, and senior—to promote career development at all stages.

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APPENDIX A

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