Workshop on Release of Research Results to Participants in Biospecimen Studies

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WORKSHOP SUMMARY

Office of Biorepositories and Biospecimen Research
National Cancer Institute
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I. Workshop Introduction and Background

Patients who contribute biospecimens to research are often interested in the composite results of studies conducted on their biospecimens as well as any individual medical information uncovered during the research process. Proponents of sharing research results contend that human research participants should have the option of receiving potentially valuable information. Opponents maintain that the purpose of research is to generate general knowledge rather than individual data, and that research laboratories are not necessarily held to the same standards as clinical laboratories.

The Centers for Medicare & Medicaid Services regulate all clinical (non-research) laboratory testing performed on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA) to ensure quality standards in the testing and results. Any personal clinical results generated in a laboratory may not, by law, be provided to patients unless they originated in a CLIA-certified laboratory. However, only a subset of research laboratories are CLIA-certified, therefore if the return of results to research participants is to be considered, issues such as how to handle results from non-certified laboratories must be addressed.

Because patients are expressing increasing interest in receiving research results and no national guidance has been offered on this subject, it is critical to generate standards addressing the complex issues associated with the return of research results—both individual and aggregate—to balance the needs of all stakeholders involved in the biospecimen research process.

The National Cancer Institute (NCI) has long recognized the need to standardize and optimize biospecimen and data collection for cancer research and has expended significant efforts to establish evidence-based best practices, which culminated in the June 2007 release of *NCI Best Practices for Biospecimen Resources* (*NCI Best Practices*). *NCI Best Practices* identify salient guiding principles for biospecimen resources[1] that promote state-of-the-science practices and adherence to ethical and legal standards in the collection, storage, and use of biospecimens in research. The current *NCI Best Practices* do not comprise detailed procedures; rather, they consist of principles that guide the development of such procedures by biospecimen resources. The recommendations contained within the document are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen resources and the availability of technological advances that improve the collection, processing, and storage of biospecimens and associated data. Although adoption of these best practices is voluntary, the NCI believes that the principles outlined in the document support the goal of optimizing biospecimens for research.

In October 2007, the NCI Office of Biorepositories and Biospecimen Research (OBBR) held a symposium-workshop titled “Custodianship and Ownership Issues in Biospecimen Research” to define the parameters of custodianship that would allow biospecimen resources to operate in a

[1] NCI defines a biospecimen resource as a collection of human specimens and associated data for research purposes, the physical entity in which the collection is stored, and all associated processes and policies. Biospecimen resources vary considerably, ranging from formal institutions to informal collections in a researcher’s freezer (*NCI Best Practices*, 2007).

culture of transparency, fairness, and accountability to all stakeholders. General consensus was reached on two aspects concerning the release of research results: (1) that exciting aggregate research results should be routinely presented using a newsletter or Web site because publicizing results enhances the public's understanding of the promise of research and builds trust; and (2) that the informed consent document should clearly indicate whether human research participants should expect to be contacted with research results, the form of communication (email, newsletter, or phone call), and the procedure for opting out of communication. The pertinent literature cautions that the option to obtain research results may be *offered* to human research participants, but that research results should not be foisted upon participants (Wolf et al. 2008).

Workshop attendees did not reach consensus concerning the provision of individual research findings to human research participants or on the specific determinants for disclosure or what constitutes clinical validity, as these issues were not the primary focus of the meeting. However, they recognized that providing individual research findings could benefit participants if the results have known clinical applicability, that is, if they could affect a participant's health or his or her family's health now or in the future.

This workshop was planned to develop much-needed best practices and guidance on the sharing of findings from research on biospecimens with human research participants because the organizers recognize that the research community does not have consistent policies or best practices on the subject; that researchers, institutions, and institutional review boards (IRBs) might not be averse to sharing research findings; and that there is even less consensus concerning the disclosure of individual research results to study participants. Following state-of-the-science presentations, the workshop engaged participants with general and breakout discussions and generated recommendations in three key areas: (1) the appropriate handling of diagnostic discrepancies or incidental findings that are discovered during the pathology review of biospecimens; (2) the mechanisms by which individual or aggregate research results might be provided to participants in clinical studies; and (3) the conditions that warrant disclosure of aggregate research findings. (The workshop agenda is included as Attachment A.)

For the purposes of this workshop, a *diagnostic discrepancy* occurs when the diagnosis made at the biospecimen resource differs from the original diagnosis reported by the biospecimen source site. An *incidental finding* is a finding outside the purpose of the study that has potential health or reproductive importance for an individual research participant. Individual findings that might be revealed in a research setting include data specific to a participant's response to medical treatment; for example, patient *A* harbors allele *B*, which leads to a condition that resists drug *C*. *Aggregate results* summarize the study's general findings; for example, the presence of biomarker *X* in patients' blood is indicative of condition *Y* in those patients. Clearly, different ethical and logistical issues are posed by the return of aggregate results compared to individual clinical information. In each of the above defined categories, the roles and responsibilities of the source site, biospecimen resource, sponsor, and research investigator need to be defined. Who should make the decisions? Who should be responsible for communicating findings? To whom should the information be given?

Prior to the formal presentations, Dr. Yassin gave an overview of the objectives of the workshop and what it was seeking to develop. She also said that the workshop was organized like a think

tank; participants were asked to join one of three panels. The workshop brought together leaders from the academic community, patient advocacy groups, and government agencies. (The list of participants in included as Attachment B.) Several experts offered perspectives during the plenary sessions prior to the three panel discussions. The deliberations from this workshop are intended to inform future revisions to *NCI Best Practices* and will form the foundation of policies on research results for the cancer Human Biobank (caHUB), a national biospecimen resource in development by the NCI.

The following is a summary of the workshop proceedings that includes new or revised recommendations regarding return of research results to participants in biospecimen studies, as well as issues that will need further discussion.

II. NCI Welcome Address: Why We Need Policies on the Release of Research Results—*NCI Best Practices* and the caHUB

Jim Vaught, PhD, National Cancer Institute

There is near-consensus in the research community that the lack of high-quality, clinically annotated human specimens has become the most significant limiting factor for translational cancer research. The NCI has taken several steps to rectify this situation: publication of *NCI Best Practices for Biospecimen Resources* (*NCI Best Practices*) to promote standards, formation of the Biospecimen Research Network (BRN) to advance this science, and development of the caHUB to provide high quality biospecimens and associated services. Of these, the caHUB is most pertinent to discussions concerning the return of results to research participants.

The current state of biobanking in the United States might perhaps best be described as "siloed." Independent repositories around the country employ varying collection, processing, and storage procedures as well as data annotation, informed consent formats, materials transfer agreement conditions, supporting information-technology structures, and access policies with differing degrees of transparency. Biospecimen resource best practices documents similarly lack coordination.

OBBR was formed in 2005 to better coordinate biobanking throughout the country. It launched the BRN the following year, and was instrumental in 2006 and 2007 in the formation and publication of *NCI Best Practices*. In 2008, the NCI Director and Deputy Director requested plans for a central biospecimen resource based on the *National Biospecimen Network Blueprint*. Much of 2009 was thus spent performing market surveys, examining organization and funding models, and measuring the risks and benefits of forming the caHUB. In June 2009, working groups were created to study caHUB planning in greater detail. This was followed by the receipt of $60 million in funding through the American Recovery and Reinvestment Act (ARRA) in early 2010 to put the plans into practice. OBBR has spent 2010 issuing requests for proposals (RFPs) and will be awarding caHUB contracts through the end of the year.

NCI Best Practices were published to unify policies and procedures for NCI-supported biospecimen resources, and to provide a baseline for operational standards. *Best Practices* include high-level recommendations for common technical, operational, and safety procedures; quality assurance and quality control programs; informatics systems; reporting mechanisms;

administration and management structures; and ethical, legal, and policy issues such as informed consent, access, privacy protection, custodianship, and intellectual property. This document has been revised for online release in 2011.

The revision process has involved recommendations from OBBR hosted workshops on custodianship, pediatric consent, and biospecimen economics; review and update of all sections with input from subject-matter experts including members of the NCI Biorepository Coordinating Committee; a new management and operations section; greatly expanded custodianship and informed consent sections; and updates to all Web and literature references. The draft was modified based on feedback from the Biorepository Coordinating Committee and other Department of Health and Human Services and NIH offices such as the Office for Human Research Protections (OHRP), Office of Intramural Research, and Office of the General Counsel. The revised document is currently posted for public comment on the OBBR Web site with a link from the *Federal Register*; after the public comment period, input will be considered and incorporated as appropriate before the document is published online.

The *National Biospecimen Network Blueprint* was the concept model for formation of the caHUB. Published in 2003, it outlines key principles for a national biospecimen resource:

- Standardized procedures for biospecimen collection and distribution
- Standardized data sets and data vocabulary
- An integrated information technology system to support all functions
- Harmonized approaches to ethical and legal issues, including standardized consent forms and materials transfer agreements
- Transparent governance and business models, including transparent access policies
- Large well designed, standardized specimen sets

The caHUB is founded on those principles with the vision to be a unique, centralized, nonprofit resource that can serve as a source of human biospecimens and associated data of *measurable high quality* acquired within an ethical framework. The vision also includes the caHUB being a source of high quality biobanking services for the scientific community.

The need for the caHUB has been clearly articulated from many sources. Surveys of NCI investigators and market research involving focus groups of academic researchers and industry decisionmakers indicate an overwhelming need for such a resource. This was echoed by feedback from the caHUB Users Workshop and interviews with commercial tissue providers and industry users in a study of economic considerations conducted by Booz Allen Hamilton. The need is also corroborated by seven years of data requests made via the NCI Specimen Resource Locator and from potential users such as the Cancer Therapy Evaluation Program, the NCI Patient Characterization Center, and numerous biomarkers programs.

As biospecimen supply and demand becomes clearer over time, operations will be modified to optimize investigator access. Current plans are for the central caHUB collection to include benchmark samples, which are biospecimens procured through standardized collection, handling, storage, processing, and distribution protocols that have strict quality control and associated metrics along with the data concerning processing variables; cases with multiple aliquots to enable

confirmation of prior studies or the opportunity to contribute information to prior studies based on new technologies; statistically valid numbers of biospecimen sets; and fully defined "patient case sets" that include tumor, adjacent normal tissue, tumor periphery (i.e., invasive border), pre- and post-operative blood samples, urine, and rich clinical data and outcome information.

Several committees comprising 210 expert participants contributed to caHUB planning. These included an overarching administrative working group and subgroups. The subgroups focused on strategic planning; normal tissue acquisition; biospecimens; facilities; informatics; partnerships and business models; and ethical, legal, and social issues (ELSI). This , workshop will continue the ELSI efforts. These committees' final reports are currently under review by OBBR and eventually will be published on the OBBR Web site as white papers, protocols, and other manuscripts.

The ELSI subgroup considered issues of governance, informed consent, normal tissue acquisition through rapid autopsy, ownership and intellectual property, access policies, data sharing, privacy and confidentiality, conflict of interest, and return of research results. They reviewed current pertinent reports, policies, and publications, identified key issues, and assigned a subgroup member to take ownership of each issue. Their discussions and recommendations are being incorporated into a white paper and informed consent template drafts. The ELSI subgroup identified the return of research results as an issue needing further discussion and additional expertise.

Implementation of the caHUB has two phases. Contracted components make up Phase 1, in which RFPs are being issued for ARRA-funded contracts. The cancer- and normal-tissue procurement contracts will be issued in fall of 2010 and spring of 2011. Thereafter, contracts will be issued for the caHUB comprehensive biospecimen resource (CBR), comprehensive data resource (CDR), and informatics alignment with the National Cancer Database (NCDB). Additional contracts will cover research and development on variables that affect biospecimen collection, processing, and storage. Such research will inform caHUB operations and revisions to *NCI Best Practices* over the next several years. The caHUB Phase 2 will involve centralizing the caHUB from the myriad dispersed Phase 1 contractors, possibly at a site on the new NCI campus. Centralization will be followed by expansion, development of special collections, training, and perhaps other services.

The caHUB is expected to be a transformative endeavor for research involving biospecimens. It should lead to more efficient product development as higher quality samples help advance biomarker research and higher quality specimens help reduce clinical trial timeframes and costs. There should be more efficient regulatory approval: the Food and Drug Administration (FDA) recognizes that "platinum" status specimens may lead to more rapid approvals for new drugs and diagnostics. It might lead to more efficient technology development and clinical implementation as standardized biospecimens allow direct performance comparisons, and benchmark biospecimens allow calibration, performance monitoring, and operator proficiency testing. It also should add clinical value through expedited transition from research standards to standards of care as well as more rapid implementation and standardization of diagnostic assays in clinical laboratories. In total, this work should result in improved outcomes for cancer patients and their quality of life, positive impacts on personal finances, savings to healthcare systems, and positive impacts on national economics.

III. Workshop Chair's Address: Return of Results—Framing the Issues

Ellen Wright Clayton, MD, JD, Vanderbilt University

There is enormous interest in issues surrounding return of results to research participants. Although these issues have been in the public consciousness since the 1980s, interest has multiplied in recent years. Many entities are expending efforts to establish equitable mechanisms for researchers and patients, including the National Heart, Lung, and Blood Institute (NHLBI), which is currently finalizing institutional guidelines; professor Susan Wolf, who has done a great deal of work about the handling of incidental findings; and the Electronic Medical Records and Genomics (eMERGE) Network, which is a recently formed consortium of biorepositories linked to electronic medical records data for conducting genomic studies. Attendees of this workshop have an enormous amount of information to contemplate as they help inform the development of NCI policies.

Many different perspectives and disciplines bear on this topic and must be considered. One perspective is ethical. Some assert that patients are entitled to any and all information pertinent to their biospecimens, and that any effort to constrain available information is paternalism. Others weigh in on the side of utility, although with many different notions of utility, arguing that information should be clinically relevant, pertinent to reproductive choices, or otherwise have personal meaning before being shared.

A great deal of research has addressed patients' opinions about obtaining research results. The Genetics and Public Policy Center has reported that people are more likely to participate in research studies if results are offered in return (Murphy et al. 2008). However, what human research participants choose when they are in the situation of deciding whether to receive results may differ from what they envision when the situation is hypothetical. This issue remains to be explored in greater depth. In any case, data from hypothetical studies should not be seen as forming but as informing policy along with a variety of other individual and systemic considerations.

Recent years have seen the development of sophisticated approaches to clinical data and their interpretation, some of which enable patients to access needed information easily, with some constraints to control the level of information. One proposal involves employing an informed cohort of participants that may access research results at their leisure (Kohane et al. 2007). This sort of set-up requires an informatics system that tracks data and allows access within the agreed-upon ethical framework, along with tools that facilitate interpretation of useful and understandable data without necessarily involving a separate appointment with a sub-specialist. Such nuanced informatics systems will be needed as sharing results with research participants becomes more common. It is generally accepted that it would be highly inappropriate to provide patients with raw data without any interpretative assistance, however, whether an informatics system would be sufficient to provide such assistance is unclear..

One issue that generated a great deal of debate recently is whether results provided to human research participants must be performed in a laboratory with Clinical Laboratory Improvements Amendments (CLIA) certification. The Centers for Medicare & Medicaid Services (CMS) require that any tests pertinent to patient care be performed in a CLIA-certified laboratory. The debate

centers on whether this standard should also apply to research assays as a prerequisite to informing the research participant of the results. This might involve re-testing results that are to be returned in a CLIA-approved laboratory, or converting the entire research enterprise to CLIA approval. This issue will be eventually regulated by CMS and should be considered beyond the purview of this workshop.

In Dr. Clayton's view, the research community has reached consensus that some research results should be returned to human research participants. Each breakout group was asked to address the following complex issues involved in defining which results should be returned and how the return of research results should be accomplished:

- Diagnostic discrepancies will be an issue of particular relevance to the caHUB, as every tissue biospecimen entering the system will be reviewed by a caHUB-pathologist prior to storage. Discrepancies could arise between the caHUB pathologist and the pathologist at the research participant's institution. Pathologists frequently address this issue in clinical practice, and the breakout group was charged with defining how to deal with it in the research setting.
- The issue of incidental findings has been evolving over time. Although returning research results to participants will certainly include information targeted by the researchers, unexpected information may be uncovered, particularly given the increasing use of high-throughput technologies such as gene chips and whole-genome sequencing. A great deal more information will be available to researchers beyond their specific investigation. Do researchers have an obligation to hunt for clinically relevant information that is not pertinent to their studies?
- As the line blurs between clinical and basic research assays, basic research information is becoming more relevant to patient-participants. Investigators increasingly have an obligation to offer participants aggregate research results, particularly in long-term cohort studies.

Each breakout group was asked to consider the mechanism by which results will be returned, covering issues such as how the process will be funded, what expertise will be required in the contactor, and whether genetic counseling will be made available and at whose expense. The individual who collected the biospecimen might not have the understanding to provide participants with an interpretation of results. It is also clear that an individual investigator should not decide on his or her own that a piece of information meets the criteria for return and then contact the participant directly. Supervisory oversight is necessary, whether that be conferring with a colleague or a more formal review mechanism discussed.

IV. Offering Individual Genetic Research Results: Context Matters

Laura M. Beskow, PhD, MPH, Duke Institute for Genome Sciences and Policy

A great deal of debate has been held on the topic of returning genetic results to study participants, and has focused on what types of information should, could, or should not be offered (Beskow and Burke 2010). The issue is challenging because reasonable people can disagree on where to draw the lines. Researchers might want to provide participants with useful information, but questions

arise as to whether that means clinically useful to a patient's own health, personally useful for life planning or personally useful because the information itself is valued even if not actionable.

Several studies have polled participants about the desire to receive results under hypothetical situations, and participants' opinions should be respected by investigators and policymakers addressing the issue. However, further research is needed to understand the nuanced preferences given varying circumstances, such as the extent of data validity or the tradeoff between using limited resources for the responsible return of results versus funding additional scientific investigation.

Additionally, what people choose in actuality frequently differs from what they choose hypothetically, and more research is needed on how participants respond to genetic information in non-hypothetical situations. These preferences might inform whether investigators should choose to offer results to participants, but should not define researchers' fundamental obligations. Continued research on how participants use and understand research results will be important to inform discussions such as those in today's workshop and for translation of policies into practice.

The discussion over whether and what research results to offer participants may be framed in terms of researchers' obligations, which will differ from those of physicians conducting medical care (see Figure 1). Ethically, there is a fundamental duty to rescue another person in imminent danger, but other less extreme contexts will have different obligations for offering genetic research results beyond the obligations of the study at hand. The duty-to-rescue includes several stipulations:

- Minimal action: Little or no risk, cost, or effort to the rescuer
- Individual action (rather than social) by someone in a position to help
- Direct confrontation with a problem (as opposed to a reason to suspect it)
- Evidence of a clear, immediate need (not self-correcting) that requires urgent action
- Prevent harm: Duty is to act, not to succeed

When applied to genetic research results, the duty-to-rescue would arise when information is obtained that clearly indicates a high probability of a serious condition for which an effective intervention is readily available. A possible example of this is identification of a mutation that confers a high risk of early-onset colorectal cancer providing the information to the participant could result in life-saving screening. Human research participants seem to have a general expectation that human decency demands that information would be provided in extreme situations. Because of the duty-to-rescue, participants should be informed that these sorts of results will be disclosed, with no choice of disclosure option, avoiding dilemmas about whether to override participants' stated wishes in extreme circumstances.

When offering research results is not required by the duty-to-rescue and is not necessary to complete the aims of the study, the researchers' obligations are less clear-cut. In the research context, data are generated to provide generalizable knowledge that will eventually contribute to improved human health. This is significantly different from the context of medical care, in which interventions are designed solely to enhance the well-being of an individual patient. When conducting experiments, researchers have the obligation to employ sound methodology and scientific integrity; minimize risks and burdens to participants; and exhibit respect for persons by

obtaining informed consent, protecting privacy, maintaining confidentiality, and ensuring the right to discontinue participation.

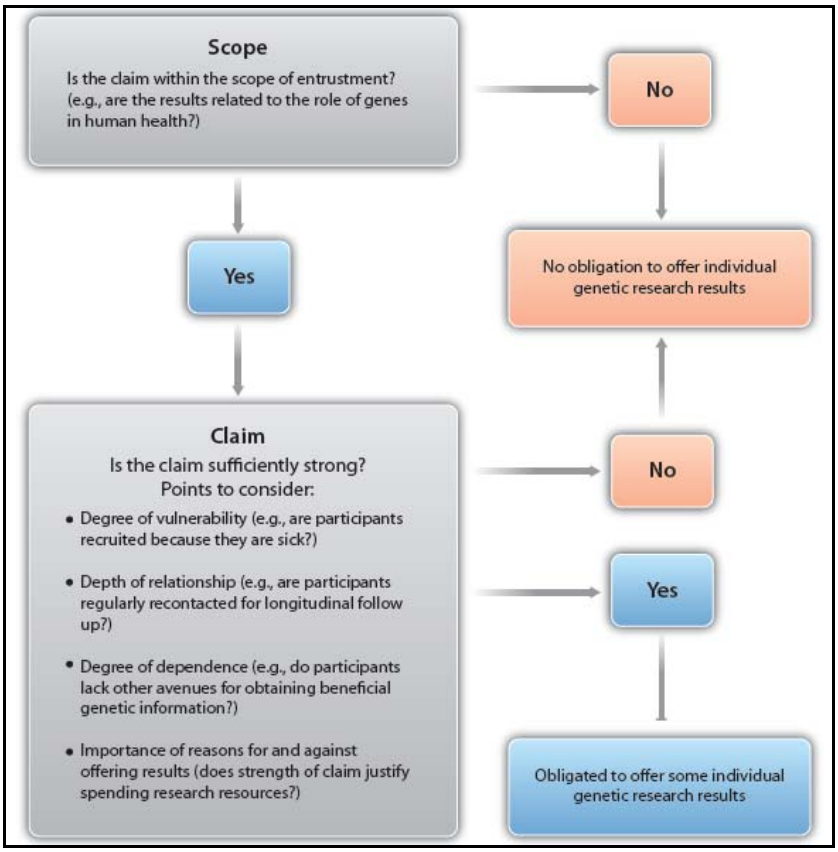

Figure 1. Flow chart illustrating return-of-results considerations

Any additional obligations in the absence of the duty-to-rescue might be considered within an ancillary care framework, that is, care that is not required by sound science, safe trial conduct, morally optional promises, or redressing subject injury. The ancillary care framework can include a continuum of situations. Examples include researchers in developing countries who might, in the absence of personal physicians, treat research participants as patients; and researchers who act as scientists and treat participants as subjects without any interaction beyond what is required for the study. Usually, some middle ground will be found between these extremes, and obligations will depend on such researcher-participant factors as the scope of entrustment and the strength of claims in terms of vulnerability, relationships, gratitude, and dependence. Another factor is the importance of reasons against returning results (Richardson and Belsky 2004; Belsky and Richardson 2004).

The scope of entrustment pertains to aspects of participants' health entrusted to researchers upon enrollment in the study. It is set by the permissions researchers obtain to carry out a study validly and safely, and thus is partial and dependent upon the nature of the study. In the context of genetic research results, permissions obtained are generally broad, stating that biospecimens and data will be used for studies of how genes affect health, or how genes affect responses to treatment. In such cases, the scope of entrustment is defined by the role of genes in human health and disease. Despite its breadth, this scope is not unlimited because it relates to health only and does not

encompass matters of personal meaning that people might apply to genetic information. The strength of claims between researchers and participants will depend in part upon permissions granted to researchers, which render participants vulnerable to researchers' discretionary power and determine the participants' degree of vulnerability. Researchers' decisions about how to respond to the information they collect or generate may affect participants' well-being. This vulnerability may be compounded when participants are ill or experiencing oppression or poverty. Thus, the nature of the study population is an important contextual consideration. This might apply to genetic research in which individuals diagnosed with a particular condition are recruited and study results are offered to foster participants' understanding of their illness, even though the results might not be clinically useful. Such decisions can be made during the study design stage, including plans to involve participants' physicians in communication about results, and included in informed consent documents.

The depth of the researcher-participant relationship will also influence the strength of claims. It varies from study to study because different protocols demand interactions of varying intensity and duration. When the researcher-participant relationship is deeper, it can be argued that researchers have stronger moral responsibility to engage with a fuller range of participants' needs. In terms of genetic research, the depth of relationship can range from no interaction to one interaction to extensive ongoing interactions. Initial assessment should be performed by the investigator who originally collects and stores the research biospecimens and data, with obligations about sharing occurring under the control of that investigator.

The degree of gratitude of the researcher toward participants also influences the strength of claims between researcher and participant. Researchers may owe a debt of gratitude to participants who have accepted uncompensated risks and burdens, or offered a rare scientific opportunity. Offering results as an expression of gratitude assumes that the information has some value to the participants, which might not be the case. This assessment of obligations is less applicable to individual genetic results because expressions of gratitude should be of uniform value to all participants, but genetic information by definition will be unique to each individual and thus is not uniform; gratitude would be more appropriately expressed through the offer of aggregate results, which would be common for all participants. Participants frequently note that they would be interested to know whether the study in which they participated was helpful to anyone. Informing them of these results expresses respect for them as individuals and acknowledges their contribution to the study.

Another determinant of the strength of claims is the degree of dependence; participants may become dependent on researchers because they might be impoverished, lack health insurance, or join a trial because it is their last hope. When considering genetic results, researchers should ask themselves, "How much difference would provision of individual genetic research results make to the participants' health?" Researchers might find themselves in a unique position to help because the genetic information is beneficial to the participants and there are limited other sources for obtaining it. However, participants must still understand that research analyses cannot be guaranteed to be returned with the same timeliness as clinical testing.

The strength of claims for ancillary obligations will differ depending on the study context. For example, strong claims could be made in family-based studies for gene discovery or assessment of

genotype-phenotype correlation, research in collaboration with rare disease advocacy organizations, or community-based participatory research with disadvantaged populations. More moderate claims would exist for studies involving population-based biospecimen resources designed to have ongoing interaction with participants, or for studies in which participants are recruited through their source of health care but without regard to disease status. Weak claims would be made in situations such as secondary analysis of data shared from a repository under the control of a third party, or studies performed using banked biospecimens left over from clinical care with de-identified medical information.

Because the research context is foreseeable at the time a study is designed, the possibility of return of results can be planned and included in research budgets and informed consent processes. Although professional judgment, the nature of the information, and participant preferences should be factored in, decisions on whether to return research results should be grounded in the researchers' sense of obligation in different contexts.

Discussion

Dr. John M. Jessup asked for clarification on the research context in which the breakout groups should be considering the possible return of results to participants. Individual institutions, cancer centers, multi-center clinical trials, and other research settings might have different biobanking strategies and funding mechanisms that inform beneficence, autonomy, and other considerations. Dr. Clayton replied that the breakout groups should consider a variety of research situations, adding that Dr. Beskow's suggestion regarding the distance between a researcher and research participant—in terms of relationships or time—and how it might alter the researcher's obligations, is not universally accepted. Dr. Vaught agreed that ideally, guidance should be developed for a variety of settings beyond the relatively narrow focus of the caHUB. Ms. Marianna Bledsoe commented that broad recommendations should consider the biobanking context involved in returning research results as well as the research context.

Dr. George Martin asked whether it would be ethically or otherwise unwise to limit participant recruitment to individuals who agree to have research results returned to them, thus avoiding dilemmas that would arise from finding critical information about a participant who stated a preference to not receive results. Dr. Beskow emphasized that the criteria for duty-to-rescue are not frequently met in research situations, and that perhaps people indicating they would not want to know results are inappropriate for research participation. Dr. Clayton agreed that research participation is not a right; therefore anyone might be excluded if that exclusion does not affect the study design and generalizability of the results.

Dr. Pearl O'Rourke asked whether the breakout groups should consider exclusively genetic results or a broader range of results. Dr. Rihab Yassin explained that the the breakout groups should address all research results, although examples have been provided concerning genetic results because this seems to be the area that has received the greatest attention. Ms. Deborah Collyar noted that the term "genetic research" should be defined for participants in the informed consent documents. The consent should also note whether the resulting information would be applicable only to the participant or might also affect the participant's genetic relatives.

Dr. Andrew Hruszkewycz commented that research laboratories do not normally have regulatory oversight of quality management and results. Therefore, the results might not be accurate enough to share with participants. Dr. Clayton suggested that the breakout groups acknowledge quality control issues in research laboratories and consider whether re-testing of results in a CLIA-approved laboratory would be an appropriate recommendation.

Dr. Lynn Dressler commented that from the point of view of the patient, information important to that patient's health has the same value whether it is revealed by an investigator with whom the participant has a relationship or someone further removed, such as a user of a publicly available database. Therefore, it might be worthwhile to consider whether and how to return research results regardless of the relationship between the researcher and the participant. Ms. Jane Perlmutter added that in the case of the caHUB, the initial recipient and custodian of the biospecimen, the caHUB would be responsible for returning any pertinent results. Common criteria should be established that apply consistently to any biospecimens collected and then dispersed by the caHUB.

As a patient advocate, Ms. Collyar noted that the context of the research to the patient should be considered. For example, individuals frequently are involved in more than one study; therefore the group should consider how results from multiple studies should be combined and communicated. Different individuals have different information needs, and the important point to consider is how a particular person can use a particular piece of information.

Dr. Yassin requested that the breakout groups work to harmonize terminology in the setting of research results.

- Dr. Elizabeth Mansfield commented that the Food and Drug Administration considers research and investigations to be distinct; research does not deliver results from a genetic device or test to the patient; an investigation involves patients to whom the risks of the investigation have been explained, for example, that the test might be incorrect.
- Dr. Beskow explained that consensus has not been reached in the field as to the definitions of such terms as "personally meaningful" or "clinical utility." Dr. Beskow uses the term "clinical utility" to refer to information upon which the participant might choose to act, for example, in seeking an intervention or making reproductive decisions; she defines results with "personal meaning" as results that might enhance one's sense of identity.

Dr. Clayton noted that ethics specialists strongly disagree whether findings with personal meaning should be returned to research participants. She added that frequent return of results will necessarily engender follow-up testing with the attendant costs and consequences; this is another aspect for the breakout groups to consider.

V. Return of Individual Research Results: Perspectives of Institutional Review Board Members and Staff

Lynn G. Dressler, PhD, The University of North Carolina at Chapel Hill

The Genetic Research Review and Issues Project (GRRIP) Consortium recently conducted an inter-CEER (Centers for Excellence in ELSI Research), multi-site study on a broad range of issues

pertaining to genetic research (Lemke et al. 2010). Although the GRRIP study focused on genetic research, the findings can be generalized. The study was conducted in three phases, all of which included a return-of-results component:

- Qualitative interviews with IRB members and genome researchers
- Quantitative national surveys with members of Public Responsibility in Medicine and Research (PRIM&R) and American Society of Human Genomics (ASHG)
- Consensus-building through partnerships with PRIM&R, ASHG, and Genetic Alliance to identify gaps and develop policy

Results of the qualitative interviews with IRB members were the subject of Dr. Dressler's presentation. The study involved semi-structured in-person or telephone interviews followed by coding of the results by the team for analysis with the goal of learning the participants' positions, concerns, criteria, and processes for judging the appropriateness of returning results to research participants. It included 6 sites throughout the United States and 31 individuals who have been active IRB members (24 participants—12 healthcare providers; 8 researchers; 1 representative each of law, ethics, and community; and 1 of unknown profession) or staff (7 participants) within the past two years and who had roles in the review of genomic research studies. There were 13 males and 18 females who had reviewed an average of zero (1 participant), between one and three (20 participants), or more than four (10 participants) genetic or genomic studies per month.

The question, "Should individual results from genetic or genomic research studies be returned to study participants?" received a spectrum of responses. All said "yes" in some form or another, many with qualifications that often pertained to the context of the research and the results in question. Many contended that individuals should have the right to choose whether or not to receive information about themselves. Others considered the risks associated with return or lack thereof, and still others expressed concern about the consequences of returning results. Many suggested considering the potential future meaning of results with currently unknown significance. One individual asserted that, as a general ethical and moral principle, all participants should be told of any information pertaining to them.

Many respondents were of the opinion that return of results depends on any number of factors, including the disease in question, the strength or validity of the results, whether an intervention is available, and the implications of imparting the information. Some stated that mutation status is not an interpretation but a fact, and contended that researchers should be permitted to inform participants that they have a particular gene. Problems arise with drawing conclusions based on information from a relatively early phase of research. These opinions reflect the dimensions of uncertainty confronting IRBs concerning results' meaning, predictive value, and utility; the negative emotional, economic, lifestyle, or other impact of knowing and acting on research results; and the potential positives of self-empowerment and intervention implementation.

The question, "What are the conditions for returning or not returning individual results?" received two general classes of responses, some relating to clinical utility and others to personal utility (Figure 2). In terms of clinical significance, several modifying conditions were discussed, including CLIA-approval of the laboratory in which the research was conducted, seriousness of the condition, available interventions, clinical significance or validation of results (however, neither of

these terms was defined), and potential negative health or clinical consequences of withholding the information. Personal utility was mentioned in terms of respect for the research subject, reciprocity, non-medical interventions such as lifestyle or reproductive choices, and possible future impact on health. All the conditions discussed revolved around the research subjects' preference to be told, and the implications of returning the findings, such as whether an infrastructure is in place to support returning results and what the return would mean for the patient, for example, in terms of potential family discord.

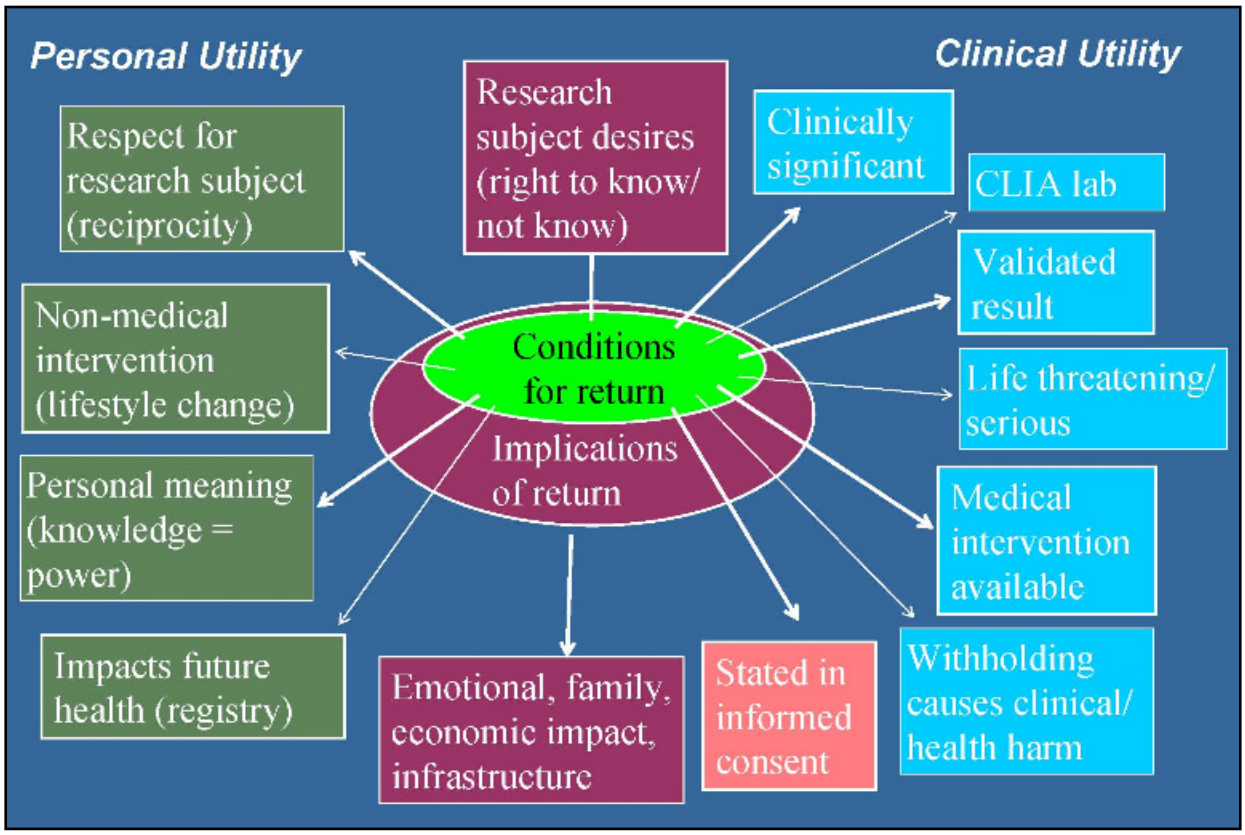

Figure 2. Opinions about conditions for the return of research results

Because actual situations rarely meet ideal conditions, GRRIP offered specific examples of situations in which results might be returned. The first involved susceptibility to blood clots or stroke, in which genes had been identified related to hyper-coagulability but the results had not been obtained nor could they be validated in a CLIA-approved laboratory because no CLIA laboratory performs the relevant assay. The general response to this situation was to favor return even though the results were not validated because there is a low risk to return and a high potential benefit in terms of interventions that might be undertaken to help prevent stroke.

The second example pertained to sub-typing for Fanconi's anemia in which the sub-typing assay could only be performed by one expert laboratory that is not CLIA-approved. The results would be important to research subjects' health because different alleles impart high risks for leukemia, solid tumors, or other ailments. The responses to this hypothetical situation were mixed, acknowledging that it would be an awkward situation. Results might be offered in a non-official capacity.

IRB members and staff were also asked about the process for return of individual research results. The consensus was that the decision should be a team effort including research investigators, scientific and medical peers, other experts, and a genetic counselor or medical geneticist. Opinions were mixed as to the role of the IRB, some stating that the IRB should be involved in making the decisions, others that it should oversee the process of decisionmaking. Little mention was made of involving research subjects or patient advocates in decisionmaking except in terms of the participants' right to know.

None of the sites has a formal process for returning research results, although several have rules, guidelines, and recommendations. Respondents expressed a desire for guidance, some wanting a general framework and others more detailed ground rules.

The guidelines in place for IRBs pertain either to the beginning of the study or later in the process. At the beginning of the study, it is the responsibility of the researcher to state his or her intentions regarding return of results and the participants' options. The IRB application should include the likelihood of obtaining meaningful results, and consider potential future meanings of results. Suggestions were made to add to the IRB application a risk-benefit analysis and the rationale for returning or not returning results. The IRB's responsibility is more problematic when return-of-results issues are not addressed until after the completion of the study. When such issues arise, guidelines state that they should be dealt with by appropriate experts on a case-by-case basis, considering the availability of medical interventions.

Rules in place for IRBs generally state that results must be validated in a CLIA-approved laboratory and communicated by a trained professional. One suggestion for dealing with after-the-fact issues involves a two-tiered optimal process. The first tier would involve the principal investigator, peers, clinicians, experts, and the IRB judging the significance, validity, and actionability of the finding. If the findings are judged to be significant, the second tier would involve the IRB, genetic counselors, the treating physician, and other experts such as psychologists and ethicists to consider the implications for the research subject. Then an appropriate process for communicating the finding should be decided upon, considering whether the research subject wants to know, how the finding should be presented—the consensus was that results should be presented in person not in writing—what support, follow-up counseling, or care would be needed, and what infrastructure, logistics, and funding would be needed.

The IRB interviews revealed a complex web of tensions and varying tolerance for uncertainty. The tensions resulted from several limitations, including experience with return-of-results analysis and decisionmaking, national guidance to help frame the analysis, and comfort with return of results decisionmaking in the context of genetic and genomic research. The increasing prevalence of genetic and genomic studies was concerning to many respondents. Other tensions resulted from conflation of research "tests" with more familiar clinical tests; the blurring of the line between research, for which IRBs are responsible, and clinical care, in which IRBs are not involved; and different risk-benefit analyses than normally performed by IRBs, which involve more tangible instances of immediate physical safety or harm and consideration of the entire research continuum (Figure 3). Often IRB guidelines recommend that results from a "fishing expedition" or preliminary data should not be returned, whereas results with clinical utility should. Perhaps the line should be drawn on the continuum somewhere between analytical and clinical validity, in

which either results with clinical utility are returned or testing in a CLIA-approved laboratory is offered.

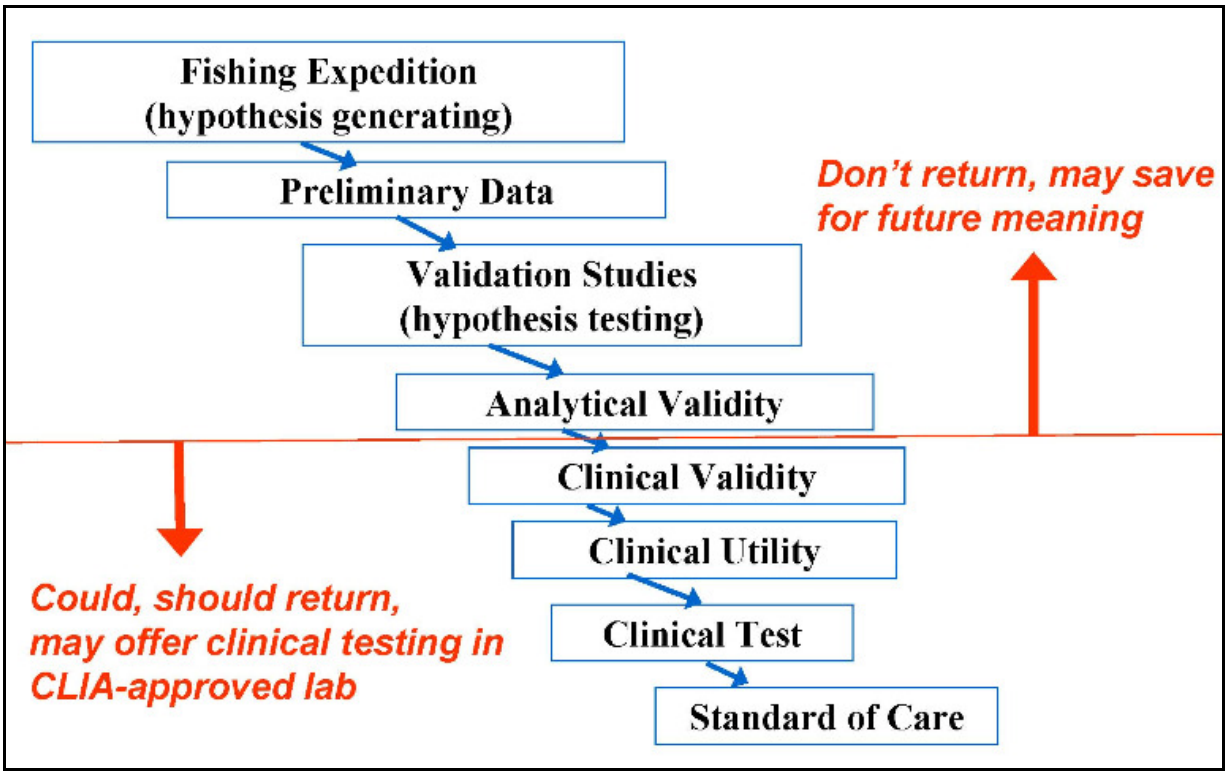

Figure 3. Return of results and the research continuum

To move IRB policy forward, the tensions and uncertainties need to be addressed, particularly the distinction, or lack thereof, between research and clinical care. A common nomenclature should be agreed upon for terms such as de-identified, clinical validity, utility, test, and research result. Finally, a different approach is needed for assessing the risks and benefits of returning an analytically valid result, considering whether the prediction of the outcome is accurate and potential changes to the significance of the results over time. IRBs need standards of reference that are consistent with the requirements of a reasonable person, the best interests of the patient, available medical interventions, and the respect for patients' rights. Case-based training would assist IRB members and staffers in considering the issue and understanding the research continuum, the basics of genetic research, and the potential impact of genetic results. The opinions represented here should help inform workshop breakout group discussions.

VI. Patient/Advocate Perspective

Mary Lou Smith, JD, Research Advocacy Network

Few clinical trial cooperative groups return research results to human research participants as part of their standard procedures. From the patients' perspective, however, there are ethical bases for doing so, including respect for participants and their contributions, the possibility that findings might affect willingness to participate, and recognizing participants as partners in research.

One survey showed that patients overwhelmingly state that they would like to be provided with aggregate research results (Partridge and Winer 2002) or at least offered the option, which few indicated they would decline. However, the participants were younger and better educated, on average, than the general population, perhaps skewing those results. Markman (2006), however, contends that providing aggregate research results risks emotional harm while offering no therapeutic benefit to the patient. Dixon-Woods et al. (2006) finds that when offered the option to request aggregate research results, only 20 percent did so; most of this group was more interested to learn which treatment group they were in, and many misunderstood the written findings they were provided. Schulz et al. (2003) and Snowdon et al. (1998) conclude that people generally want to know aggregate research results even when the information might be emotionally distressing.

Both Partridge and Winer (2002) and Fernandez et al. (2003b) evaluated potential benefits of returning aggregate results to research participants. They concluded that it increases patient satisfaction, has a potential impact on patients' future health, improves patient perception of research itself, improves the research accrual process and outcome, improves patient-physician communication, increases research visibility and awareness, and enhances public and potential participants' understanding of the promise of research. Patient concerns about receiving research results are that they might get information they did not want to receive, might not understand the results reported, will experience anxiety related to reliving a difficult time, will learn they were at risk or treated for an ailment, or will learn that they or their child has an increased risk for health problems. Researcher concerns focus on giving patients bad news, clinician and staff time needed, recontacting patients, and potential conflicts with researchers concerning individual versus generalizable knowledge.

In a survey of 10 patients in a kidney cancer support group that asked directly whether respondents would want individual research results, all indicated that they would: four would want the information to be provided by their doctors, two by the researcher, two by a genetic counselor, and two by the researcher along with a genetic counselor. Patients generally are concerned with themselves as individuals, whereas patient advocates are interested in benefiting everyone with a particular disease. When 100 patient advocates were asked whether individual genetic research results should be given to participants, more than 30 percent responded. Of the 37 percent saying yes, 63 percent said it depends, and none said no outright.

The "it depends" respondents indicated the following mitigating factors: if there is full explanation in the informed consent documents, if the patient wants the information, if the information is clinically relevant and validated, if an expert is available to discuss the results, if lawsuits are a possibility, correlative science, and whether the results pertain to children of the participants. Opinions about who should provide the results were again mixed, with 29 percent saying it should be a genetic counselor, 23 percent the participant's physician, 19 percent the researcher, 3 percent the tissue bank staff, and 26 percent other, which included the person most qualified and/or someone who has a relationship with the patient. Some patients might consider their specialist, such as an oncologist, rather than their primary care physician the appropriate physician to return research results.

This same group of advocates was asked whether information on diagnostic discrepancies should be provided to individuals who donated their tissue for research. One individual responded no,

approximately 70 percent responded yes, and 30 percent said that it depends on one or more of these factors:

- Whether the discrepancy would be clarified
- Whether the discrepancy impacts health, welfare, or emotional well-being
- What the findings are and the impact they will have on the individual, to be judged case-by-case
- Whether the physician knows about and is prepared to discuss the results with the patient
- Whether the person wants to receive individual genetic results

Another consideration is that the information might not be available until months or years after the biospecimen is donated.

When asked whether information about incidental findings should be provided to individuals who donated their tissue for research purposes, 80 percent said yes, one individual said no, and 20 percent said that it depends upon the purpose of the research and what is in the informed consent document. This group added that the findings should be provided if they impact future medical care of the individual or his family, an ailment could be prevented or detected early, and the patient elected to receive them. An alternative offered by one respondent is to send the participant a letter stating, "We believe it would be appropriate for you to have (name of test needed) performed by your physician's lab."

A question pertaining to the return of aggregate results from clinical studies resulted in approximately 70 percent saying yes, 30 percent saying it depends, and one individual saying no. The "it depends" group mentioned that the rationale for returning results is to validate and show respect for research participants, but the results might be overwhelming for patients in treatment and would require more explanation by the physician. The individual's contribution to the study should be clarified. Results should be returned only if desired by the participant.

The advocate group was next asked whether individual results from clinical studies using biospecimens should be provided to participants; 34 percent said yes, 16 percent no, and 50 percent said it depends. The mitigating factors noted in this instance were whether:

- The option was included in the informed consent document and the participant wants the results
- The results would impact the participant's health, welfare, or emotional well-being
- The study was complete, unblinded, and published
- The results would offer benefits such as alerting the participant to a health problem that could and needs to be addressed
- It would be feasible to return results to participants
- An explanation would be given by the participant's physician and a genetic counselor

One respondent suggested that the data set not be de-identified so that information can be linked back to individual participants.

When asked whether research results should be analytically and clinically validated prior to being returned, 84 percent said yes and 16 percent said no; whether participants should be offered the opportunity to decide if they want results returned, 97 percent said yes and 3 percent said no; and whether genetic counseling should be offered before and after returning results, 66 percent said yes and 34 percent said no. Respondents also noted that participants should sign a disclaimer; incomplete research results would only cause anxiety and should not be offered; training , including cultural competency, should be offered to those providing the results; and that there should be an opportunity to have the information included in a patient's medical chart. Other comments were that returning research results is helpful and encourages participation, and that families and participants want aggregate results because trials are group research not individual treatment plans.

Holding workshops such as this one and forming guidance on the return of results to research participants offers the opportunity for partnership between the research and advocacy communities. Additional studies are needed to understand fully what patients want, which might differ between hypothetical scenarios and real situations.

Discussion

Dr. Jennifer Hunt commented that another issue for the breakout groups to consider is that some assays, such as that for the BRCA mutation, are patented, and this might influence the disclosure of research results.

Dr. Susan Wolf sought clarification as to whether the information presented by Dr. Dressler included incidental findings as part of the research results to be returned. Dr. Dressler explained that this was left open to interpretation by the IRB respondents, many of whom considered incidental findings as defined by Dr. Wolf in her publications, and that IRBs would benefit from consistent definitions of such terms as incidental findings and diagnostic discrepancies. Dr. Wolf noted that many recommendations make a distinction between diagnostic discrepancies and incidental findings, a distinction that is important for biospecimen resources, because clinical and analytical validity—as discussed by Dr. Dressler—might differ.

Dr. Wolf noted with interest the two-tiered approach to returning results outlined by the IRB respondents. The breakout groups have several models to consider, including models outlined by Kohane et al. (2007), some of which are more driven by participant involvement and preferences. She added that the desire for more Federal guidance is shared by many, and encouraged the breakout groups to attempt to achieve high-level guidance and uniformity in the recommendations. Dr. Dressler agreed, commenting that the caHUB ELSI working group discussed that biospecimen source sites should not be expected to devise their own policies on returning results. Therefore, the recommendations produced by this workshop should be viewed as best practices that can be applied or adapted as appropriate at contributing sites.

Dr. Kenneth Mandl commented that new high-throughput technologies allow thousands or millions of tests to be performed simultaneously, thus involving IRBs in the return-of-results decisionmaking process could rapidly overwhelm IRB committees. Perhaps this issue is beyond the purview of an IRB, and a parallel oversight structure that remains linked to IRBs should be

considered. Dr. O'Rourke concurred, and added that non-research clinicians might be polled for their opinions on returning research results, because they frequently express a desire not to be burdened with involvement beyond referring patients to studies. IRBs would be useful resources for information about regulations, for example, concerning patient contact, but Dr. Dressler agreed that a non-IRB oversight board that interacts with IRBs would likely be welcomed by IRBs; a great deal of the contention and concern expressed by IRB members stems from their uncertainty about whether issues related to return of results to research participants are their responsibility.

Dr. Perlmutter observed that multiple IRBs are frequently asked to consider the same question, for example, when a study spans regions overseen by more than one IRB. Creating a parallel oversight board might lead to similar duplication of effort.

Ms. Bledsoe asked whether Dr. Dressler's survey included any examples of situations in which researchers found a result in a non-CLIA-approved laboratory and recommended that participants have the test redone by a CLIA-approved laboratory. This was not an example offered in that survey, but was a path recommended by some respondents. Validation of results might involve repeating testing in CLIA-approved laboratories, but a contentious issue is whether the researcher should seek such validation or pass the onus and cost on to the participant by merely recommending that the participant (via his physician or some other third party) have the test performed.

Dr. Perlmutter commented on the idea that results with little utility now might have more utility later because the store of knowledge is increasing. She suggested that a return-of-results model might include a portal for participants to access that fills over time with information from their donated biospecimen. Dr. Clayton added that some participants balk at the idea of an individual or group filtering what information is made available to them; a consideration for the breakout groups is whether this might be more acceptable if expert scientists serve as the filtering agent. Another consideration is whether a filtering agent might be acceptable if it only judges analytical or clinical validity. Dr. Perlmutter explained that a scientific filter would judge the merit of the information. A different type of filter would be needed to judge the ethical rationale for returning results or not. Ms. Smith added that more research on patient preferences will be needed to understand what patients mean when they say they do not want filters on the information.

Dr. Clayton posed several additional situations for patient advocates to consider:

- If a researcher that has no relationship with the participant, such as a downstream user of banked data, learns something of value about the participant, does that researcher have an obligation to notify the participant if possible?
- If information about a participant today becomes significant in 10 years, is anyone, even the participant's physician, required to unearth the 10-year-old data? If any piece of collected data imparts an obligation to return results to the participant any time in the future no matter where the participant might be, that is a huge responsibility.

Dr. Perlmutter contended that the caHUB, rather than individual researchers, should address such issues and have arrangements in place to implement whatever is decided. Dr. Helen Moore noted that science is constantly progressing, and a genetic variant that has clinical relevance might be

discovered years from now. If a user of a public database uncovers the presence of such a variant years down the road, should it be the responsibility of the biospecimen resource to facilitate contacting the participant? That would place a great deal more responsibility on the research community than is currently the case.

Dr. Martin stated that as a patient, if he were at risk for macular degeneration, he would want to know because sometime in the future there might be a preventative treatment he could seek. Dr. Martin added that involvement of IRBs in determining the process for the return-of-results decisionmaking will lead to enormous heterogeneity, which is counter to the desire the community has for standards and Federal guidance. Dr. Dressler replied that this effort should be informed by the current IRB guidelines in the Code of Federal Regulations. Without an efficiency test in which the same case is sent to multiple IRBs, heterogeneity is likely. This workshop should result in best practice recommendations that might be agreed upon by IRBs and collectors and users of biospecimens. Putting these recommendations into practice in the caHUB will reveal any problems or issues that remain to be addressed and will inform how IRBs handle this issue in general.

Ms. Collyar commented that it is not feasible to expect individual researchers to contact individual participants about individual results 10 years after the biospecimen collection. To date, the research community has not done a good job of studying expectations in advance of issues arising. This workshop and the formation of the caHUB offer an opportunity to set expectations, for example, to give participants aggregate results accompanied by the best interpretation possible at the time and to help physicians provide specific information to individuals. Once a workable framework has been established, it will guide IRBs to an extent. She urged the breakout groups to discuss bare-bones issues so that guidance might be developed to set general expectations at all levels: for patients, physicians, and researchers.

VII. Breakout 1: Appropriate Handling of Diagnostic Discrepancies or Incidental Findings in the Context of Pathology

Chair: Jared N. Schwartz, MD, PhD, Aperio Technologies, Inc.
Co-Chair: Nicole C. Lockhart, PhD, National Cancer Institute, NIH

Members:

Joy Boyer
Lynn Dressler, DrPH
Symma Finn, PhD
Marianne Henderson, MS
Jennifer Hunt, MD, MEd
Jennifer Loud, CRNP, DNP
Mary A. Majumder, PhD, JD
Mary Lou Smith, JD
Sheila Cohen Zimmet, JD

Session Focus: Provide recommendations concerning the processes for communicating diagnostic discrepancies or incidental findings discovered during the pathology review of biospecimens contributed for research.

Diagnostic discrepancies or incidental findings constitute unique concerns to established biospecimen resources and to the planned caHUB. At these resources, every biospecimen obtained would undergo pathologic review by preeminent, board-certified pathologists. In most cases, the review would confirm the original diagnosis made at the source site. However, on rare occasions, a

different diagnosis may be reached or new incidental findings revealed that differ from what was reported by the source site. The caHUB ELSI subgroup recommended that the informed consent document should notify individuals that their samples will be reviewed by the caHUB and any clinically relevant information regarding diagnosis will be communicated to them via their institution.

While significant work has been done on the classification of incidental findings discovered in the course of research (Wolf et al. 2008; Table 1), work on human biospecimens presents additional challenges and considerations. Depending on how the biospecimens are collected, human research participants may be unaware that their biospecimens are being used in research, particularly in the case of residual biospecimens originally obtained for clinical purposes (Clayton 2008).

Table 1. Recommended Classification of Incidental Findings (Table 5 in Wolf et al. 2008: 235)

Category	Relevant Incidental Findings	Recommended Action
Strong Net Benefit	• information revealing a condition likely to be life-threatening • information revealing a condition likely to be grave that can be avoided or ameliorated • genetic information revealing significant risk of a condition likely to be life-threatening • genetic information that can be used to avoid or ameliorate a condition likely to be grave • genetic information that can be used in reproductive decisionmaking: (1) to avoid significant risk for offspring of a condition likely to be life-threatening or grave or (2) to ameliorate a condition likely to be life-threatening or grave	Disclose to research participant as an incidental finding, unless s/he elected not to know.
Possible Net Benefit	• information revealing a nonfatal condition that is likely to be grave or serious but that cannot be avoided or ameliorated, when a research participant is likely to deem that information important • genetic information revealing significant risk of a condition likely to be grave or serious, when that risk cannot be modified but a research participant is likely to deem that information important • genetic information that is likely to be deemed important by a research participant and can be used in reproductive decisionmaking: (1) to avoid significant risk for offspring of a condition likely to be serious or (2) to ameliorate a condition likely to be serious	May disclose to research participant as an incidental finding unless s/he elected not to know.
Unlikely Net Benefit	• information revealing a condition that is not likely to be of serious health or reproductive importance • information whose likely health or reproductive importance cannot be ascertained	Do not disclose to research participant as an incidental finding.

A participant who may have been given no prior opportunity to opt out of receiving incidental findings would be suddenly confronted with a decision on whether to receive potentially important information. Even if the research participant consented for use of a biospecimen in research, the consent may be broad or unclear (Clayton 2008). From the researcher's perspective, if biospecimens are collected for the purpose of broad future research, it is difficult to determine what information about incidental findings should be included in the informed consent document because the range of possible findings could vary widely. In some instances, biospecimens may be completely anonymized; reporting incidental findings would be impossible.

In addition to considerations concerning the return of diagnostic discrepancies or incidental findings, a variety of operational issues regarding how these processes would occur should also be addressed. The mechanism by which this type of information is transmitted from the biospecimen resource to the biospecimen source site needs to be established. Additional considerations include whether agreements between biospecimen resources and source sites should stipulate that patients must be informed of any discrepancy or incidental findings and outline the conditions under which discrepancies or new diagnoses are imparted to patients. For example, this would be done only in instances when a differential diagnosis would have treatment implications. Other issues to consider are how differences in opinion between the biospecimen source site and the biospecimen resource will be resolved and whether affected patients will be encouraged to seek additional opinions.

A. Areas of General Consensus

The group began by agreeing on the definitions of key terminology and the scope of its charge.

- A *biospecimen* is any human biological material that might be saved in some manner for research, such as solid tissue, cells, blood, spinal fluid, or hair. A *sample* is a portion or aliquot of a biospecimen.
- A *biospecimen resource* is any institution that banks biospecimens, from an individual scientist with biospecimens in a laboratory freezer to a large, multi-site tissue procurement and storage organization.
- A *diagnostic discrepancy* is any diagnosis made on the biospecimen that is different from the clinical diagnosis, that is, the diagnosis listed in the annotation associated with the biospecimen from the biospecimen source site. This might reflect a difference of opinion and does not imply that the initial diagnosis was incorrect. An example of a diagnostic discrepancy is a clinical diagnosis of leiomyosarcoma that is later determined to be pleomorphic sarcoma during pathology review at the biospecimen resource.
- An *incidental finding* is any clinically relevant information about a biospecimen that was not noted at the biospecimen source site. “Incidental” should not be taken to mean unimportant or insignificant. It is simply unexpected in the medical context of the biospecimen and/or study. An example of an incidental finding is detection of leukemia cells in a bone-marrow sample from a patient who was not believed to have leukemia.

The group next agreed that its charge included not only cancer patients but also all potential patient-donors. General recommendations should encompass any diseased as well as non-diseased, normal biospecimens. Discrepant diagnoses or incidental findings are most likely to occur on solid tissue biospecimens because they are most likely to undergo pathology review at the biospecimen resource. However, the recommendations should cover all biospecimen types because, for example, experimentation conducted on cells extracted from nearly any biospecimen have the potential to result in diagnostic discrepancies or incidental findings. On the other hand, this does not mean that every biospecimen entering a biospecimen resource must be reviewed; blood, urine, and other biospecimen types are not routinely given pathology review prior to storage, nor do best practices recommend that they necessarily should.

1. Diagnostic Discrepancies

Best practices recommend that pathology review is performed on every solid tissue biospecimen before it leaves the biospecimen source site and as it enters the biospecimen resource. Such reviews should be performed by a board-certified pathologist or a panel of the same. Participants acknowledged that in practice, biospecimen resources do not always have the ability in terms of funding and/or staff to perform pathology review on all incoming biospecimens. Additionally, a portion of a tumor is sometimes sent to the hospital pathology department for clinical diagnosis and a different portion, one that has not been evaluated onsite by a pathologist, is reserved for research. In this case, the source site pathologist might not welcome contact about a potential discrepant diagnosis on a sample he or she has never seen. Another potential confounder in the consideration of discrepant diagnoses arises if the biospecimen received by the biospecimen resource is not reviewed immediately but after months or years in storage. In such a situation, difficulties might arise in locating the patient. Additionally, returning information concerning a diagnostic discrepancy might be moot because treatment will likely have been completed. For these reasons, untimely notification of discrepant diagnoses might not engender cooperation from the source site pathologist. The group made the following recommendations based on best practices.

> **Recommendation 1.1:** A pathology report should be prepared for any biospecimen that has undergone pathology review at the biospecimen source site. This report should include a statement that the biospecimen or a portion thereof was transferred to the biospecimen resource.
>
> **Recommendation 1.2:** If a biospecimen source site changes the diagnosis pertaining to a biospecimen or portion thereof that has been sent to a biospecimen resource, the biospecimen resource should be notified of the change and the reasons for the change.
>
> **Recommendation 1.3:** If a biospecimen is delivered to the biospecimen resource *after or concurrent with* a primary pathology clinical interpretation, a secondary pathology quality assurance evaluation should be performed, using standard best practice assays (for example, hematoxylin-and-eosin stain or cytology preparation), prior to banking and within a clinically reasonable period of time. It is recognized that intake quality assurance is not always feasible, but good science requires good biospecimens, for which documentation of biospecimen quality is critical.
>
> > **Recommendation 1.3.a:** A study should be conducted comparing the cost of quality assurance pathology review at intake with the cost of long term storage of poor- or unknown-quality biospecimens.
> >
> > **Recommendation 1.3.b:** A study should be performed assessing the cost to scientific progress and credibility generated by publishing data derived from biospecimens of unknown quality.

Occasionally a test performed in the process of patient diagnosis, such as an immunohistochemical assay for estrogen or progesterone receptors might be repeated by the biospecimen resource or in

the course of research. The group decided that discrepant results in such a situation should be handled in the same manner as diagnostic discrepancy.

> **Recommendation1.4:** Biospecimen resources and researchers are not obligated to repeat clinical tests. However, if an assay is repeated and the results do not concur with those of an initial clinical assay, this should be treated as a diagnostic discrepancy and handled according to the steps outlined in Recommendation 1.6.

2. Incidental Findings

Biospecimens upon which prior pathology review has not been conducted are certain to be sent to biospecimen resources. These might include tissue samples from non-disease controls or fluid biospecimens such as blood or urine. Although biospecimen resources and researchers do not have an obligation to perform pathology review on such biospecimens, best practices recommend that solid tissue biospecimens, at least, undergo review prior to long term storage.

> **Recommendation 1.5:** If a tissue biospecimen is received upon which no primary pathology clinical interpretation has been performed, a pathology intake evaluation should be performed using standard best practice assays (for example, hematoxylin-and-eosin stain or cytology preparation) prior to banking and within a clinically reasonable period of time.

Occasionally, such biospecimens might reveal previously unknown information pertinent to the patient-donor's health. For example, a malignant melanoma might be identified on a skin biospecimen from a presumed healthy donor. Additionally, biospecimens are frequently screened for infectious disease upon entry to a biospecimen resource. Biospecimen resources are not required to perform such screening, but if they do, the process might reveal pertinent information, for example, the presence of hepatitis in a blood biospecimen that was collected in conjunction with a tumor biospecimen from a cancer patient. Information concerning such incidental findings should be returned to the biospecimen source site, patient's physician, and/or the patient through the same mechanism as diagnostic discrepancies (see below).

3. Process for Returning Diagnostic Discrepancies or Incidental Findings

The group based the process for returning information about diagnostic discrepancies and incidental findings upon similar processes currently employed in clinical settings. Pathologists frequently seek second opinions pertaining to a particular diagnosis, and occasionally the second opinion does not concur with the first. In this situation, the pathologists typically confer, discussing the reasons for the discrepancy. If no agreement is reached, a third (or more) pathologist might be consulted. Such discussions are documented for legal purposes. Each institution has procedures in place for informing the physician of the patient in question about any discrepancies so appropriate action may be taken. With that in mind, the group devised a flow chart (Figure 4) illustrating the steps to follow in the cases of diagnostic discrepancies or incidental findings.

> **Recommendation 1.6:** Adopt an established protocol for handling any diagnostic discrepancy or incidental finding that has the potential to impact the patient-donor's health. The protocol should include verification of analysis and diagnosis, proper notification of

the principal investigator of the study and the pathologist(s), re-review if necessary, and adherence to the biospecimen source site's institutional patient-notification protocols, as appropriate.

Recommendation 1.6.a: If the biospecimen resource personnel and the original pathologist do not reach agreement, an impartial and knowledgeable third party should be consulted. If that third party agrees with the biospecimen resource personnel, the original diagnosis should be amended and the patient notified as appropriate using existing institutional procedures. If no agreement is reached, the biospecimen resource should be notified so that a decision may be made about further storage and use of the biospecimen.

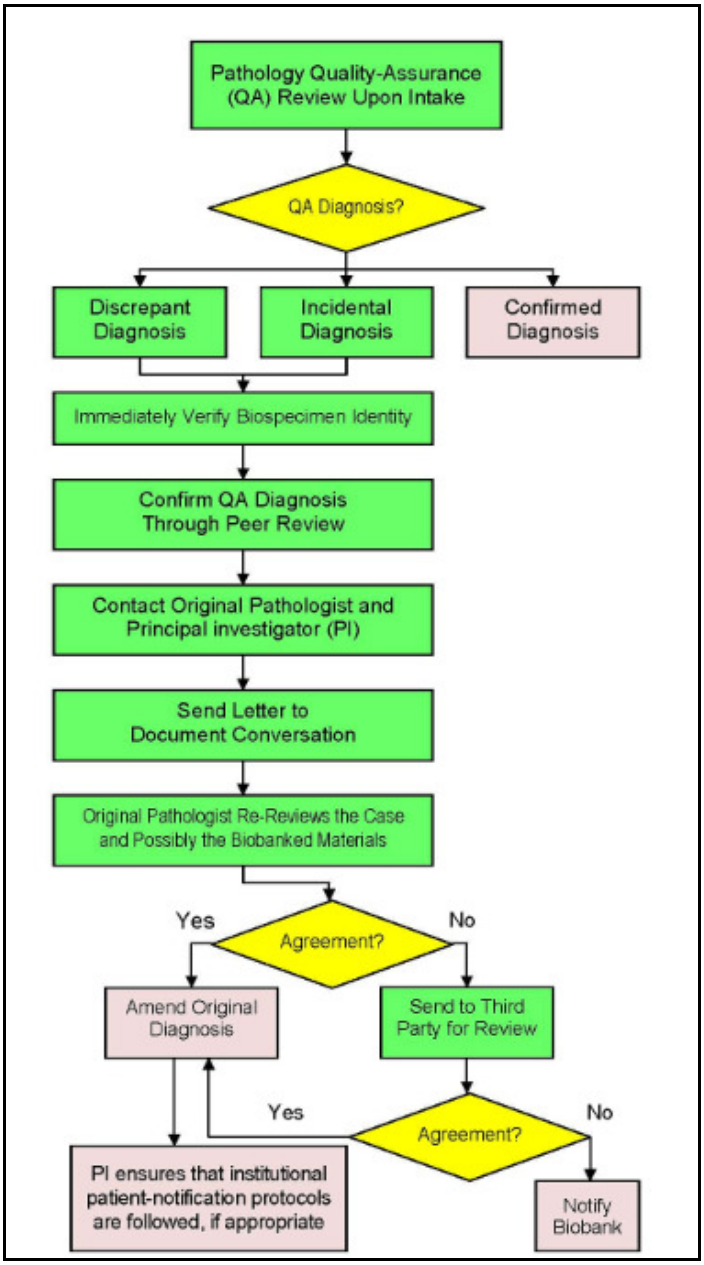

Figure 4. Flow chart proposing protocol for handling diagnostic discrepancies or incidental findings

Finally, the group discussed patient expectations in terms of discrepant results and incidental findings, and concluded that patients should know whether their biospecimens will be banked and/or used for research, and whether there is a possibility that a discrepant diagnosis or incidental finding might be identified.

Recommendation 1.7: Informed consent documents should include a general statement as to whether clinically significant differences of opinion pertaining to the diagnosis or other information related to the patient's health will be returned. Consent documents should be simplified and the above statement should only be included if diagnostic discrepancies or incidental findings will be reported back to the patient.

Recommendation 1.8: Generally, a link to patient identifiers should be maintained at the biospecimen collection site so that diagnostic discrepancies or incidental findings may be handled in the manner most beneficial to the patient-donor. If biospecimens are to be anonymized and used for research, this should be disclosed in the informed consent documents.

B. Issues for Further Discussion

There were no issues identified for further discussion.

VIII. Breakout 2: Release of Research Results from Clinical Studies

Chair: Pearl O'Rourke, MD, Partners Healthcare System, Inc.
Co-Chair: John M. Jessup, MD, National Cancer Institute, NIH

Members:

Christine D. Berg, MD	Jean E. McEwen, PhD, JD
Andrew Hruszkewycz, MD, PhD	Tracy L. McGregor, MD
Penny Keller	Jane Perlmutter, PhD, MBA
Irina Lubensky, MD	Katherine Schneider, MPH, GCG
Elizabeth Mansfield, PhD	Richard Schwab, MD
Karen Maschke, PhD	Susan M. Wolf, JD

Session Focus: Provide recommendations concerning the conditions and processes for releasing individual or aggregate research findings from biospecimens collected for/in the course of clinical studies.

With the new scientific endeavors such as genome-wide association studies, epigenetic studies, and whole genome-sequencing, the line between research and medicine has become less distinct. The biomedical research community's traditional reluctance to provide individual research findings to human research participants has been challenged by the increased likelihood that clinically actionable and relevant findings could be revealed. Strong arguments persist both in support of and against the disclosure of research information to biospecimen contributors (Dressler 2009; Table 2). The same ethical principles of respect for persons, beneficence, and non-malficence support both sides of the argument (Shalowitz and Miller 2005; Dressler 2009).

Table 2. Arguments for and against disclosure of individual research results (Table 2 in Dressler 2009: 4272)

A. Arguments Supporting Disclosure
   - Respect for persons
     i. Self-determination, autonomy
     ii. Consideration of value of research result to research subject
   - Beneficence/nonmaleficence
     i. Empowerment/proactive lifestyle-changing behavior
     ii. Information should not be withheld when it provides evidence of immediate risk to or significant health information for individual participants
     iii. Withholding information is acceptable if:
       a. disclosure would predictably compromise the safety of a participant or third party, OR
       b. disclosure would compromise scientific validity

B. Arguments against Disclosure
   - Respect for persons
     □ Informed consent: participation under conditions of nondisclosure
   - Beneficence/nonmaleficence (maximize benefits, minimize harms)
     i. Research findings must be confirmed, validated, and proven clinically useful, otherwise risk false reassurances or unnecessary scares, do more harm than good
     ii. In the United States, by law, only CLIA-approved laboratories can provide information that will be used in treatment decisions (Clinical Laboratory Improvement Act, 1988).
   - Contrary to the intent of research
     i. To create generalizable knowledge, not necessarily to benefit individual research subject

Those in favor of disclosing research-derived information to individual biospecimen contributors cite respect for individual autonomy, empowerment of research participants, and treatment of research participants as partners in the research process. Opponents express concern about the risk of harm to individuals resulting from disclosure, citing unclear scientific validity, inconclusive results, and the unknown psychosocial implications of disclosure. Opponents also contend that disclosure of individual results is contrary to the concept of research, which is to provide generalizable information (Clayton and Ross 2005; Dressler 2009).

Few studies have evaluated patients' opinions about receiving individual research findings (Dressler 2009). A survey of 40 potential biospecimen contributors in North Carolina indicated that research participants understand that investigators generally do not provide individualized information to participants. However, a majority indicated that they would expect investigators to contact them or their physicians concerning any information with serious health implications (Beskow and Dean 2008; Beskow and Smolek 2009).

Policies on returning individual research findings have evolved over the past decade (Wolf et al. 2008; Table 3). In a recent review, Knoppers and Kharaboyan (2009) concluded that "international policies are converging towards an ethical duty to return individual genetic research results to subjects, provided there is proof of validity, significance, and benefit." This reflects the general consensus among Federal, professional, advisory, commercial, and advocacy groups that research results must be analytically and clinically validated prior to any disclosure (Renegar et al. 2006; Avard et al. 2009; Dressler 2009). These groups also agree that the investigator should not make this decision alone but in conjunction with an IRB and other experts, and the intent to disclose or not disclose results should be made clear to biospecimen contributors in the informed consent

process (Renegar et al. 2006; Avard et al. 2009; Dressler 2009). *NCI Best Practices* do not include recommendations on this topic, and the caHUB ELSI subgroup did not reach consensus on who may be responsible for determining whether research results should be communicated to the biospecimen contributor or on the process for communicating such results. Other unresolved topics include disclosure to family in the case of a deceased biospecimen contributor and disclosure in a health area unrelated to the original objective of the project.

Table 3. Comparison of Recommendations on Returning Individual Research Results (Table 3 in Wolf et al. 2008: 230)

National Bioethics Advisory Commission (NBAC)*	Return results only if: (a) "the findings are scientifically valid and confirmed" (b) "the findings have significant implications for the subjects' health concerns" and (c) "a course of action to ameliorate or treat these concerns is readily available."
Centers for Disease Control [and Prevention] (CDC)**	Criteria for returning individual results in population-based genetic research: "When the risks identified in the study are both valid and associated with a proven intervention for risk reduction, disclosure may be appropriate."
National Heart, Lung, and Blood Institute (NHLBI)***	Criteria for returning individual genetic results: (1) "The risk for the disease should be significant, i.e. relative risk>2.0. Variants with greater penetrance or associated with younger age of onset should receive priority." Note: "Genetic test results should not be reported to study participants and their physicians as clinically valid tests unless the test(s) was performed in a CLIA-certified laboratory. If the test was performed in a non-CLIA-certified laboratory, a CLIA-certified laboratory should be sought to confirm results by redrawing a sample and performing the test within the CLIA-certified laboratory. Results reported by a research laboratory should be identified as 'research' results." (2) "The disease should have important health implications, i.e. fatal or substantial morbidity or should have significant reproductive implications" and (3) "Proven therapeutic or preventive interventions should be available."
National Research Council & Institute of Medicine (NRC & IOM) ****	In human embryonic stem cell research, the duty to report individual research results "depends in large part on the reliability of the findings and the significance of the information to human health." "CLIA regulations do not permit the return of research results to patients or subjects if the tests were not conducted in a CLIA-approved laboratory."
National Human Genome Research Institute (NHGRI)*****	Upon their request, "[r]esearch participants should have access to experimental research data except when…[t]he research results are of unproven clinical validity and the IRB has judged that there is no benefit to the research subjects."

* National Bioethics Advisory Commission (NBAC), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (Rockville, MD: 1999), I: at 72.
** L.M. Beskow et al. "Informed Consent for Population-Based Research Involving Genetics," *JAMA* 286, no. 18 (2001): 2315-2321, at 2320.
*** National Heart, Lung, and Blood Institute, *NHLBI Working Group on Reporting Genetic Results in Research Studies*, Meeting Summary, Bethesda, MD, July 12, 2004, available at <http://www.nhlbi.nih.gov/meetings/workshops/gene-results.htm> (last visited January 8, 2008).
**** National Research Council and Institute of Medicine Committee on Guidelines for Human Embryonic Stem Cell Research, *Guidelines for Human Embryonic Stem Cell Research* (Washington, D.C.: National Academies Press, 2005): at 89-90.
***** National Human Genome Research Institute, *Federal Policy Recommendations Including HIPAA*, available at <http://www.genome.gov/11510216> (last visited January 8, 2008).

In analyses of key ethics sources, Wolf et al. (2008) concluded that researchers have an obligation to ensure that research participants are made aware, in informed consent documents, of the possibility that important medical information might be discovered in the course of research, with possible benefit to their health or well-being. Additionally, researchers should establish a mechanism for communicating pertinent individual findings to participants, and the informed consent documents should clarify this mechanism (Wolf et al. 2008). Ravitsky and Wilford (2006) proposed a nuanced approach to providing individual findings to human research participants. It entails analysis of the analytic validity and clinical utility of the results in the context of the study

and the personal meaning of the findings to the recipient. The approach also accounts for the investigator's ability to disclose the findings appropriately, the investigator's relationship with the research participant, and whether the research participant would have access to the information through other means.

The persistent discussions around disclosure of individual research results in bioethics publications suggest a continuing lack of consensus, particularly on the specific determinants for disclosure or what constitutes clinical validity. One key factor in the decision of whether to disclose or not disclose individual research results should be the preference of the research participant. Accordingly, it would be necessary to seek input from the research participants' community to assess what would be useful information to return (Dressler 2009).

A. Areas of General Consensus

The breakout group began by noting that the term "biospecimen resource" is ambiguous because biorepositories or tissue banks vary in size and scope. A biospecimen resource could range from a single freezer containing biospecimens from one study to a separate entity into which researchers deposit biospecimens that have been collected for many studies. Breakout group members noted that clarifying what is meant by "biospecimen resources" is necessary to better articulate who is responsible for reporting research results. They agreed that the IRB should review and approve proposed mechanisms for the return of research results and that the institution with which the research participant signed consent for biospecimen collection is ultimately responsible for communicating research results. "Research results" is another term that must be clarified. In some studies, what constitutes a research result is clear, but for others, in which someone enrolls in a protocol to donate a biospecimen for unspecified future research, the research result is poorly defined.

1. Determining Responsibility for Return of Research Results

For the purposes of discussion, the breakout group established a model in which biospecimen source sites (primary researchers) collect and store biospecimens under IRB-approved protocols and informed consent processes. These sites deposit biospecimens in the biospecimen resource, which then provides samples and coded data to accessing investigators (secondary researchers) for use in further research. Secondary researchers would not be able to re-identify samples and data, and therefore, secondary research would not be considered human subjects research. However, samples and data can still be linked, with either the biospecimen source site or the biospecimen resource itself holding the links. Research results can be generated at three levels: by the primary researcher, by the biospecimen resource conducting internal reviews of the biospecimen, and by secondary researchers using samples of the biospecimen. Although the recommendations generated could be applied to other biospecimen resources, the breakout group focused on the caHUB model, which is intended to bank a collection of high-quality biospecimens and data. The breakout group agreed that even results obtained from secondary research should be returned to human research participants if the results meet certain criteria. Although the group acknowledged that some secondary researchers, particularly commercial entities, might hesitate to report such results because of patent or intellectual property issues, it agreed that the biospecimen resource should require, as a condition for receiving a specimen, that secondary institutions have a mechanism for identifying and alerting the resource of potentially returnable results. Group

members suggested that such a requirement be included with other expectations outlined in materials transfer agreements for secondary institutions.

> **Recommendation 2.1:** Collecting institutions should use clear informed consent language to describe the circumstances under which research participants may receive individual, clinically relevant research findings and the mechanisms for communicating such findings.
>
> **Recommendation 2.2:** The informed consent document for biospecimen collection should provide an opportunity for research participants to opt out of obtaining individual research results.
>
> **Recommendation 2.3:** The cost and any associated staffing required for disclosing individual research results should be accounted for in the planning of a biospecimen resource.

Group members noted that the possible return of research results should be considered before the study begins. In addition, although the research investigator is most familiar with the study results and is ultimately responsible for identifying those that might be returnable, the investigator should not make this determination alone. Both Federal and institutional guidance is needed, and a mechanism should be in place before the study begins so that, if a potential returnable result is discovered, the responsibility and process are clearly defined. Thus, the investigator is responsible for anticipating study results that might be returnable and for proposing a mechanism by which those results should be reviewed and returned, consulting available Federal and institutional guidance. The IRB overseeing the study is then responsible for reviewing this proposal during the initial review of the protocol. When a potentially returnable research result arises, the investigator should notify the IRB and seek guidance on whether the result should be returned. Although some potentially returnable results can be anticipated during study design, the possibility of unanticipated results should also be acknowledged.

The breakout group agreed that in instances in which the duty-to-rescue is invoked, research investigators are ethically bound to return research results. On the other hand, sharing some information desired by some research participants might be unethical. The bulk of the initial breakout discussion therefore focused on a "smart filter," defined as a list of criteria that would serve as guidance for the research investigator and IRBs. Such a filter would prompt the investigator to identify potentially returnable results, and would be used by the IRB to evaluate the validity of the results and determine whether the results should be returned. Breakout group members agreed that a filter should include information specified in the informed consent documents (e.g., return the result or not; what types of information would be shared), analytic validity, clinical or health significance or seriousness, and whether a result is clinically actionable. They also agreed that "clinically actionable" should be viewed in its broadest sense; knowing the result might not lead to obtaining a cure, for example, but it might help participants in planning for the future or in better understanding their diseases or conditions. The group acknowledged that for many existing biospecimen resources, informed consent for future research use of banked biospecimens may not have been obtained.

There was some debate as to whether all four principles should be met or whether there should be a matrix of "high-medium-low" that could be applied on a case-by-case basis. Some members supporting use of a matrix noted that the four core principles are not always bimodal and suggested, for example, that a result scoring high on all four principles would be returned, whereas one scoring high on some and low on others would require a judgment call. Other members noted, however, that unless the lines between high, medium, and low could be clearly drawn, using a matrix would foster disagreements and thus be counterproductive. The group agreed to recommend that all four principles be met, although members acknowledged the possibility of tradeoffs in some cases.

The group also debated whether reproductive or personal significance should be included in the filter. Many members agreed on the importance of sharing results that might inform a research participant's reproductive decisions, but they also noted the high probability of finding actionable results in genetic or genome-wide association studies and the large amount of information a patient might receive. For example, some members pointed out that for every sample taken from a patient, these studies could generate five to ten alleles associated with a severe trait that requires genetic counseling. With respect to personally meaningful results, some group members expressed concern that providing research results that would not improve health outcomes or help participants understand their conditions might produce unintended costs that could have an impact on policy or societal resources. Others thought returning personally meaningful results would be acceptable if analytic validity has been established. Cost-benefit was also raised as a potential component of the filter, but it was not clear whose perspective—research participant, institution, or researcher—should take precedence. The breakout group agreed that reproductive and personal significance should be considered as warranted by the situation and by the preferences of the participant. Recommendations for filtering should be limited to research in which return of results is not an experimental aim of the study.

The breakout group agreed that all research investigators, whether primary or secondary, are responsible for proposing a mechanism for return of research results and triggering that mechanism once a result is generated. For primary researchers collecting biospecimens during the course of their research, the investigator is responsible for identifying potentially returnable results. The IRB is ultimately responsible for evaluating the results' validity and determining whether they should be returned to research participants. The breakout group agreed that the IRB might need guidance from an advisory group with relevant expertise in the assays used by the investigator. The group also acknowledged that funding would be needed to support the additional activities of the investigator and IRB.

The biorepository itself should apply the filter as it reviews the validity of potentially returnable results generated by internal reviews of stored specimens. However, although the filter would be the same, oversight (i.e., who does the filtering) at the level of secondary research is not clear. The breakout group agreed that responsibility for filtering should not lie with local IRBs at secondary institutions, but there was some debate as to whether the filtering should be done by the biospecimen resource or by the primary researchers that had collected the biospecimens. Although existing models state that the institution that obtains consent and collects the biospecimen is ultimately responsible for informing participants of research results, the group also acknowledged that such a responsibility could constitute an unfair burden when these institutions have no control

over downstream research. The possibility that secondary research might use biospecimens from multiple sources is an additional complication.

The breakout group thus agreed that the biospecimen resource can no longer be a passive entity that stores biospecimens. The biospecimen resource should assume responsibility for applying the filter when potentially returnable results are discovered in the course of secondary research. Although the biospecimen resource might elect to take responsibility for applying the filter itself, it might be more likely to delegate that responsibility to a separate entity. In that case, it should still be responsible for ensuring that filtering is done and for updating the filter as needed. In addition, secondary institutions should assume some responsibility for the results they generate. They should be required by the biospecimen resource to ascertain the quality of the data they generate, and take responsibility for triggering the process for evaluation and return of results. The breakout group thus agreed that the biospecimen resource should take on a coordinating role that includes input from both the primary and secondary institutions. Mechanisms such as material transfer agreements could be used to specify the responsibilities of all parties and what types of results should be brought back to the biospecimen resource.

> **Recommendation 2.4:** When a research study protocol is submitted to the IRB for initial review, the research investigator should anticipate potentially returnable results that might arise from the research and propose a mechanism for review and return of those results to research participants.
>
> **Recommendation 2.5:** For both anticipated and unanticipated research results, a "smart filter," defined as a list of criteria, should be used to determine whether to return results to research participants. This filter will be used by the research investigator to identify potentially returnable results, and by the IRB to evaluate the validity of the results and determine whether those results should indeed be returned to participants. The filter should include the following core principles:
>
> - The research participant agreed in the consent process to receive research results.
> - The result is analytically valid.
> - The result is clinically significant or serious for the participant.
> - The result is clinically actionable. "Clinically actionable" should be interpreted broadly. For example, the result might not lead to a cure, but it could help the participant better understand a clinical condition or plan for the future.
>
> While in general, all four principles should be met, in some cases, tradeoffs between the criteria may be required.
>
> > **Recommendation 2.5.a:** Although the costs and benefits of returning a research result were proposed for inclusion in the filter, more research is needed. For example, it is not clear whether the perspective of the research participant, the investigator, or the research institution should take precedence when considering the costs of returning a result.

Reproductive significance and personal meaning might also be considered on a case-by-case basis. The filter should not be static; it should evolve based on what is learned from the process for returning results.

> **Recommendation 2.6:** For results discovered by primary researchers or the biospecimen resource, the IRB at the primary institution is responsible for evaluating the validity and significance of research results. The IRB may seek guidance from an advisory committee that includes members with expertise in the techniques used by the research investigator. For results discovered by secondary researchers, the biospecimen resource is responsible for ensuring that validity of these results is evaluated and for coordinating the process of evaluation, or applying the filter. This coordination should be done with input from the primary and secondary researchers.
>
> > **Recommendation 2.6.a:** Agencies such as the Office for Human Research Protections and the Food and Drug Administration could provide some guidance to IRBs in reviewing proposed mechanisms for returning research results and in applying filters once a result is obtained.
>
> **Recommendation 2.7:** For new biospecimen resources, mechanisms for filtering and returning research results should be established before biospecimens are collected. Existing biospecimen resources should seek to incorporate a filtering mechanism for return of research results.

2. Assuring Analytic Validity of Research Results

The group proposed a model, similar to the one used by data safety monitoring boards, to apply in the event a potentially returnable result is discovered. In this model, the research investigator would use the filter to identify potentially returnable results, and then alert the IRB of the result, in line with a previously agreed-upon process for evaluating and communicating results (see Recommendation 2.4). The IRB would then review the result and determine whether it should be returned to participants. The breakout group acknowledged that to fulfill this added responsibility, the IRB might need additional guidance from people with relevant expertise in the assays used by the investigator. Thus, the breakout group suggested that IRBs could seek such guidance from laboratory groups, internal committees resembling an Informed Consent Oversight Board, or external, topic-focused advisory groups. The breakout group also noted that the additional responsibilities of the IRB would require more funding.

It was noted that analytic validity could be a stopping point for many researchers, because results most likely will be discovered in non-CLIA-approved laboratories, laboratories often cannot harmonize results, and standards for reproducibility are poor. Several breakout members suggested adhering to the current standard, which requires results obtained in non-CLIA-approved laboratories to be verified in CLIA-approved laboratories, except in the case of orphan diseases for which CLIA certification might be impossible. However, even in clinical practice, many tests do not meet high standards of care or are not clinically valid. Investigators who verify research results in non-CLIA-approved laboratories should assure the analytic validity and safety of the test they use. The group also agreed that the informed consent document should notify participants of their

right to receive results associated with their biospecimen and caution that some results might be obtained in non-CLIA-approved laboratories.

> **Recommendation 2.8:** Results obtained in a non-CLIA-approved laboratory should be verified in a CLIA-approved laboratory, except for cases in which such verification is impossible. If verification cannot take place in a CLIA-approved laboratory, investigators should ensure the analytic validity and safety of the test they use.

3. Who Should Inform Research Participants of a Result

In terms of responsibility for communicating individual research results to human research participants, and the role of the biospecimen resource in coordinating the communication between researchers and the biospecimen source site, participants agreed that primary collecting institutions should inform research participants of the results from primary studies. However, who should inform research participants of research results from secondary studies is a complex question. The primary collecting site might have a relationship with the participant, or the participant might feel more comfortable hearing results from that institution. However, this site has no control over secondary research, thus the responsibility for informing participants of research results might constitute an unfair burden.

Biospecimens used in secondary research might come from multiple sites. Because the biospecimen resource stores biospecimens and controls downstream uses, taking responsibility for informing research participants of secondary research results could be seen as part of responsible stewardship. However, distance from and lack of prior contact with the research participant could pose a problem. If biospecimen resources are responsible for informing research participants of research results, they must have a mechanism to access identifiers, either by direct access from biospecimen source sites or by creating a data repository that would be in a separate location but parallel to the biospecimen repository. In addition, whether this would constitute "human subjects research" on the part of the biospecimen resource would have to be assessed.

Conventional wisdom has held that when secondary researchers discover returnable results, the primary institutions are responsible for reporting these results to the research participant, because these institutions hold the identification codes and have a history of contact with the individuals. However, breakout group members expressed concern about making primary institutions responsible for communicating results they did not discover. Group members felt such a responsibility constitutes an unfair burden when the primary institution has no control over how secondary institutions use the specimens in their research. Yet the breakout group also acknowledged that secondary researchers alone should not be held responsible for reporting results to individuals they cannot contact. The group thus agreed that biospecimen resources can fulfill their responsibilities in communicating research results obtained from secondary studies by taking a coordinating role involving both primary and secondary researchers in the communication process.

There was some debate concerning the effects of receiving significant information from the biospecimen resource. Some group members noted that many patients will not care who gives them the information, that making the biospecimen resource responsible for communication might

offer some consistency, and that the biospecimen resource would be better able to understand the research results generated by secondary researchers. However, others expressed concern about patients hearing potentially life-changing information from a stranger. Other members noted that not all research participants are patients; some are healthy volunteers with no ongoing relationship with an institution. Time, or how long it has been since a biospecimen was collected, might also be considered in determining who should be responsible for communicating the research result. Adding information to the informed consent document about who might communicate research results was suggested.

For the biospecimen resource to assume responsibility for communicating research results from secondary research, it will need to have access to links to re-identify biospecimens. Breakout group members suggested a cooperative group model in which a data repository or statistical center that is separate from the biospecimen repository would hold the links.

> **Recommendation 2.9:** Primary collecting sites are responsible for communicating to the research participant results discovered during primary research at that institution or during internal review at the biospecimen resource. The biospecimen resource is responsible for ensuring that communication occurs and for coordinating the process by which secondary research results obtained with biospecimens from the resource are communicated to research participants. This coordination should include input from the primary and secondary institutions.

4. How Research Participants Should Be Informed

Novel communication strategies, such as Web-based mechanisms, should be explored. The breakout group agreed that once a research result has been determined to be returnable, the result should be communicated using a three-step process. In the first step, research participants should be alerted that a potentially significant research result has been discovered, and they should have an additional opportunity to opt out. In discussing the significance, the first contact should describe potential implications without disclosing the result, and communicate the significance in such a way that participants can be proactive in getting more information. Once participants choose to receive the result, the second step should involve a person who is knowledgeable about the study or field and who can present a consistent message using an agreed-upon script. The script should describe the result using language the participant can understand, and it should inform participants where they can go for more information. Although an in-person interaction might be ideal at this point, it is not required. In the third step, a separate presentation of results in writing should take place. Information should be shared only with the research participant and not with the physician, unless the participant shares the information or gives permission for it to be shared.

The breakout group agreed that the return of research results should not be the only communication that research participants receive. Instead, results should be part of ongoing communications about aggregate issues and the status of the research in which they participated.

The group further agreed that research participants should be proactive and responsible for keeping their contact information current if they consent to provide biospecimens for future, unspecified research. This will reduce the burden of locating participants if a significant research result is

discovered and validated. In cases where duty-to-rescue applies, the biospecimen resource or primary collecting site might be responsible for finding participants and communicating results.

Whether the communication of research results constitutes a clinical or research interaction was a subject of debate. Some group members suggested that the research result should be communicated with the participant and not recorded in the medical record. These members expressed concern that turning this information into clinical care might attribute too much value to it or to a component of a multi-factorial process or condition. However, other group members noted that where the line is drawn could influence the filter and that the processes of applying the filter and returning a clinically significant finding constitute clinical care. The group eventually agreed that research results should be reported without noting them in the medical record.

> **Recommendation 2.10:** Research results should be communicated to the participant in a three-step process:
>
> - A "second chance" to opt out of receiving research results. This step should mention potential implications of the result, and should require participants to proactively move to the next step.
> - A scripted communication by a knowledgeable person (e.g. genetic counselor) about the research result and where the participant can obtain more information. Although an in-person interaction is ideal, it is not required.
> - A written follow-up of the communication by the knowledgeable person.
>
> **Recommendation 2.10.a:** New communication strategies, such as Web-based approaches, should be explored further, particularly for cases in which the biospecimen resource is responsible for communicating research results.
>
> **Recommendation 2.10.b:** The distinction between clinical care and research is an important issue that should be discussed further.
>
> **Recommendation 2.10.c:** Whether to allow patients to opt out in the event that duty-to-rescue is invoked needs further discussion.
>
> **Recommendation 2.11:** Although the results might trigger a clinical interaction, they should be communicated with participants but not shared with participants' physicians unless the participants give permission. The distinction between research and clinical care should be discussed further.

B. Issues for Further Discussion

From the point of view of the FDA, the biospecimen resource is not responsible for results generated from the testing of biospecimens, but it is responsible for who obtains the biospecimens and for what use. Thus, if a secondary research result turns out to be wrong, it is the responsibility of that institution and not the biospecimen resource. The breakout group noted that although regulations and guidance from the FDA and OHRP can be applied to return of research results, they do not define the entire ethical space. It further emphasized that biospecimen resources can no

longer be passive institutions. The breakout group debated how regulations could be adopted. Some members felt that only a legislative act could establish additional regulations, whereas others argued that OHRP, for example, should take a more proactive role in defining or clarifying existing guidance.

The issue of initial oversight at the level of secondary research is also not clear. All investigators should be responsible for anticipating return of research results, proposing mechanisms for review and return, and triggering those mechanisms. Whereas primary investigators work with their IRBs, it is not clear who secondary researchers should work with. If researchers receive samples and coded data and are unable to re-identify samples, their studies do not constitute human subjects research under current OHRP guidance and might not require IRB review. On the basis of their participation in the planning of some biospecimen resources, some breakout group members suggested that an oversight mechanism that is transparent and accountable to the public be established before contracts are signed and biospecimens collected. However, oversight of secondary research needs to be discussed and clarified further.

There was some disagreement about the distinction between clinical practice and conduct of research. The breakout group agreed that although the return of research results might trigger a clinical interaction, it should be considered a research finding and not entered into the medical record. However, members did express some discomfort with the distinction between clinical and research interactions, because the intersection is becoming more ambiguous. Some workshop participants noted that insisting that a result is still a research result after it has been taken through a filter to determine clinical import is disingenuous, and suggested that research participants be educated about the nature of research data and given access to all of it. Other workshop participants thought that it is reckless to provide results directly to participants without involving physicians or others who could interpret the results. Reporting of CLIA-approved laboratory test results is done under the guidance of a physician; workshop participants felt that physicians also should be involved in the reporting of results from non-regulated tests. In addition, some research participants might be healthy volunteers, so the recommendation cannot be “one size fits all.”

Whether to allow patients to opt out in the event that duty-to-rescue is invoked needs further discussion. Some breakout and workshop participants felt that research participants should be allowed to opt out in the event that duty-to-rescue is invoked, and they noted examples in which individuals can refuse a genetic test even if a predisposing mutation is present in their families. Some institutions have explained to potential research participants that everything cannot be anticipated, that research participants might be re-contacted, and that on some occasions (for example, duty-to-rescue), the institution might override permissions. Potential research participants thus sign the consent only if they are comfortable with these caveats. However, recent publications on duty-to-rescue avoid the idea of overriding participants’ consent. In addition, it is not clear whether parents can decline information pertaining to their children. In some states, failure to obtain appropriate medical care is viewed as neglect or abuse.

There are logistical issues that must be addressed prior to implementing the “filter” concept. Some group members suggested that the filter should differ by population, but others stressed that all participants in a project or study should receive equivalent information. Further, it is not clear whether it is feasible to make the biospecimen resource responsible for direct interactions with

research participants. Moreover, the types of research results described in the consent under which biospecimens are collected differ from the types of results obtained in secondary research studies, and it is not clear whether this difference should be accounted for in the filter. The breakout group also proposed this filter on the assumption that secondary researchers are at academic institutions. The model becomes more complicated if researchers working for commercial organizations are hesitant to return research results. "Duty to hunt" and the ease by which a diagnosis can be obtained should be included in further discussions of logistical issues associated with the filter.

Although the breakout group agreed on four principles or criteria that should be included in the filter, other principles such as personal utility, reproductive significance, and unanticipated financial burden should be discussed further.

The breakout group also discussed the issue of re-testing a finding before informing research participants. Offering the participant an option to come in for CLIA-approved testing was suggested as one mechanism for re-testing. Obtaining an extra biospecimen as a validation sample at the time of collection was also suggested. Although having a second sample for re-testing would be ideal, it might not be feasible, particularly in cases of research results obtained from secondary research. The group did not reach consensus but acknowledged that such a judgment most likely will depend on the situation and possibly the type of sample. An additional blood sample might be easily obtained, but an additional tumor sample might not.

IX. Breakout 3: Release of Research Results from Basic Studies

Chair: Charis Eng, MD, PhD, The Cleveland Clinic
Co-Chair: Rihab Yassin, PhD, National Cancer Institute, NIH

Members:

Laura M. Beskow, PhD, MPH
Marianna J. Bledsoe, MA
Deborah Collyar
Richard Fabsitz, PhD
Kenneth Mandl, MD, MPH
George Martin, MD
Lopa Mishra, MD
Ellen Richmond, RN, MS, AOCN
Joan Scott, MS, CGC
Richard Sharp, PhD
Barbara Spalholz, PhD
Asad Umar, DVM, PhD
Carol Weil, JD

Session Focus: Provide recommendations concerning the conditions and processes for releasing aggregate research findings from de-identified biospecimens contributed for research, including biospecimens collected for future research.

Traditionally, research has been considered by scientists to be a distinct endeavor from clinical medicine when it comes to communicating findings to research participants. However, the Internet has allowed individuals greater access to information than ever before, which perhaps underlies the desire and expectation of many research participants to be informed of results. Thus, over the past several years, bioethicists and other stakeholders have been debating whether and how research results might be provided to research participants (Dressler 2009).

Because the majority of basic research may be conducted through secondary use of biospecimens

that have been de-identified, and occurs in laboratories that are not CLIA-approved, the return of individual results from these studies may have additional constraints. As such, the return of aggregate results that summarize overall findings may be an appropriate alternative that demonstrates the value and significance of human research participants' contributions. Please refer to the introduction section of panel II for more discussions on the support for and drawbacks of sharing research results.

The soon-to-be-released new iteration of *NCI Best Practices* recommends that summaries of aggregate results should be made available to biospecimen contributors and the general public on a publicly accessible Web site. This would enable individuals who have contributed biospecimens to be aware of the research findings in which their biospecimens might have played a part (Yassin et al. 2010). A similar recommendation has also been reached by the caHUB ELSI subgroup. Whether this should entail access to PDF files of journal articles or summaries written in plain language was not specified, nor was the responsibility of creating plain language summaries, that is, the site conducting the research or the biospecimen resource itself.

A. Areas of General Consensus

Sharing of aggregate research results with research participants demonstrates respect and gratitude for their contributions and fosters public trust and support for research funding. The breakout group recognized that providing aggregate results, even when written in plain language and passively provided, may not always be welcomed by biospecimen contributors. Best practices are meant to strike a balance in the judicious sharing of aggregated de-identified research results. In the interest of transparency, biospecimen resources should be encouraged to make aggregate results available as broadly as possible, but as appropriate depending on the nature, size, and scope of the biospecimen resource. Aggregate results should be peer-reviewed and provided with a plain-language abstract.

Given the diversity of study approaches, the group refrained from being too prescriptive, preferring to state the desired outcome without necessarily providing explicit guidance on methods. At a minimum, study principals must declare whether aggregate results will be made available. The group also concluded that biospecimen contributors ***could*** have access to aggregate findings from basic research studies, and that the NCI should develop best practices outlining human research participants' rights to aggregate findings from research on their biospecimens. The group also discussed that in rare circumstances, a researcher may believe it is appropriate to contact study participants about aggregate findings.

> **Recommendation 3.1:** Biospecimen source sites should develop a process to review researchers' requests to contact study participants about aggregate findings and decide whether aggregate findings should be communicated and in what manner. Researchers should be encouraged to communicate important aggregate findings when possible, and in plain language.

1. Informed Consent Process

Discussion centered initially on what should be communicated during the informed consent

process, as distinct from the informed consent document. The informed consent document should be understandable, concise, and clearly state ***whether*** aggregate results will be provided. If aggregate research results will be directly sent to biospecimen contributors, it is important to offer a way for research participants to opt out of receiving this information. For cases in which study directors plan not to share aggregate research results, future sharing of aggregate research findings should not be precluded if exceptional circumstances arise that justify release.

Although highlighting how and when information or results will be shared can help forestall unwelcome surprises for biospecimen contributors, being specific about the process for sharing aggregate research results *a priori* can be problematic for some investigators. The group, therefore, considered it acceptable for information about ***how and when*** aggregate research findings can be shared to be contained in ancillary material that is not necessarily part of the informed consent document.

Aggregate results must be anchored in time because understanding about what constitutes a finding might change with the accumulation of knowledge. Recommendations are, therefore, meant to apply prospectively, since it might be impossible to locate a biospecimen contributor from decades ago.

> **Recommendation 3.2:** When biospecimens are collected prospectively, biospecimen resources should inform research participants in clear, plain language through the informed consent process that they may have access to aggregate information about the research conducted on the biospecimens. The manner of access may be placed in ancillary material.
>
> **Recommendation 3.3:** The informed consent process for biospecimen collection should provide an opportunity for research participants to opt out of being directly contacted about aggregate research results if there are plans to actively return aggregate results.

2. Responsibility of the Biospecimen Resource for Sharing Aggregate Research Findings

The group indicated that the biospecimen resource should establish a mechanism to receive or collect aggregate research findings from researchers in peer-reviewed publications and plain language summaries. The findings should be made publicly available on the biospecimen resource Web site, for example, for interested individuals to access. Doing so benefits the biospecimen resource by demonstrating its value, which is essential for its continued funding and use. Additionally, the biospecimen resource should outline in its funding applications the resources needed for making aggregate research findings publicly available.

For most biospecimen resources, it will be logical to post a list of peer-reviewed publications on their Web site. However, it was noted that negative results often do not get published, so there should not be singular reliance on publications. For this reason, another type of summary would document the number and characteristics of biospecimen users (e.g., pharmaceutical companies) and protocols that have accessed the biospecimen resource. It was also noted that descriptive information about a study is important for ethical reasons. I—it provides the option for people to withdraw if they do not agree with how researchers plan to use biospecimens.

Biospecimen source sites that have an ongoing relationship with research participants might consider publishing a newsletter that could be posted on their Web sites. The biospecimen resource (e.g., the caHUB) would be responsible for notifying biospecimen source sites when there is a new posting.

Paralleling the return of individual results, it is important to differentiate between aggregate results that may have clinical implications and those that may be of general interest to participants. A tiered type of communication may make sense, depending on the nature of the finding. Some data would always be on a study Web site while other information would be communicated to the biospecimen source site to share with the patient or donor, as appropriate.

As mentioned previously, the recommendations are meant to apply prospectively to enable biospecimen resources to plan for the additional costs.

> **Recommendation 3.4:** The cost and any associated staffing required for making aggregate research results available should be accounted for in the planning of a biospecimen resource.

> **Recommendation 3.5***:* Biospecimen resources should be encouraged to make the following information available:

- Data on the usage of samples, such as summaries of projects accessing the resource
- Peer-reviewed publications based on the biospecimen resource, with a summary in plain language

3. Responsibility of Researcher for Sharing Aggregate Research Findings

Public trust and support for funding of research is enhanced by greater awareness of the important scientific role played by biospecimen resources. It is legitimate to insist that publications derived from the use of a resource's samples be shared with the biospecimen resource. It is the researcher's responsibility to provide a copy of his or her publication(s) to the biospecimen resource, along with plain-language summaries and contact information. The researcher also should work with his or her IRB to decide if forwarding of aggregate results to the biospecimen source site is indicated.[2]

Greater understanding of research results can be facilitated by the provision of summaries written in language understandable to the general public, including biospecimen contributors, news organizations, advocacy groups, and researchers from other fields.

> **Recommendation 3.6:** Plain-language summaries should be regularly prepared by investigators, because they offer the opportunity to communicate aggregate research findings to the public and other stakeholders.

[2] A concrete example of such a situation might arise if a gene mutation is found to be causative of a particular condition or disease based on aggregated data from 10 individuals in 80 percent of cases, none in controls. Should those 10 individuals be contacted to alert them to this finding and encouraged to seek additional testing? The nature of the aggregate result must be a factor in this decision. Some findings could be quite concerning to individuals

4. Developing Standards for Communicating Aggregate Research Results

The group endorsed the expectation that aggregate research results in the form of peer-reviewed publications be made available through the biospecimen resource, but recognized that it may be asking too much for the biospecimen resource to determine if a finding is clinically significant. It would be helpful to provide researchers with guidelines stating when a finding based on aggregate data is considered sufficiently clinically important to justify communication with biospecimen contributors (through the biospecimen resource or biospecimen source site), and when that communication should occur. The group recognized that establishing communication standards will elevate the need to retain medical care providers and personnel adept at communicating information in appropriate ways during the informed consent process, and in referring readers of aggregate findings to their physicians for further discussion.

It was noted that the American Congress of Obstetricians and Gynecologists (ACOG) makes available plain-language summaries of findings from its publications. There was a call for the NCI to ensure the preparation of plain-language summaries for NCI-funded research publications. One meeting participant called for an even higher authority to issue a template approach because the NCI is only one funder of biospecimen resources. Biospecimen resources might consider linking their publications to PubMedCentral. Many existing online resources (e.g., NIH Reporter) can be leveraged to make available information about a particular biospecimen resource or to create an indexing scheme.

For purposes of transparency, Clinicaltrails.gov requires results of clinical trials to be published online for use by the scientific community; it does not require that the results be communicated to individuals. A similar mechanism (e.g., biospecimens.gov) could be developed to serve as an authoritative clearinghouse of information related to a biospecimen resources and studies, including plain-language summaries.

> **Recommendation 3.7:** The NIH and NCI should explore analogies to clinicaltrials.gov and NIH Reporter for making plain-language summaries of research generated from biospecimens available to the public.
>
> **Recommendation 3.8:** The NCI should pilot a study of the most effective ways to share aggregate research results with human research participants who contribute biospecimens.
>
> **Recommendation 3.9**: The NCI should develop standards for communicating aggregate results from biospecimen source sites to individual subjects. Other initiatives could inform this process at a later time.

5. Building Support for Use of Biospecimens for Research

Another point of discussion was the need for a public dialogue about the benefits of research participation, contributions of biospecimen resources to both individual and public health, and interpretation of research results. The public needs to be engaged to support the sharing of electronic health records for research purposes. It is not enough to rely on individual researchers to

have this kind of communication skill. Some group members called for the NCI, perhaps in collaboration with other Federal agencies, to create a public relations campaign on the benefits of biobanking for research, and obtain feedback to develop a template for moving forward.

> **Recommendation 3.10:** The NCI should study how to inform, engage, and garner support by the public and the scientific and medical communities for continued research advances made possible with biospecimens.

B. Issues for Further Discussion

Some members of the panel advocated strongly that aggregate research findings should be considered only as such, and not be treated as clinically actionable or personally communicated to the donor. Because conclusions about individual outcomes are difficult to draw from aggregate results, it is important to present aggregate results in appropriately cautionary terms to preclude misinterpretations.

Discussion about whether and how aggregate results are communicated to research participants was not pursued. The group deferred to the discussion in Breakout Group 2 covering whether and how individual results should be communicated to research participants.

Additional discussion is needed about the added costs and liabilities assigned to biospecimen resources, including appropriate limits on the extent of the biospecimen resource's responsibility in terms of what researchers do with biospecimens. If sharing aggregate research results and what users do with the biospecimens obtained from the resource are outside the purview of an individual biospecimen resource's responsibility, some contended that the NCI should be the central authority to filter research results. Others cautioned that use of the NCI imprimatur may lend greater credence to preliminary results and unnecessarily promote premature changes in therapy.

X. Conclusion and Next Steps

Workshop participants made significant progress in formulating concrete recommendations for returning results to research participants, although some issues remain to be resolved. The deliberations and recommendations of the breakout groups were grounded by plenary presentations and discussions that included perspectives from researchers, biospecimen administrators, IRBs, and the advocacy community. Areas upon which the greatest contention remains include the distinction between clinical care and research findings, the right of human research participants to opt out of obtaining research results even when the duty-to-rescue principle might apply, and the responsibilities of secondary researchers who might be removed in space and time from human research participants. Several recommendations called for additional research focused on economic considerations, such as the cost of banking biospecimens of poor or unknown quality and the costs and benefits of providing individual information to research participants. Others recommended studies to identify the best strategies for communicating research results.

The recommendations formulated in this workshop will be used to develop guidance for publication in a future edition of *NCI Best Practices* as well as for policies for the caHUB and its biospecimen source sites. The NCI OBBR-led activities complement related efforts by other NIH

Institutes and Centers (ICs), including the NHLBI and the National Human Genome Research Institute (NHGRI). For example, in 2004 the NHLBI Working Group on Reporting Genetic Results in Research Studies met and published their recommendations as the first step toward establishing formal guidelines (Bookman et al. 2006). In 2009, the NHGRI solicited grant applications for two-year pilot programs focused on re-contact issues in genotype and genome-wide association studies (http://www.genome.gov/27530574). NCI collaboration with these ICs, agencies such as the Office for Human Research Protections and the Food and Drug Administration, and the workshop participants will inform individual efforts and ensure harmonization of resulting recommendations as well as future guidelines. Stakeholders are encouraged to visit the NCI OBBR Web site (http://biospecimens.cancer.gov/) for updates on these issues and to submit comments to nciobbr@mail.nih.gov.

X. References

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XI. Attachments

ATTACHMENT A

Office of Biorepositories and Biospecimen Research
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Workshop on
Release of Research Results to Participants in Biospecimen Studies

July 8-9, 2010
Bethesda North Marriott Hotel & Conference Center
5701 Marinelli Road
Bethesda, MD 20852

AGENDA

Statement of the Workshop: *This workshop is convened to provide recommendations concerning the conditions and processes for releasing biospecimen research results to human research participants who contribute biospecimens. Three areas will be examined: diagnostic discrepancies and incidental findings, results from clinical studies, and results from basic research studies. The workshop will bring together leaders from the academic community, patient advocacy groups, and government agencies. The goal is to generate guiding principles for the development of NCI Best Practices on the release of research results and policies for the cancer Human Biobank (caHUB), a national biospecimen resource in development by the NCI.*

Thursday, July 8

7:30 a.m. - 8:30 a.m. **Registration**

8:30 a.m. **Opening of the Workshop**

8:30 a.m. - 12:10 p.m. **Plenary Session I**
Chair: Ellen Wright Clayton, M.D., J.D.
Vanderbilt University

8:30 a.m. - 8:40 a.m. ***Welcome and Workshop Overview***
Rihab Yassin, Ph.D.
National Cancer Institute, NIH

8:40 a.m. - 9:10 a.m. ***NCI Welcome Address: Why We Need Policies on the Release of Research Results - NCI Best Practices and caHUB***
Jim Vaught, Ph.D.
National Cancer Institute, NIH

9:10 a.m. - 9:40 a.m. ***Workshop Chair's Address: Framing the Issues***
Ellen Wright Clayton, M.D., J.D.
Vanderbilt University

Thursday, July 8 *(continued)*

9:40 a.m. - 10:10 a.m. ***Offering Individual Genetic Research Results: Context Matters***
Laura M. Beskow, Ph.D., M.P.H.
Duke Institute for Genome Sciences and Policy

10:10 a.m. - 10:30 a.m. ***Questions and Answers***
All Presenters

10:30 a.m. - 10:50 a.m. **Coffee Break**

10:50 a.m. - 11:20 a.m. ***Perspectives of IRBs on Return of Individual Research Results***
Lynn G. Dressler, Ph.D.
The University of North Carolina at Chapel Hill

11:20 a.m. - 11:50 a.m. ***Perspectives from the Advocacy Community***
Mary Lou Smith, J.D.
Research Advocacy Network

11:50 a.m. - 12:10 p.m. ***Questions and Answers***
All Presenters

12:10 p.m. - 1:15 p.m. **Lunch Break**

1:15 p.m. - 5:30 p.m. **Breakout Sessions**

1:15 p.m. - 2:45 p.m. ***Session I***

Breakout 1: Diagnostic Discrepancies and Incidental Findings
Session Focus: Provides recommendations concerning the processes for communicating diagnostic discrepancies and incidental findings discovered during the pathology review of biospecimens contributed for research.

Chair: Jared N. Schwartz, M.D., Ph.D.
Aperio Technologies, Inc.

Co-Chair: Nicole C. Lockhart, Ph.D.
National Cancer Institute, NIH

Breakout 2: Release of Research Results from Clinical Studies
Session Focus: Provides recommendations concerning the conditions and processes for releasing individual or aggregate research findings from biospecimens collected for/in the course of clinical studies.

Chair: Pearl O'Rourke, M.D.
Partners Healthcare System, Inc.

Co-Chair: John M. Jessup, M.D.
National Cancer Institute, NIH

Thursday, July 8 *(continued)*

Breakout 3: Release of Research Results from Basic Studies
Session Focus: Provides recommendations concerning the conditions and processes for releasing aggregate research findings from biospecimens collected for basic research studies.

Chair: Charis Eng, M.D., Ph.D.
The Cleveland Clinic

Co-Chair: Rihab Yassin, Ph.D.
National Cancer Institute, NIH

2:45 p.m. - 3:00 p.m. **Coffee Break**

3:00 p.m. - 4:30 p.m. ***Session I*** *(continued)*

Breakout 1: Diagnostic Discrepancies and Incidental Findings
Chair: Jared N. Schwartz, M.D., Ph.D.
Aperio Technologies, Inc.

Co-Chair: Nicole C. Lockhart, Ph.D.
National Cancer Institute, NIH

Breakout 2: Release of Research Results from Clinical Studies
Chair: Pearl O'Rourke, M.D.
Partners Healthcare System, Inc.

Co-Chair: John M. Jessup, M.D.
National Cancer Institute, NIH

Breakout 3: Release of Research Results from Basic Studies
Chair: Charis Eng, M.D., Ph.D.
The Cleveland Clinic

Co-Chair: Rihab Yassin, Ph.D.
National Cancer Institute, NIH

4:30 p.m. - 5:30 p.m. ***Sessions Conclusion, Preparation of Talking Points for Day 2***

5:30 p.m. **Day 1 Adjournment**

Friday, July 9

8:00 a.m. - 10:00 a.m. **Plenary Session II**
Chair: Ellen Wright Clayton, M.D., J.D.
Vanderbilt University

Reports from Breakout Session Chairs
Reports: 20 minutes; Q&A: 10 minutes

8:00 a.m. - 8:30 a.m. ***Diagnostic Discrepancies and Incidental Findings***
Jared N. Schwartz, M.D., Ph.D.
Aperio Technologies, Inc.

8:30 a.m. - 9:00 a.m. ***Release of Research Results from Clinical Studies***
Pearl O'Rourke, M.D.
Partners Healthcare System, Inc.

9:00 a.m. - 9:30 a.m. ***Release of Research Results from Basic Studies***
Charis Eng, M.D., Ph.D.
The Cleveland Clinic

9:30 a.m. - 10:00 a.m. ***Overall Discussions***
All Participants

10:00 a.m. - 10:20 a.m. **Coffee Break**

10:20 a.m. - 12 noon **Breakout Sessions**

Session II: Discussion of Unresolved/New Issues and Overlap between Sessions

Breakout 1: Diagnostic Discrepancies and Incidental Findings
Chair: Jared N. Schwartz, M.D., Ph.D.
Aperio Technologies, Inc.

Co-Chair: Nicole C. Lockhart, Ph.D.
National Cancer Institute, NIH

Breakout 2: Release of Research Results from Clinical Studies
Chair: Pearl O'Rourke, M.D.
Partners Healthcare System, Inc.

Co-Chair: John M. Jessup, M.D.
National Cancer Institute, NIH

***Friday, July 9** (continued)*

Breakout 3: Release of Research Results from Basic Studies
Chair: Charis Eng, M.D., Ph.D.
The Cleveland Clinic

Co-Chair: Rihab Yassin, Ph.D.
National Cancer Institute, NIH

12 noon - 12:15 p.m. **Coffee Break**

12:15 p.m. - 1:30 p.m. **Plenary Session II** (continued)
Chair: Ellen Wright Clayton, M.D., J.D.
Vanderbilt University

Final Recommendations from Breakout Sessions and Workshop Deliverables
Reports from Breakout Session Chairs
Reports: 10 minutes; Q&A: 5 minutes

12:15 p.m. - 12:30 p.m. ***Diagnostic Discrepancies and Incidental Findings***
Jared N. Schwartz, M.D., Ph.D.
Aperio Technologies, Inc.

12:30 p.m. - 12:45 p.m. ***Release of Research Results from Clinical Studies***
Pearl O'Rourke, M.D.
Partners Healthcare System, Inc.

12:45 p.m. - 1:00 p.m. ***Release of Research Results from Basic Studies***
Charis Eng, M.D., Ph.D.
The Cleveland Clinic

1:00 p.m. - 1:15 p.m. ***Overall Discussions***
All Participants

1:15 p.m. - 1:30 p.m. **Workshop Conclusion**
Ellen Wright Clayton, M.D., J.D.
Vanderbilt University

1:30 p.m. **Day 2 Adjournment**

ATTACHMENT B

List of Participants

Christine D. Berg, M.D., Detection Research Group Division of Cancer Prevention, NCI, NIH

Laura M. Beskow, Ph.D., M.P.H., Duke Institute for Genome Sciences

Leslie G. Biesecker, M.D., Genetic Disease Research Branch, National Human Genome Research Institute, NIH

Marianna J. Bledsoe, M.A., Office of Biotechnology Activities, Office of the Director, Office of Science Policy, NIH

Joy Boyer, National Human Genome Research Institute, NIH

Ellen Wright Clayton, M.D., J.D., Center for Biomedical Ethics and Society, Vanderbilt University

Deborah Collyar, Patient Advocates in Research

Lynn G. Dressler, Dr.P.H., The University of North Carolina at Chapel Hill

Charis Eng, M.D., Ph.D., Genomic Medicine Institute, The Cleveland Clinic

Richard R. Fabsitz, Ph.D., National Heart, Lung, and Blood Institute, NIH

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George M. Martin, M.D., Department of Pathology, University of Washington Health Sciences

Karen Maschke, Ph.D., The Hastings Center

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Jerry Menikoff, M.D., Ph.D., Office for Human Research Protections, U.S. Department of Health and Human Services

Lopa Mishra, M.D., Department of Gastroenterology, Hepatology and Nutrition, The University of Texas, M.D. Anderson Cancer Center

Pearl O'Rourke, M.D., Human Research Affairs Partners Healthcare System, Inc.

Wendy Patterson, J.D., Technology Transfer Center, NCI, NIH

Jane Perlmutter, Ph.D., M.B.A., Patient Advocate Gemini Group

Laura Lyman Rodriguez, Ph.D., National Human Genome Research Institute, NIH

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Joan A. Scott, M.S., CGC, Genetics and Public Policy Center, Johns Hopkins University

David Shalowitz, M.D., Department of Obstetrics and Gynecology, Brigham and Women's Hospital and Massachusetts General Hospital

Richard Sharp, Ph.D., Bioethics Research, The Cleveland Clinic

Anna M. Smith, CCRP, Clinical Monitoring Research Program, SAIC-Frederick, Inc., NCI, NIH

Mary Lou Smith, J.D., Research Advocacy Network

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