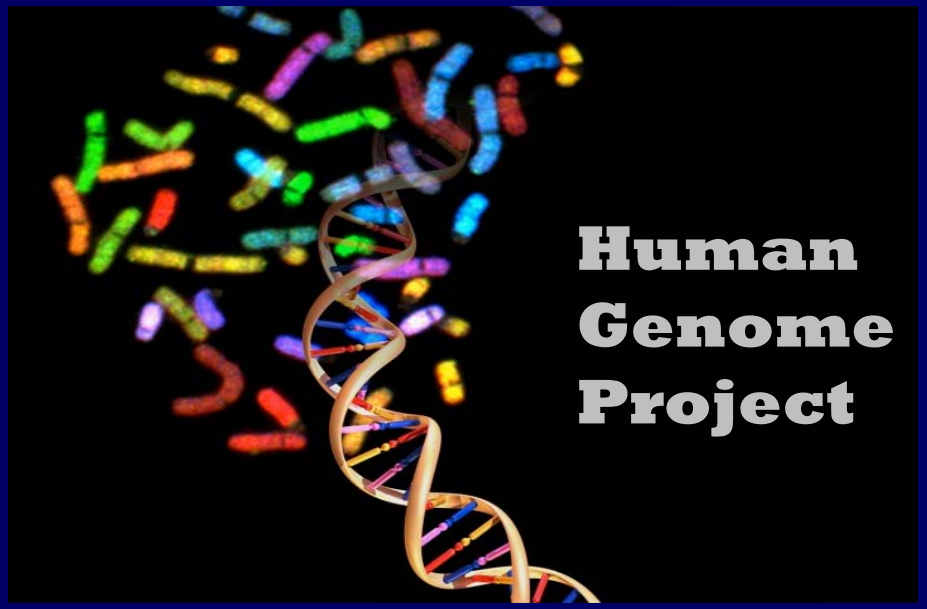
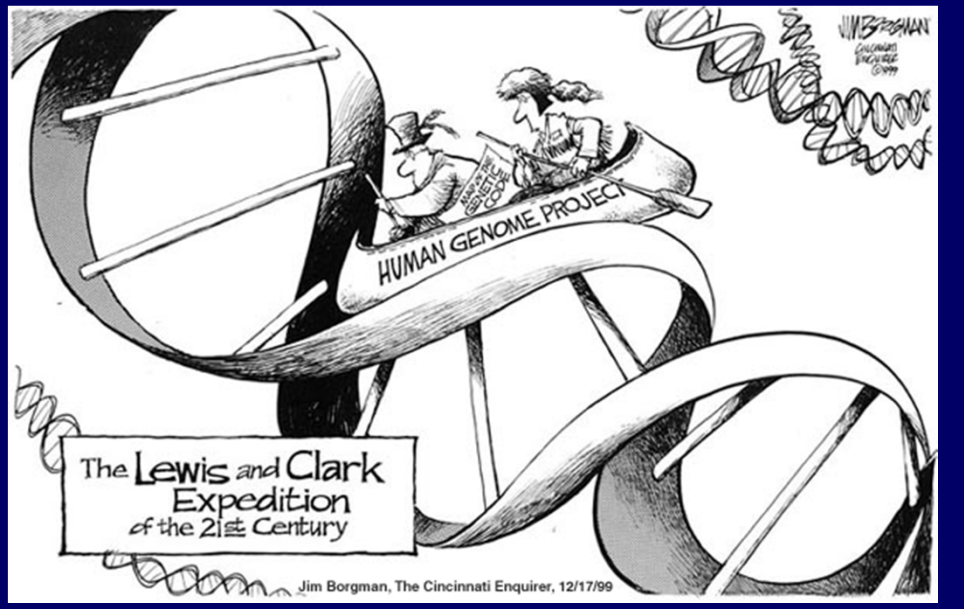
Genomics and Undiagnosed Disease

Eric Green, M.D., Ph.D.
Director, NHGRI

~21 Years Ago

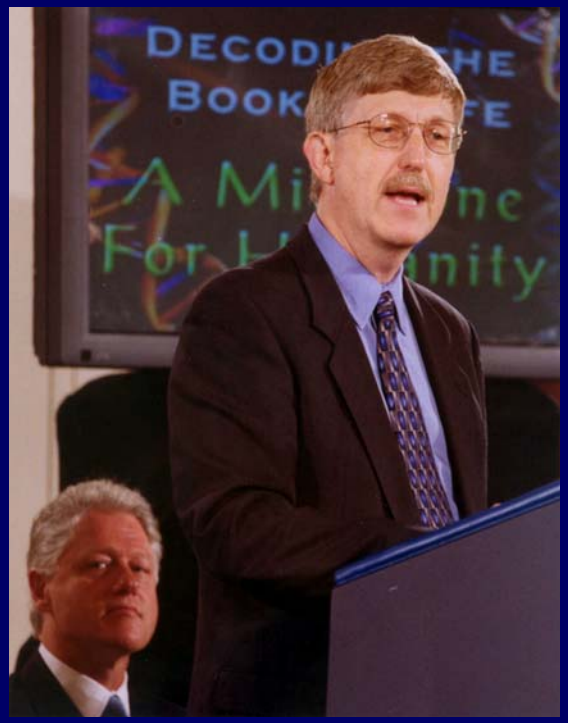


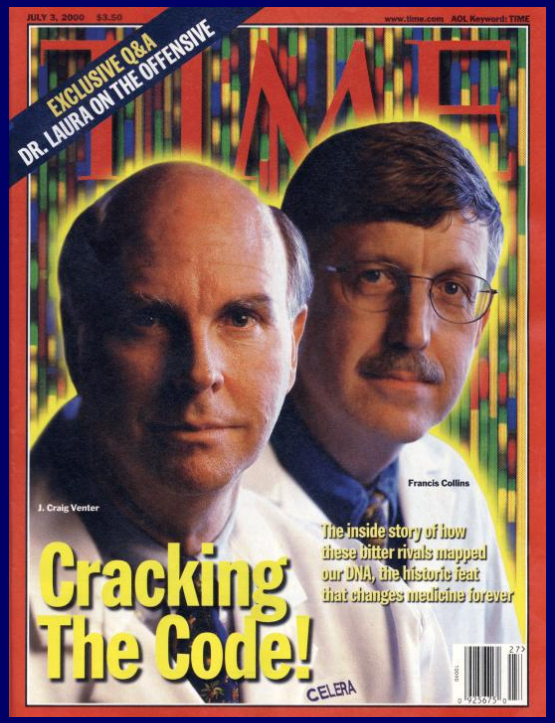


October 1990

Human Genome Project Begins

~11 Years Ago

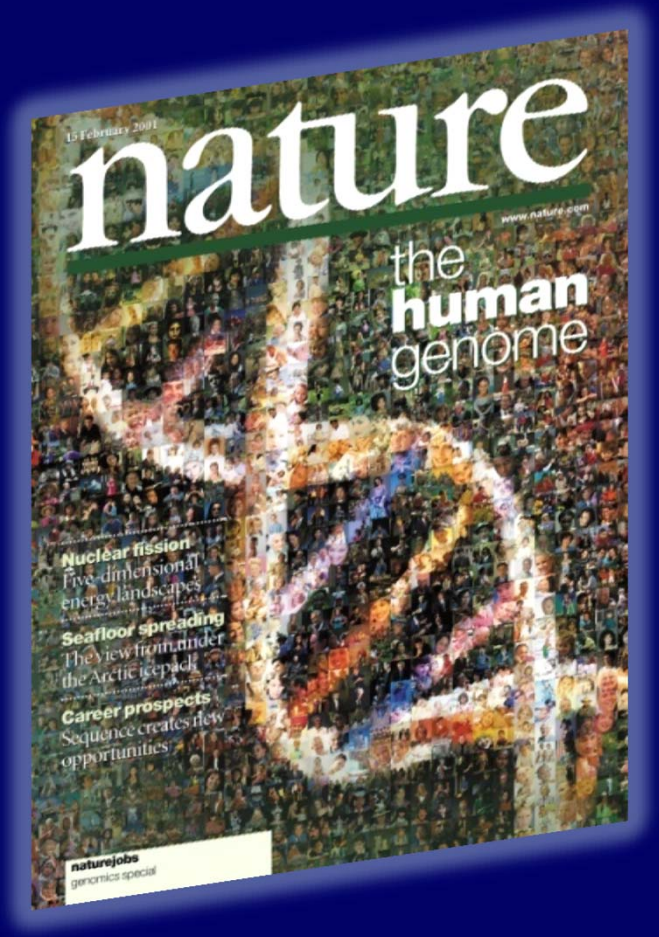




June 2000

Draft Human Genome Sequence Announced

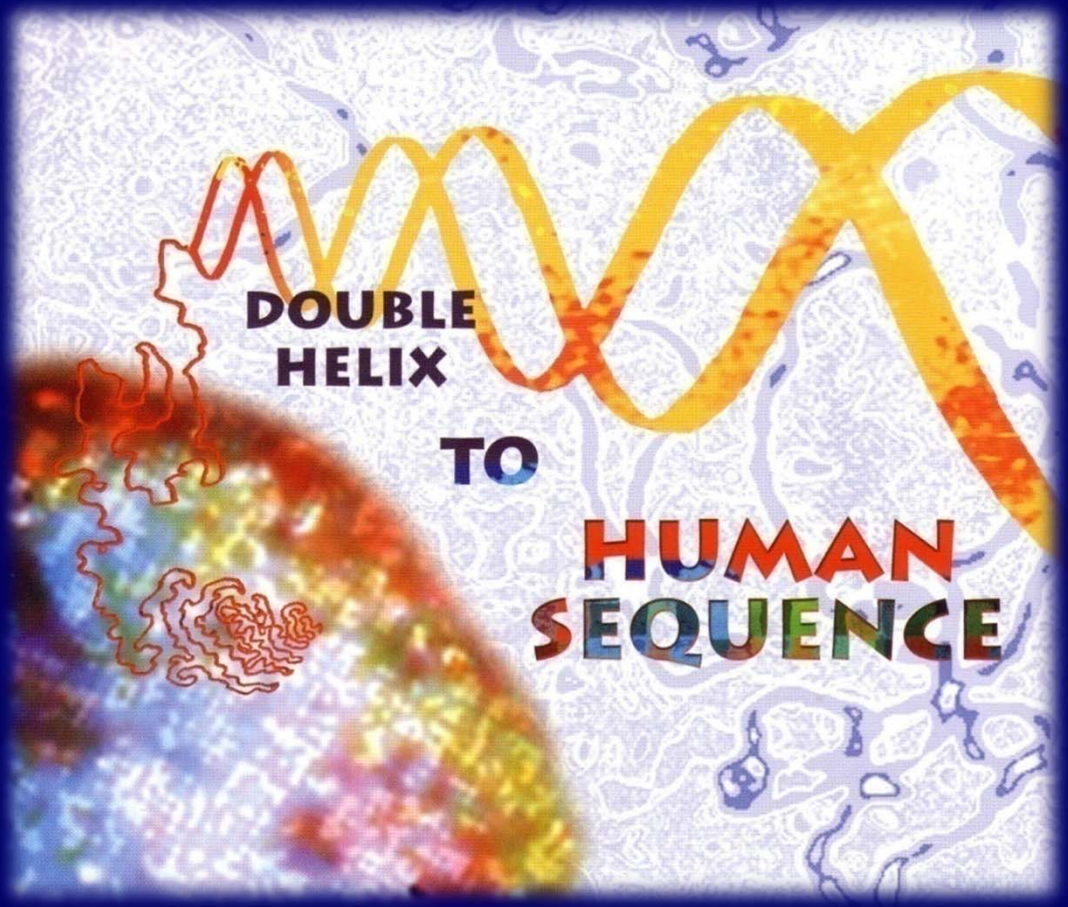
~11 Years Ago



February 2001

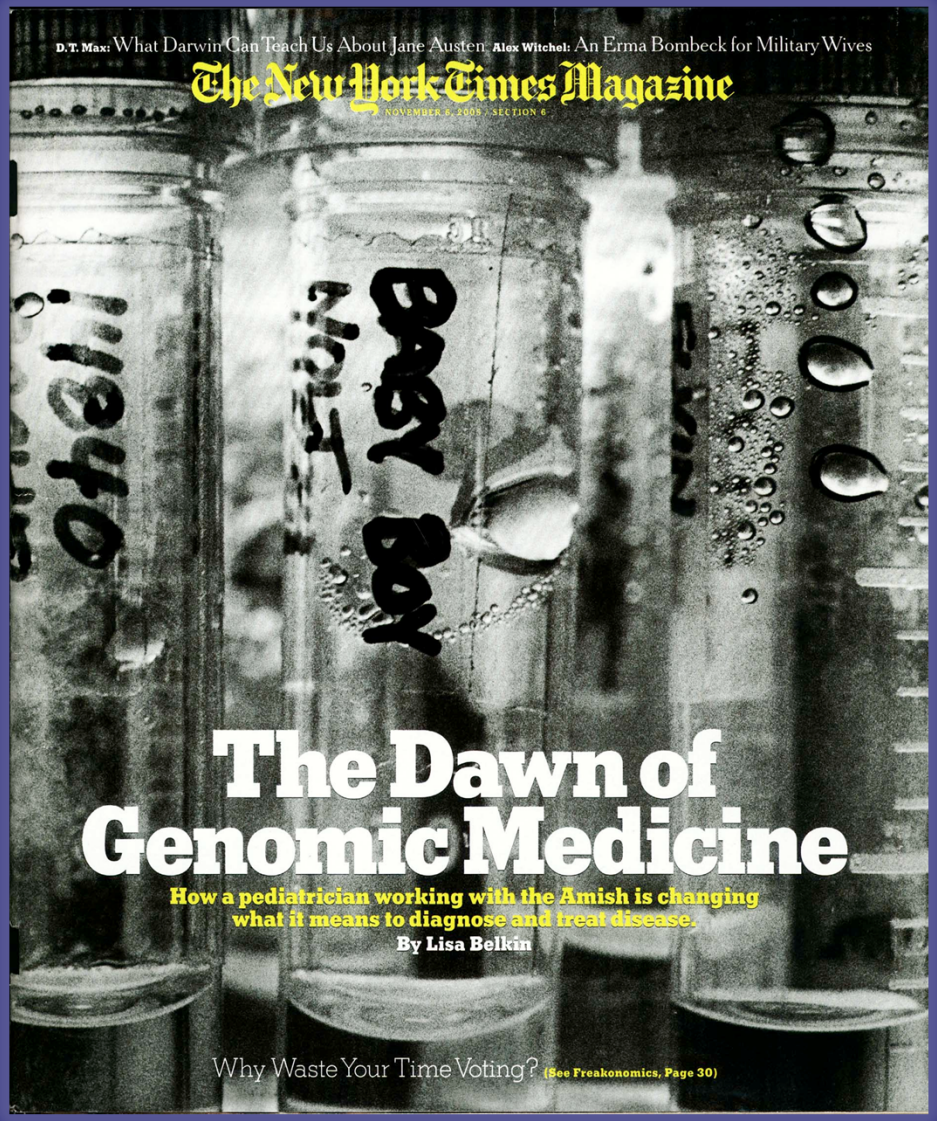
Draft Human Genome Sequence Published

~9 Years Ago



April 2003

Human Genome Project Ends

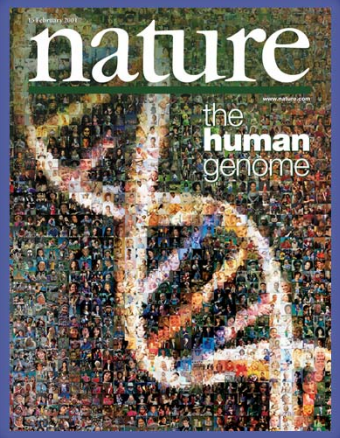

D.T. Max: What Darwin Can Teach Us About Jane Austen Alex Witchel: An Erma Bombeck for Military Wives
The New York Times Magazine
NOVEMBER 6, 2005 · SECTION 6
The Dawn of Genomic Medicine
How a pediatrician working with the Amish is changing what it means to diagnose and treat disease.
By Lisa Belkin
Why Waste Your Time Voting? (See Freakonomics, Page 30)


Science
24 October 2003
Vol. 302 No. 5645
Pages 517–728 $10
Genomic Medicine
American Association for the Advancement of Science

Genomic Medicine

Healthcare tailored to the individual based on genomic information

The Path to Genomic Medicine



Human Genome Project

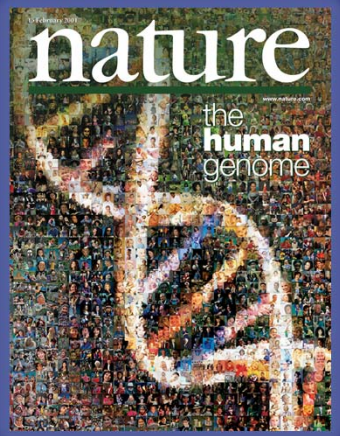
→ → ? → →

Realization of Genomic Medicine

"Fulfilling the Promise"

The Path to Genomic Medicine

Function of the Human Genome Sequence



Human Genome Project

Realization of Genomic Medicine

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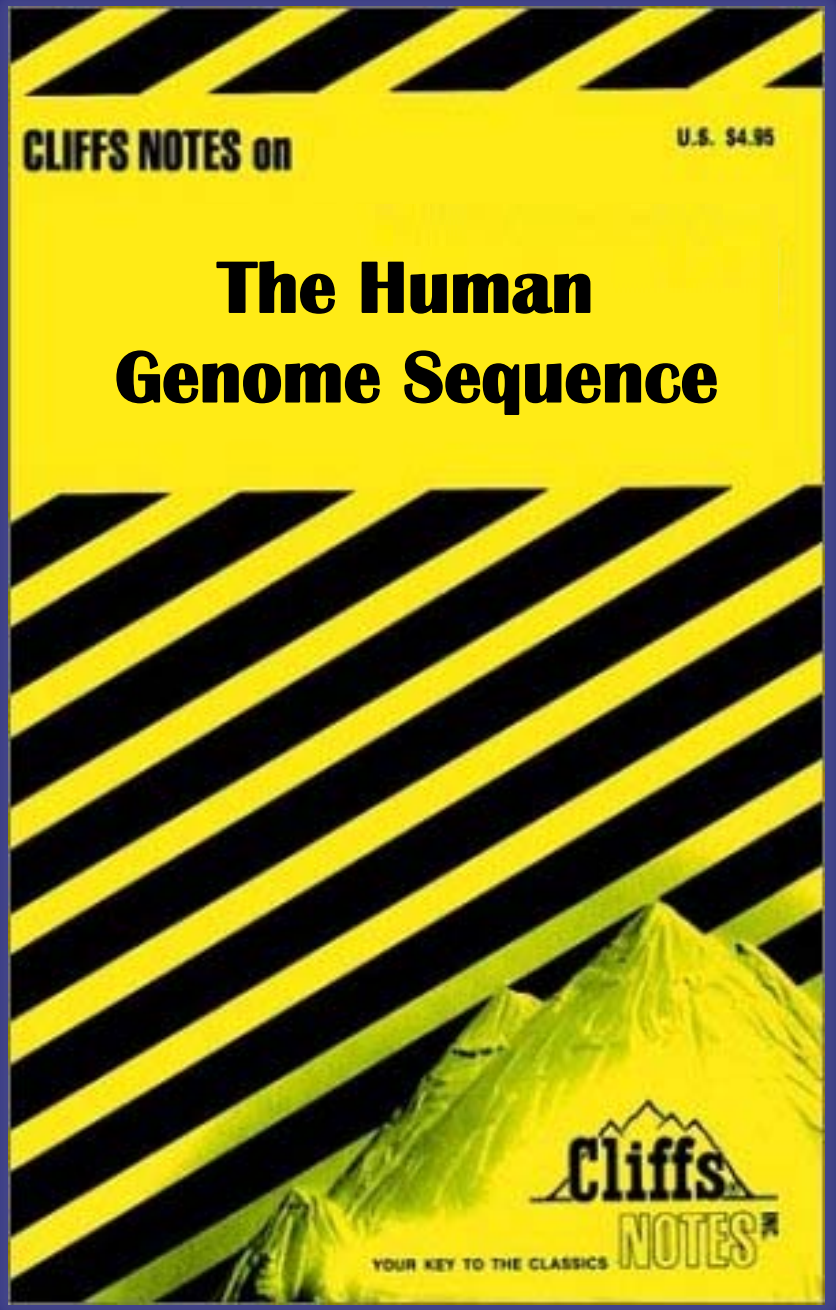
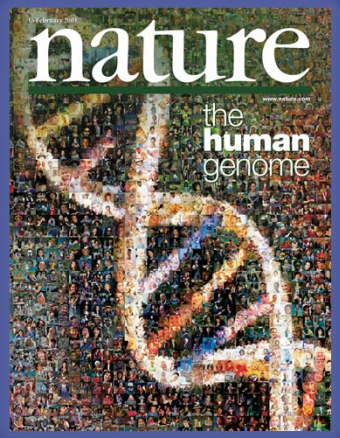


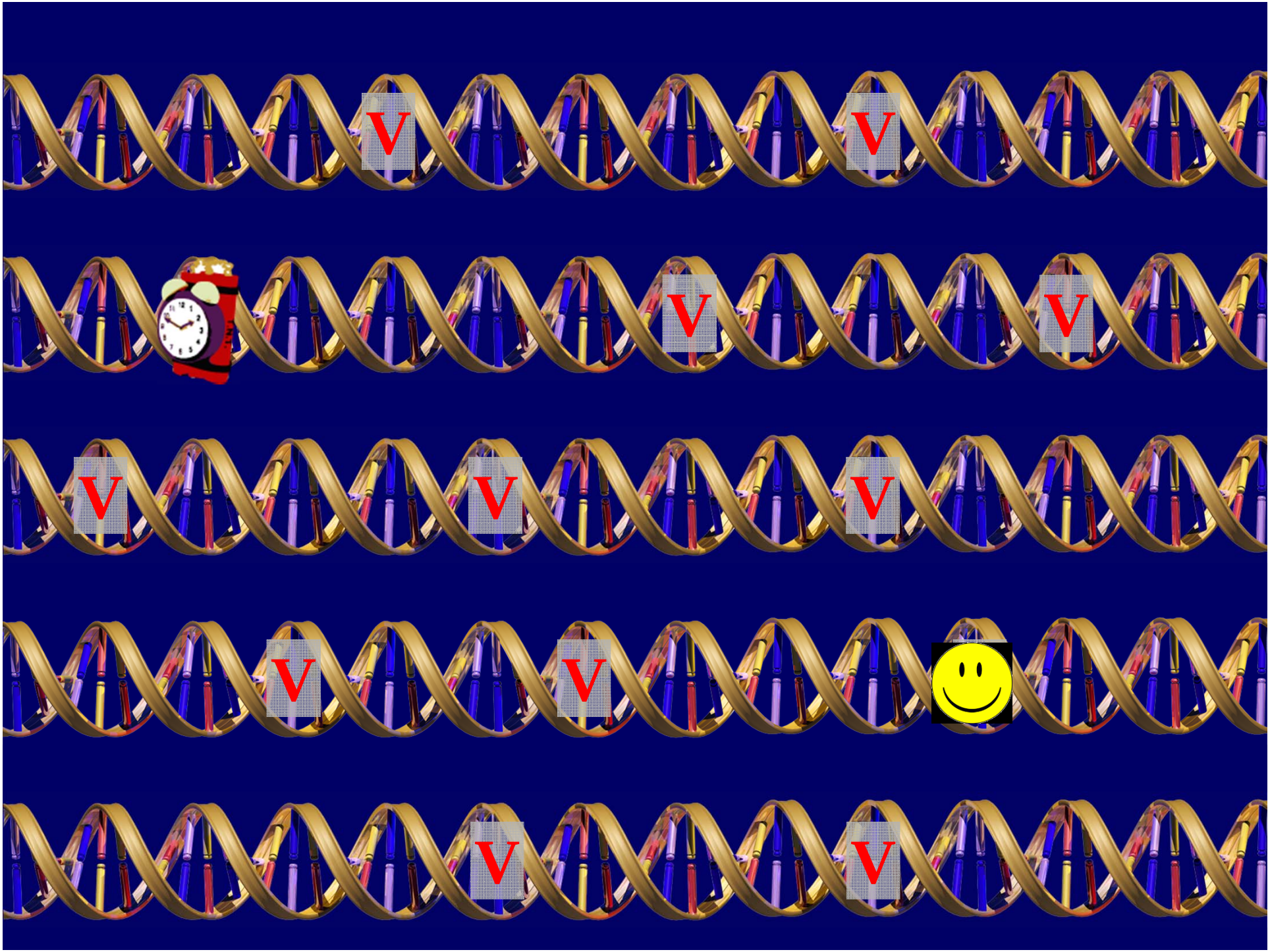
The Path to Genomic Medicine

Human Genomic Variation



Human Genome Project

Realization of Genomic Medicine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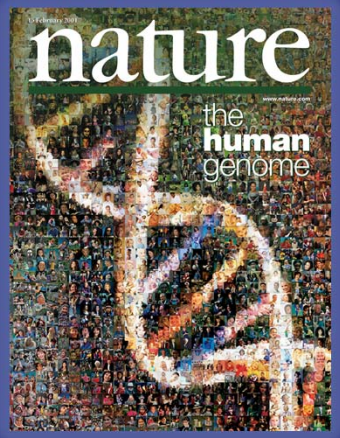
The Path to Genomic Medicine

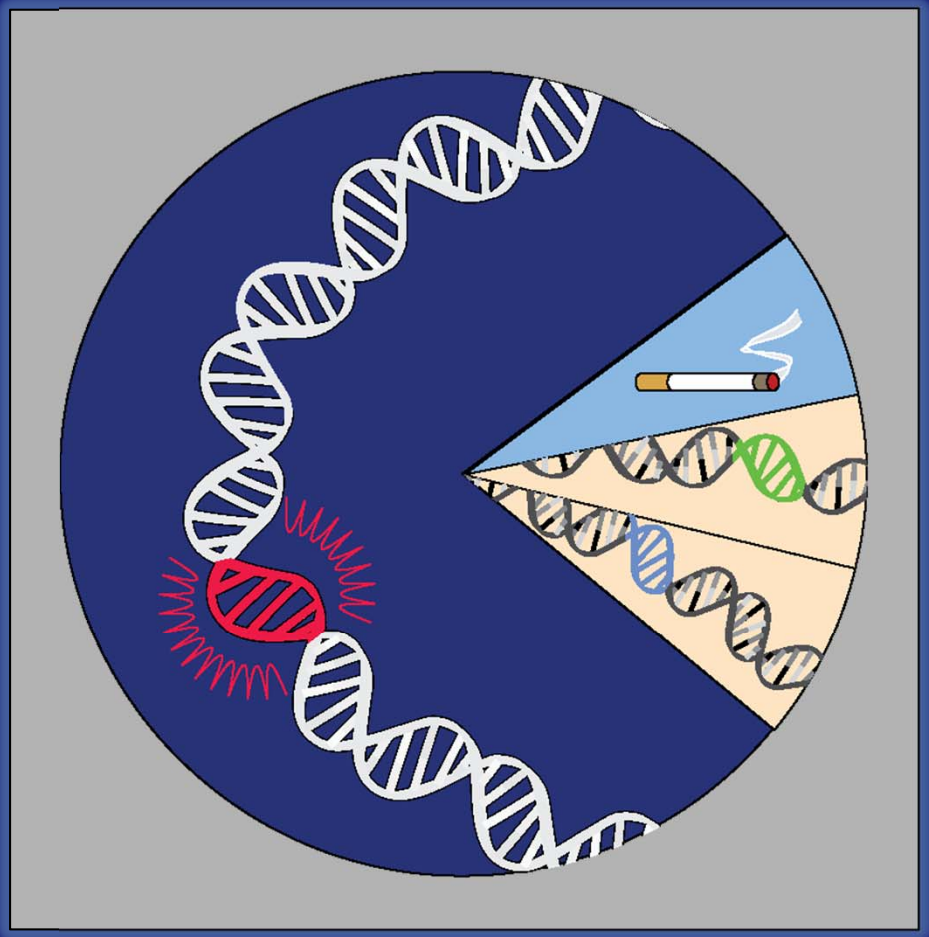
Genomic Basis for Human Diseases



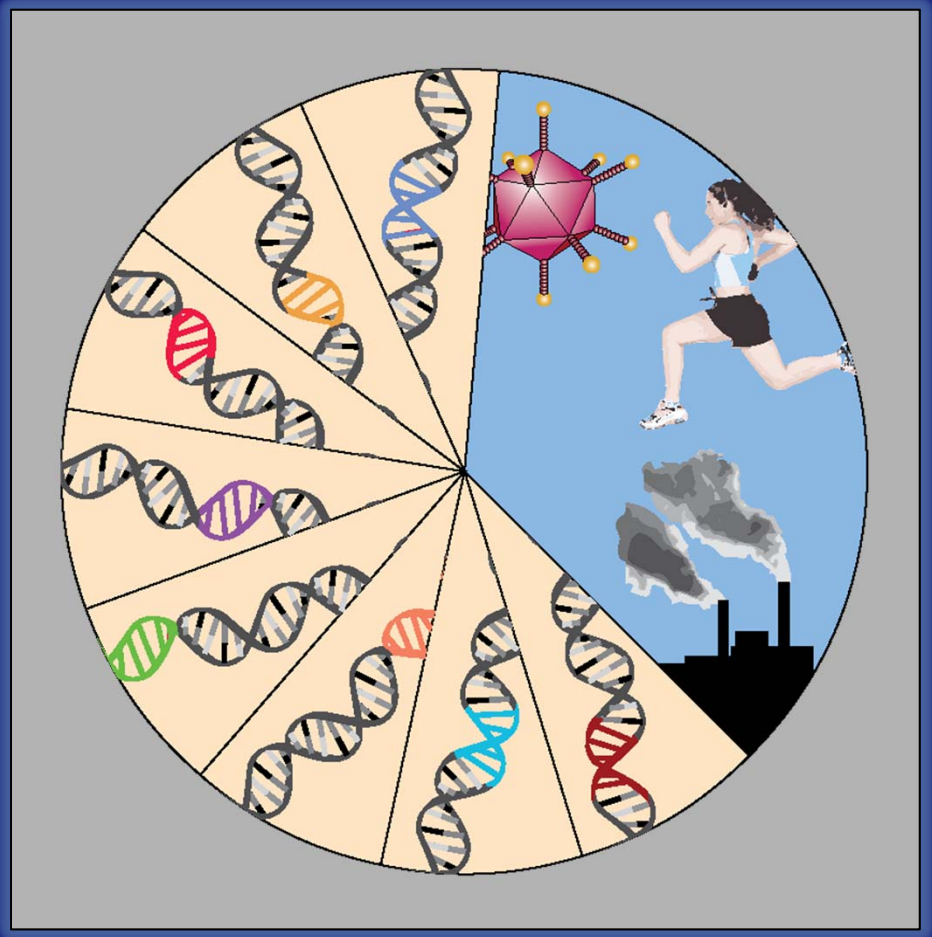
Human Genome Project

Realization of Genomic Medicine

Genomic Architecture of Genetic Diseases

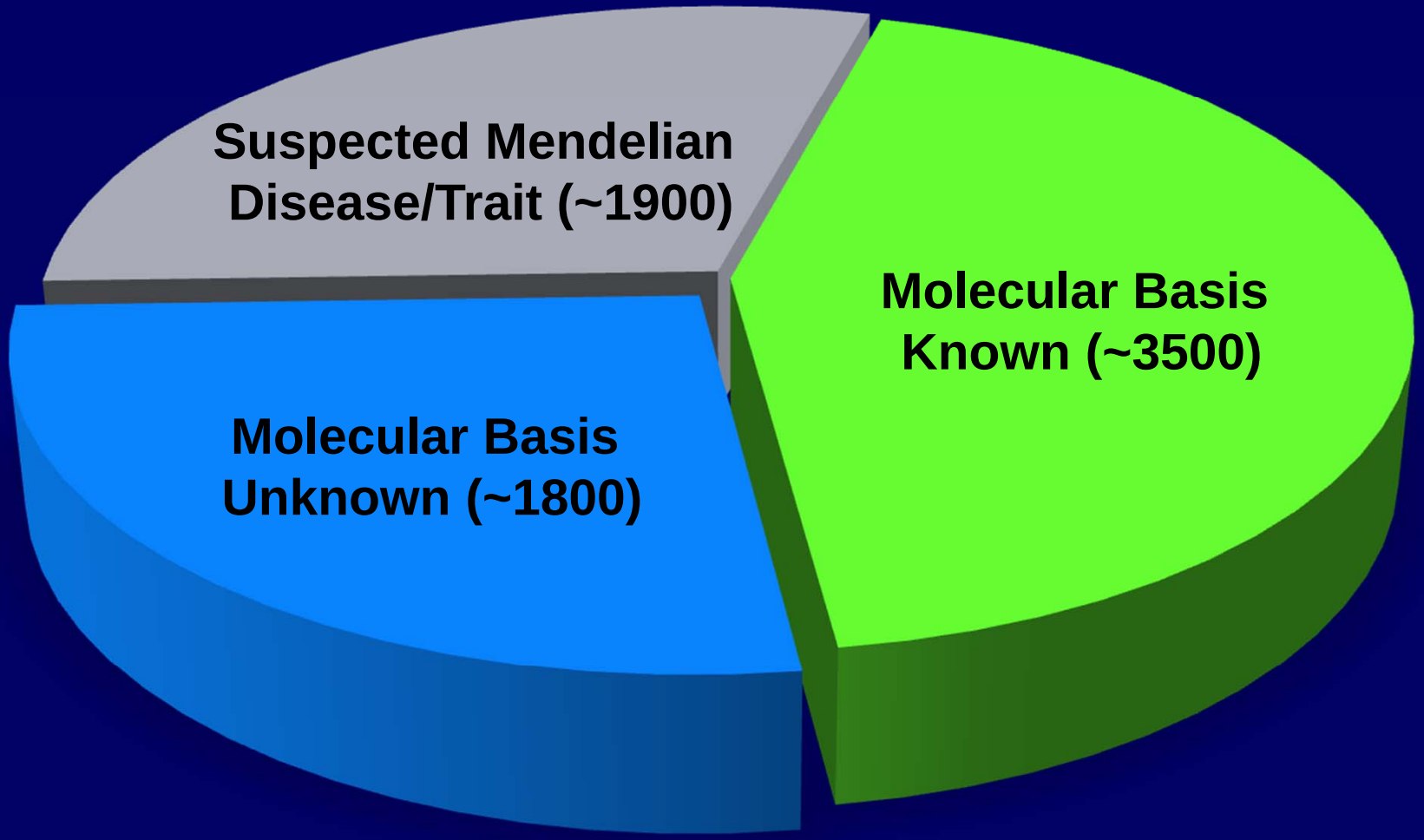


Rare, Simple, Monogenic, Mendelian…

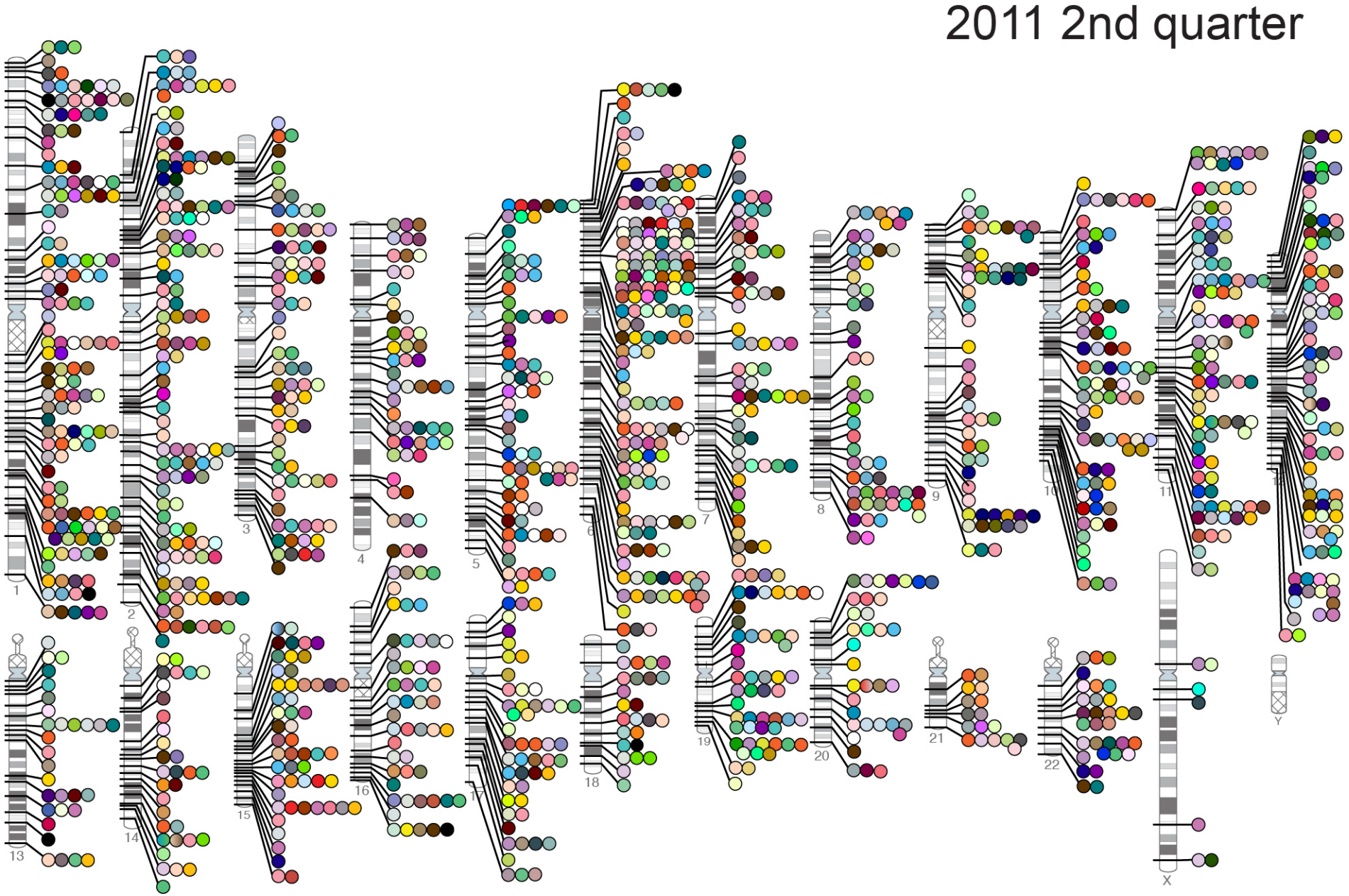


Common, Complex, Multigenic, Non-Mendelian…

Mendelian Diseases/Traits

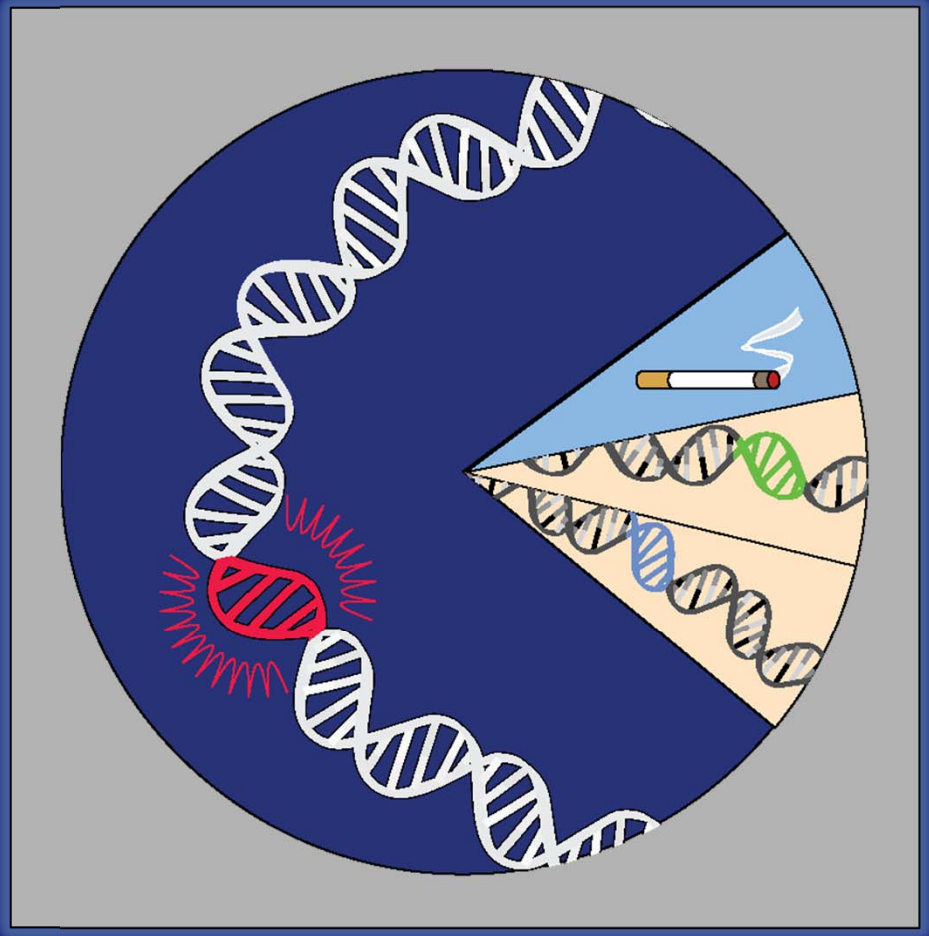


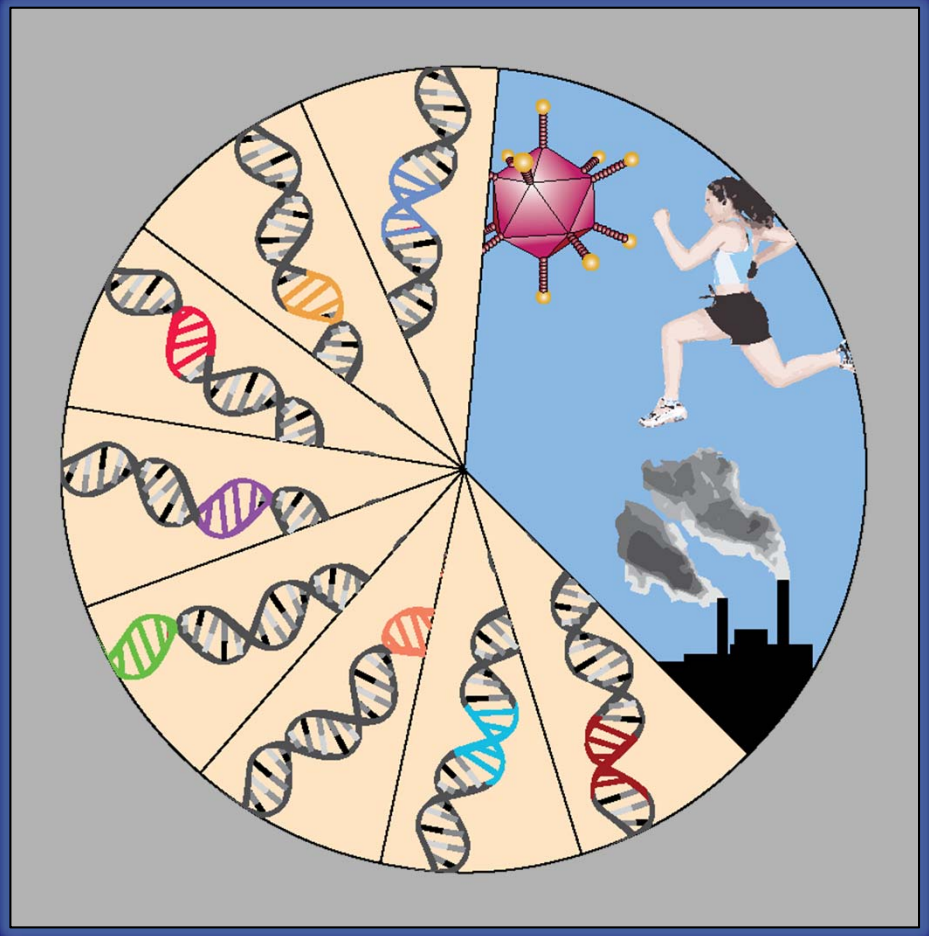
Source: *Online Mendelian Inheritance in Man* (www.ncbi.nlm.nih.gov/omim)



genome.gov/gwastudies

Genomic Architecture of Genetic Diseases





Rare, Simple, Monogenic, Mendelian…

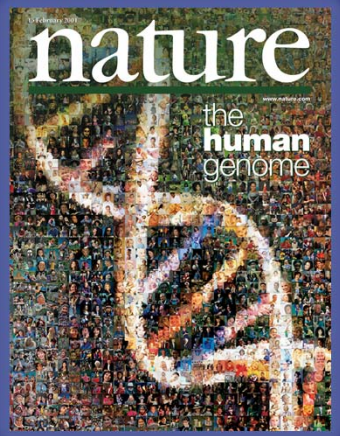
Common, Complex, Multigenic, Non-Mendelian…

Mostly *Coding* Mutations

Mostly *Non-Coding* Mutations

The Path to Genomic Medicine

Routine Whole-Genome Sequencing

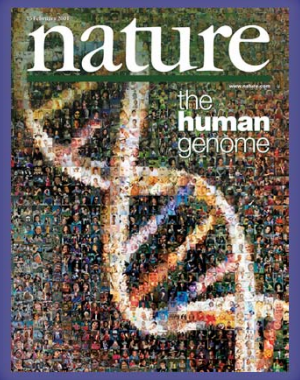


Human Genome Project

Realization of Genomic Medicine

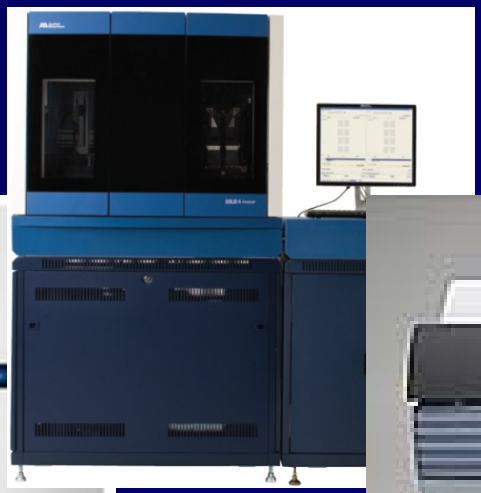
Human Genome Sequence

~$1,000,000,000



~$1,000

"The $1000 Genome"

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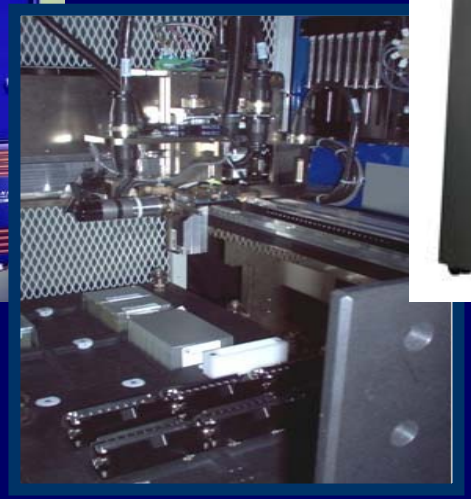
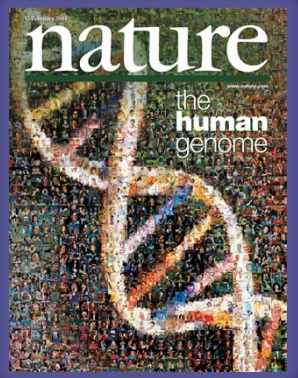


Human Genome Sequence



~$1,000,000,000

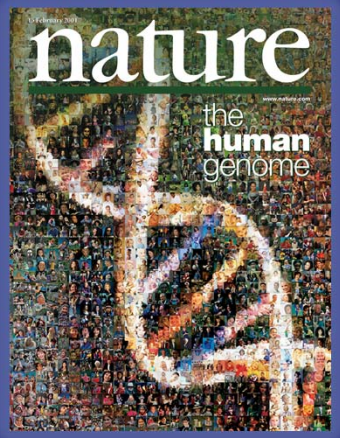
Current Cost

~$1,000

"The $1000 Genome"

The Path to Genomic Medicine

Routine Analysis of Genome Sequences



Human Genome Project

Realization of Genomic Medicine

The Computational Bottleneck

The Informational Bottleneck

Ten Years On — The Human Genome and Medicine

Harold Varmus, M.D.

On a June day nearly 10 years ago, the leaders of the United States and the United Kingdom, accompanied by the leaders of the public and private teams deciphering the human genome, announced that a draft sequence had been completed. That occasion was rich with promises of new and more powerful ways to understand, diagnose, prevent,

Human Genome Project has not yet directly affected the health care of most individuals."[2]

In this issue, the *Journal* begins another series of articles on genomic medicine.[3] Is it appropriate for the *Journal* to be taking stock so soon? It is, and for the following reasons.

First, readers will want to know the state of

Physicians are still a long way from submitting their patients' full genomes for sequencing, not because the price is high, but because the data are difficult to interpret.

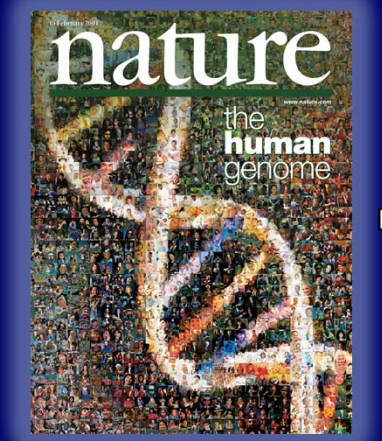
some strong genetic markers for assessing drug responsiveness, risk of disease, or risk of disease progression — have entered routine medical practice. And most of these can be traced to discoveries that preceded the unveiling of the human genome. As Francis Collins, formerly the leader of the publicly funded sequencing efforts, recently commented: "the consequences for clinical medicine . . . have thus far been modest . . . the

influential haplotypes, and in general, other implicated susceptibility haplotypes collectively account for only a small fraction of the apparent heritable risk. Clearly, more than one decade of genomics will be required to understand the inborn risks of most common disorders, such as diabetes and hypertension.

Second, readers will enjoy learning from these articles how rapidly the engines of genomics and

***NEJM* (2010)**

The Path to Genomic Medicine



Human Genome Project

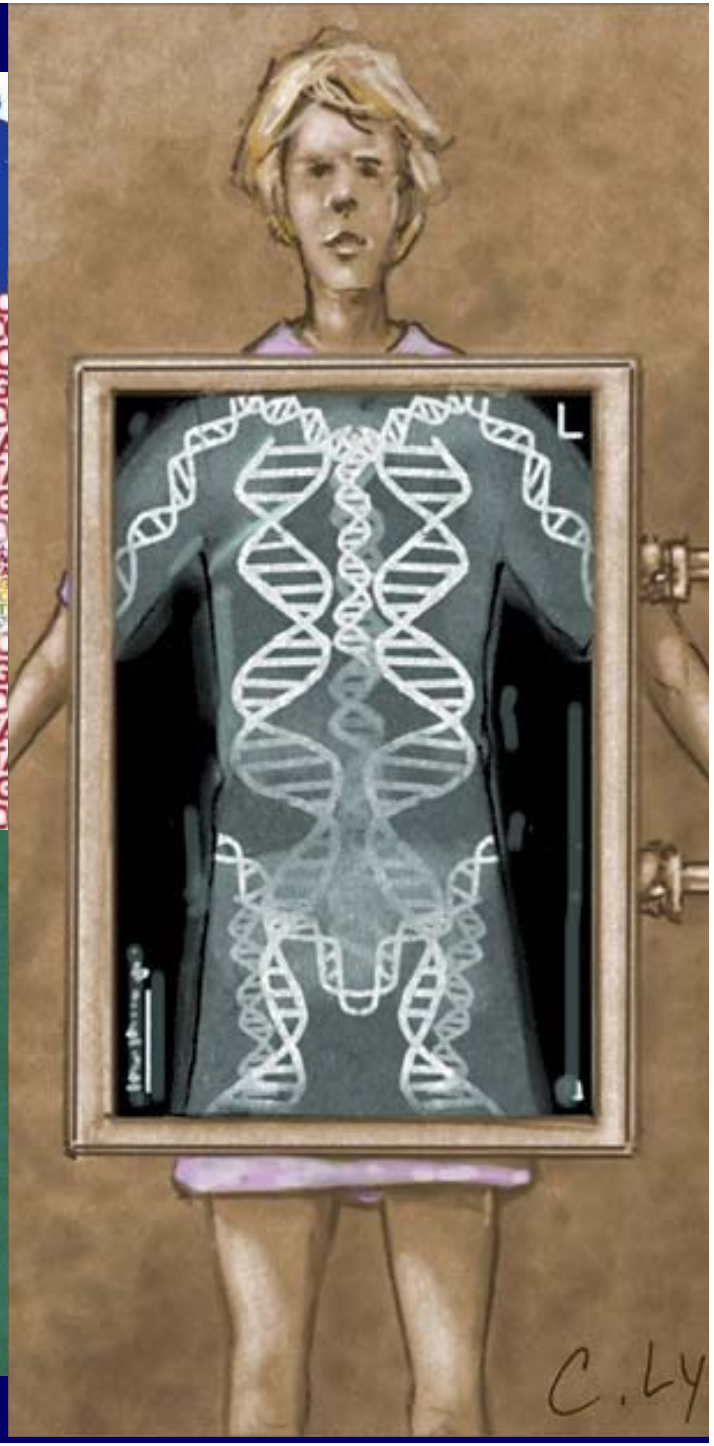
New Diagnostics

New Therapeutics

New Preventions

???

Realization of Genomic Medicine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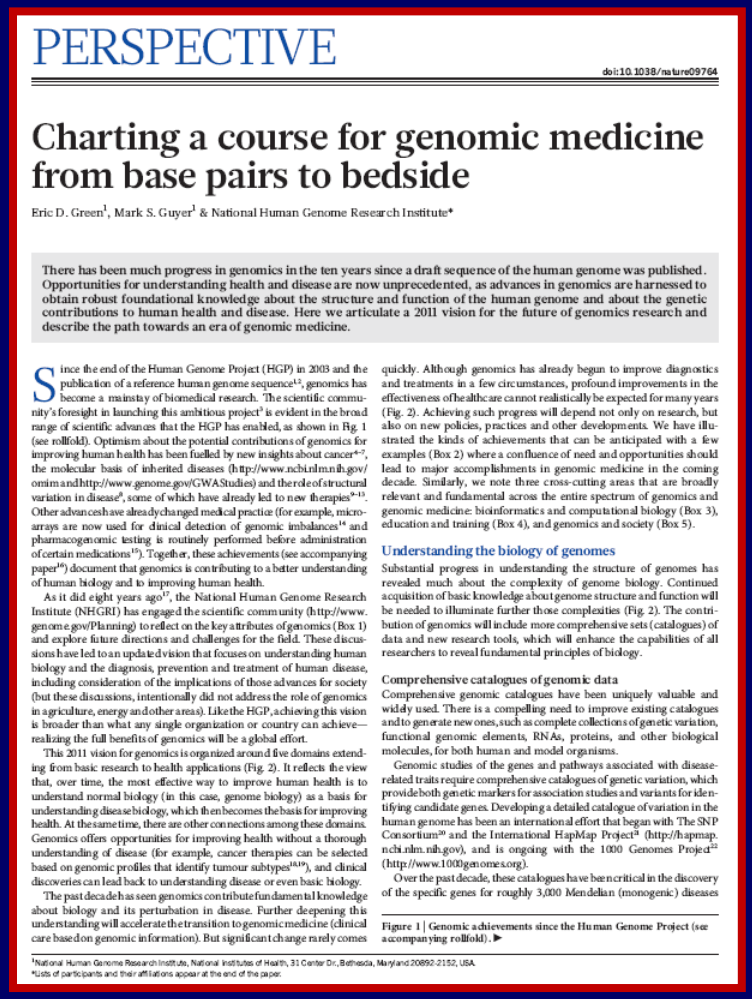
~11 Months Ago



PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[3] is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer[4–7], the molecular basis of inherited diseases (http://www.ncbi.nlm.nih.gov/omim and http://www.genome.gov/GWAStudies) and the role of structural variation in disease[8], some of which have already led to new therapies[9–13]. Other advances have already changed medical practice (for example, microarrays are now used for clinical detection of genomic imbalances[14] and pharmacogenomic testing is routinely performed before administration of certain medications[15]). Together, these achievements (see accompanying paper[16]) document that genomics is contributing to a better understanding of human biology and to improving human health.

As it did eight years ago[17], the National Human Genome Research Institute (NHGRI) has engaged the scientific community (http://www.genome.gov/Planning) to reflect on the key attributes of genomics (Box 1) and explore future directions and challenges for the field. These discussions have led to an updated vision that focuses on understanding human biology and the diagnosis, prevention and treatment of human disease, including consideration of the implications of those advances for society (but these discussions, intentionally did not address the role of genomics in agriculture, energy and other areas). Like the HGP, achieving this vision is broader than what any single organization or country can achieve—realizing the full benefits of genomics will be a global effort.

This 2011 vision for genomics is organized around five domains extending from basic research to health applications (Fig. 2). It reflects the view that, over time, the most effective way to improve human health is to understand normal biology (in this case, genome biology) as a basis for understanding disease biology, which then becomes the basis for improving health. At the same time, there are other connections among these domains. Genomics offers opportunities for improving health without a thorough understanding of disease (for example, cancer therapies can be selected based on genomic profiles that identify tumour subtypes[18,19]), and clinical discoveries can lead back to understanding disease or even basic biology.

The past decade has seen genomics contribute fundamental knowledge about biology and its perturbation in disease. Further deepening this understanding will accelerate the transition to genomic medicine (clinical care based on genomic information). But significant change rarely comes quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should lead to major accomplishments in genomic medicine in the coming decade. Similarly, we note three cross-cutting areas that are broadly relevant and fundamental across the entire spectrum of genomics and genomic medicine: bioinformatics and computational biology (Box 3), education and training (Box 4), and genomics and society (Box 5).

Understanding the biology of genomes

Substantial progress in understanding the structure of genomes has revealed much about the complexity of genome biology. Continued acquisition of basic knowledge about genome structure and function will be needed to illuminate further those complexities (Fig. 2). The contribution of genomics will include more comprehensive sets (catalogues) of data and new research tools, which will enhance the capabilities of all researchers to reveal fundamental principles of biology.

Comprehensive catalogues of genomic data

Comprehensive genomic catalogues have been uniquely valuable and widely used. There is a compelling need to improve existing catalogues and to generate new ones, such as complete collections of genetic variation, functional genomic elements, RNAs, proteins, and other biological molecules, for both human and model organisms.

Genomic studies of the genes and pathways associated with disease-related traits require comprehensive catalogues of genetic variation, which provide both genetic markers for association studies and variants for identifying candidate genes. Developing a detailed catalogue of variation in the human genome has been an international effort that began with The SNP Consortium[20] and the International HapMap Project[21] (http://hapmap.ncbi.nlm.nih.gov), and is ongoing with the 1000 Genomes Project[22] (http://www.1000genomes.org).

Over the past decade, these catalogues have been critical in the discovery of the specific genes for roughly 3,000 Mendelian (monogenic) diseases

Figure 1 | Genomic achievements since the Human Genome Project (see accompanying rollfold). ▶

[1]National Human Genome Research Institute, National Institutes of Health, 31 Center Dr., Bethesda, Maryland 20892-2152, USA.
*Lists of participants and their affiliations appear at the end of the paper.

February 2011

NHGRI Published New Vision for Genomics

Five Domains of Genomics Research

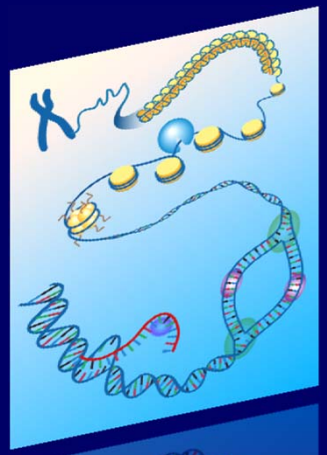
Understanding the Structure of Genomes

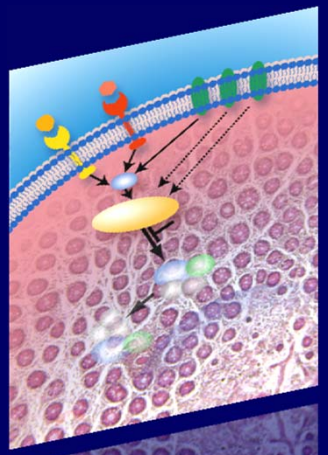
Understanding the Biology of Genomes

Understanding the Biology of Disease

Advancing the Science of Medicine

Improving the Effectiveness of Healthcare





Base Pairs to Bedside

Helix to Health

Genomic Accomplishments Across Domains

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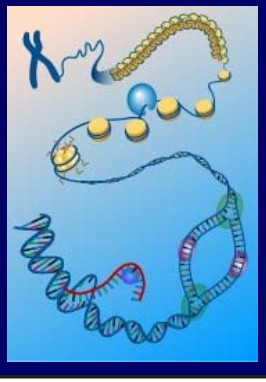
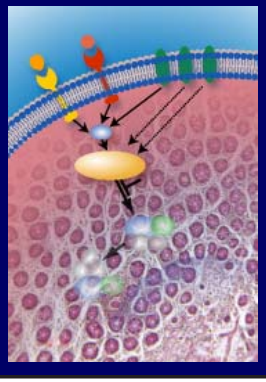
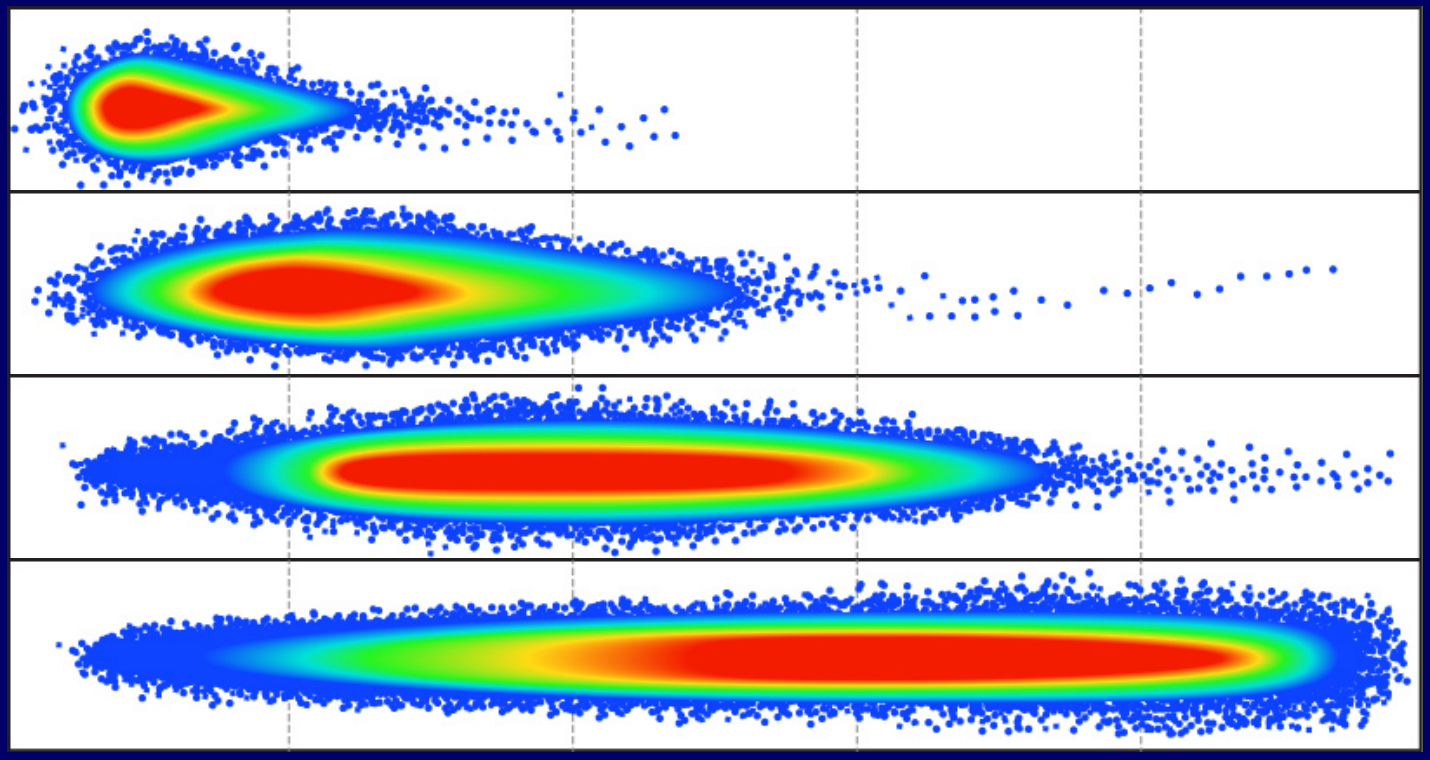
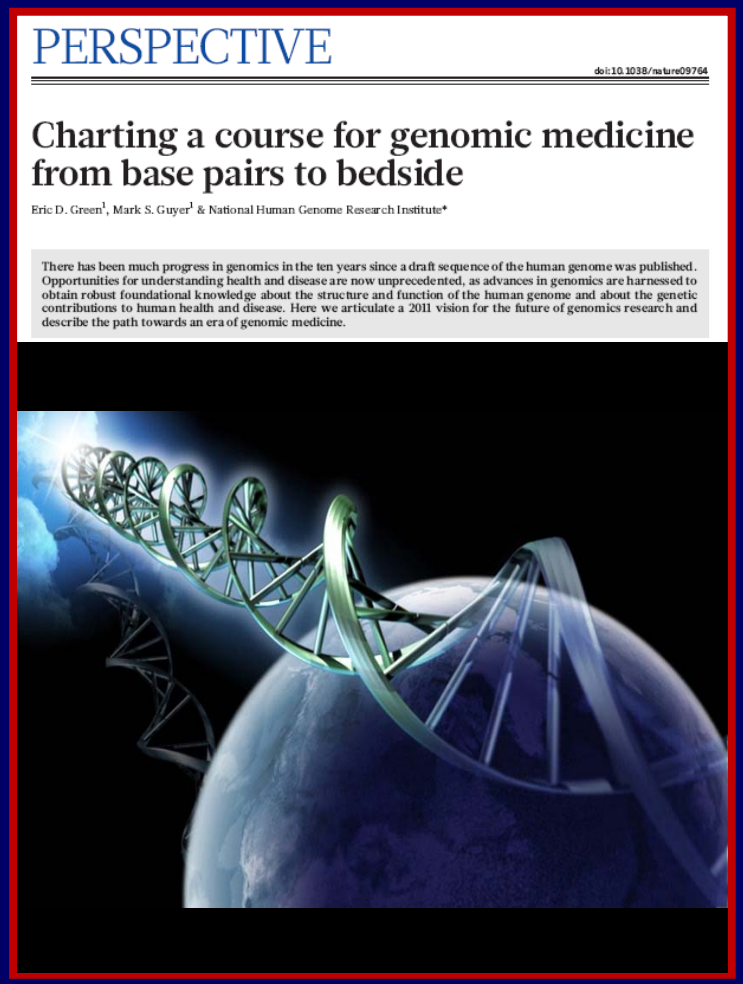
					
1990-2003 *Human Genome Project*					
2004-2010					
2011-2020					
Beyond 2020					

2011 NHGRI Strategic Plan for Genomics



PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

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>>>

NHGRI

BOX 2

Imperatives for genomic medicine

Opportunities for genomic medicine will come from simultaneously acquiring foundational knowledge of genome function, insights into disease biology and powerful genomic tools. The following imperatives will capitalize on these opportunities in the coming decade.

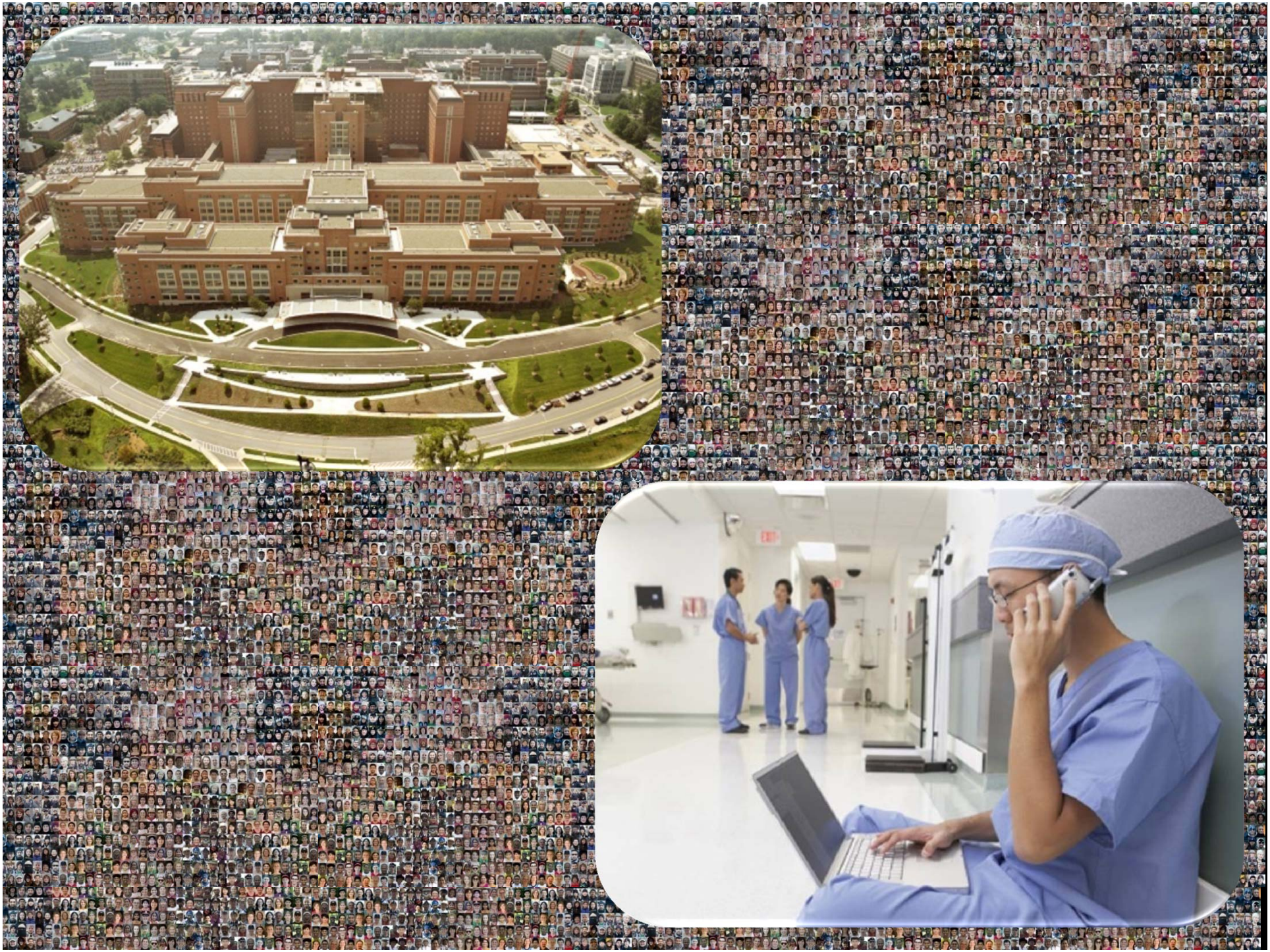
Making genomics-based diagnostics routine. Genomic technology development so far has been driven by the research market. In the next decade, technology advances could enable a clinician to acquire a complete genomic diagnostic panel (including genomic, epigenomic, transcriptomic and microbiomic analyses) as routinely as a blood chemistry panel.

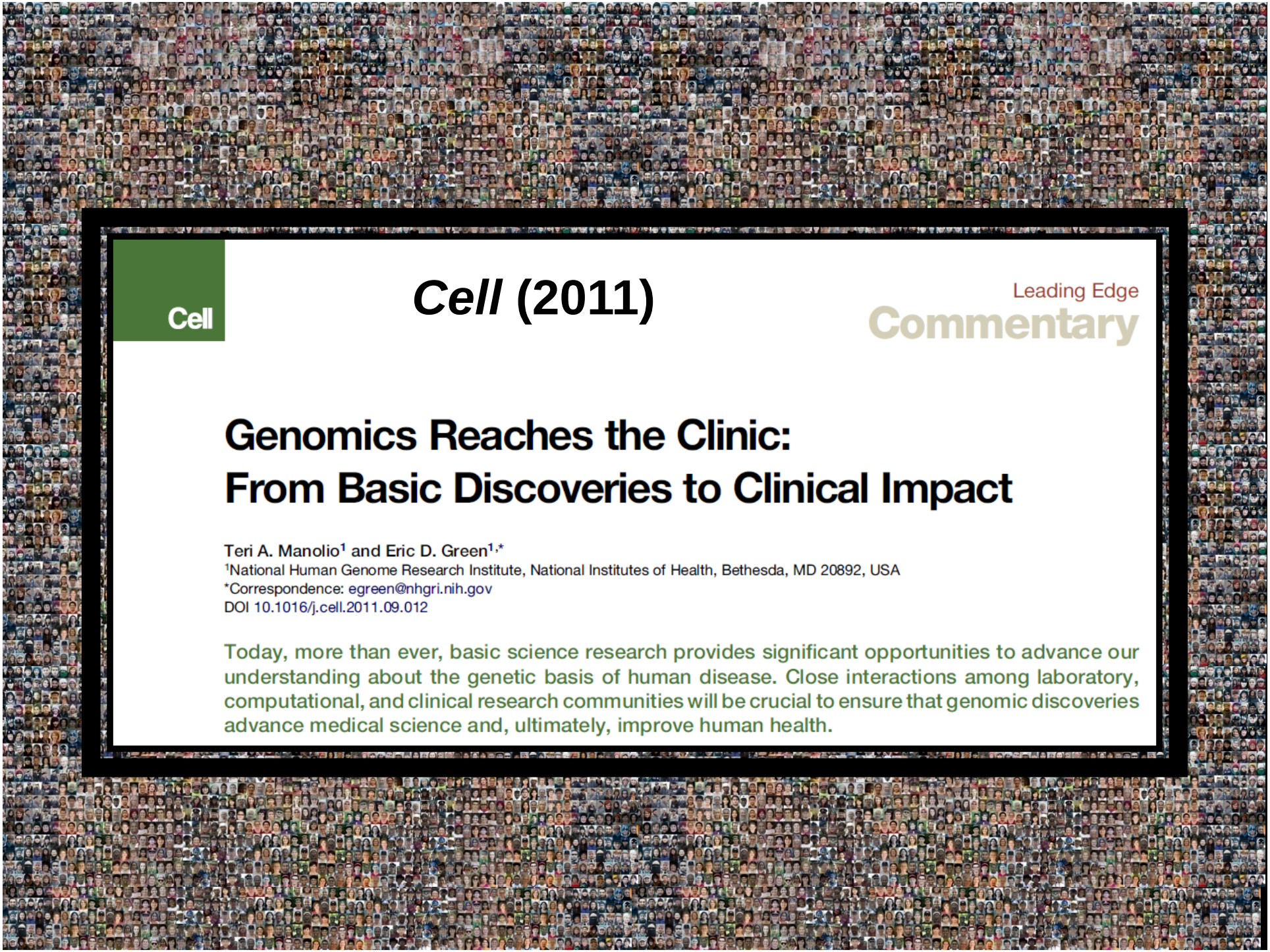
Defining the genetic components of disease. All diseases involve a genetic component. Genome sequencing could be used to determine the genetic variation underlying the full spectrum of diseases, from rare Mendelian to common complex disorders, through the study of upwards of a million patients; efforts should begin now to organize the necessary sample collections.

Comprehensive characterization of cancer genomes. A comprehensive genomic view of all cancers[4–7] will reveal molecular taxonomies and altered pathways for each cancer subtype. Such information should lead to more robust diagnostic and therapeutic strategies and a roadmap for developing new treatments[74,75].

Practical systems for clinical genomic informatics. Thousands of genomic variants associated with disease risk and treatment response are known, and many more will be discovered. New models for capturing and displaying these variants and their phenotypic consequences should be developed and incorporated into practical systems that make information available to patients and their healthcare providers, so that they can interpret and reinterpret the data as knowledge evolves.

The role of the human microbiome in health and disease. Many diseases are influenced by the microbial communities that inhabit our bodies (the microbiome)[101]. Recent initiatives[102,103] (http://www.human-microbiome.org) are using new sequencing technologies to catalogue the resident microflora at distinct body sites, and studying correlations between specific diseases and the composition of the microbiome[104]. More extensive studies are needed to build on these first revelations and to investigate approaches for manipulating the microbiome as a new therapeutic approach.





Cell

Cell (2011)

Leading Edge

Commentary

Genomics Reaches the Clinic: From Basic Discoveries to Clinical Impact

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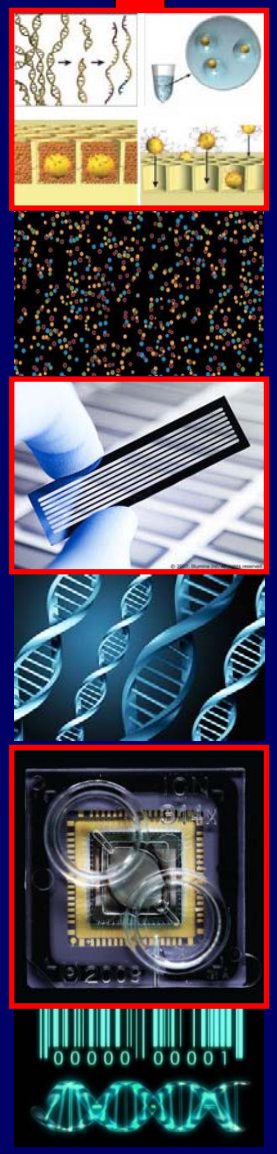
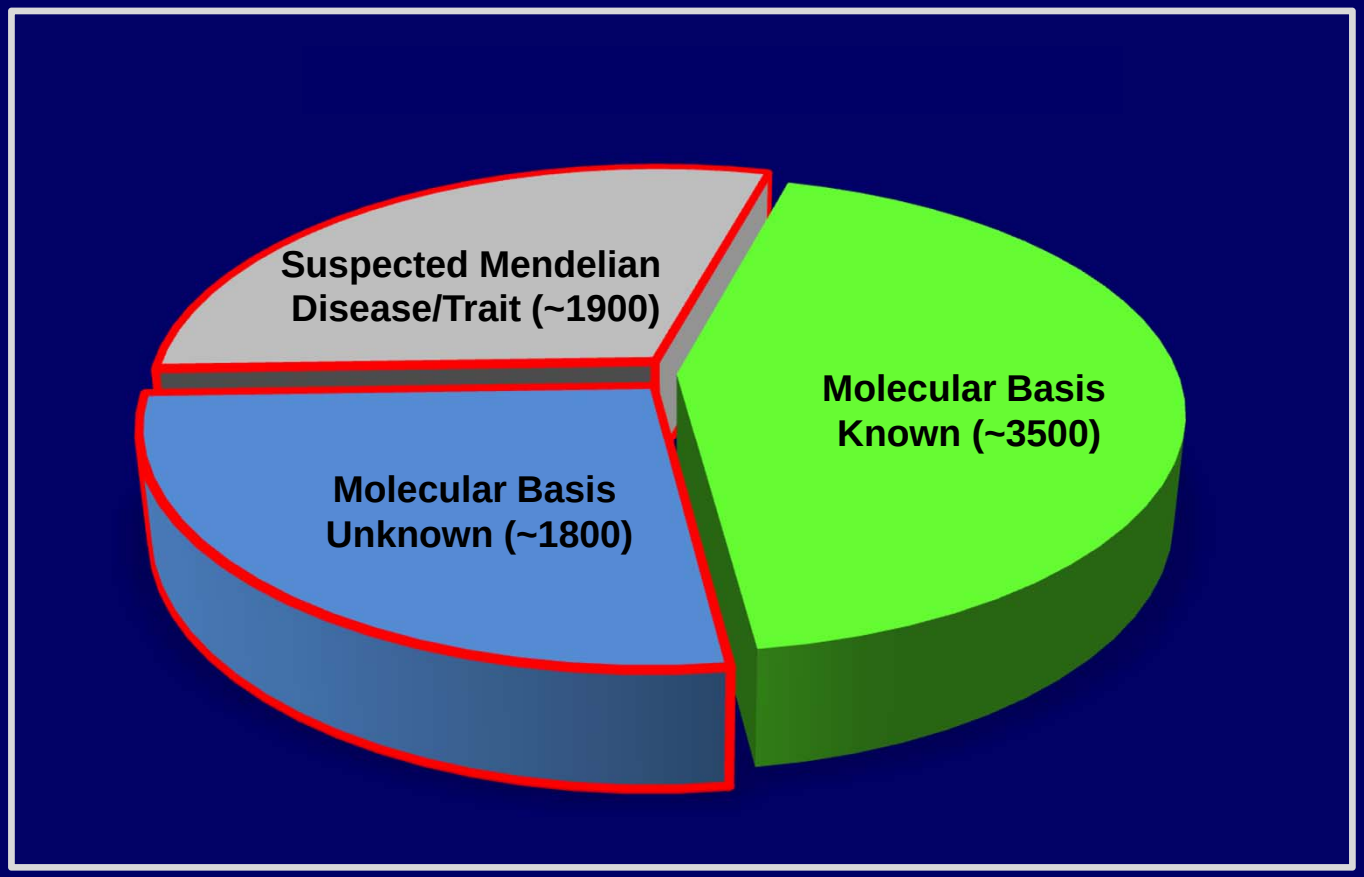
DOI 10.1016/j.cell.2011.09.012

Today, more than ever, basic science research provides significant opportunities to advance our understanding about the genetic basis of human disease. Close interactions among laboratory, computational, and clinical research communities will be crucial to ensure that genomic discoveries advance medical science and, ultimately, improve human health.

The Future: Genome Sequencing

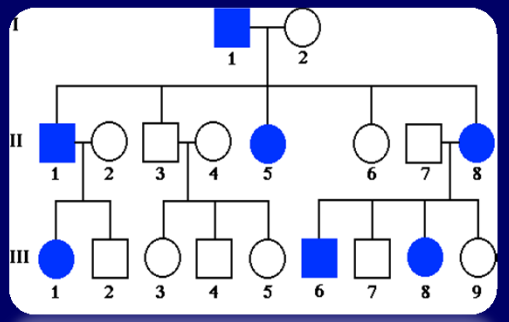




Mendelian Diseases/Traits

Mendelian Disorders Genome Centers

- Discover genetic basis of as many Mendelian disorders as possible (sample solicitation, sequencing, and data analysis)
- Establish and disseminate study designs and methods for the elucidation of the genetic basis of Mendelian phenotypes
- Create and maintain a public list of human samples as a point of coordination for broad-based discovery efforts



Mendelian Genome Centers

AGTC

Finding the genes underlying human Mendelian conditions

The Mendelian Genome Centers will apply next-generation sequencing and computational approaches to discover the genes and variants that underlie Mendelian conditions.

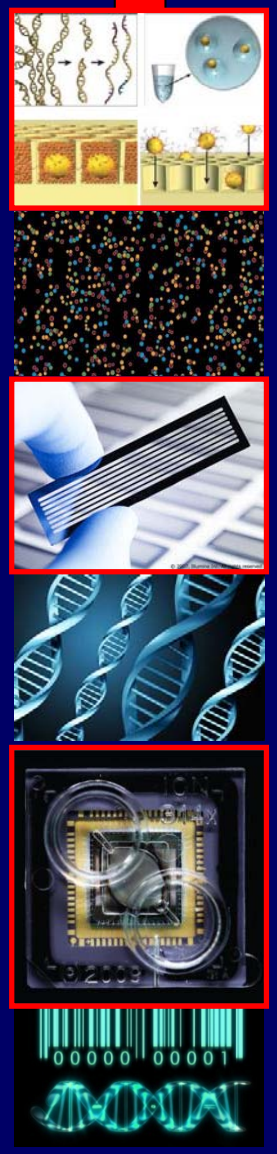
Our vision is to discover new genes that cause Mendelian conditions. As a result, we will expand our understanding about their biology to facilitate their diagnosis, and potentially indicate new treatments.

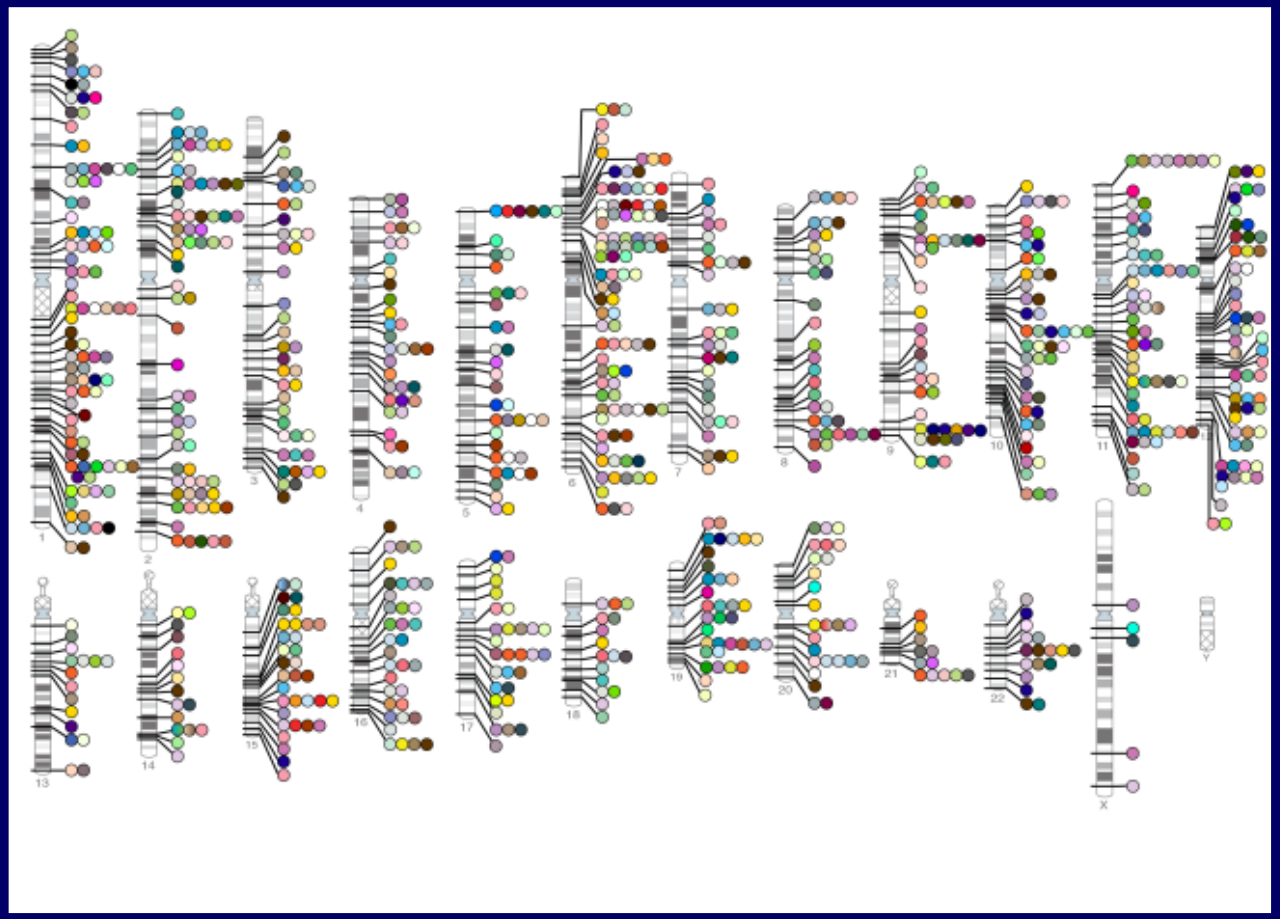
University of Washington Center for Mendelian Genomics
(coordinating center)

Yale Center for Mendelian Disorders

Baylor-Johns Hopkins Center for Mendelian Genetics

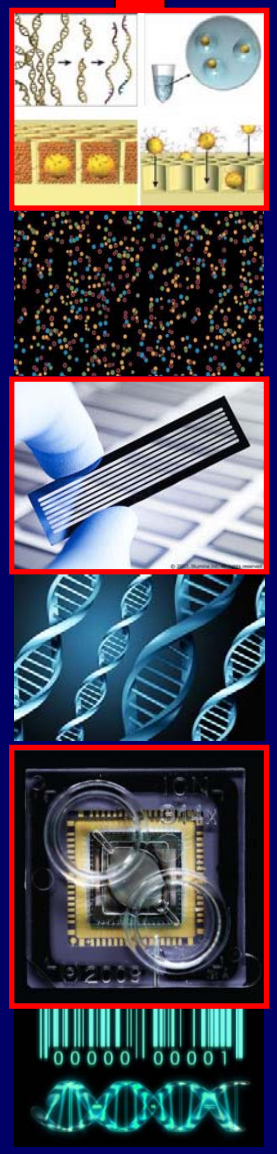
The Future: Genome Sequencing





Complex Diseases/Traits

The Future: Genome Sequencing



National Cancer Institute | National Human Genome Research Institute

The Cancer Genome Atlas — *Understanding genomics to improve cancer care*

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About Cancer Genomics

Explore information and resources to improve your understanding of cancer genomics, the importance of tumor samples in genomic research and the role of cancer genomics in personalized medicine.

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News Releases and Announcements

February 22, 2011
The Cancer Genome Atlas Announces Sessions at the AACR 2011 Annual Meeting

Leadership Update

February 2011
TCGA: A Future Arrived
Brad Ozenberger, Ph.D., TCGA Program Director for the National Human Genome Research Institute (NHGRI), talks about TCGA.

Launch Data Portal

The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

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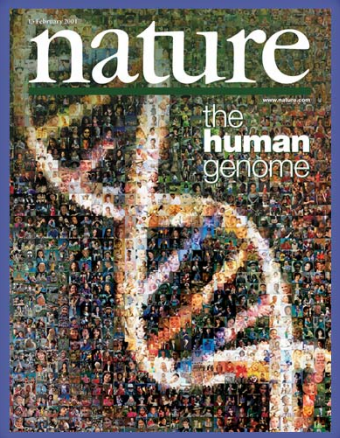
Clinical Genomic Information Systems

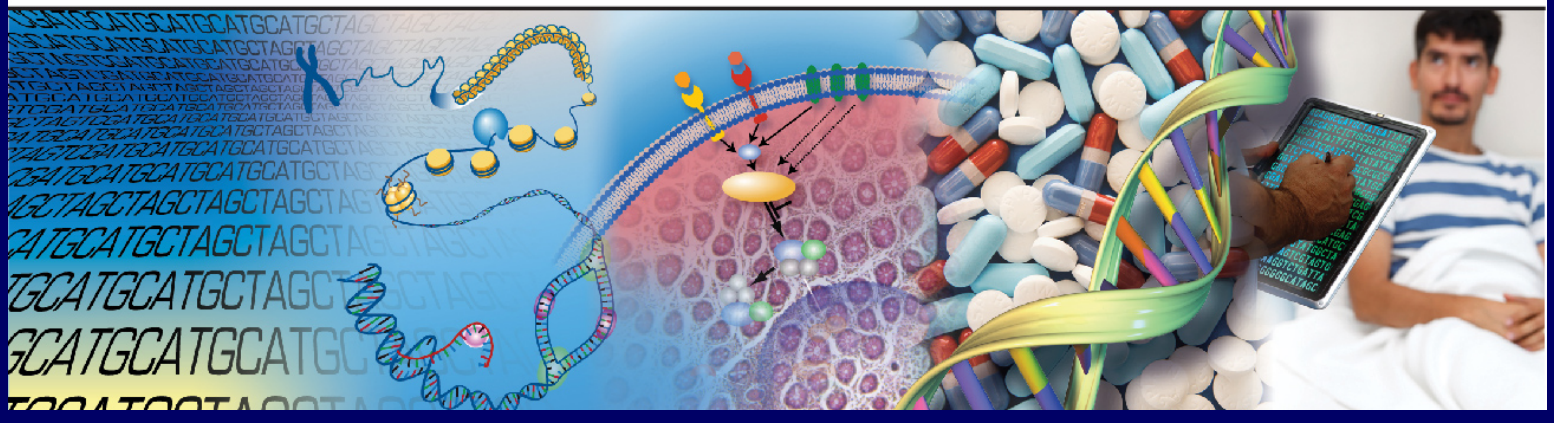
The Path to Genomic Medicine



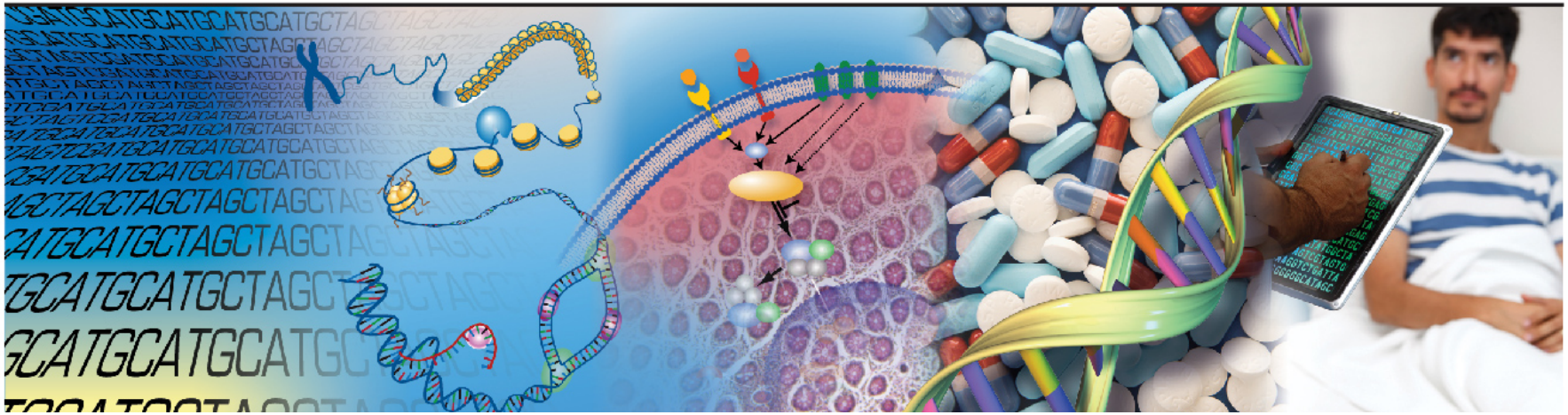
Human Genome Project

Realization of Genomic Medicine

Understanding the Structure of Genomes	Understanding the Biology of Genomes	Understanding the Biology of Disease	Advancing the Science of Medicine	Improving the Effectiveness of Healthcare



Understanding the Structure of Genomes | Understanding the Biology of Genomes | Understanding the Biology of Disease | Advancing the Science of Medicine | Improving the Effectiveness of Healthcare



A pessimist sees the difficulty in every opportunity.

An optimist sees the opportunity in every difficulty.

--Winston Churchill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