



NHGRI's Genomic Medicine Research Portfolio

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



NHGRI's Genomic Medicine Definition

An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the other implications of that clinical use

- **Purposefully narrow definition**
- **By 'genomic,' NHGRI means direct information about DNA or RNA; downstream products outside the immediate view**
- **Metaphorically viewed as a key 'destination' for attaining NHGRI's mission of improving health through genomics research**

The Path to Genomic Medicine



**Human
Genome
Project**



**Realization of
Genomic
Medicine**

A vision for the future of genomics research

A. Chapman et al.

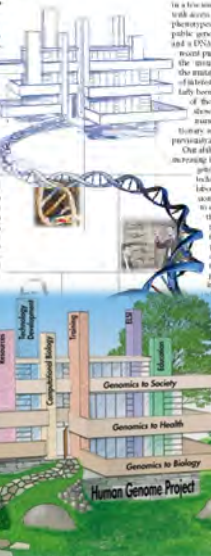
Francis S. Collins, Eric D. Green, Alan E. Guttmacher and Mark S. Guyer are leaders of the US National Human Genome Research Institute*

The completion of a high-quality, comparative sequence of the human genome, in the fifth anniversary year of the discovery of the double-helical structure of DNA, is a landmark event. The genome era is now dawning.

In contemplating a vision for the future of genomics research, it is important to consider the remarkable path that has brought us here. The initial (Figure 1) shows a timeline of landmark accomplishments in genetics and genomics, beginning with Gregor Mendel's discovery of the laws of heredity and their rediscovery by the early days of the twentieth century. The discovery of DNA as the hereditary material, determination of its structure, elucidation of the genetic code, development of recombinant DNA technology, and establishment of the molecularly amenable methods for DNA sequencing mark the stage for the Human Genome Project (HGP) to begin in 1990 (see also www.nature.com/nature/1990). Thanks to the vision of the scientific community, the creation of the HGP is now a reality. The initial objectives of the project, as defined by the HGP, are to determine the sequence of the human genome, to identify all genes, and to understand the function of the human genome.

The project's experimental strategy is already well advanced, and the public genome sequence is being assembled. The project's initial objectives are being met, and the project is well on its way to achieving its goals. The project's initial objectives are being met, and the project is well on its way to achieving its goals.

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feature

In a review by a single graduate student with access to DNA samples and associated phenotypes, an indirect connection to the public genome databases, a formal review and a DNA-sequencing machine. With the recent publication of a draft sequence of the mouse genome, identification of the mutations underlying a vast number of interesting mouse phenotypes has naturally been simplified. Comparison of the human and mouse sequences shows that the proportion of the mammalian genome under positive natural selection is more than twice that previously assumed.

Our ability to explore genetic diversity is increasing in parallel as each subsequent genome is sequenced. Microarray technologies have accelerated many laboratory and clinical experiments, and of these in two years in a month the expression of tens of thousands of genes in a single experiment. Clinical applications for gene-based personalized medicine of diagnosis and adverse drug response are emerging at a rapid pace, and the therapeutic promise of genomics has taken on an exciting phase of expansion.

As it did eight years ago*, the National Human Genome Research Institute (NHGRI) has a vision for the future of genomics research. The NHGRI is committed to the HGP and to exploring the future directions of genomics research. The NHGRI is committed to the HGP and to exploring the future directions of genomics research. The NHGRI is committed to the HGP and to exploring the future directions of genomics research.

Nature

PERSPECTIVE

doi:10.1038/nature09716

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green¹, Mark S. Guyer¹ & 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, and 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 sequence¹, genomics has become a mainstay of biomedical research. The scientific community's insight in launching this ambitious project is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see ref. 2). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer³, the molecular basis of inherited diseases (http://www.nchad.nih.gov/continuing/genome.gov/QA/Stroke) and the role of structural variation in disease⁴, some of which have already led to new therapies^{5,6}. Other advances have already changed medical practice (for example, microarrays are now used for clinical detection of genomic imbalances⁷ and pharmacogenomic testing is routinely performed before administration of certain medications^{8,9}). Together, these achievements (see accompanying paper)¹⁰ document that genomics is contributing to a better understanding of human biology and to improving human health.

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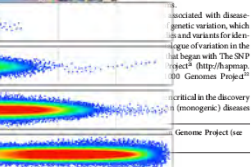
The 2011 vision for genomics research is to explore the future directions of genomics research. The NHGRI is committed to the HGP and to exploring the future directions of genomics research. The NHGRI is committed to the HGP and to exploring the future directions of genomics research.

quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of health care 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 identified the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunity 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

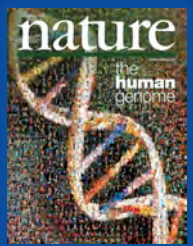
Substantial progress in understanding the structure of genomes has revealed much about the complexity of genome biology. Continued sequencing of basic types of genomes (see Fig. 2). The continuing expansion of genome catalogs (catalogues) of the capabilities of all genomes.

Genomics research is uniquely valuable and is creating a catalog of genetic variation, and other biological information, that is associated with disease. The NHGRI is committed to the HGP and to exploring the future directions of genomics research.



*National Human Genome Research Institute (NHGRI) has a vision for the future of genomics research.

Nature



2003

2011



NHGRI Strategic Vision for Genomics



PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green¹, Mark S. Guyer¹ & 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 sequence¹, genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project² is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rolloff). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer³⁻⁷, 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 disease⁸, some of which have already led to new therapies⁹⁻¹⁵. Other advances have already changed medical practice (for example, microarrays are now used for clinical detection of genomic imbalance¹⁶ and pharmacogenomic testing is routinely performed before administration of certain medications¹⁷). Together, these achievements (see accompanying paper¹⁸) document that genomics is contributing to a better understanding of human biology and to improving human health.

As it did eight years ago¹⁷, 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^{19,20}), 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 health care 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 catalogue 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 Consortium²¹ and the International HapMap Project²² (<http://hapmap.ncbi.nlm.nih.gov>), and is ongoing with the 1000 Genomes Project²³ (<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 rolloff). ▶

*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.

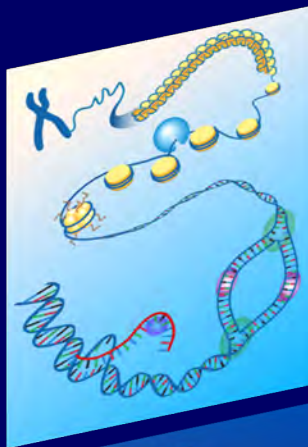
February 2011

Five Domains of Genomics Research

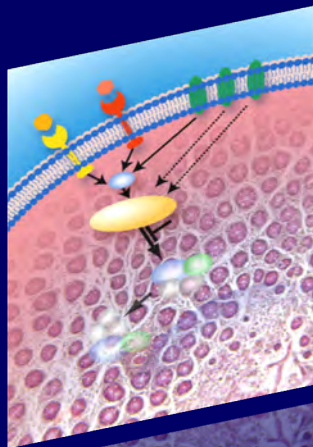
Understanding the Structure of Genomes



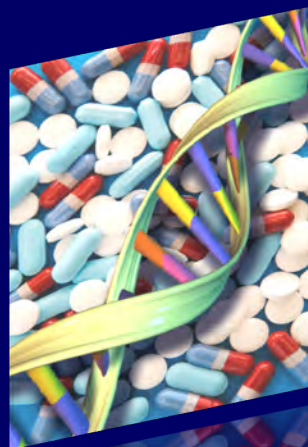
Understanding the Biology of Genomes



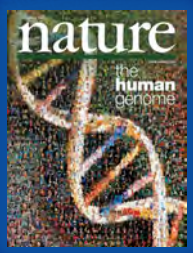
Understanding the Biology of Disease



Advancing the Science of Medicine



Improving the Effectiveness of Healthcare



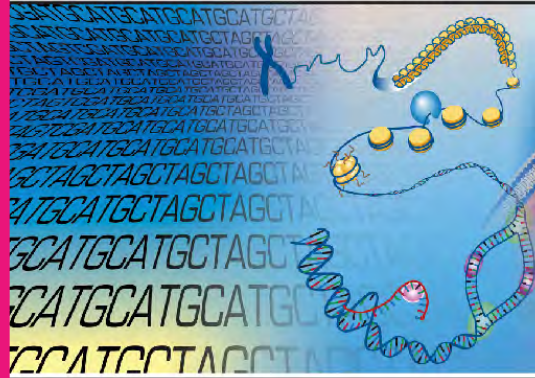
Understanding
the Structure of
Genomes

Understanding
the Biology of
Genomes

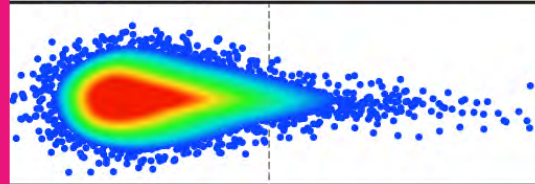
Understanding
the Biology of
Disease

Advancing
the Science of
Medicine

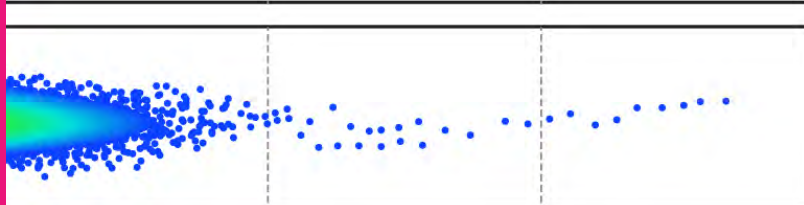
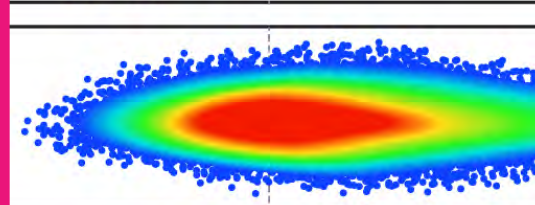
Improving the
Effectiveness of
Healthcare



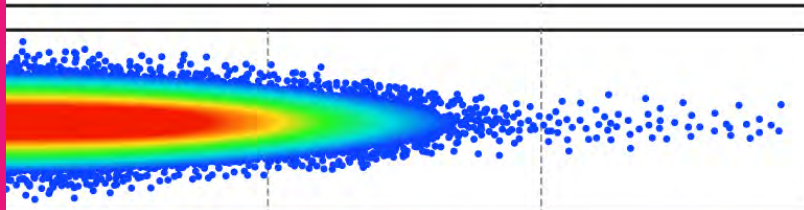
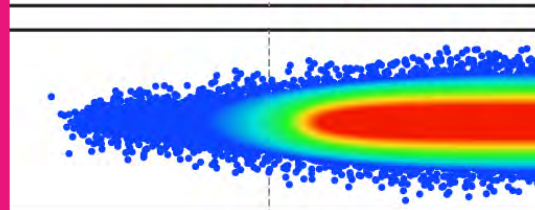
1990-2003
Human Genome Project



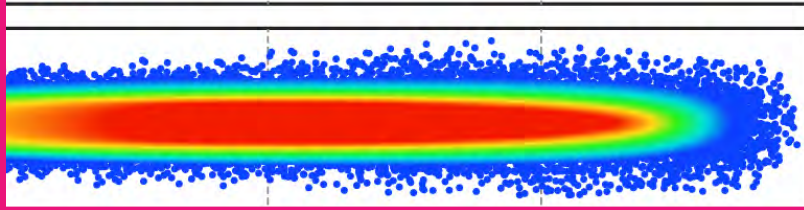
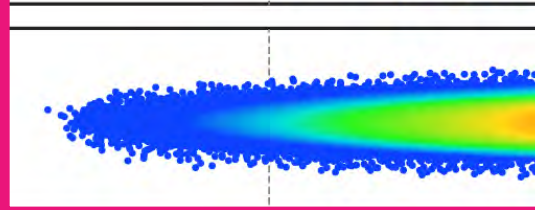
2004-2010



2011-2020



Beyond 2020



Disease-Related Genomics Research

Domain 3

Discovery Research

Establish genotype-phenotype associations for human diseases

- Identify persons at increased risk of disease based on their genomic variants
- Find all variants related to a given phenotype or disease
- Characterize variants known to be related to disease or treatment response

Domain 4

Clinical Validation

Assess outcomes from using genomic information for clinical care

- Assess impact on health outcomes and care utilization
- Identify causes of rare or undiagnosed diseases
- Validate drug targets and develop improved therapeutics

Domain 5

Clinical Implementation

Develop processes for using genomic information for clinical care

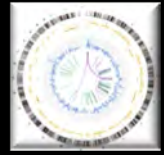
- Develop processes for using genomic information
- Educate clinicians and patients about use of genomic information
- Define and disseminate information on actionable clinical variants and relevant evidence base

Genomic Medicine

NHGRI Programs in Genomic Medicine



Cancer Genomics



Pharmacogenomics



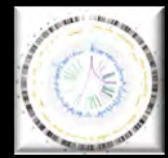
**eMERGE Network
& eMERGE-PGRN**

Dan Roden

NHGRI Programs in Genomic Medicine



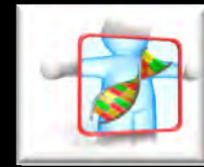
Cancer Genomics



Pharmacogenomics



Genomic Medicine
'Test Drive' Programs



Clinical Sequencing
Exploratory Research (CSER)

Lucia Hindorff

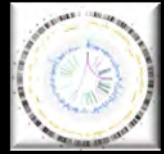
Implementing Genomics in
Practice (IGNITE)

Geoff Ginsburg

NHGRI Programs in Genomic Medicine



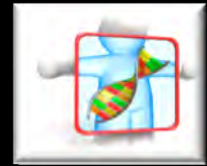
Cancer Genomics



Pharmacogenomics



Genomic Medicine
'Test Drive' Programs



Newborn Genomic
Analysis

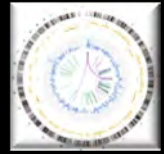


Newborn Sequencing Program
Anastasia Wise

NHGRI Programs in Genomic Medicine



Cancer Genomics



Pharmacogenomics



**Genomic Medicine
'Test Drive' Programs**



**Newborn Genomic
Analysis**



**Clinical Genomics
Information Systems**



Clinical Genomics Information Systems



Clinical Genome Resource (ClinGen)

New NIH-funded resource focuses on use of genomic variants in medical care



Bethesda, Md., Wed., Sept. 25, 2013 - Three grants totaling more than \$25 million over four years will help three research groups to develop authoritative information on the millions of genomic variants relevant to human disease and the hundreds that are expected to be useful for clinical practice. The awards are from the National Institutes of Health.

More and more medical and research centers are sequencing the DNA of whole genomes (the body's entire genetic blueprint) or exomes (the genome's protein-coding region) of patients. Each time, millions of DNA differences in genes and the regions between the genes are detected. But doctors struggle to know which of those differences, called variants, are relevant to disease and for a patient's medical care. As a result, information on few genomic variants is used in clinical practice.

The grants will support a consortium of research groups to develop the Clinical Genome Resource (ClinGen). The investigators will design and implement a framework for evaluating

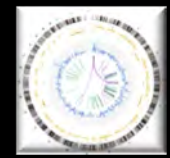
which variants play a role in disease and those that are relevant to patient care, and will work closely with the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM), which will distribute this information through its ClinVar database. The grants are funded by the National Human Genome Research Institute (NHGRI) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which, along with NCBI and NLM, are part of NIH. ClinGen was developed from NHGRI's Clinically Relevant Variants Resource program.

genome.gov

NHGRI Programs in Genomic Medicine



Cancer Genomics



Pharmacogenomics



**Genomic Medicine
'Test Drive' Programs**



**Newborn Genomic
Analysis**



**Clinical Genomics
Information Systems**



**Ultra-Rare Genetic
Disease Diagnostics**



Ultra-Rare Genetic Disease Diagnostics

Exome Sequencing: Dual Role as a Discovery and Diagnostic Tool

Chee-S **Clinical application of exome sequencing in undiagnosed genetic conditions**



Anna C I **Next-Generation Sequencing for Clinical Diagnostics**
Kevin V S

Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

Ya **Genomics in Clinical Practice: Lessons from the Front Lines**
Matth
Alicia
Matthe
Magalie S

Howard J. Jacob,^{1,5,6*} Kelly Abrams,¹² David P. Bick,^{1,5,10} Kent Brodie,¹ David P. Dimmock,^{1,5,10} Michael Farrell,³ Jennifer Geurts,^{1,7} Jeremy Harris,^{1,5} Daniel Helbling,^{1,5} Barbara J. Joers,¹² Robert Kliegman,⁵ George Kowalski,¹ Jozef Lazar,^{1,2} David A. Margolis,⁵ Paula North,^{4,9,11} Jill Northup,¹ Altheia Roquemore-Goins,¹¹ Gunter Scharer,^{1,5,10} Mary Shimoyama,^{1,7} Kimberly Strong,^{1,8} Bradley Taylor,¹ Shirng-Wern Tsaih,¹ Michael R. Tschannen,¹ Regan L. Veith,^{1,10} Jaime Wendt-Andrae,¹ Brandon Wilk,^{1,5} Elizabeth A. Worthey^{1,5,9}



Undiagnosed Diseases Network (UDN)



- **Build upon the successful experience with the NIH Undiagnosed Diseases Program to improve the diagnosis and care of patients with undiagnosed diseases**
- **Facilitate research into the etiology of undiagnosed diseases**
- **Create a highly collaborative research community to identify best practices for the diagnosis and management of undiagnosed diseases**

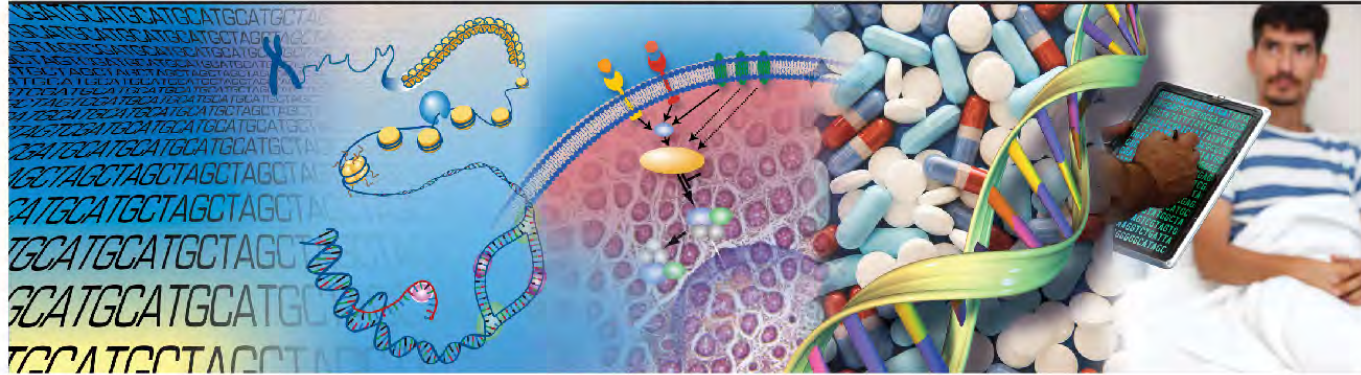
Understanding
the Structure of
Genomes

Understanding
the Biology of
Genomes

Understanding
the Biology of
Disease

Advancing
the Science of
Medicine

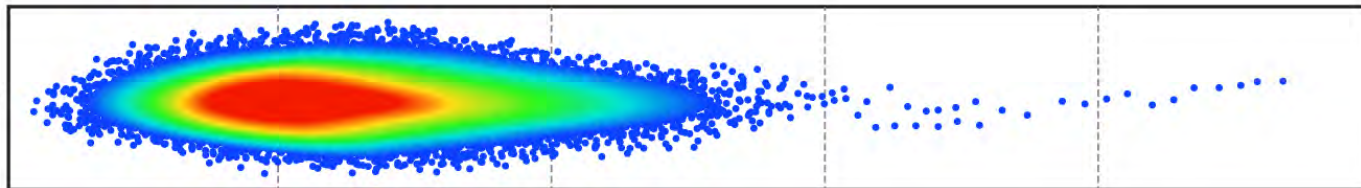
Improving the
Effectiveness of
Healthcare



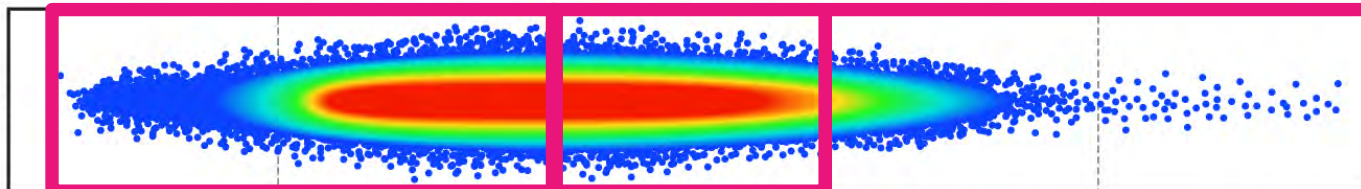
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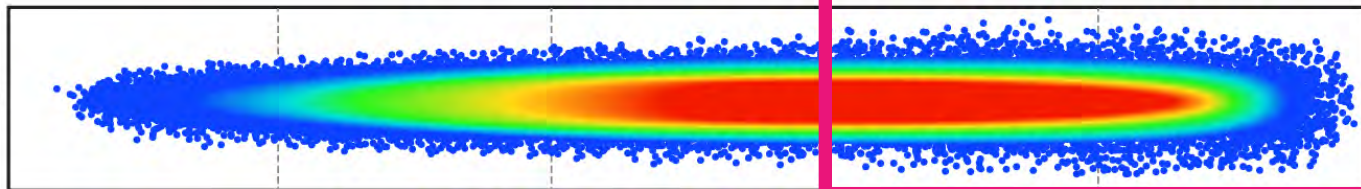
2004-2010



2011-2020



Beyond 2020



The Genomics Landscape

A monthly update from
the NHGRI Director



October 21, 2013

I am pleased to debut a new means of communicating information from the National Human Genome Research Institute (NHGRI) — *The Genomics Landscape*. In response to encouragement that I have received from various stakeholders to provide more regular personal updates about topics of interest, I am starting a monthly email message that aims to disseminate information from the NHGRI Director to the broader genomics community and other interested recipients. Each month, I will endeavor to highlight two to four topics, typically featuring one in greater detail.

To subscribe, follow link from:
genome.gov/Director

NHGRI-Smithsonian Genome Exhibition

GENOME
UNLOCKING
LIFE'S
CODE



National Human Genome
Research Institute



Smithsonian
National Museum of Natural History



- **Opened June 14, 2013**
- **~4400 square foot exhibition**
- **Hall 23 (adjacent to Hope Diamond)**
- **Resident in Smithsonian NMNH for ~1 year**
- **Subsequently will tour North America for 4-5 years**

NHGRI-Smithsonian Exhibition: Website



unlockinglifescode.org

Exhibition Opening June 14, 2013

GENOME
UNLOCKING
LIFE'S
CODE

EXHIBIT FEATURES DONORS

The image shows a screenshot of a website for the NHGRI-Smithsonian Exhibition. The main visual is a photograph of an older man in a blue shirt and glasses pointing upwards at a large, glowing orange DNA double helix structure. A young child in a light blue shirt is looking up at the man. The background is a blurred cityscape. The text on the page includes the exhibition opening date, the title 'GENOME UNLOCKING LIFE'S CODE', and navigation buttons for 'EXHIBIT FEATURES' and 'DONORS'. The browser address bar shows 'unlockinglifescode.org' and the search engine is Google.

unlockinglifescode.org



NATIONAL HUMAN GENOME RESEARCH INSTITUTE



***Advancing human health
through genomics research***