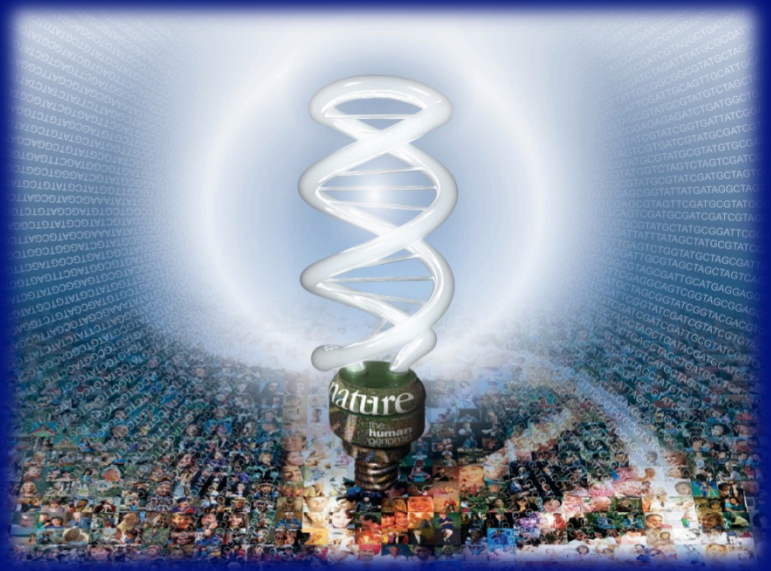
Integrating Genomic Sequencing into Clinical Care: CSER and Beyond



Setting the Context

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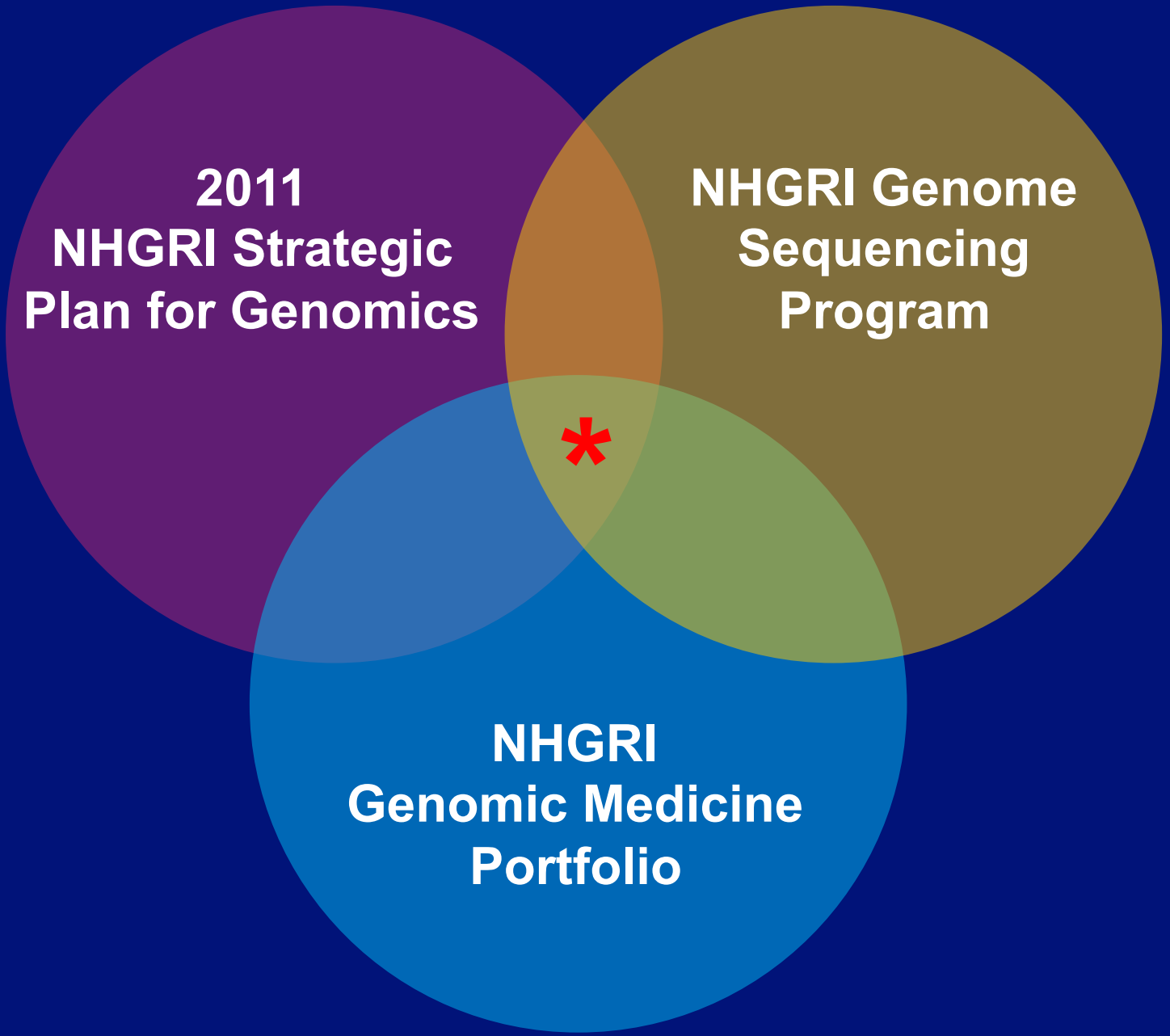
Director, NHGRI

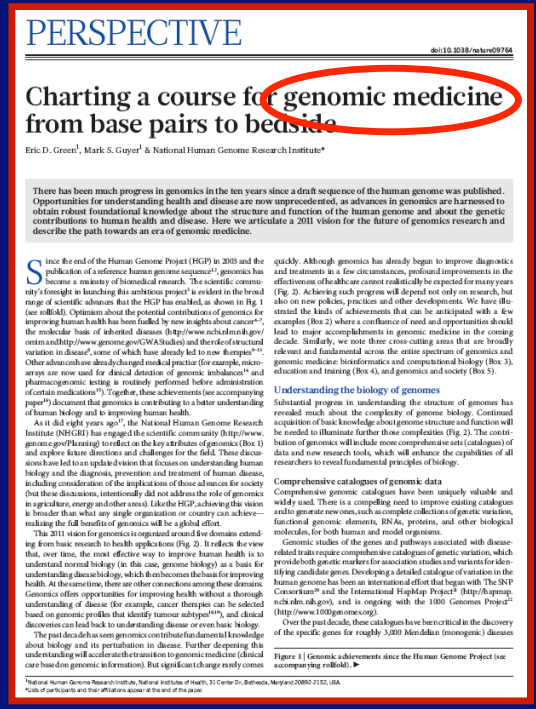
NIH National Human Genome Research Institute

Dodged the Bullet…
(for now)!

25th Anniversary of the Launch of the Human Genome Project

Getting Oriented





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], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[2] 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[3–7], 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/Pfunding) 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 update division 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[9,10]), 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[18] and the International HapMap Project[19] (http://hapmap.ncbi.nlm.nih.gov), and is ongoing with the 1000 Genomes Project[20] (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). ▶

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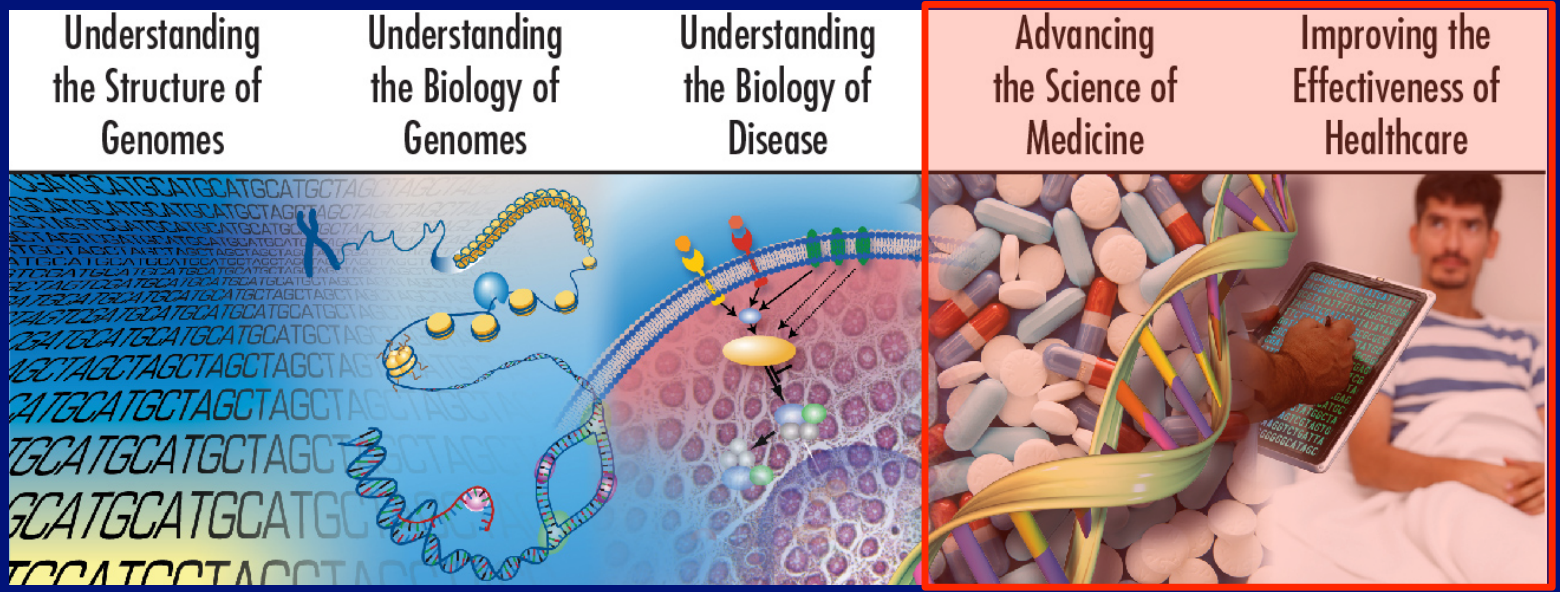
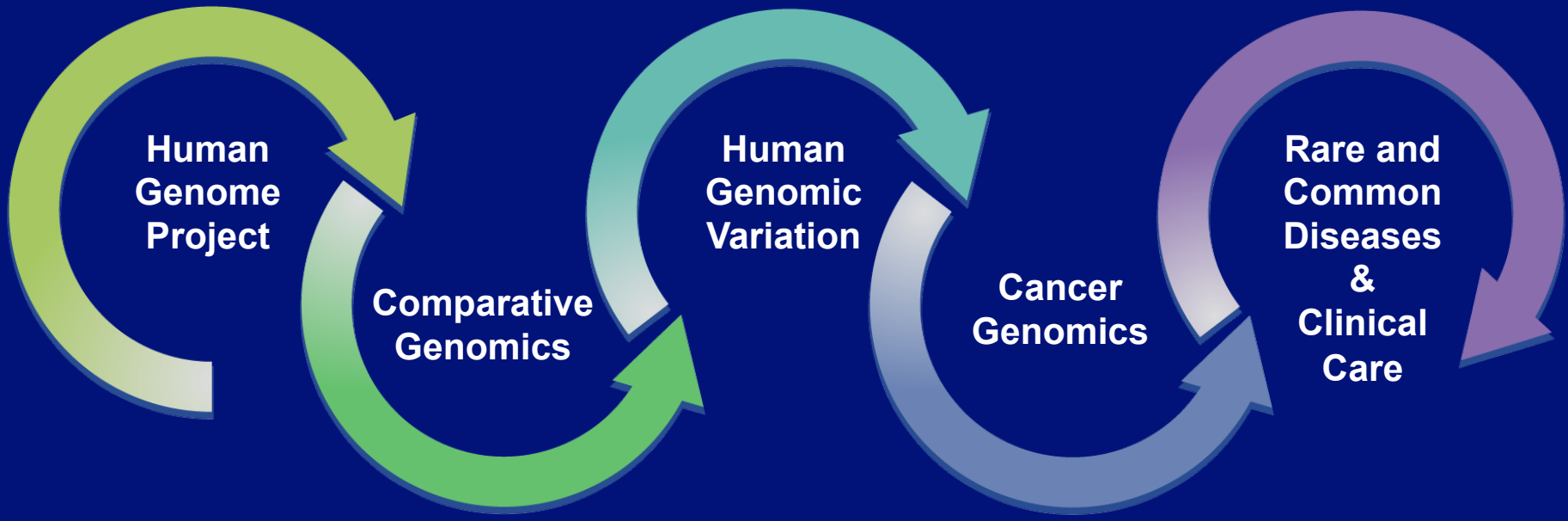
*Lists of participants and their affiliations appear at the end of the paper.



NHGRI Genome Sequencing Program

At the cutting edge of genome analysis



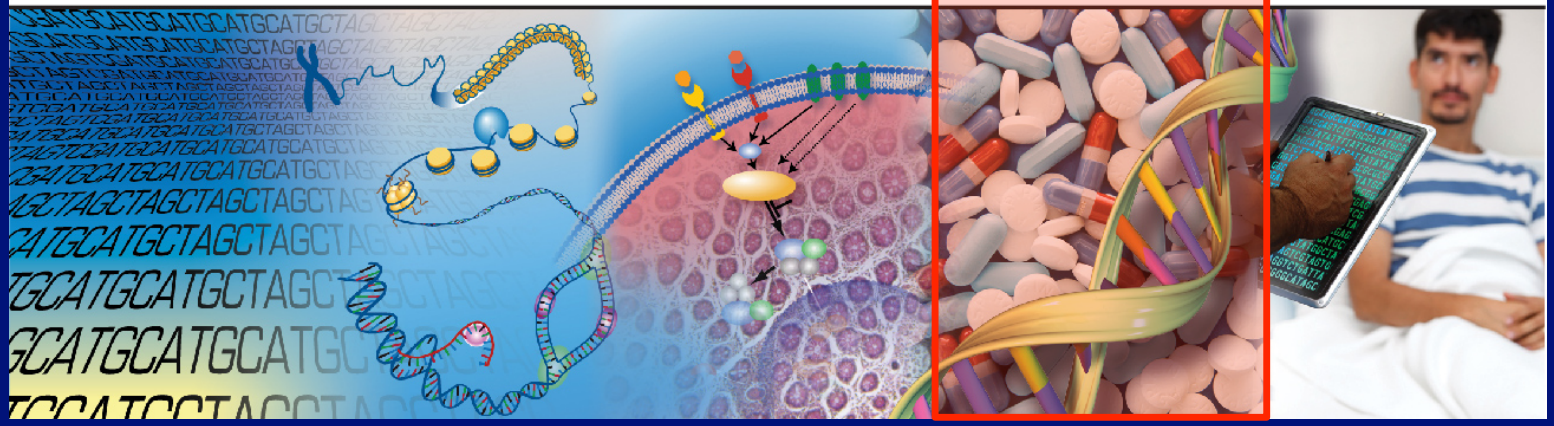
NHGRI Genome Sequencing Program
Circa 2012-2015

Large-Scale Genome Sequencing and Analysis Centers

cser

Clinical Sequencing Exploratory 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



NHGRI Genome Sequencing Program
Circa 2016-2019

Centers for Common Disease Genomics

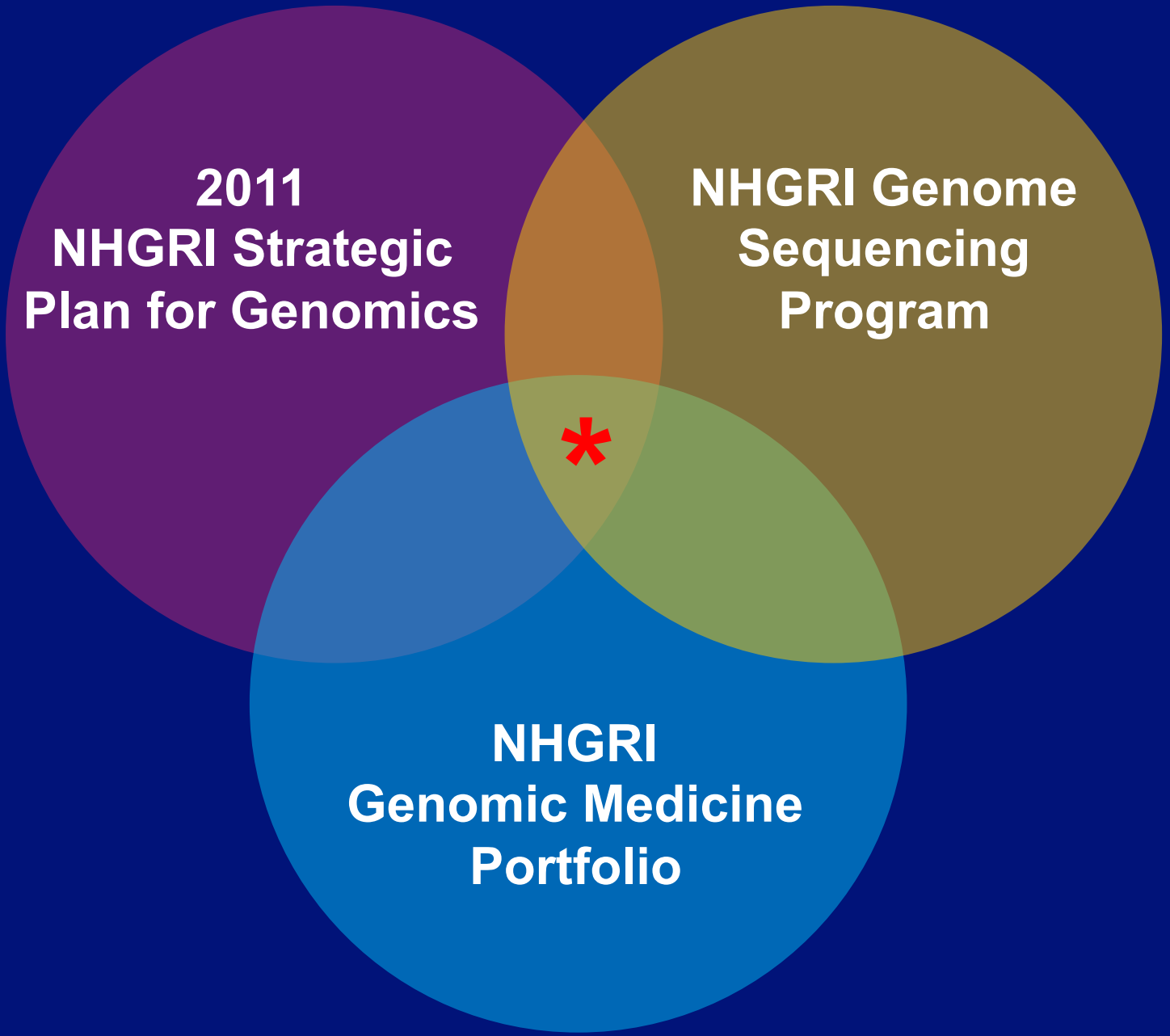
Centers for Mendelian Genomics

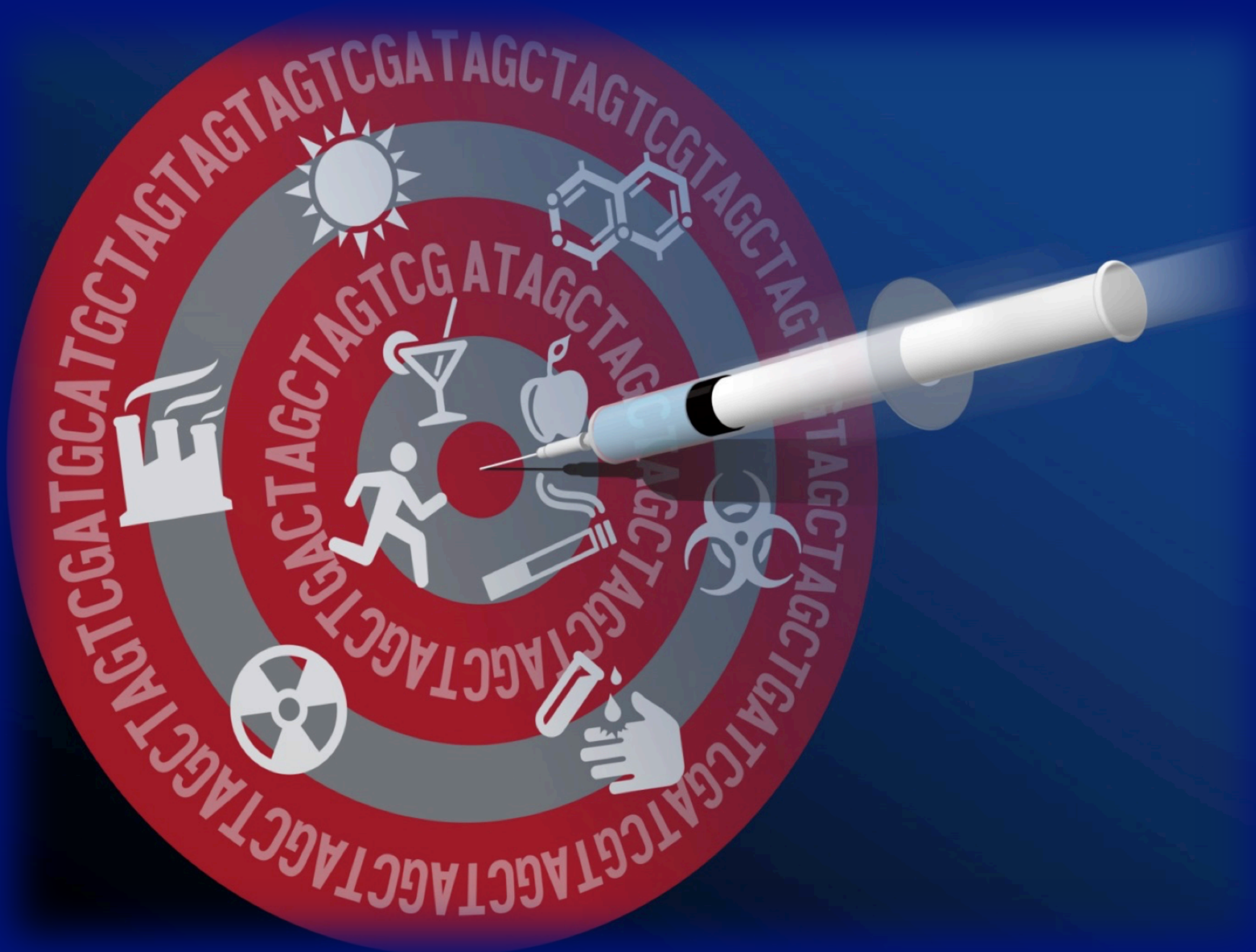
Coordinating Center

Genome Sequencing Program Analysis Centers

Human & Non-Human Primate Genome Sequences

Getting Oriented





Precision Medicine

"…[the] new Precision Medicine Initiative [will bring] America closer to curing diseases like cancer and diabetes, and gives all of us access, potentially, to the personalized information that we need to keep ourselves and our families healthier."

President Barack Obama
January 30, 2015

The NEW ENGLAND JOURNAL of MEDICINE

January 30, 2015

Perspective

A New Initiative on Precision Medicine

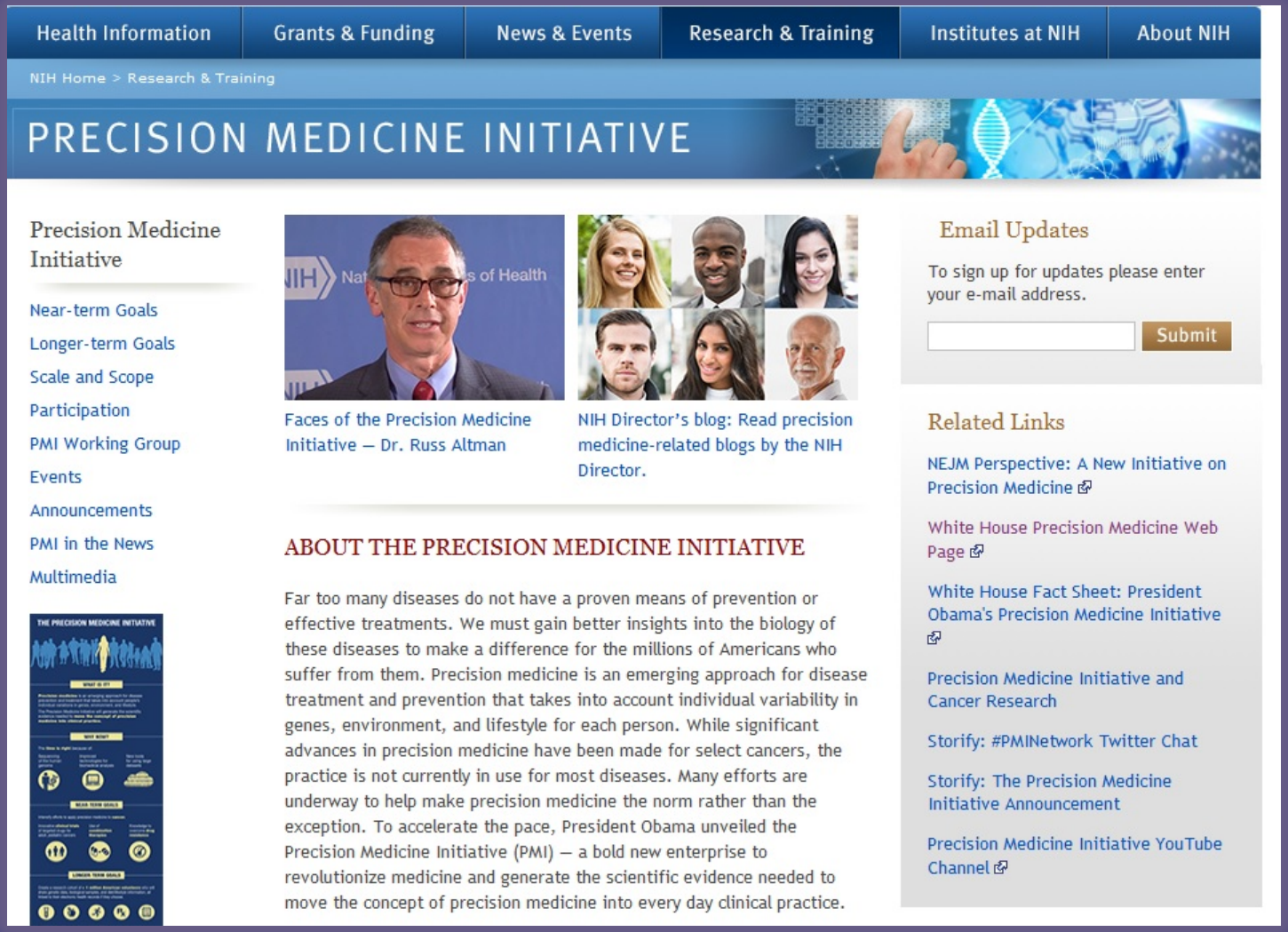
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

The proposed initiative has two main components: a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease. Both components are now within our reach because of advances in basic research, including molecular biology, genomics, and bioinformatics. Furthermore, the initiative


THE PRECISION MEDICINE INITIATIVE

Precision Medicine Initiative



www.nih.gov/precisionmedicine

National Research Cohort

Report on Precision Medicine Initiative Cohort Program

The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine

Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH

September 17, 2015

For Immediate Release: Thursday, September 17, 2015

NIH framework points the way forward for building national, large-scale research cohort, a key component of the President's Precision Medicine Initiative

The National Institutes of Health Advisory Committee to the Director (ACD) today presented to NIH Director Francis S. Collins, M.D., Ph.D., a detailed design framework for building a national research participant group, called a cohort, of 1 million or more Americans to expand our knowledge and practice of precision medicine. Dr. Collins embraced the design recommendations made by the ACD, noting the need to remain nimble and adaptable as the Initiative progresses. He also thanked the Committee for their recommendations on policy issues and welcomed the opportunity to review them. NIH plans to move quickly to build the infrastructure so that participants can begin enrolling in the cohort in 2016, with a goal of enrolling at least 1 million participants in three to four years.

Program Review Meeting: Objectives

- To summarize and evaluate key scientific contributions of the CSER Program
- To identify and prioritize scientific opportunities and questions for the next 5-10 years that would address informed integration of genomic sequencing into clinical care
- To identify optimal organizational features of a potential follow-up program

NHGRI is Listening to Your Input

- Workshop Participants
- Members of the National Advisory Council for Human Genome Research
- Other NIH Institutes
- Broader Research Community (via live webcast)


National Human Genome
Research Institute
Advancing human health
through genomics research