NHGRI's Genomic Medicine Research Portfolio

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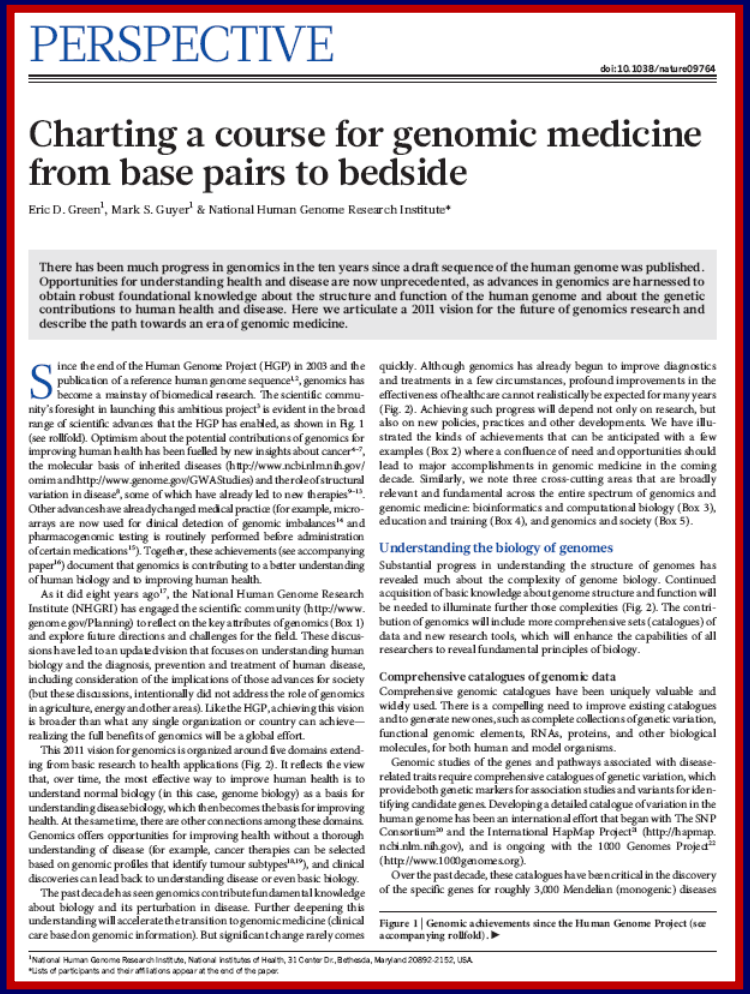
NHGRI Strategic Vision for Genomics



PERSPECTIVE

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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). ▶

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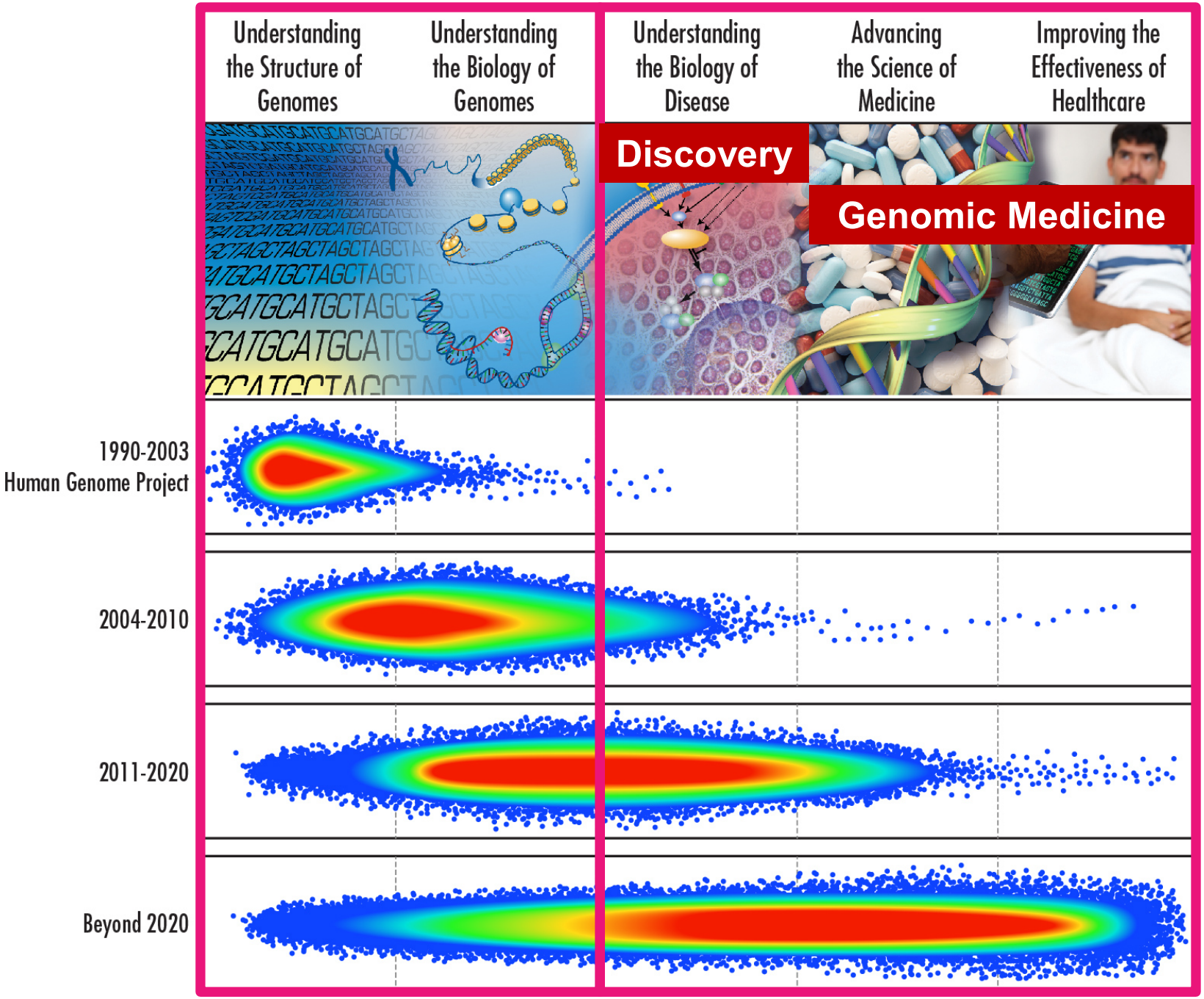
*Lists of participants and their affiliations appear at the end of the paper.

February 2011

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

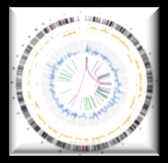
- Purposefully narrow definition
- By 'genomic,' NHGRI means direct information about DNA or RNA; downstream products outside the immediate view
- Metaphorically viewed as a key 'destination' for attaining NHGRI's mission of improving health through genomics research



Green et al. 2011

NHGRI Programs in Genomic Medicine

Cancer Genomics

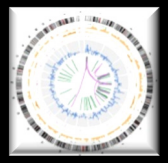


Pharmacogenomics

eMERGE Network
& eMERGE-PGRN

NHGRI Programs in Genomic Medicine

Cancer Genomics



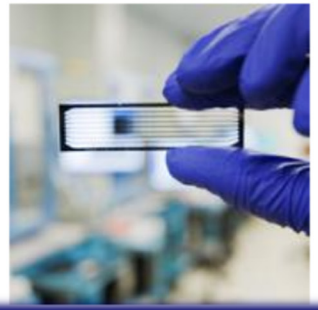
Pharmacogenomics

Genomic Medicine
'Test Drive' Programs

Clinical Sequencing Exploratory Research (CSER)

cser
Clinical Sequencing
Exploratory Research

Moving the genome into the clinic



In the past, standard medical practice for genetic testing involved looking at one gene at a time. With new advances in our understanding of the genomic basis of health and disease and in technology, it is now possible to test all of our genes at once using tests called whole exome or whole genome sequencing. Medical uses of genome sequencing are being applied and adapted on a case-by-case basis, but research to study the optimal uses and implementation of these tests is needed.

cser-consortium.org

Implementing Genomics into Clinical Practice Network (IGNITE)

Share Print

Implementing Genomics in Practice (IGNITE)

Overview

Findings from the genomics field have slowly started to find applications in clinical care. The field of "genomic medicine" could potentially improve patient health and treatment strategies or better predict the likelihood of disease.

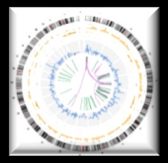
The Implementing Genomics in Practice (IGNITE) consortium (RFA-HG-12-006, RFA-HG-12-007 and RFA-HG-13-004) was created to enhance the use of genomic medicine by supporting the development of methods for incorporating genomic information into clinical care and exploration of the methods for effective implementation, diffusion and sustainability in diverse clinical settings.

These demonstration projects will incorporate genomic information into the electronic medical record (EMR) and provide clinical decision support (CDS) for implementation of appropriate interventions or clinical advice. The sites will work together to develop new methods and projects and disseminate their findings to the public. Dissemination of these methods and developing best practices for implementation is a key goal so that the information generated from the program will contribute to the growing knowledge base of using genomic information in patient care.

genome.gov/27554264

NHGRI Programs in Genomic Medicine

Cancer Genomics



Pharmacogenomics

Genomic Medicine
'Test Drive' Programs

Newborn Genomic
Analysis

Genomic Sequencing in Newborn Healthcare

NIH program explores the use of genomic sequencing in newborn healthcare

Bethesda, Md., Wed., Sept. 4, 2013 - Can sequencing of newborns' genomes provide useful medical information beyond what current newborn screening already provides? Pilot projects to examine this important question are being funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health. Awards of $5 million to four grantees have been made in fiscal year 2013 under the Genomic Sequencing and Newborn Screening Disorders research program. The program will be funded at $25 million over five years, as funds are made available.

"Genomic sequencing has potential to diagnose a vast array of disorders and conditions at the very start of life," said Alan E. Guttmacher, M.D., director of NICHD. "But the ability to decipher an individual's genetic code rapidly also brings with it a host of clinical and ethical issues, which is why it is important that this program explores the trio of technical, clinical, and ethical aspects of genomics research in the newborn period."

The awards will fund studies on the potential for genome and exome sequencing to expand and improve newborn health care. Genomic sequencing examines the complete DNA blueprint of the cells, and exome sequencing is a strategy to selectively sequence exons, the short stretches of DNA within our genomes that code for proteins.

genome.gov

Sequenced from the start

Four US studies are set to explore how genomic data can best help healthy and ill newborns. They must also settle some questions of ethics.

Genetic sequencing has established itself as a powerful tool for diagnosis, but it is not yet clear how useful it will be for disease prevention or health management. A US$25-million project announced last week aims to explore that issue in perhaps the most high-stakes patient group: newborn babies.

In the Genomic Sequencing and Newborn Screening Disorders (GSNSD) programme, four teams will sequence the exomes — the protein-coding portions of the genome — or the whole genomes of more than 1,500 babies, including not only infants who are ill, whether or not the disease has been diagnosed, but also healthy babies. The programme is funded by the US National Human Genome Research Institute and the Eunice Shriver Kennedy National Institute of Child Health and Human Development (NICHD). The studies will examine how useful sequencing information is for families and doctors, and whether it is superior to data gathered through conventional newborn-screening methods, which check for about 60 genetic disorders.

plans to give the raw genetic data to the children's families, even though that could allow the children to benefit from it throughout their lives.

Finally, should the data be shared with other researchers? This would be the best way for scientists to help tackle the tough question of how genes contribute to disease. But it is increasingly difficult to guarantee the privacy of genetic data (see *Nature* **493**, 451; 2013), and this is an important issue for babies, whose information will be known for their entire lives even though they themselves have not consented to the disclosure. One of the GSNSD projects will share data with the NICHD's Newborn Screening Translational Research Network, and another with the National Center for Biotechnology Information's Database of Genotypes and Phenotypes. The other two are still deciding.

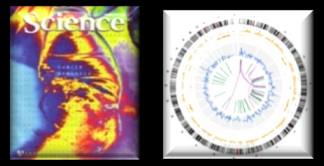
"The day when all children will be sequenced at birth — if not before — draws ever nearer."

As researchers explore these questions, sequencing costs continue

***Nature* (2013)**

NHGRI Programs in Genomic Medicine

- Cancer Genomics



- Pharmacogenomics

- Genomic Medicine 'Test Drive' Programs

- Newborn Genomic Analysis

- Clinical Genomics Information Systems


GTACT
CAAGT
CTA
TAC
CCGA
TAGG
ATCC
TGG
ATCC
S. Myers

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.

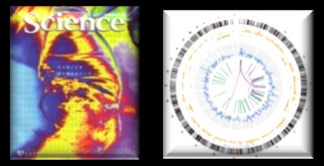
More and more medical and research centers are sequencing the DNA of whole genomes (the body's entire genetic blueprint) or exomes (the genome's protein-coding region) of patients. Each time, millions of DNA differences in genes and the regions between the genes are detected. But doctors struggle to 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

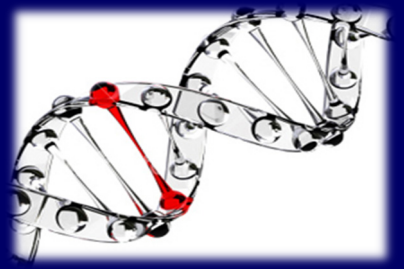
Exome Sequencing: Dual Role as a Discovery and Diagnostic Tool

Chee-S

Clinical application of exome sequencing in undiagnosed genetic conditions

Anna C
Kevin V

Next-Generation Sequencing for Clinical Diagnostics



Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders

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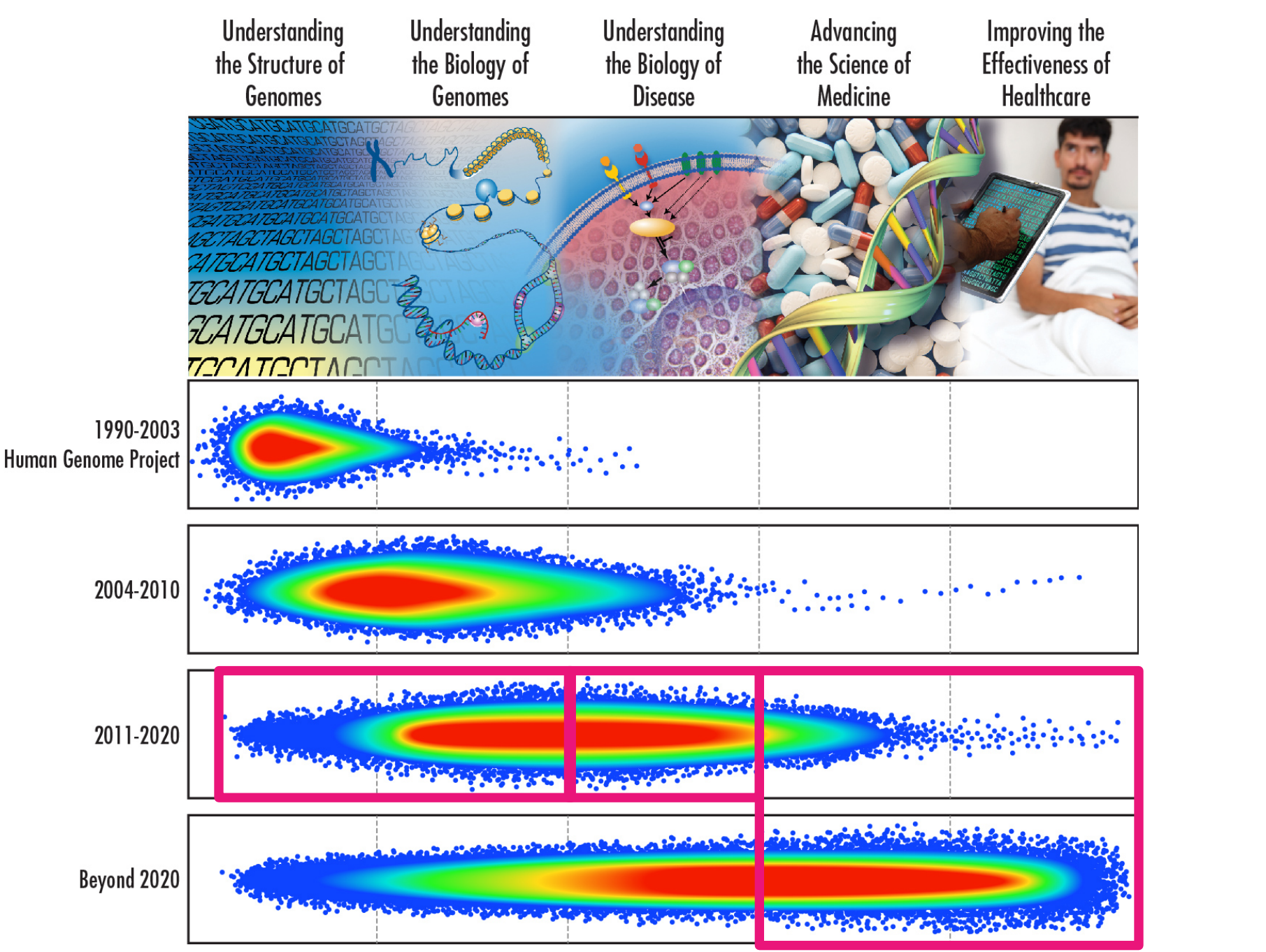
Genomics in Clinical Practice: Lessons from the Front Lines

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]

Sci Transl Med (2013)

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



Green et al. 2011

January 7, 2014

Happy New Year!

I start 2014 with mixed feelings. I continue to marvel at the spectacular advances seen in genomics each and every year, to struggle with the ongoing difficult budgetary circumstances for NIH and NHGRI, and to latch on to a few optimistic signs suggesting that our budgetary problems might be finally 'bottoming out' and that things will soon start to improve. I suspect the stories we feature in *The Genomics Landscape* during 2014 will capture elements of these mixed feelings.

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National Human Genome
Research Institute
Advancing human health
through genomics research