

Future Opportunities for Genome Sequencing... and Beyond



Welcome, Charge, and Context

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



Thank You

Maake Asante Shukria Dhanyavadagalu Manana Dankon

Kam Sah Hammida ٱر كٲش Mauruuru Biyan Matondo

Dank Je Dankscheen Kiiitos Vinaka kőszőnőm

Blagodaram Ngiyabonga Dziekuje Tack Taiku

Juspaxar Arigato Chokrane Diolch i Chi Terima Kasih

நன்றி Bedankt Dakujem dhanyavad cam ơn ban Mochchakkeram

Ua Tsaug Rau Koj Grazas Gratias Tibi

Suksama Dėkuji Nirringrazzjak Hvala Welalin Di Ou Mėsi Kia Ora Kop Khun Khap Paldies Obrigado

Misaotra Rahmat Matur Nuwun 谢谢 xBala Danke Mercı Go Raibh Maith Agat Djiere Dieuf Eskerrik Asko

Najis Tuke

NHGR: Guided by Strategic Planning

Understanding Our Genetic Inheritance

The U.S. Human Genome Project

The First Five Years FY 1991-1995



POLICY FORUM

A New Five-Year Plan for the U.S. Human Genome Project

Francis Collins and David Galas*

The U.S. Human Genome of an international effort to determine the genetic and physical maps and DNA sequence of the human genome of several million people. Thanks to advances in technology focused effort, the track with respect to its initial goals is well advanced. Because 3 years have elapsed goals were set, and because sophisticated and detailed what needs to be done and how available, the goals have been extended to cover the (through September 1998) genome initiative.

In 1990, the Human Genome of the National Institutes of Health and the Department of Energy developed a joint research plan for the first 5 years (FY 1991-95) of the U.S. Human Genome Project (HGP). It has served as a guide for both the research and the agencies' administrative and executing the goals and assessing its progress. Great strides have been achieved in the initial particularly with respect to:

Physical maps of the human genome of certain areas developing improved technology sequencing and information defining the most urgent set, and social issues associated with the use of large-scale genetic information.

Progress toward achieving goals for the genome project on schedule or, in some cases ahead of schedule. Further logical improvements that have been anticipated in 1990 have changed the scope of the project, and the most ambitious approach this year, it was therefore decided and extended the initial goals of genome research.

F. Collins is the director of the National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892. D. Galas is the director of the Center for Environmental Research, Case Western Reserve University, Cleveland, OH 44106. *A version of this article appeared in *Genetics*, Vol. 150, No. 2, pp. 1-10, 1998.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

U.S. DEPARTMENT OF ENERGY
Office of Energy Research
Office of Health and Environmental Research

1991-1995

1993-1998

1998-2003

2003-2010

2011-Present

SPECIAL SECTION

GENOME

1. J. A. Hill, D. W. Brown, C. C. Chang, *Nature* 351: 671 (1994).
2. J. A. Hill, D. W. Brown, C. C. Chang, *Nature* 351: 671 (1994).
3. S. E. Hyman and R. E. Pratt, *Science* 229: 1234 (1995).
4. C. E. Hill, *Genetics* 149: 473 (1998).
5. C. E. Hill, *Genetics* 149: 473 (1998).
6. C. E. Hill, *Genetics* 149: 473 (1998).
7. C. E. Hill, *Genetics* 149: 473 (1998).
8. C. E. Hill, *Genetics* 149: 473 (1998).
9. C. E. Hill, *Genetics* 149: 473 (1998).
10. C. E. Hill, *Genetics* 149: 473 (1998).
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19. C. E. Hill, *Genetics* 149: 473 (1998).
20. C. E. Hill, *Genetics* 149: 473 (1998).
21. C. E. Hill, *Genetics* 149: 473 (1998).

physical maps; (iii) the definition of the sequence tagged sites (STS) as a common unit of physical mapping; and (iv) improved technology and automation for DNA sequencing. Further substantial improvements in technology are needed in all areas of genome research, especially in

A vision for the future of genomics research

A blueprint for the future of genomics research

PERSPECTIVE

New

Francis S. Collins, Eric D. Green, and Mark S. Guyer*

The Human Genome Project's major goals in its current 1993-98 plan for the first 5 years of the U.S. Human Genome Project (HGP) have been achieved in the initial particularly with respect to:

Physical maps of the human genome of certain areas developing improved technology sequencing and information defining the most urgent set, and social issues associated with the use of large-scale genetic information.

Progress toward achieving goals for the genome project on schedule or, in some cases ahead of schedule. Further logical improvements that have been anticipated in 1990 have changed the scope of the project, and the most ambitious approach this year, it was therefore decided and extended the initial goals of genome research.

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602

feature

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green*, Mark S. Guyer* & 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 biological research. The scientific community's foresight 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 rolloff). Optimism about the potential contributions of genomics to improving human health has been fueled by new insights about cancer², the molecular basis of inherited disease³ (<http://www.ncbi.nlm.nih.gov/omim>) and HIV⁴ (see rolloff), and the need to understand variation in disease⁵, some of which have already led to new therapies⁶. Other advances are already changing medical practice (for example, microarrays are now used for prenatal detection of genomic imbalances⁷ and pharmacogenomics testing is routinely performed before administration of certain medications⁸). Together, these achievements (see accompanying paper⁹) document that genomics is contributing to a better understanding of human biology and to improving human health.

As it did eight years ago¹⁰, 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 update to a vision that focuses on understanding human biology and the diagnosis, prevention and treatment of human disease, including consideration of the implications of these advances for society (see accompanying paper⁹). In this vision, 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 directions 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 drug targets^{11,12}), and clinical diagnostics can lead back to understanding disease or even basic biology.

The 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 directions 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 drug targets^{11,12}), and clinical diagnostics can lead back to understanding disease or even basic biology.

The past decade has seen genomics contribute fundamental knowledge about biology and its part 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 improvement in the effectiveness of therapy 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 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 genomics

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, DNA, 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 Consortium¹³ and the International HapMap Project¹⁴ (<http://hapmap.ncbi.nlm.nih.gov>), and is ongoing with the 1000 Genomes Project¹⁵ (<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 (Fig. 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. [†]List of articles and their affiliations appear at the end of this issue.

NHGRI's Current Strategic Plan



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*

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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 that 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.

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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 this paper.

February 2011

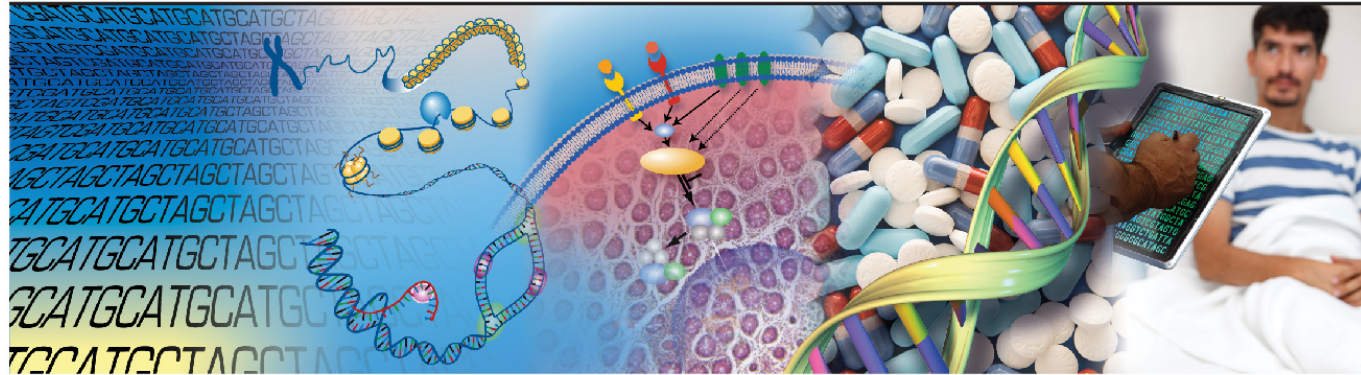
Understanding
the Structure of
Genomes

Understanding
the Biology of
Genomes

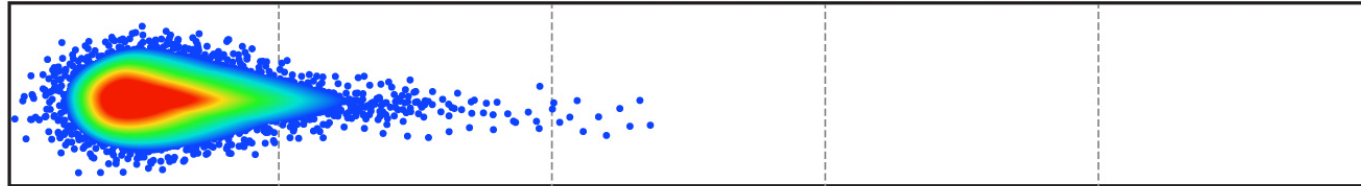
Understanding
the Biology of
Disease

Advancing
the Science of
Medicine

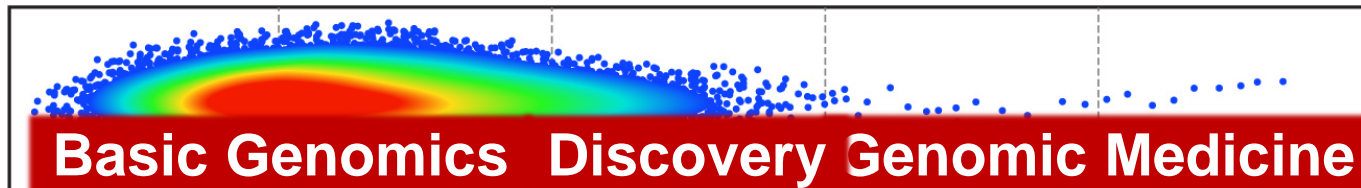
Improving the
Effectiveness of
Healthcare



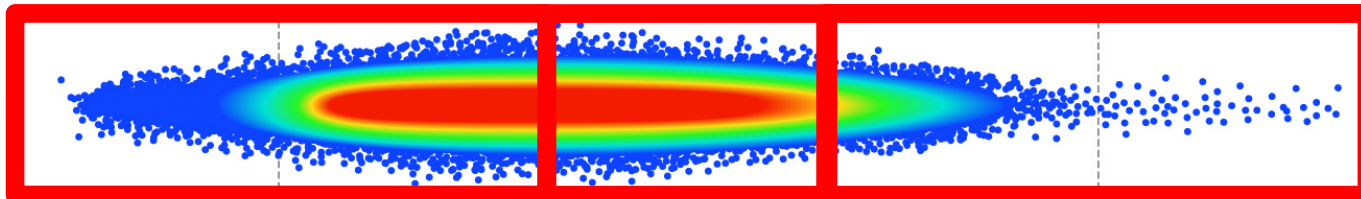
1990-2003
Human Genome Project



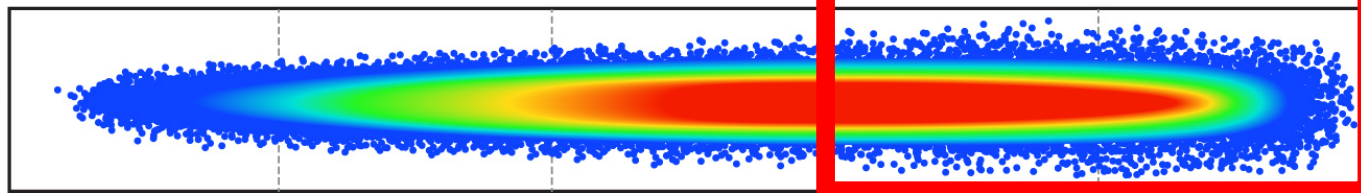
2004-2010



2011-2020



Beyond 2020



NHGRI's 'Flagship': The Genome Sequencing Program



1. History

2. Characteristics

NHGRI's 'Flagship': The Genome Sequencing Program



1. History

2. Characteristics

Post-HGP
Planning

~2002



Program Review
Workshop

2005



2003

2006

2012

2016

Human
Genome
Project

1990-2003

“Large-Scale
Genome
Sequencing
Centers”

2003-2006



Comparative Genomics
HapMap Project

June 2005 Program Review Workshop

Workshop on the Future of the Large-Scale Sequencing Program



June 13, 2005

Executive Summary

The National Human Genome Research Institute convened a workshop to obtain opinions from the scientific community on the current status and potential future directions of the NHGRI large-scale sequencing program. Participants were asked to consider the scientific, technological, and strategic opportunities in evaluating NHGRI's future investment in sequencing, and to specifically address several general questions and challenges:

- Given what has already been accomplished - very high quality assembled genome sequences of the human and major model organisms, draft sequence assemblies of genomes representing many of the nodes of the metazoan lineage, concerted application of comparative sequencing to annotate mammalian genomes - what are the best future opportunities for large-scale sequencing? What is the proper balance of these types of projects going forward? Should other kinds of large-scale sequencing projects be considered? What is the continuing priority of large-scale sequencing as a source of genomic data compared with other types of genomic data?
- Disruptive technologies appear to be promising enough that a significant reduction in the cost of DNA sequencing could occur within the next three years. What are the realistic prospects for the introduction of such a disruptive technology? How should it be anticipated and encouraged? How would it affect sequencing costs and capacity? How would it affect the types of scientific questions that can be addressed? How should the possibility of future significant cost reductions affect the decisions about the types of sequencing projects that should be initiated in the next two to three years?
- How should NHGRI evaluate the ongoing value of its investment in a large-scale sequencing program? How should it assess the contribution that continued sequencing will make to scientific research overall and genomic research in

genome.gov/16015129

Post-HGP
Planning

~2002



Program Review
Workshop

2005



Program Review
Workshop

2009



2003

2006

2012

2016

Human
Genome
Project

1990-2003

“Large-Scale
Genome
Sequencing
Centers”

2003-2006

“Large-Scale
Genome
Sequencing
Centers”

2006-2011



Comparative Genomics

HapMap Project

Microbiome

1000 Genomes

Cancer Genomics (TSP, TCGA)

Medical Sequencing

Pathogens & Vectors

March 2009 Program Review Workshop

Workshop Report

The Future of DNA Sequencing at the National Human Genome Research Institute March 23-24, 2009

What are the most important biomedical questions that can be addressed with large-scale sequence data? What are the most compelling sequence-based community resources that should be generated? What are the consequences of the rapid increase in sequencing capacity, and the rapid decrease in cost, afforded by the new technology platforms? In order to answer these questions, the National Human Genome Research Institute (NHGRI) convened a workshop to discuss the future of large-scale sequencing as one component¹ of the Institute's current two-year planning process for all of its scientific programs.

The need for this workshop was particularly underscored by the recent and ongoing rapid changes in sequencing technology, propelled by the "next generation" sequencing platforms. Introduced into production activities less than two years ago, the new sequencing platforms have already afforded an increase in throughput² of two orders of magnitude over the previous platforms, and this is likely to increase by nearly another order of magnitude in the next year or two. Furthermore, yet newer technologies are being developed and are expected to be available in the next three to five years. These rapid changes offer incredible new opportunities as well as major new challenges for the use of sequencing technology in general and to NHGRI's sequencing program specifically. As the technology continues to improve, new applications of genomic sequencing are constantly being developed, for example the sequencing of genomes from large numbers of individuals for disease and population studies, quantitative transcriptional analysis and epigenomics.

The 'disruptive' technological change has many other consequences. Most obviously, the ability to apply large-scale sequencing efficiently towards a larger number of problems will result in unprecedented demands on scientists' ability to find enough samples that are appropriate to addressing an expanded range of questions. To date, the most difficult problem has been obtaining samples for human disease or population studies that are properly consented for the work. One can also foresee

Post-HGP
Planning

~2002



Program Review
Workshop

2005



Program Review
Workshop

2009



2003

2006

2012

2016

Human
Genome
Project

1990-2003

“Large-Scale
Genome
Sequencing
Centers”

2003-2006

“Large-Scale
Genome
Sequencing
Centers”

2006-2011

4-Component
“Genome
Sequencing
Program”

2012-2015



Comparative Genomics

HapMap Project

Microbiome

1000 Genomes

Cancer Genomics (TSP, TCGA)

Medical Sequencing

Pathogens & Vectors

NHGRI Genome Sequencing Program

Circa 2012-2015



**Large-Scale
Genome
Sequencing and
Analysis Centers**

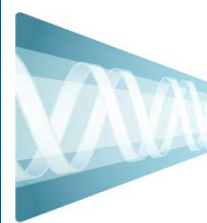


Centers for Mendelian Genomics



cser

Clinical Sequencing
Exploratory Research



iSEQTOOLS

Post-HGP
Planning

~2002



Program Review
Workshop

2005



Program Review
Workshop

2009



Program Review
Workshop

2014



2003

2006

2012

2016

Human
Genome
Project

1990-2003

“Large-Scale
Genome
Sequencing
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2003-2006

“Large-Scale
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2006-2011

4-Component
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Sequencing
Program”

2012-2015



Comparative Genomics

HapMap Project

Microbiome

1000 Genomes

Cancer Genomics (TSP, TCGA)

Medical Sequencing

Pathogens & Vectors

Common Diseases

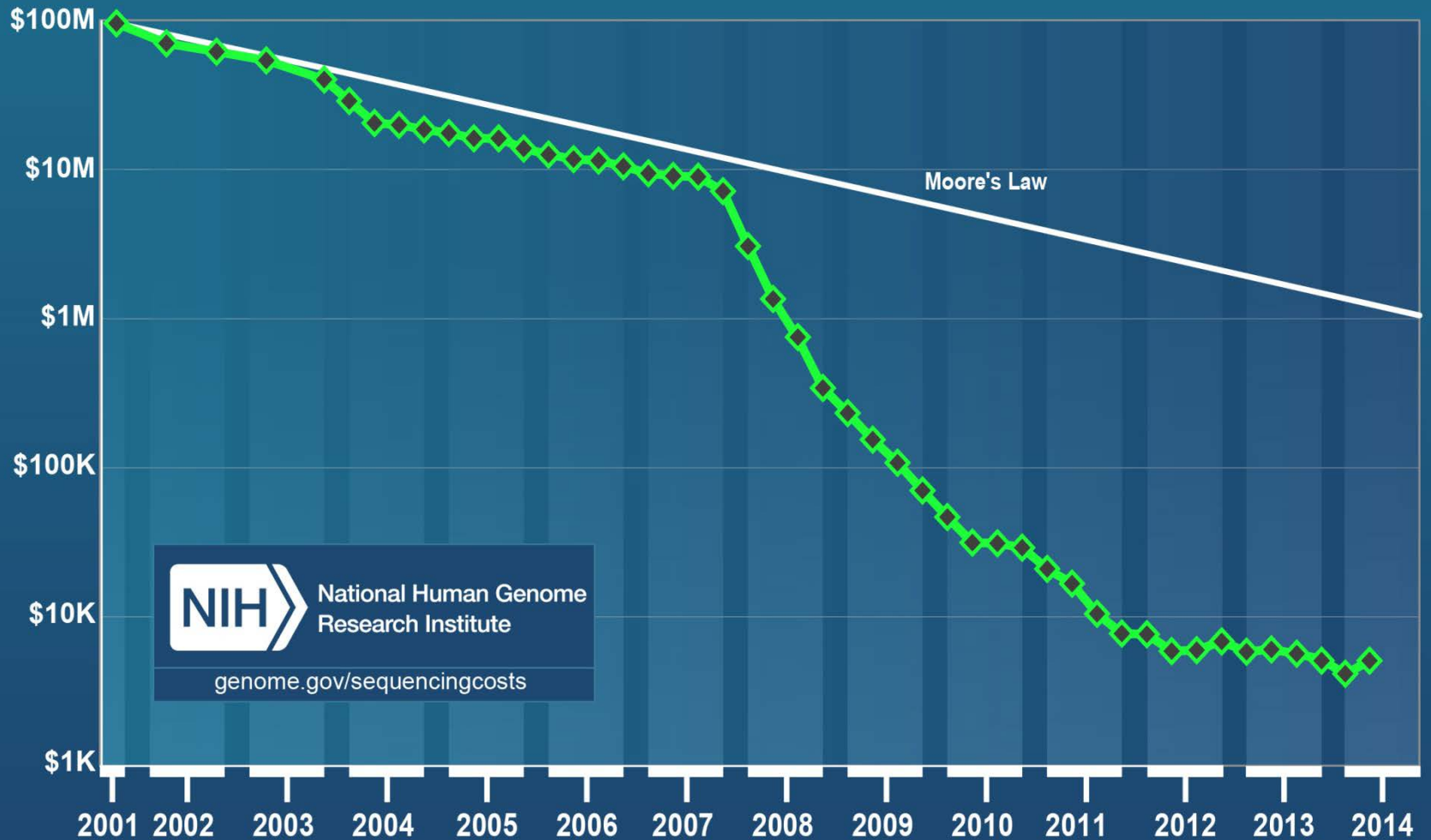
Mendelian Diseases

Clinical Genomics

Computational Tools

Plummeting Cost of Genome Sequencing

Cost per Genome



Post-HGP
Planning

Program Review
Workshop

Program Review
Workshop

Program Review
Workshop



~2002

2005

2009

2014



2003

2006

2012

2016

Human
Genome
Project

“Large-Scale
Genome
Sequencing
Centers”

“Large-Scale
Genome
Sequencing
Centers”

4-Component
“Genome
Sequencing
Program”

To Be
Determined

1990-2003

2003-2006

2006-2011

2012-2015

2016-???



Comparative Genomics

Microbiome

HapMap Project

1000 Genomes

Cancer Genomics (TSP, TCGA)

Medical Sequencing

Pathogens & Vectors

Common Diseases

???

Mendelian Diseases

???

Clinical Genomics

???

Computational Tools

???

NHGRI's 'Flagship': The Genome Sequencing Program



1. History

2. Characteristics

NHGRI Genome Sequencing Program: Characteristics (To Date)

Large (i.e., Scale)

Consortia-oriented

Highly managed

Resource-generating

'Technology'-advancing

Scientifically/medically relevant

Nimble

Going Forward: What Does NHGRI Want?

- Continue being 'genomics trailblazers'
- Alignment with strategic vision/plan
- Impact that correlates with program size
- If continuation of a major program, then retain 7 characteristics (previous slide)
- Importance of 'moving on' past initial catalytic role (e.g., organism sequencing, microbes, microbiome, and cancer)
- Increased 'cost-sharing' to broaden impact

NHGRI and Cost-Sharing

- **Genomics = Huge; NHGRI = Small**
- **NHGRI cannot support 'everything genomics'**
- **Partnerships are key (past and future)**
- **Consider formalizing an approach for cost-sharing in large-scale NHGRI-funded genomics projects**

Purpose of Workshop

- 1. For Starters: It's what we do...**
- 2. General: Natural time for strategic input (e.g., 3 years since 2011 strategic plan)**
- 3. Critical: Synchronize strategic thinking in light of rapidly changing (and complicated) landscape**
- 4. Practical: Fiscal Year 2016 and ~\$100M (~25% of extramural funds)**

Highest Priority: Discussion about Areas Associated with:



**Large-Scale
Genome
Sequencing and
Analysis Centers**



Also Important: Discussion about Areas Associated with:



cser
Clinical Sequencing
Exploratory Research



Questions to Address (Among Many)

1. What are the 'grand opportunities' appropriate for a 'flagship' NHGRI program(s)?
2. What is NHGRI not doing that it should be doing?
3. How to balance 'democratization' of genome sequencing and benefits of consortia-based, large-scale pursuits?
4. How to properly tune a 'flagship' program's(s') funding level with its impact?
5. Should NHGRI develop a formal cost-sharing approach for large non-generic (e.g., disease-specific) projects?
6. How should NHGRI more efficiently obtain 'commodity' genome sequencing to meet programmatic needs?

Going Forward (Quickly)...



TOUGH DECISION AHEAD

S

The image shows a blue rectangular sign mounted on a metal post. The sign has the text 'TOUGH DECISION AHEAD' in a white, bold, serif font. A small white letter 'S' is positioned above the letter 'A' in 'AHEAD'. The sign is set against a background of a cloudy sky with a blue gradient at the top and bottom.

There are Likely Too Many Good Options





NATIONAL HUMAN GENOME RESEARCH INSTITUTE



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