Bringing Genomic Medicine into Focus

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Director, NHGRI

The Relevance of Genomics

Biomedical Researchers
Healthcare Professionals
Patients (and Friends & Relatives of Patients)

Human Genomics Landscape

Past  Present  Future
Genomics: Some Basics...

April, 1953

Discovery of Double-Helical Structure of DNA

1960’s
The Genetic Code

1980’s
DNA Cloning
The DNA Alphabet

A Adenine
T Thymine
G Guanine
C Cytosine

Human Genome:
~3 billion bases (‘letters’)

October, 1990

Draft Human Genome Sequence Announced

Human Genome Project Begins

June, 2000
February, 2001

Draft Human Genome Sequence Published

April, 2003

Human Genome Project Ends

Myriad Applications of Genomics

- Agriculture
- Ancestry
- Livestock
- Infectious Agents
- Forensics
- Bioenergy
Turning discovery into health
NIH
Advancing human health through genomics research

Genomic Medicine
An emerging medical discipline that involves using an individual’s genomic information as part of their clinical care

The Path to Genomic Medicine
Human Genome Project
Realization of Genomic Medicine
“Fulfilling the Promise”
New NHGRI Vision for Genomics Published

Five Domains of Genomics Research

Genomic Accomplishments Across Domains
Function of the Human Genome Sequence

~3,000 bp (0.0001%) of Human Genome Sequence

Comparative Genome Sequencing
~3,000 bp (0.0001%) of Human Genome Sequence

The Epigenomic Landscape

TECHNOLOGY FEATURE
READING THE SECOND GENOMIC CODE

Nature (2012)
Eric Green
NHGRI Director

- A haplotype map of the human genome
  2005
- A second-generation human haplotype map of over 3.5 million SNPs
  2007
- Integrating common and rare genetic variation in diverse human populations
  2010

- 1000 Genomes
  A Deep Catalog of Human Genetic Variation

- An integrated map of genetic variation from 1,092 human genomes
  Nature (2012)

Your Genome: By the Numbers

- ~6B nucleotides
- ~3-5M single-nucleotide variants
  - ~150K not in databases
  - ~60 not in either parent
- ~10-20K structural variants
- ~100 ‘disruptive’ variants in genes
- ~20 completely inactivated genes (both copies)
Genomic Basis for Human Diseases

Manolio et al., J Clin Invest (2008)

Monogenic Diseases/Traits *

Source: Online Mendelian Inheritance in Man (www.omim.org)
Monogenic Diseases/Traits *

<table>
<thead>
<tr>
<th>Suspected Mendelian Disease/Trait (~1900)</th>
<th>Genomic Basis Known (~4800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic Basis Unknown (~1800)</td>
<td></td>
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</table>

Source: Online Mendelian Inheritance in Man (www.omim.org)

Genome-Wide Association Studies (GWAS)

The First GWAS Success Story: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration
Genomic Architecture of Genetic Diseases

- Rare, Simple, Monogenic, Mendelian...
- Mostly Coding Mutations

- Common, Complex, Multigenic, Non-Mendelian...
- Mostly Non-Coding Mutations

Routine Whole-Genome Sequencing
“...'technological leaps' that seem so far off as to be almost fictional but which, if they could be achieved, would revolutionize biomedical research and clinical practice.

[For example,]...the ability to sequence DNA at costs that are lower by four to five orders of magnitude than the current cost, allowing a human genome to be sequenced for $1,000 or less.”

Human Genome Sequence

~$1,000,000,000

~$1,000  “The $1000 Genome”
Cost per Sequenced Human Genome

Human Genome Sequence

~$1,000,000,000
~$1,000

“The $1000 Genome”
Eric Green
NHGRI Director

Sequencing a Human Genome

<table>
<thead>
<tr>
<th></th>
<th>HGP (1st Sequence)</th>
<th>Immediate Post-HGP</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>~6-8 years</td>
<td>~3-4 months</td>
<td>~2-3 days</td>
</tr>
<tr>
<td>Cost</td>
<td>~$1B</td>
<td>~$10-50M</td>
<td>~$4-6K</td>
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And Yet Newer Technologies...

Search for Perfection
The Largest Current Bottleneck in Genomics...

The Computational Bottleneck
The Informational Bottleneck

Ten Years On — The Human Genome and Medicine

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.

The $1,000 genome, the $100,000 analysis?

Genome Med (2010)
Technology Advances Drive Science

- Astronomy
- Cell Biology
- Radiology
- Genomics

Genomic Accomplishments Across Domains

<table>
<thead>
<tr>
<th>1990-2003</th>
<th>Human Genome Project</th>
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<tr>
<td>2004-2010</td>
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<td>2011-2020</td>
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<tr>
<td>Beyond 2020</td>
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</table>
The Future: Genome Sequencing

Mendelian Diseases/Traits

- Suspected Mendelian Disease/Trait (~1,900)
- Generic Basis Unknown (~1,800)
- Generic Basis Known (~4,000)
The Future: Genome Sequencing

Complex Diseases/Traits

The Future: Genome Sequencing

Cancer Genomics

Eric Green
NHGRI Director
Eric Green
NHGRI Director

Genomic Medicine: Cancer Diagnostics

Now

Future

Because Everyone Responds Differently.
All patients with same diagnosis

No response

Toxic side effects

Response without toxic side effects

McLeod & Evans, Ann Rev Pharmacol Toxicol 41:101-121, 2001

New NHGRI Genomic Medicine Initiatives

- Pharmacogenomics
- Clinical Sequencing Exploratory Research
- Genomic Medicine Demonstration Projects
- Newborn Genome Sequencing
- Clinically Relevant Variants Resource
The Role of Both the Genome and the Environment in Human Disease

Genome Analysis Technologies >>> Environmental Monitoring Technologies

The Human Microbiome
The Future: Genome Sequencing

Microbiome

Genomic Medicine: Clinical Microbiology

Now

Future

Bringing Genomic Medicine into Focus

~1990  ~2003  ~2011  ~2020
A pessimist sees the difficulty in every opportunity. An optimist sees the opportunity in every difficulty.

—Winston Churchill
Eric Green
NHGRI Director

genome.gov/HGP10

NHGRI-Smithsonian Genome Exhibition

Opening in June 2013
Smithsonian National Museum of Natural History