



The Genomic Landscape *Circa 2012*



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



JOHNS HOPKINS
MEDICINE

CONTINUING MEDICAL EDUCATION

Current Topics in Genome Analysis 2012

Eric Green

***No Relevant Financial Relationships with
Commercial Interests***



NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research

Outline

- I. Historical Context for Genomics
- II. Major Achievements since the Human Genome Project
- III. The Human Genomics Landscape: 2012 and Beyond

>>> Goal: Place Future Speakers into a Broader Context <<<

Foundational Milestones in Genetics & Genomics



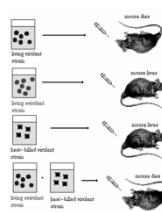
Mendel

1865



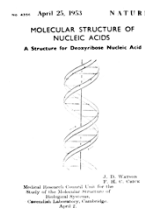
Miescher

1871



Avery

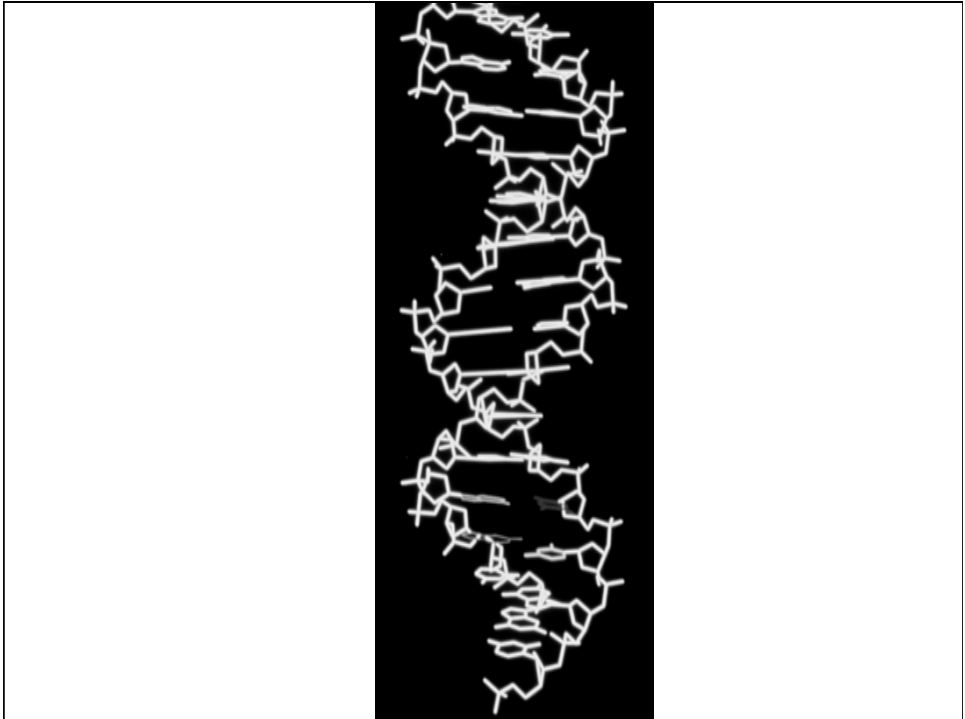
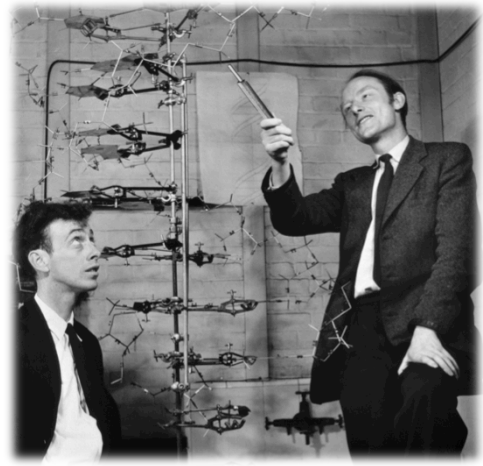
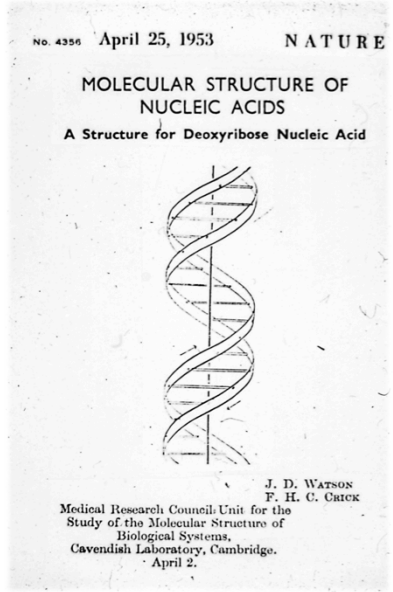
1944



Watson & Crick

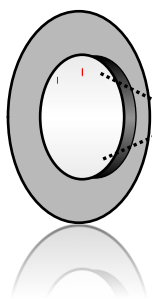
1953

April, 1953



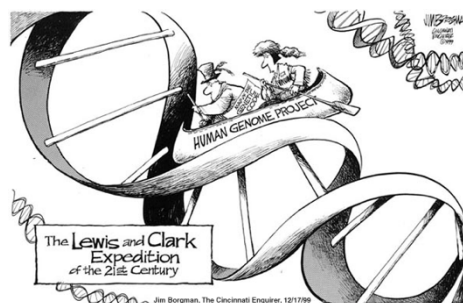
The DNA Alphabet

G **Guanine**
A **Adenine**
T **Thymine**
C **Cytosine**



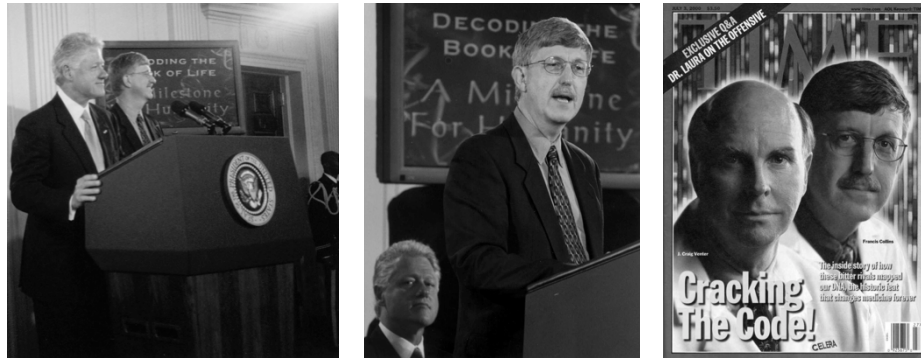
Human Genome: ~3 billion bases ('letters')

~21 Years Ago



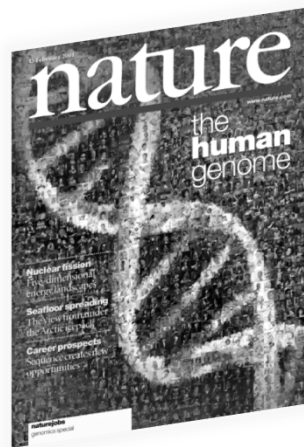
October 1990
Human Genome Project Begins

~11 Years Ago



June 2000
Draft Human Genome Sequence Announced

~11 Years Ago



February 2001
Draft Human Genome Sequence Published

~9 Years Ago



April 2003

Human Genome Project Ends

guardian.co.uk



Adam Rutherford

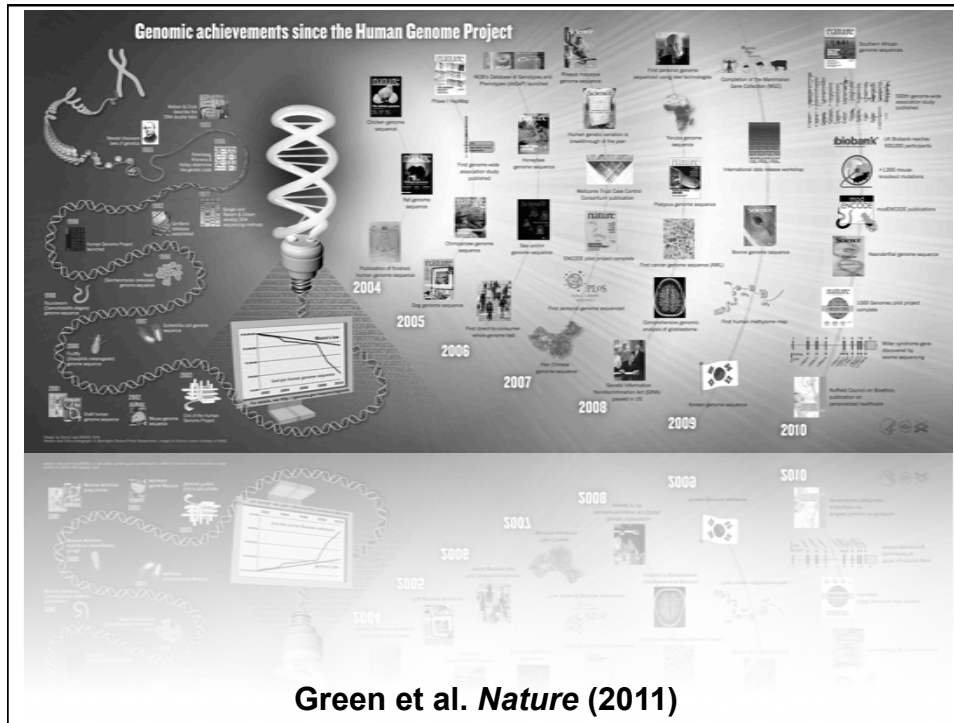
guardian.co.uk, Thursday 21 April 2011 09.59 BST

[A](#) [larger](#) | [smaller](#)

The Human Genome Project was just the starting point

April 2011

“But the mistake that we often make is [saying that the Human Genome Project] was an end point. In fact, the Human Genome Project was a pregnancy... Ten years later, we now have a clue what we don’t yet know. The Human Genome Project may be finished, but understanding our genome is only just beginning.”



Genomic Medicine

Healthcare tailored to the individual based on genomic information



The Path to Genomic Medicine



Human Genome Project

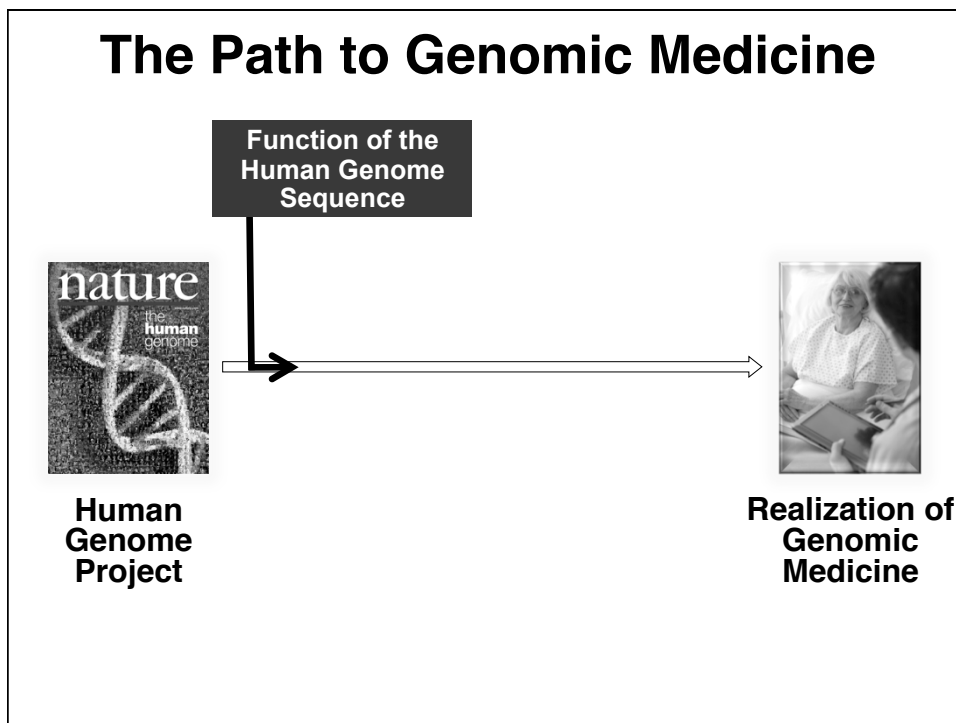
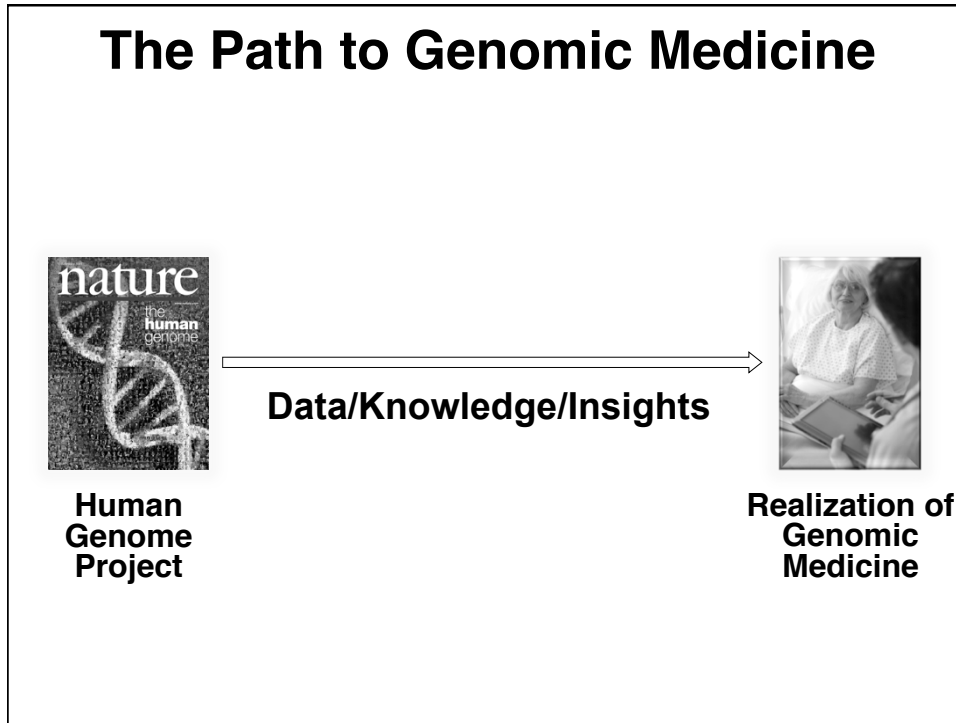


Realization of Genomic Medicine

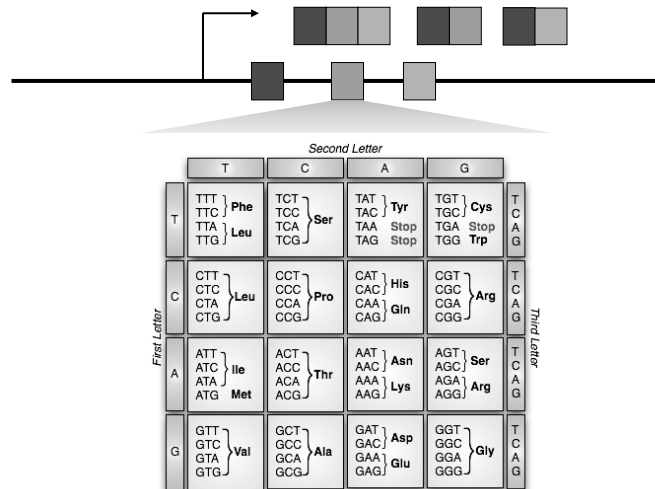


“Fulfilling the Promise”





Coding Sequences (i.e., Genes)

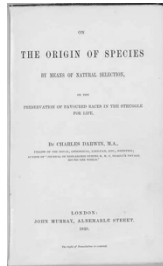


The Genetic Code

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

```
TGCCCGGAACTTTTCGGCTCTAAGGCTGATTTTGGATACGAAAGGCACATTTTCCTCCCTTTTCAAATGCACCTTGCAACGTAACAG
GAACCCGACTAGGATCATCGGAAAAGGAGGAGGAGGAAAGGCAGGCTCCGGGAAGCTGGTGGCAGCGGGTCTGGGTCTGGCGGACCCCTGA
CCGCAAGAGGGTCTAGGAAGCTCTCCGGGAGCCGGTTCCTCCGCGGGTGGCTTCTCTGTCTCCAGCGTTGCCAAGTAAAGAGAGG
CCGCGACTGTCGCCACCTGCGGGATGGCCCTGGTCTGGCGGTAAGGACACGGACCTGGAAGGAGCGCGCGGAGGGAGGGCTGGGAGTC
AGAATCGGAAAGGAGGCTCGGGCGCGGAGGAGCGAAGGAGGAGGAGGAGGAGCGGGAGGGCTGCTGGCGGGGTGCTAGTGGGTGGA
GAAAGCCGCTAGAGCAAATTTGGGGCCGACAGGCAGCAGCTCGGCTTTAACTGGGCGAGTGAAGCGGGGAAAGAGCAAAGGAAGGGGTG
TGTGCGGAGTAGGGTGGTGGGGGAATTGGAAGCAAATGACATCACAGCAGGTCAGAGAAAAGGGTGGAGCGGACGCCACAGATAGTAG
GTCTTTGGCATTAGGAGCTTGAGCCAGAGCCCTAGCAGGACCCAGCGCCGAGAGACCATGCAGAGTTCGCTCTGAAAAGGCCAGCGT
TGTCCTCAAACCTTTTTTCAGGTGAGAAGGTGGCCAACCGAGCTTCGGAAGACACGTCGCCACGAAAGAGGAGGGCGTGTGTATGGGTGGGT
TGGGTAAAGGAATAGCAGTTTTTAAAAGATGCGCTATCATTCATTTGTTTGAAGAAAATGTGGCTATTCTAGAAATAAACAGAAAGCATT
AGAAGAGATGAAGAATGAAGTGAAGCTGATTAATAGAGAGCCACTACTTGAAGTAAAGTAAAGTAAAGTAAAGTAAAGTAAAGTAAAGTAA
ATGCACCTGTTTTTATTTTCAATTTTCAAGAACTAAAAAATCTGTTAATAAGTACCTAAGTATGGTTATTTGGTTTTCCCTTCATGCTTGG
ACACTTGAATGCTCTTGGCACATACAGGTGCCATGCCATAGTATAGTAAAGTCTCAGAAAACATTTCTTGAAGTAAATCAGCCAAACAAAAT
TTGGGTAGGTAGAAAATATATGCTTAAAGTATTTATTTGTTATGAGACTGGATATATCTAGTATTTGTCACAGTAAATGATTTCTCAAATTTG
AAAGCAAATTTGTTGAATATTTATTTGAAAAGTTACTTCAAGCTATAAATTTTAAAGCCATAGGAATAGATCCGAAAGTATATCCAA
CTGACATTTAATAAATTTGATTCATAGCCTAATGTGATGACCCAGAAAGCTTGCAAACTTTAATGAGATTTTAAAAATAGCATCTAAGTTCGG
AATCTTAGGCAAGTGTGTTAGATGAGCACTTCATATTTGAAGTGTCTTTGGATATGTCATCTACTTTGTTCTGTATATATACCTGGTGTGA
ATGAATGAATAGTACTGCTCTCTTGGGACATTAACGACATAATTAACCAATGAATAGCACTACTGAGGTATCAAAAAGTCAAAATATGT
TATAATAGCTCATATATGTGTGAGGGGGAAGGAATTTAGCTTTCACATCTCTTATGTTTAAAGTCTCTGATGTCAGTAAATCTCTGGAAC
TCCGCTGCTAAGGAGAGCTGTTGGCCCTGGAAGGAGCTTCTCCCTGTTGGATGAGAGAGAAGGACTTACTCTTTGGAATATCTTTTGGT
TGATGTTATCCACTTTTGTACTCCACTATAAAATCGGCTTATCTATTGATCTGTTTTCCTAGTCCTATAAAGTCAAAATGTTAATTTGGCAT
AATTTATAGCTTTTTTAGCAGAGAATTTGAGAACCTTAAATGCCAACCACTTAAATGCAGTTTTTCAGAAAGTAAATGATTTTCAATGATA
GTCTAAATACTAATGAATTTAAAATAGCTTACTATTGATCTGTCAAAGTGGTTTTTATATAAATTTCTTTTACAAATCACCTGACACATTT
AATATAGTTAAAAATGCTATCAGGCTGGTTTGAAGAAAATGTATTACAAAGGCTGCTAAGTGTGTAAGAGCATACTCTTTCTGTTCTCC
AAAATATTTCAATAGGCTTTAAGAAATAGGATGTTTTTAAAAGTTAAGTCTTACTATTTTATAGGAATGCAATCACCTAAAATACCAATGA
TTCAAACCTCTCTGCGCTTCTGACTGCAATTTAAAAGTGAATAAACATATTTTCTGCATTAAGTGGCAGTATTGCTTAGTTTTCAA
GTGGTAGCTTTGGAGTCAGATTTTGTATCAGATCTACATCTACTGTTTGTAGTACTGTTGCGCTGAGGAGGTCCTTAACATCTCTGTG
TGACTTGAACCTTTAAAATTTGGAGACTGTCAAGGGTAAATCCCTTGAGAAAATGAATGTGAAAAGTTAGCCTAATGTTAATCTGATTTAT
ATGATAGCTAAAAATTTCAATTCATCACAGTACATGCACCTGTTAATAAAGATGCTCAATTCATCTTTGAGTATAAATTTGAGCTCTCAAT
CTGGATATGCAATGAGTGGCCGTGATGAGAAATTAATTTATGAAAATTTGCTTTTCAATGCGCTTACCAGATATACAGGAAACACCTCACATG
TTTCTATTGTATGTTTAAATGCCTTAGAATTTAATTTCTGAATAGGATCCCTTCAGTTTGGAGTCAATAAAGAGTAAAATTTATGTTAT
```

Foundational Milestones in Genetics & Genomics



Darwin

1859



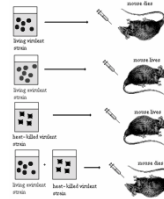
Mendel

1865



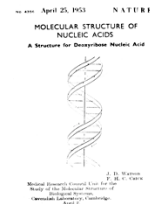
Miescher

1871



Avery

1944

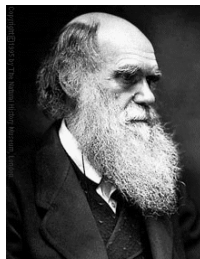


**Watson
& Crick**

1953

"It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change."

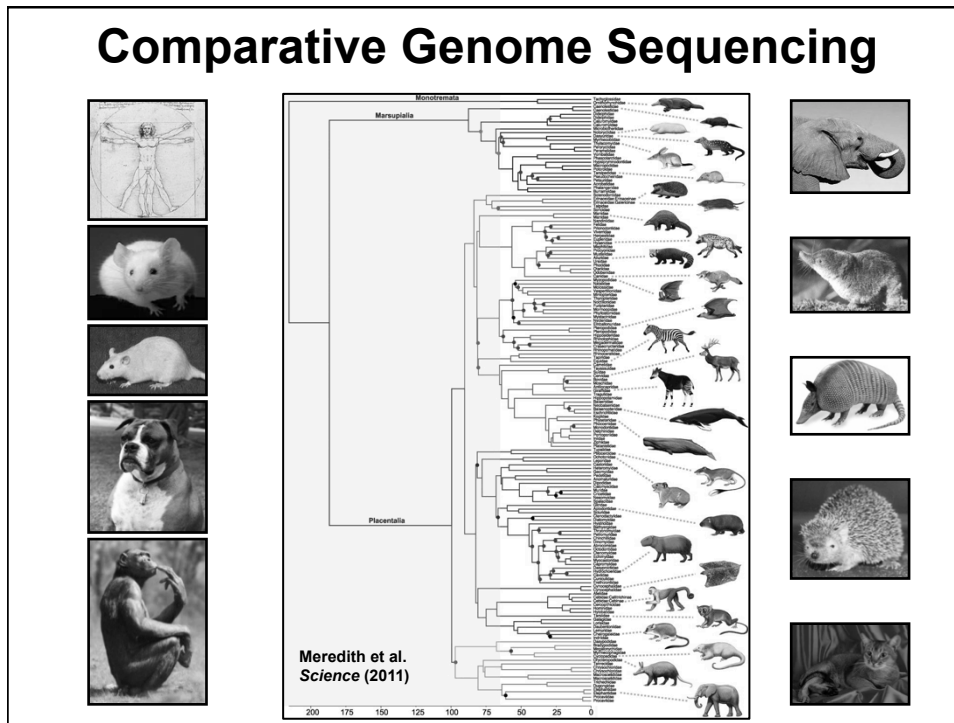
(Attributed to Darwin)



Charles Darwin (1809-1882)

"For the last three and a half billion years, evolution has been taking notes."

—Eric Lander



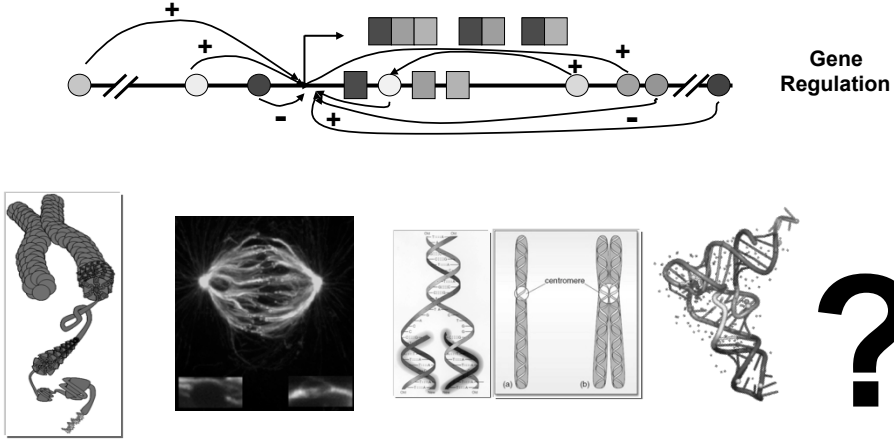
Comparative Genome Sequencing

A high-resolution map of human evolutionary constraint using 29 mammals


Kerstin Lindblad-Toh^{1,2}, Manuel Garber^{1*}, Or Zuk^{1*}, Michael F. Lin^{1,3*}, Brian J. Parker^{4*}, Stefan Washietl^{3*}, Pouya Kheradpour^{1,3*}, Jason Ernst^{1,3*}, Gregory Jordan^{5*}, Evan Mauceli^{1*}, Lucas D. Ward^{1,3*}, Craig B. Lowe^{6,7,8*}, Alisha K. Holloway^{9*}, Michele Clamp^{7,10*}, Sante Gnerre⁹, Jessica Alföldi¹, Kathryn Beal⁵, Jean Chang¹, Hiram Clawson⁶, James Cuff¹, Federica Di Palma¹, Stephen Fitzgerald⁹, Paul Flicek⁵, Mitchell Guttman¹, Melissa J. Hubisz¹², David B. Jaffe¹, Irwin Jungreis³, W. James Kent⁹, Dennis Kostka⁹, Marcia Lara¹, Andre L. Martins¹², Tim Massingham⁵, Ida Moltke¹, Brian J. Raney⁶, Matthew D. Rasmussen³, Jim Robinson¹, Alexander Stark¹³, Albert J. Vilella⁵, Jiayu Wen¹, Xiaohui Xie¹, Michael C. Zody¹, Broad Institute Sequencing Platform and Whole Genome Assembly Team†, Kim C. Worley¹⁴, Christie L. Kovar¹⁴, Donna M. Muzny¹⁴, Richard A. Gibbs¹⁴, Baylor College of Medicine Human Genome Sequencing Center Sequencing Team†, Wesley C. Warren¹⁵, Elaine R. Mardis¹⁵, George M. Weinstock^{14,15}, Richard K. Wilson¹⁵, Genome Institute at Washington University†, Ewan Birney⁵, Elliott H. Margulies¹⁶, Javier Herrero⁵, Eric D. Green¹⁷, David Haussler^{6,8}, Adam Siepel¹², Nick Goldman⁵, Katherine S. Pollard^{9,18}, Jakob S. Pedersen^{4,19}, Eric S. Lander¹ & Manolis Kellis^{1,3}

Nature (2011)

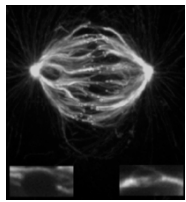
Non-Coding Functional Sequences



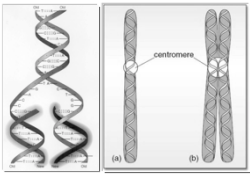
Gene Regulation




Chromosome Packaging



Chromosome Segregation



Chromosome Replication



Non-Coding RNAs

The Human Genome... by the Numbers

~5% of Human Genome Sequence is Constrained Across Mammals (and Presumed Functional)

5% of 3B Bases = ~150M Bases
 Do NOT Yet Know the Position of these ~150M Functional Bases
 Lower Bound for the Amount that is Functional

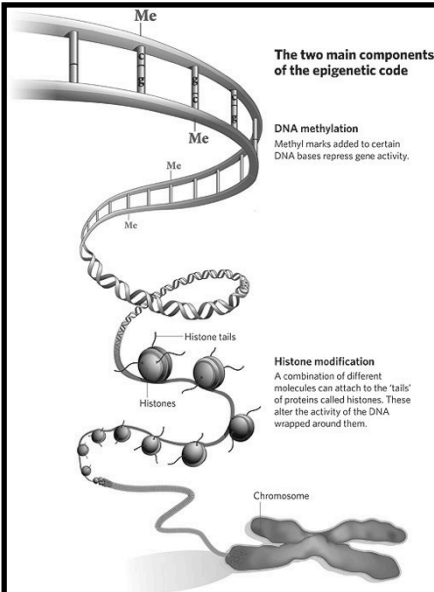
~1.5% Encodes for Protein (Genes)

Corresponds to ~18-22K Genes
 Many More than ~22K Different Proteins

~3.5% Functional But Non-Coding

Gene Regulatory Elements
 Chromosomal Functional Elements
 Undiscovered Functional Elements (NOT Yet in Textbooks!)

The Epigenomic Landscape



The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.


Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

Me


Histone tails

Histones

Chromosome

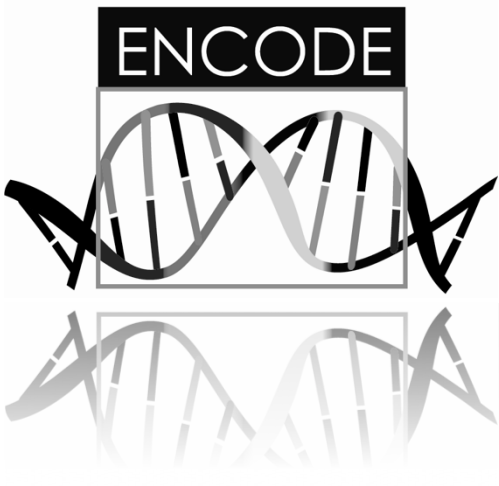


Science
28 October 2011 \$10
Epigenetics

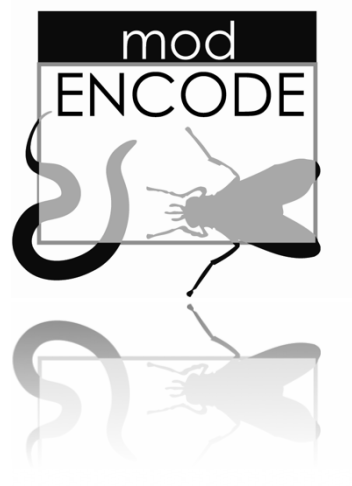


TheScientist
MAGAZINE OF THE LIFE SCIENCES
MARCH 2011
Epigenetics
CANCER
BEHAVIOR & MEMORY
PLANT FLOWERING
GENE IMPRINTING
PLURIPOTENCY
TESTING A TENET
PLUS
BEST PLACES
TO WORK FOR
POSTDOCS

The ENCODE Portfolio



ENCODE



mod
ENCODE

OPEN ACCESS Freely available online PLoS BIOLOGY

A User's Guide to the Encyclopedia of DNA Elements (ENCODE)

The ENCODE Project Consortium*

Abstract

The mission of the Encyclopedia of DNA Elements (ENCODE) Project is to enable the scientific and medical communities to interpret the human genome sequence and apply it to understand human biology and improve health. The ENCODE Consortium is integrating multiple technologies and approaches in a collective effort to discover and define the functional elements encoded in the human genome, including genes, transcripts, and transcriptional regulatory regions, together with their attendant chromatin states and DNA methylation patterns. In the process, standards to ensure high-quality data have been implemented, and novel algorithms have been developed to facilitate analysis. Data and derived results are made available through a freely accessible database. Here we provide an overview of the project and the resources it is generating and illustrate the application of ENCODE data to interpret the human genome.

PLoS Biol (2011)

The image shows a screenshot of a PLoS Biology article. At the top, it says 'OPEN ACCESS Freely available online' and 'PLOS BIOLOGY'. The title is 'A User's Guide to the Encyclopedia of DNA Elements (ENCODE)' by 'The ENCODE Project Consortium*'. There is an 'Abstract' section with text describing the mission of the ENCODE project. Below the abstract, there are two genomic tracks showing data from the ENCODE project. The citation 'PLOS Biol (2011)' is prominently displayed in the bottom right of the article preview.

Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) National Institutes of Health • U.S. Department of Health and Human Services

The NIH Common Fund

Home Common Fund Programs Funding Opportunities Funded Research News & Events About the Common Fund

Back to: [Common Fund Home](#) > [Programs](#)

Epigenomics

- Overview
- Implementation Group Members
- Program Initiatives
- Funding Opportunities
- Funded Research
- Meetings
- Press Releases
- Science News
- Science Publications

OVERVIEW

Epigenetics is an emerging frontier of science that involves the study of changes in the regulation of gene activity and expression that are not dependent on gene sequence. For purposes of this program, epigenetics refers to both heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable. While epigenetics refers to the study of single genes or sets of genes, epigenomics refers to more global analyses of epigenetic changes across the entire genome.

Related Information

- What is Epigenomics?
- Scientific Illustration of How Epigenetic Mechanisms Can Affect Health
- PRS: A Tale of Two Mice (text translation)
- Variate Black-Red Concentrates.co


nihroadmap.nih.gov/epigenomics

The NIH Roadmap Epigenomics Mapping Consortium

Bradley E Bernstein, John A Stamatoyannopoulos, Joseph F Costello, Bing Ren, Aleksandar Milosavljevic, Alexander Meissner, Manolis Kellis, Marco A Marra, Arthur L Beaudet, Joseph R Ecker, Peggy J Farnham, Martin Hirst, Eric S Lander, Tarjei S Mikkelsen & James A Thomson

Nature Biotechnology (2010)

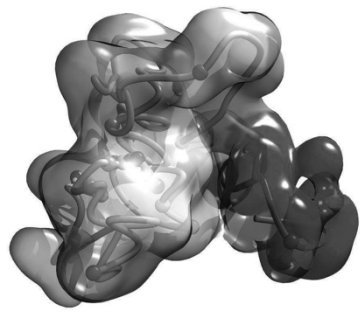
The image shows a screenshot of the NIH Roadmap Epigenomics Mapping Consortium website. At the top, it says 'Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) National Institutes of Health • U.S. Department of Health and Human Services'. The main heading is 'The NIH Common Fund'. There is a search bar and a navigation menu with items like 'Home', 'Common Fund Programs', 'Funding Opportunities', 'Funded Research', 'News & Events', and 'About the Common Fund'. Below that, there is a breadcrumb trail 'Back to: Common Fund Home > Programs'. The main content area is titled 'Epigenomics' and has a sidebar with a list of links: 'Overview', 'Implementation Group Members', 'Program Initiatives', 'Funding Opportunities', 'Funded Research', 'Meetings', 'Press Releases', 'Science News', and 'Science Publications'. The main text area has an 'OVERVIEW' section with a paragraph about epigenetics and a 'Related Information' section with links to 'What is Epigenomics?', 'Scientific Illustration of How Epigenetic Mechanisms Can Affect Health', 'PRS: A Tale of Two Mice (text translation)', and 'Variate Black-Red Concentrates.co'. Below the screenshot, the URL 'nihroadmap.nih.gov/epigenomics' is displayed. The title 'The NIH Roadmap Epigenomics Mapping Consortium' is followed by a list of names: 'Bradley E Bernstein, John A Stamatoyannopoulos, Joseph F Costello, Bing Ren, Aleksandar Milosavljevic, Alexander Meissner, Manolis Kellis, Marco A Marra, Arthur L Beaudet, Joseph R Ecker, Peggy J Farnham, Martin Hirst, Eric S Lander, Tarjei S Mikkelsen & James A Thomson'. At the bottom, the citation 'Nature Biotechnology (2010)' is shown.



TECHNOLOGY FEATURE

GENOMES IN THREE DIMENSIONS

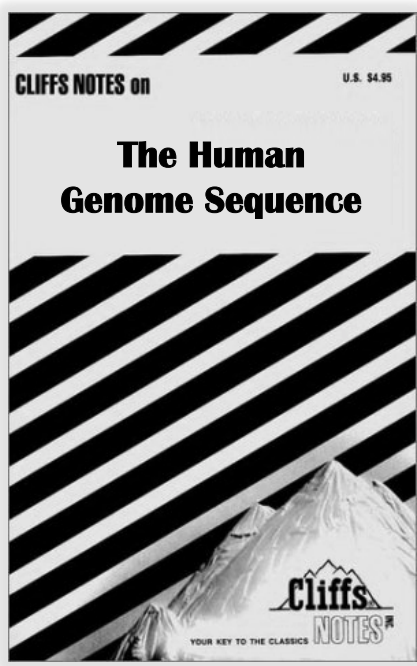
A DNA sequence isn't enough; to understand the workings of the genome, we must study chromosome structure.



Nature (2011)

```

TGCCCGGAACCTTTTCGGCTCTCTAAGGCTGTATTTTGATAT
ACGAAAGGCACATTTTCCTTCCCTTTTCAAATGCACCTTGC
AAACGTAACAGGAACCCGACTAGGATCATCGGAAAAGGAGG
AGGAGGAGGAAGCGAGGCTCCGGGGAAGCTGGTGGCAGCGGG
TCCTGGGTCTGGCGGACCTGACCGGAAGGAGGGTCTAGGAA
GCTCTCCGGGAGCCGGTTCTCCCGCGGTGGCTTCTTCTGT
CCTCAGCGTTGCCAACTGGACCTAAAGAGAGGCCCGACTG
TCGCCACCTGCGGGATGGGCTGGTCTGGCGGTAAGGAC
ACGGACCTGGAAGGAGCGCGCGAGGGAGGGAGGCTGGGAG
TCAGAAATCGGAAAAGGAGGTGCGGGGCGCGAGGGAGCGAA
GGAGGAGAGGAGGAAGGAGCGGGAGGGGTGCTGGCGGGGTG
CGTAGTGGGTGGAGAAAGCCGCTAGAGCAAATTTGGGCCGG
ACCAGGCAGCACTCGGCTTTTAACTGGGCACTGAAGGCGGG
GAAAGAGCAAAAAGGAGGGGTGGTGTCCGAGTAGGGTGG
GTGGGGGAATTGGAAGCAAATGACATCACAGCAGGTGAGAG
AAAAAGGTTGAGCGGCAGGCACCCAGAGTAGTAGGTTCTTG
GCATTAGGAGCTTGAGCCAGACGGCCCTAGCAGGGACCCCA
CGCCCCAGAGACCATGCGAGAGTCCCTCTGAAAAGGCCA
CGCTGTCTCCAACTTTTTTTCAGGTGAGAGGTGGCCAA
CGAGCTTCGGAAGACAGCTGCCACGAAAGAGGAGGGCGTG
TGTATGGTTGGTTTTGGGTAAGGAATAAGCAGTTTTTAA
AAAGATGCGCTATCATTGTTTTGAAAGAAAATGTGGGT
ATTGTAGAATAAACAGAAAGCATTAGAAGAGATGGAAGAA
TGAAGTGAAGCTGATTGAATAGAGGCCACATCTACTTGCAA
CTGAAAAGTTAGAATCTCAAGACTCAAGTACGCTACTATGCA
CTGTTTTATTTCATTTTTTCTAAGAACTAAAAACTTGT
AATAAGTACCTAAGTATGGTTTATGGTTTTCCCGCTCATG
CCTGGACACTTGATTGTCTTCTGGCACATACAGGTGCCAT
GCCTGCATATAGTAAAGTCTCAGAAAACATTTCTGACTGAA
TTCAGCCAACAAAAATTTGGGTAGGTAGAAAATATATGCT
TAAAGTATTTATGTTATGAGACTGGATATATCTAGTATTTG
TCACAGGTAATGATTTCTCAAATAATGAAAGCAAATTTGT
GAAATATTTATTTGAAAAAGTTACTTCACAGCTATAAAT
TTTTAAAGCCATAGGAATAGATCCGAAGTTATATCCAACG
ACATTTA
                
```



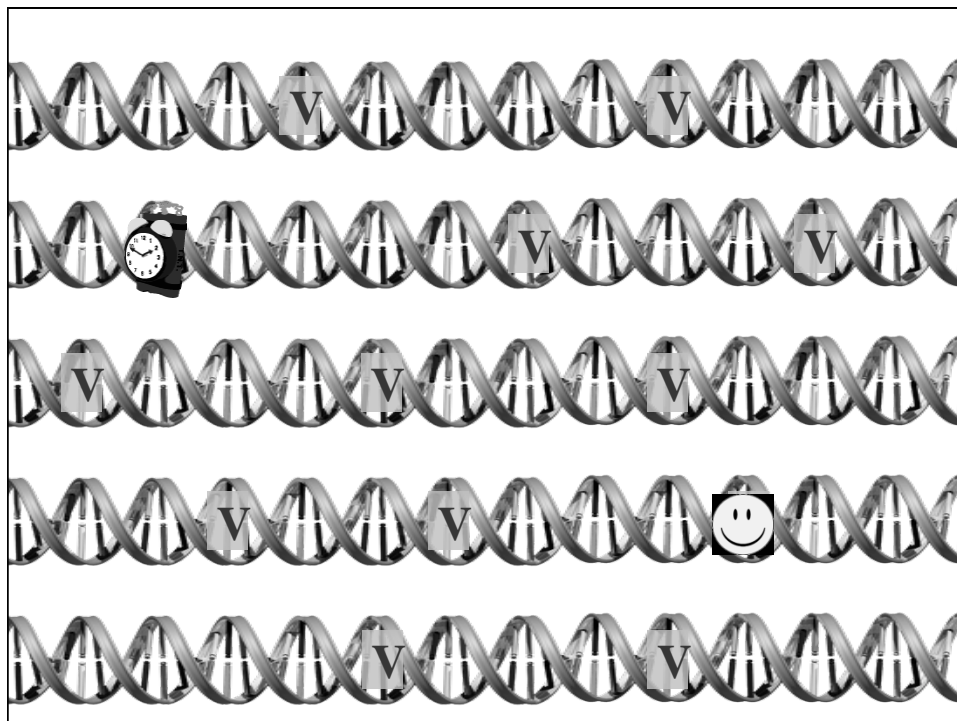
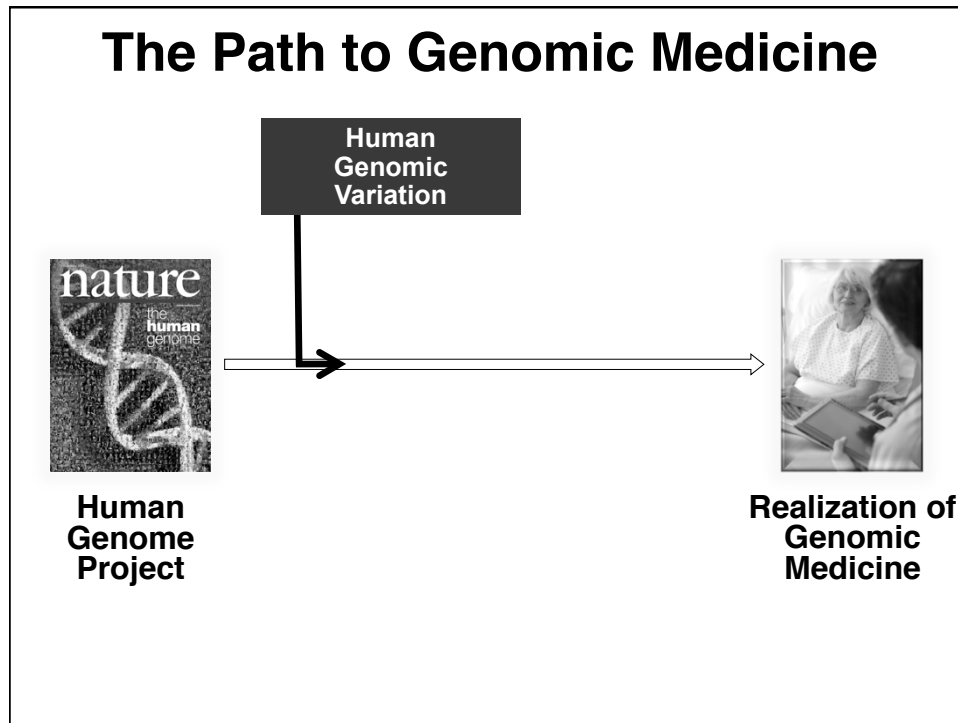
The Genomics of Human Evolution



Genome 10K: A Proposal to Obtain Whole-Genome Sequence for 10 000 Vertebrate Species

GENOME 10K COMMUNITY OF SCIENTISTS*

J. Heredity (2009)







A haplotype map of the human genome
 The International HapMap Consortium*
2005

Inherited genetic variation has a critical but as yet largely uncharacterized role in human disease. Here we report a public database of common variation in the human genome: more than one million single nucleotide polymorphisms (SNPs) for which accurate and complete genotypes have been obtained in 269 DNA samples from four populations including ten 500-kilobase regions in which essentially all information about common DNA variation has been extracted. These data document the generality of recombination hotspots, a block-like structure of linkage disequilibrium and low haplotype diversity, leading to substantial correlations of SNPs with many of their neighbours. We show how the HapMap resource can guide the design and analysis of genetic association studies, shed light on structural variation and recombination, and identify loci that may have been subject to natural selection during human evolution.

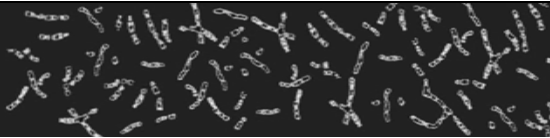
A second generation human haplotype map of over 3.1 million SNPs
 The International HapMap Consortium*
2007

We describe the Phase II HapMap, which characterizes over 3.1 million human single nucleotide polymorphisms (SNPs) genotyped in 270 individuals from four geographically diverse populations and includes 25–30% of common SNP variation in the populations surveyed. The map is extended to capture untyped common variation with an average maximum r^2 of between 0.9 and 0.96 depending on population. We demonstrate that the current generation of commercial genome-wide genotyping products captures common Phase II SNPs with an average maximum r^2 of up to 0.8 in African and up to 0.96 in non-African populations, and that potential gains in power in association studies can be obtained through imputation. These data also reveal novel aspects of the structure of linkage disequilibrium. We show that 10–30% of pairs of individuals within a population share at least one region of extended genetic identity arising from recent ancestry and that up to 1% of all common variants are untagable, primarily because they lie within recombination hotspots. We show that recombination rates vary systematically around genes and between genes of different function. Finally, we demonstrate increased differentiation at non-synonymous, compared to synonymous, SNPs, resulting from systematic differences in the strength of natural selection between populations.

Integrating common and rare genetic variation in diverse human populations
 The International HapMap 3 Consortium*
2010

Despite great progress in identifying genetic variants that influence human disease, most inherited risk remains unexplained. A more complete understanding requires genome-wide studies that fully examine less common alleles in populations with a wide range of ancestry. To inform the design and interpretation of such studies, we genotyped 1.6 million common single nucleotide polymorphisms (SNPs) in 1,184 reference individuals from 11 global populations, and sequenced ten 500-kilobase regions in 492 of these individuals. This integrated data set of common and rare alleles, called 'HapMap 3', includes both SNPs and copy number polymorphisms (CNPs). We characterized population-specific differences among low-frequency variants, measured the improvement in imputation accuracy afforded by the larger reference panel, especially in imputing SNPs with minor allele frequency of 1%, and demonstrated the feasibility of imputing newly discovered CNPs and SNPs. This expanded public resource of genome variants in global populations supports deeper interrogation of genetic variation and its role in human disease, and serves as a step towards a high-resolution map of the landscape of human genetic variation.

1000 Genomes
 A Deep Catalog of Human Genetic Variation





ARTICLE
 doi:10.1038/nature09534

A map of human genome variation from population-scale sequencing
 The 1000 Genomes Project Consortium*

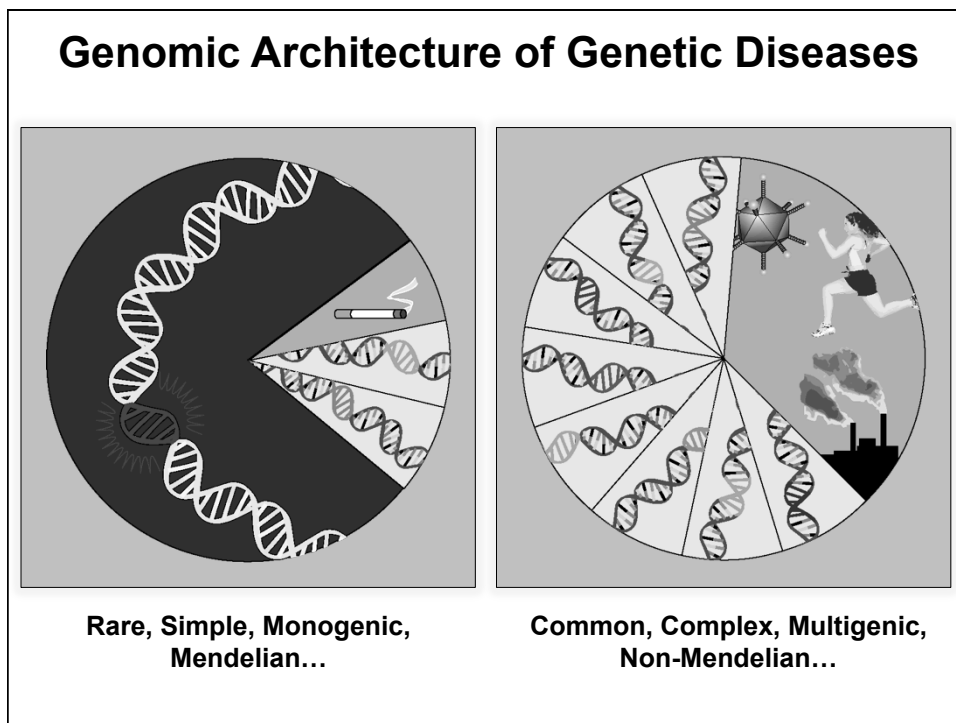
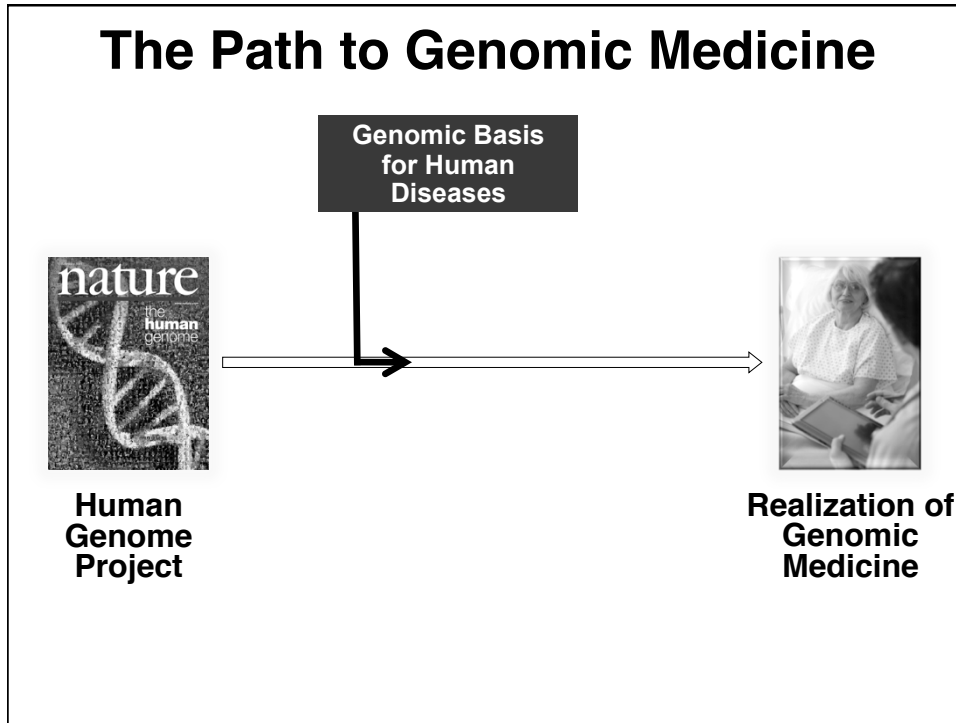
The 1000 Genomes Project aims to provide a deep characterization of human genome sequence variation as a foundation for investigating the relationship between genotype and phenotype. Here we present results of the pilot phase of the project, designed to develop and compare different strategies for genome-wide sequencing with high-throughput platforms. We undertook three projects: low-coverage whole-genome sequencing of 179 individuals from four populations; high-coverage sequencing of two mother-father-child trios; and exon-targeted sequencing of 697 individuals from seven populations. We describe the location, allele frequency and local haplotype structure of approximately 15 million single nucleotide polymorphisms, 1 million short insertions and deletions, and 20,000 structural variants, most of which were previously undescribed. We show that, because we have catalogued the vast majority of common variation, over 95% of the currently accessible variants found in any individual are present in this data set. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders. We demonstrate how these results can be used to inform association and functional studies. From the two trios, we directly estimate the rate of de novo germline base substitution mutations to be approximately 10^{-8} per base pair per generation. We explore the data with regard to signatures of natural selection, and identify a marked reduction of genetic variation in the neighbourhood of genes, due to selection at linked sites. These methods and public data will support the next phase of human genetic research.

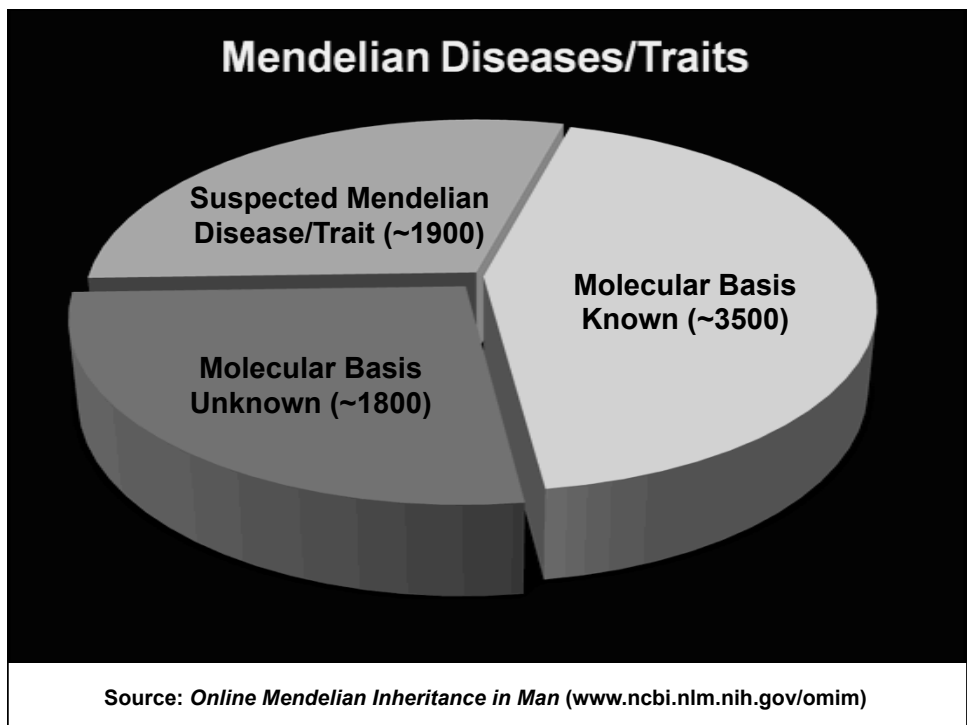
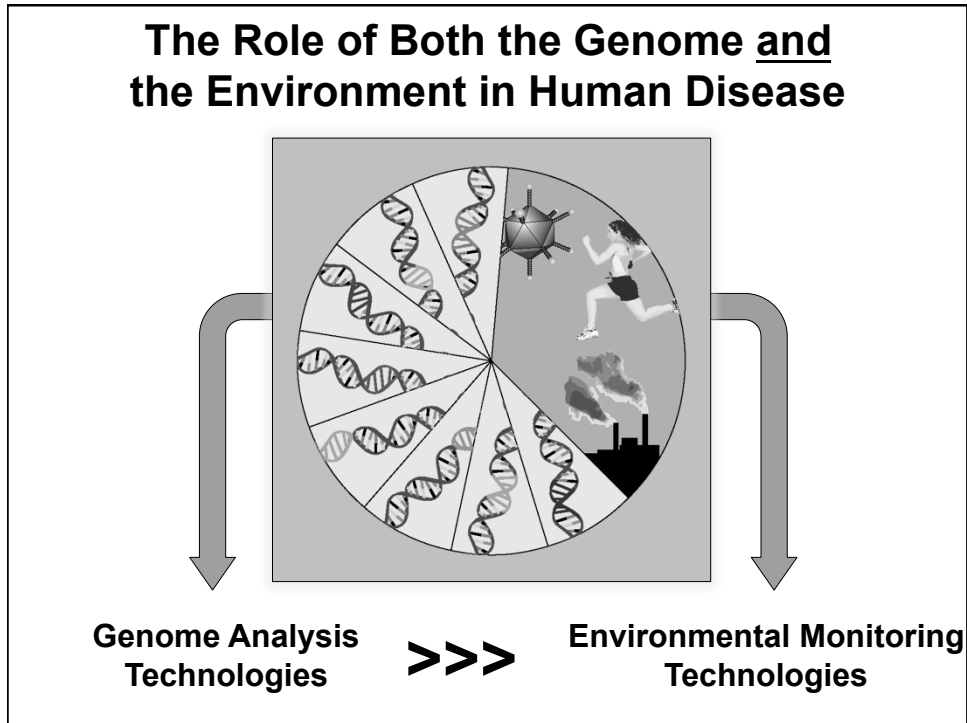
Nature 2010

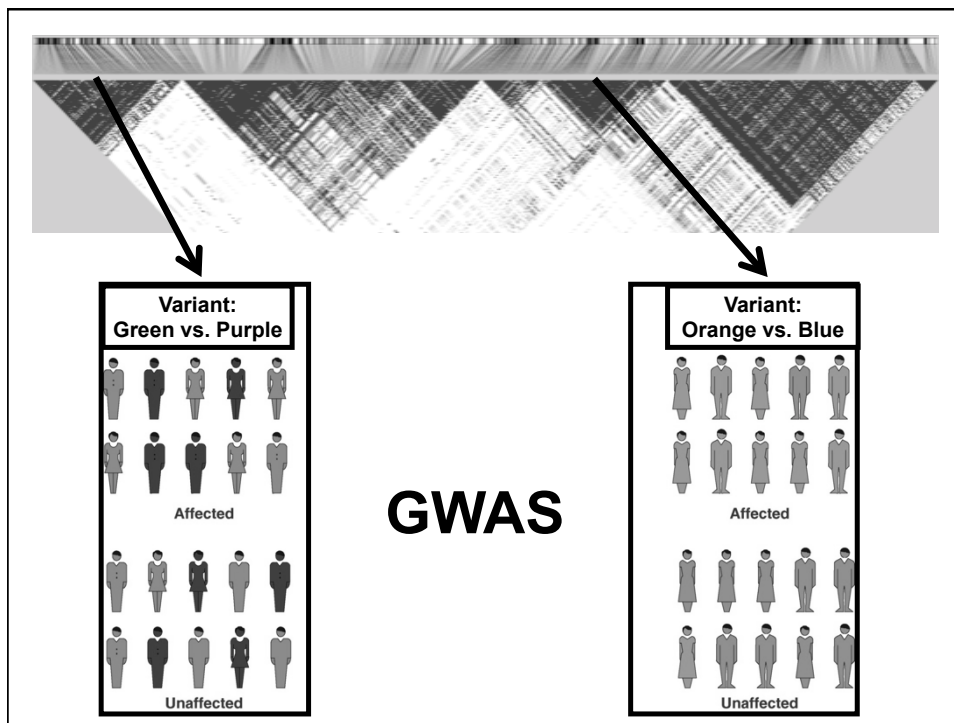
HUMAN STRATEGIES
BEYOND THE COURT CASE
 Implications for the law, industry and ethics
PAGE 102

CLIMATE PRODUCTIVITY
PHOSPHATE DOWN THE AGES
 Key nutrient plentiful after "snowball" earth
PAGE 103 & 104

RETURN BOOKS
THE RECURRING UNIVERSE
 Lee Smolin on Roger Penrose's grand idea
PAGE 104







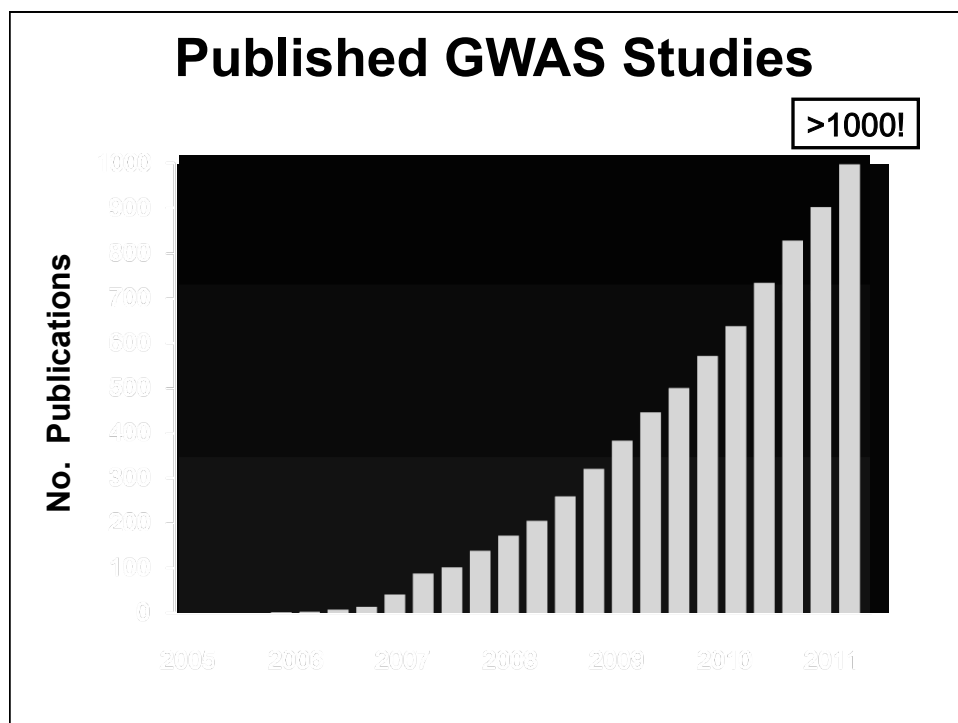
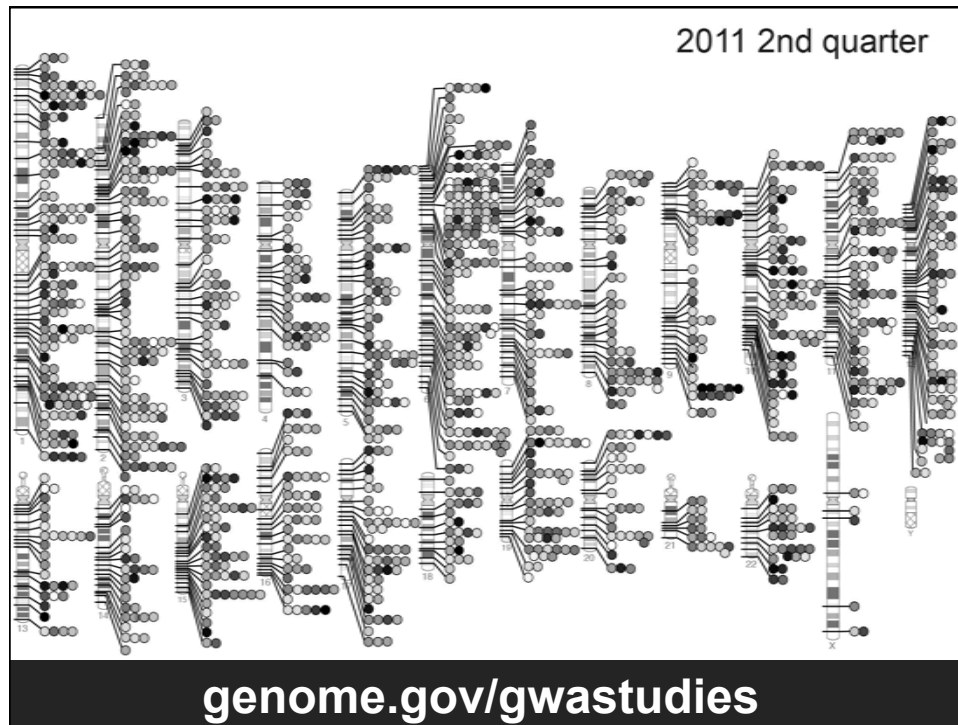
The First GWAS Success Story: Age-Related Macular Degeneration

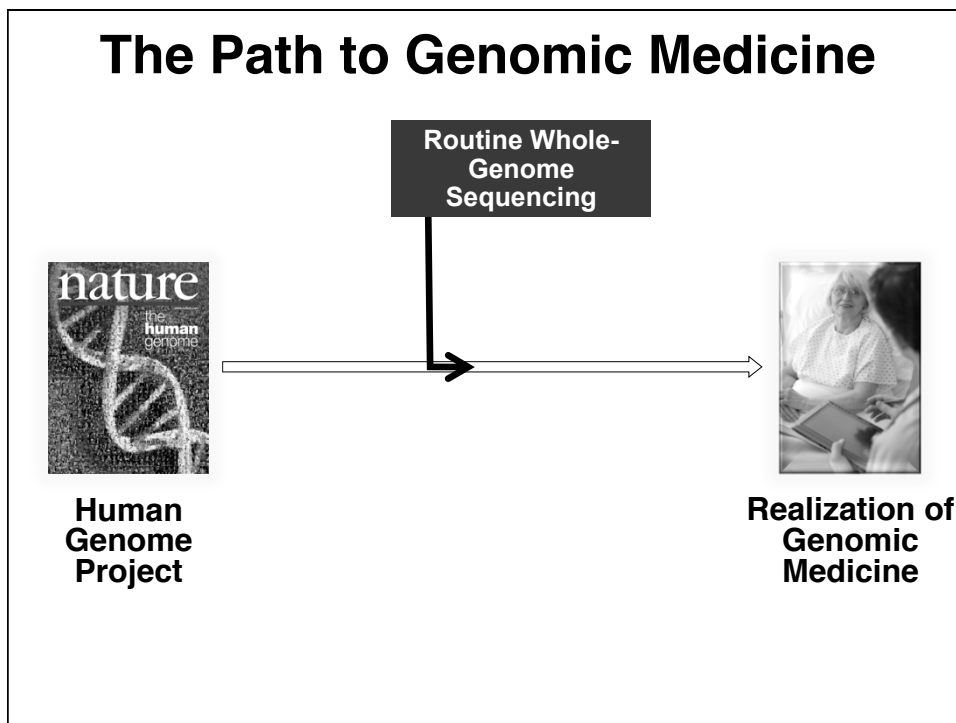
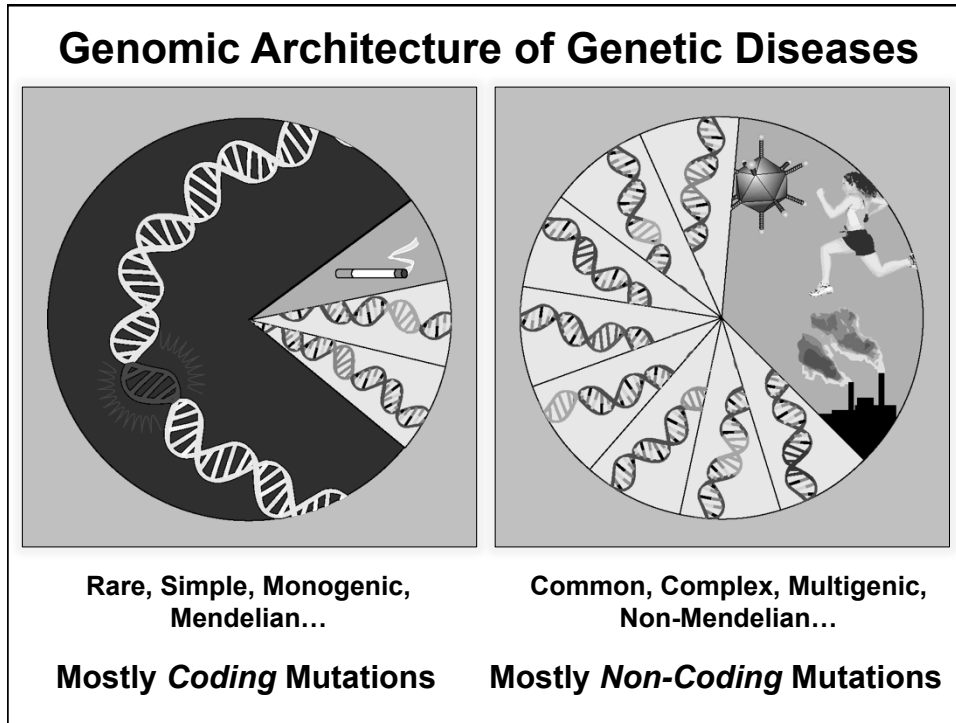
Complement Factor H Polymorphism in Age-Related Macular Degeneration

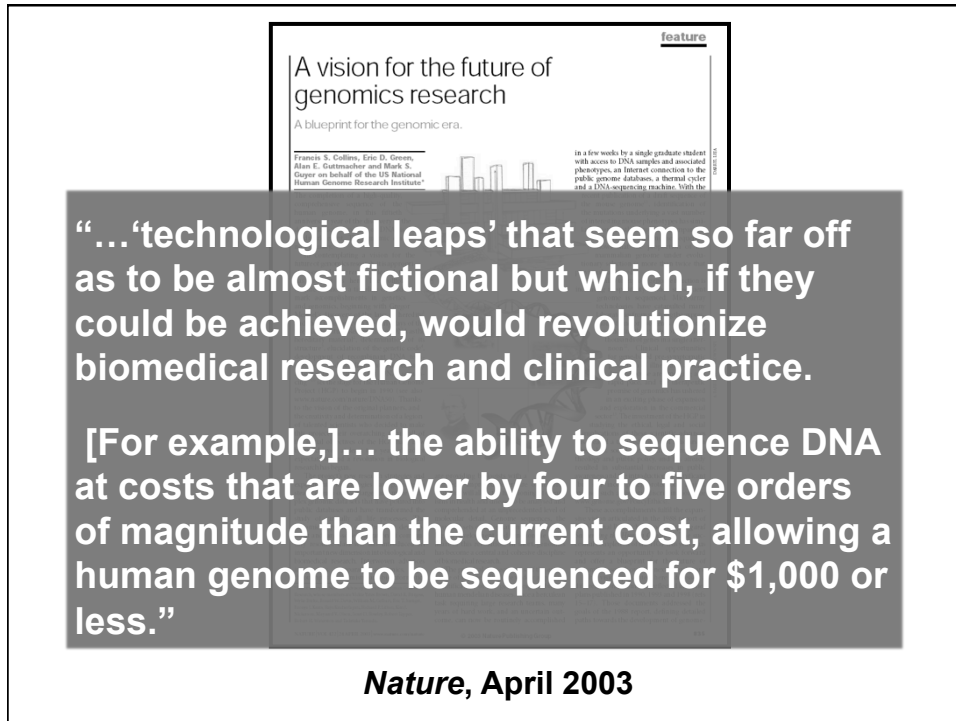
Robert J. Klein,¹ Caroline Zeiss,^{2*} Emily Y. Chew,^{3*} Jen-Yue Tsai,^{4*} Richard S. Sackler,¹ Chad Haynes,¹ Alice K. Henning,⁵ John Paul SanGiovanni,³ Shrikant M. Mane,⁶ Susan T. Mayne,⁷ Michael B. Bracken,⁷ Frederick L. Ferris,³ Jurg Ott,¹ Colin Barnstable,² Josephine Hoh^{7†}

Science (2005)










“...‘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.”


***Nature*, April 2003**

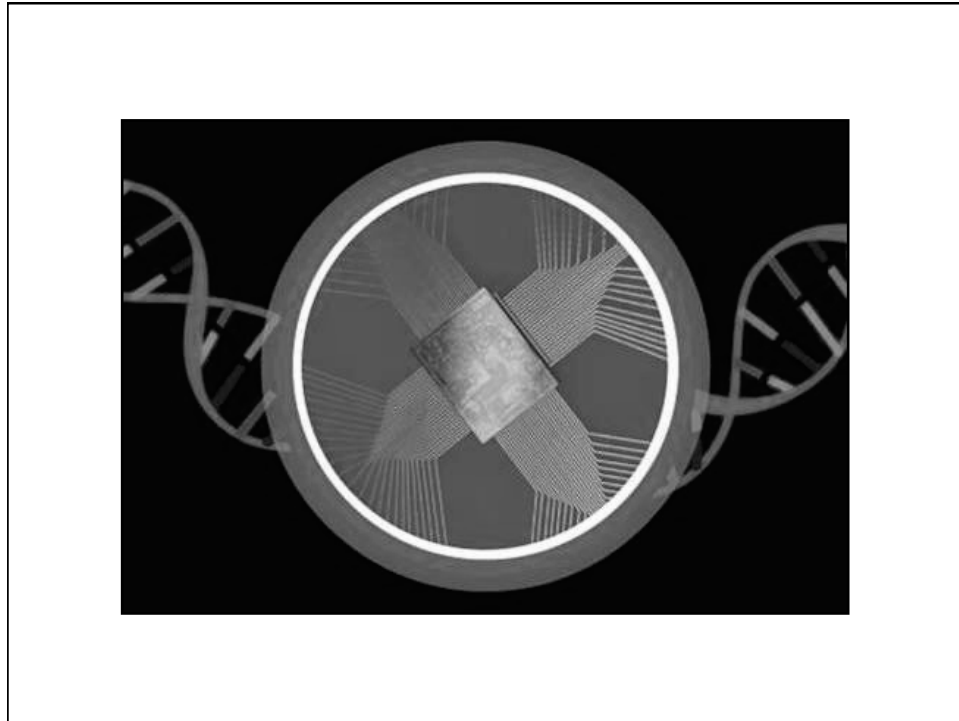
Human Genome Sequence

~\$1,000,000,000



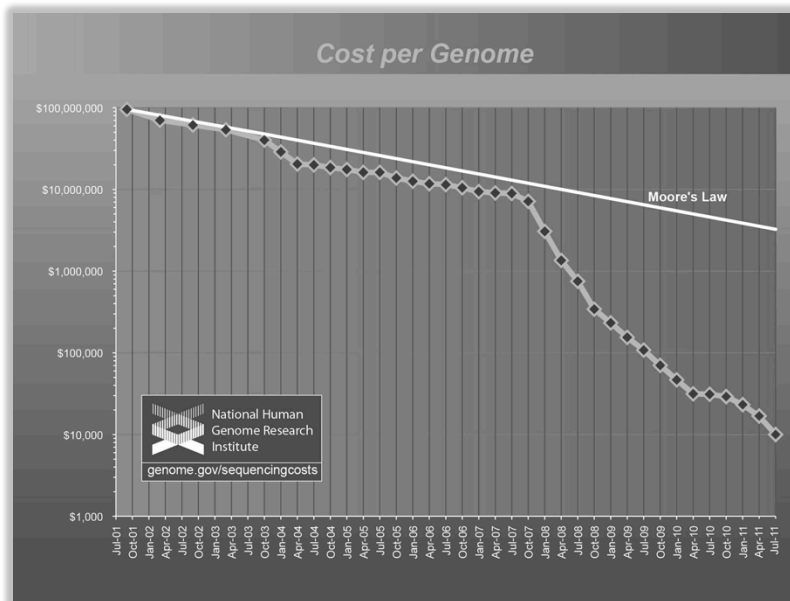
~\$1,000 “The \$1000 Genome”







Cost per Sequenced Human Genome



Human Genome Sequence

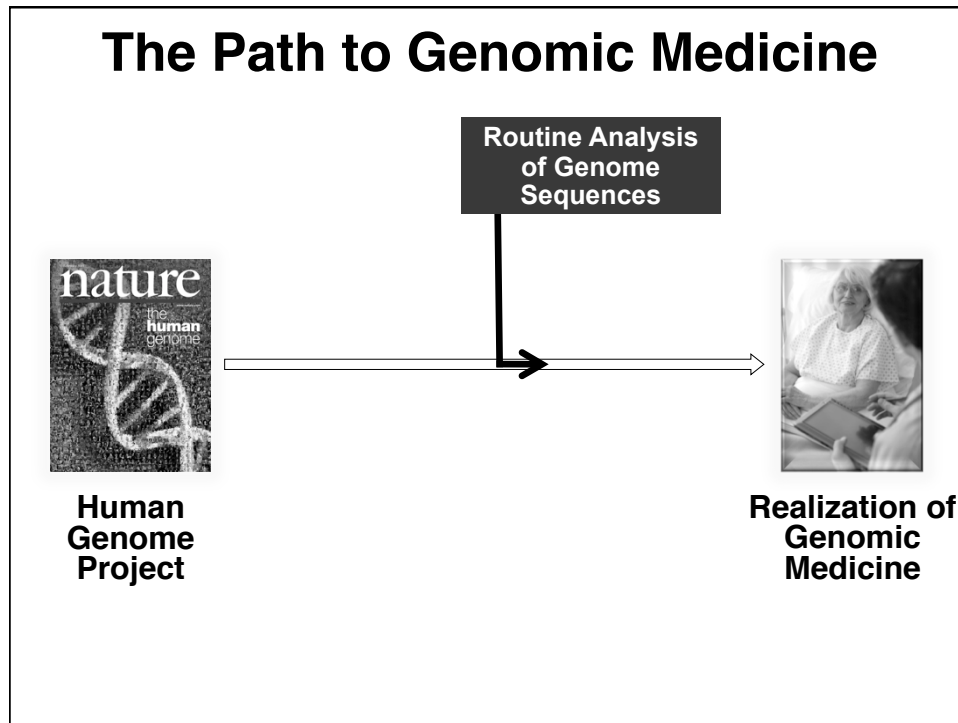
~\$1,000,000,000

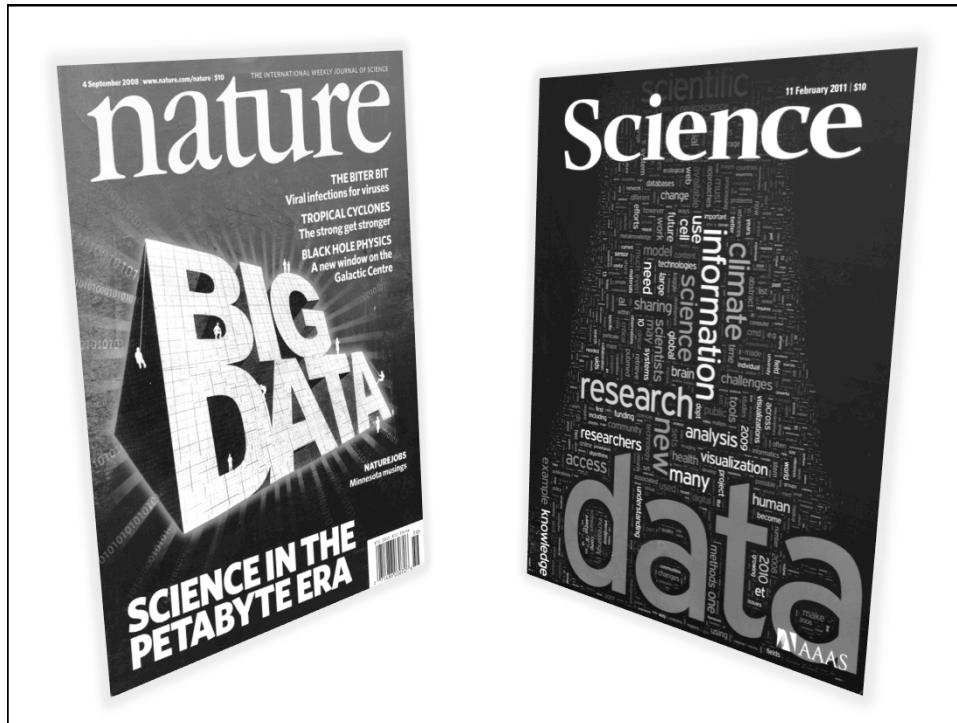
~\$1,000

Current Cost

“The \$1000 Genome”

Genome Sequencing as a ‘Commodity’





The Computational Bottleneck



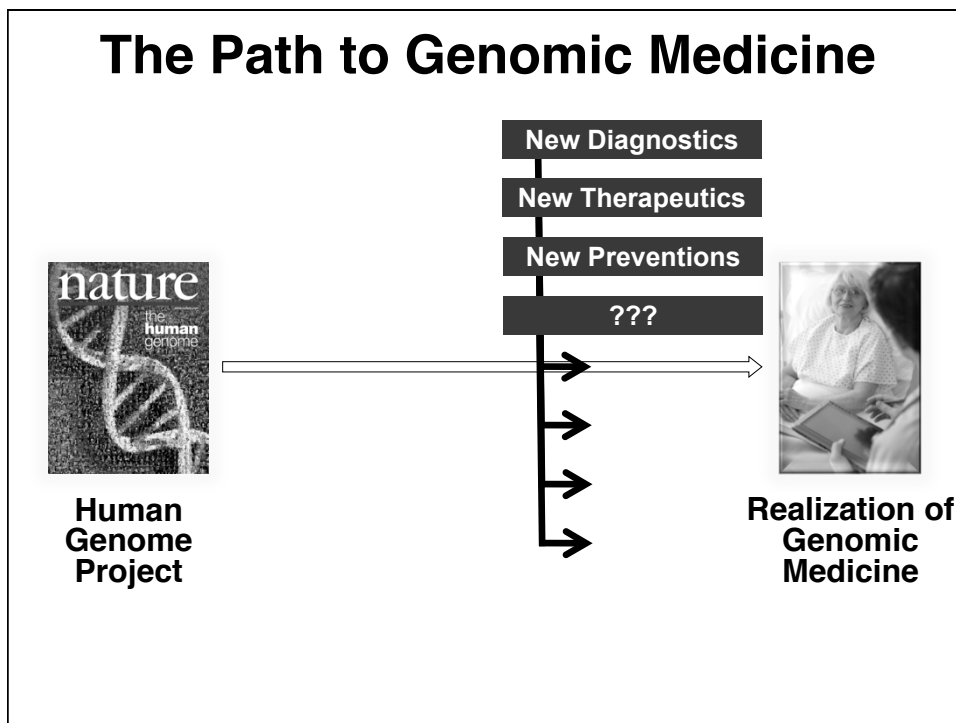
Ben didn't have an informatics bottleneck.

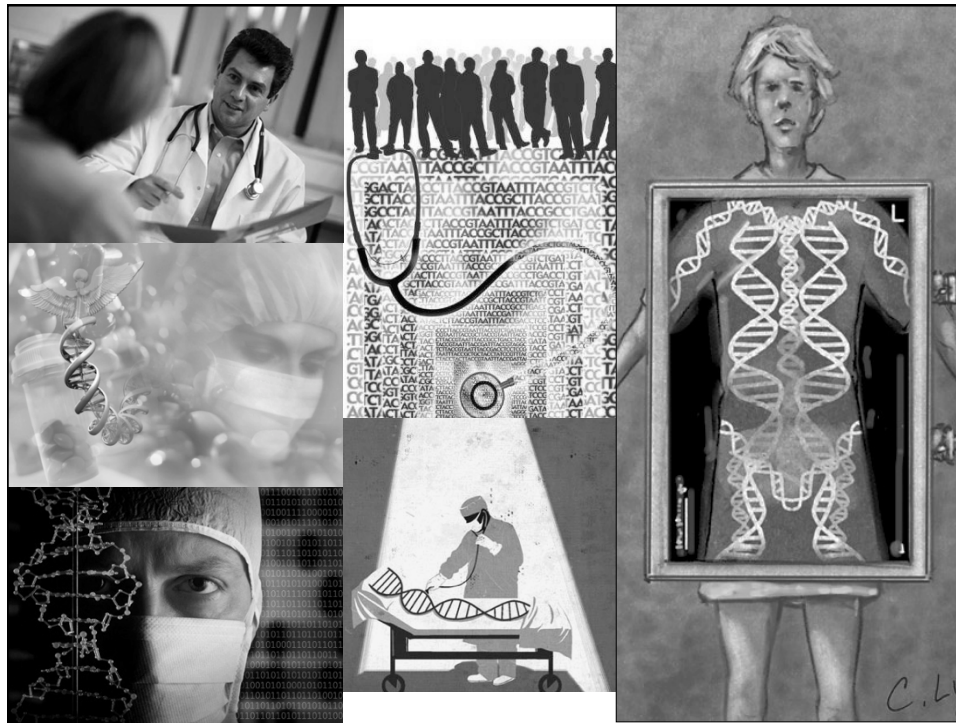
SPECIAL PRICING | **\$3,750** per genome | Includes whole genome sequencing (30x), downstream informatics & interpretation tools

Introducing knomeBASE™, an informatics service that transforms raw sequence data from human genomes into a format optimized for desktop interpretation. knomeBASE annotates, compares, and displays sequence data—addressing the primary informatics challenges that typically bottleneck the process of interpreting whole genomes. Clients also receive a suite of software tools, scripts, and libraries that give geneticists unprecedented flexibility to query, visualize, and interpret multiple genomes.

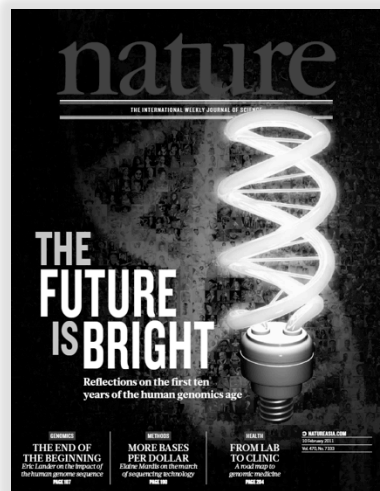
Knome
The human genome interpretation company™

Downstream informatics & interpretation tools for geneticists: visit www.knome.com

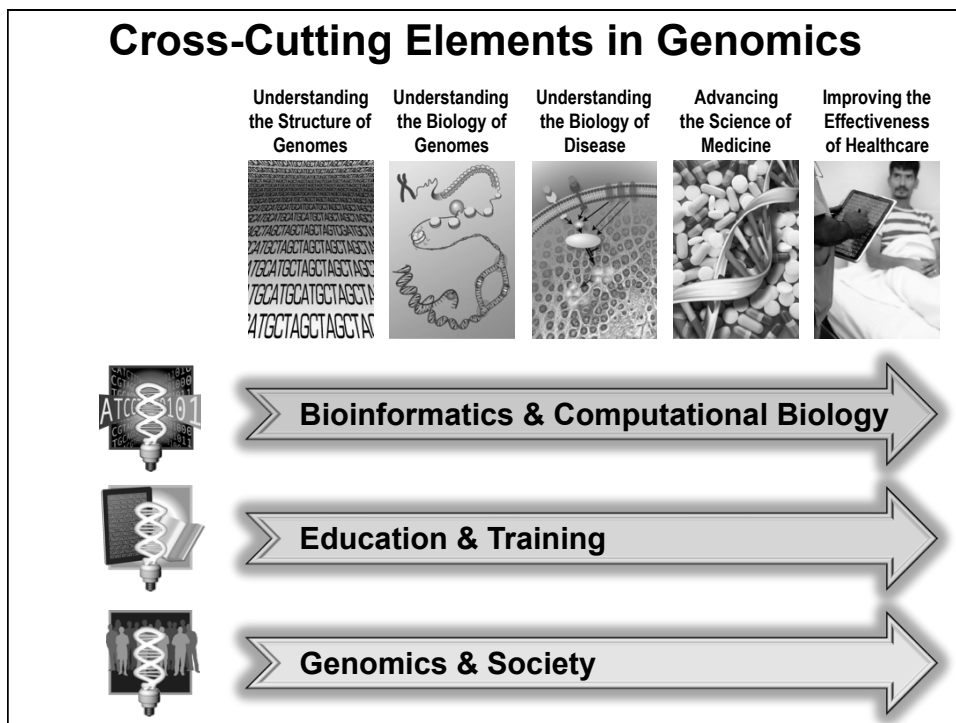
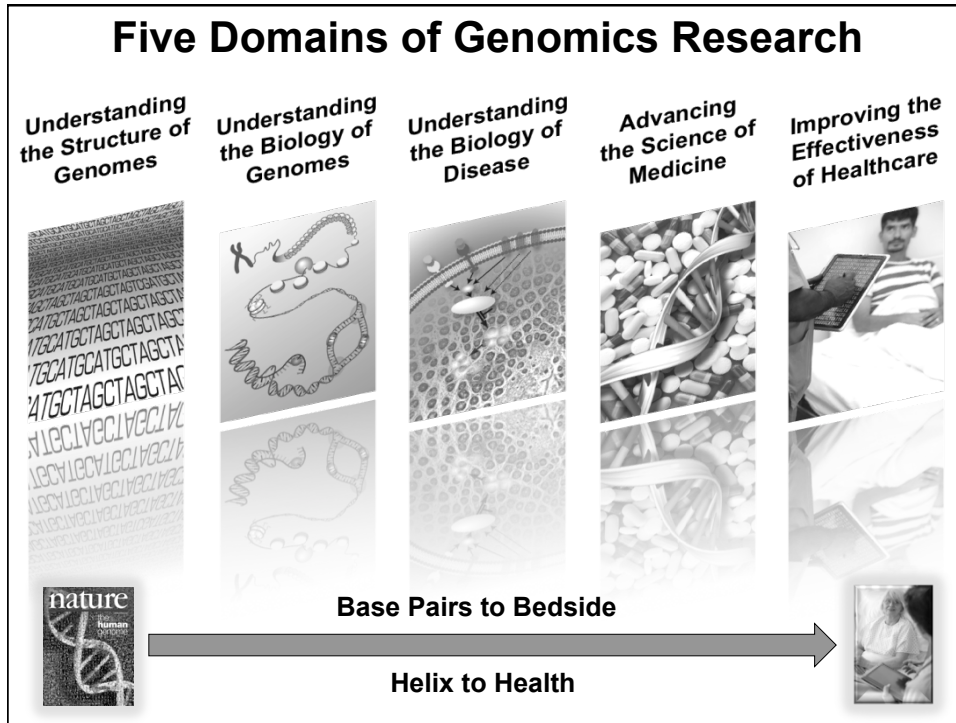


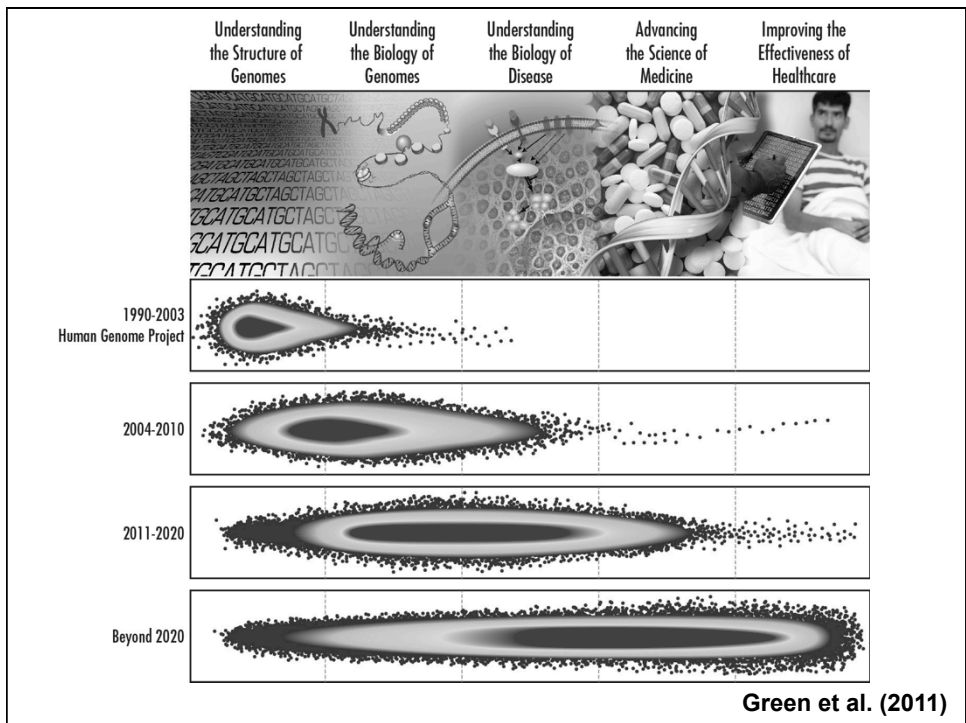
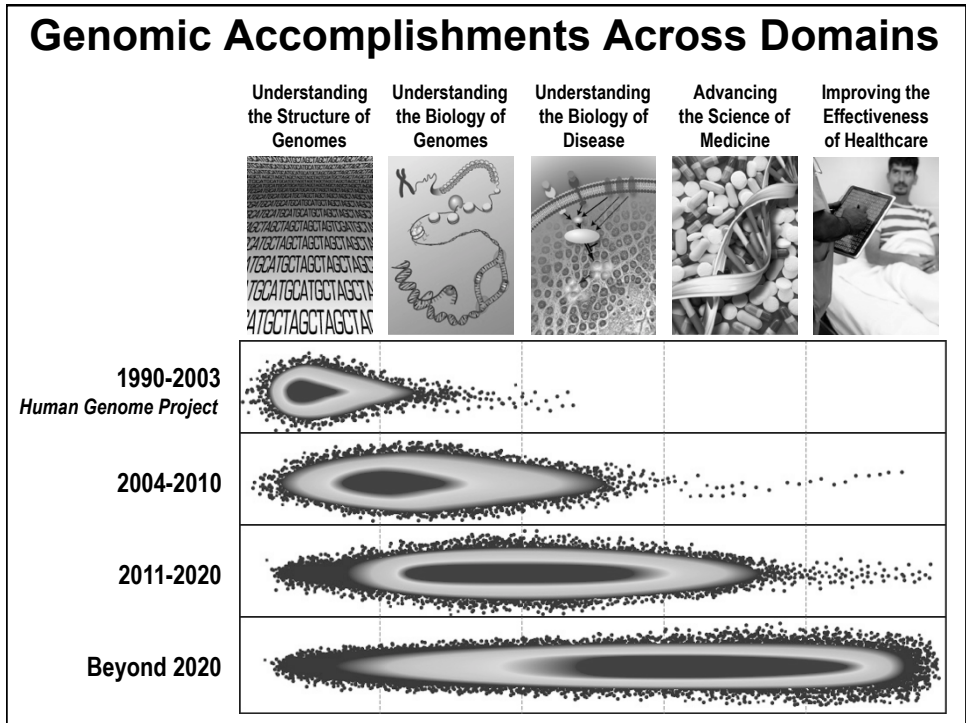


~11 Months Ago

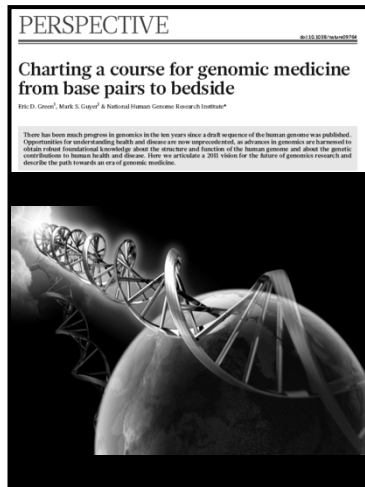


February 2011 NHGRI Published New Vision for Genomics





2011 NHGRI Strategic Plan for Genomics



BOX 2

Imperatives for genomic medicine

Opportunities for genomic medicine will come from simultaneously acquiring foundational knowledge of genome function, insights into disease biology and powerful genomic tools. The following imperatives will capitalize on these opportunities in the coming decade.

Making genomics-based diagnostics routine. Genomic technology development so far has been driven by the research market. In the next decade, technology advances could enable a clinician to acquire a complete genomic diagnostic panel (including genomic, epigenomic, transcriptomic and microbiomic analyses) as routinely as a blood chemistry panel.

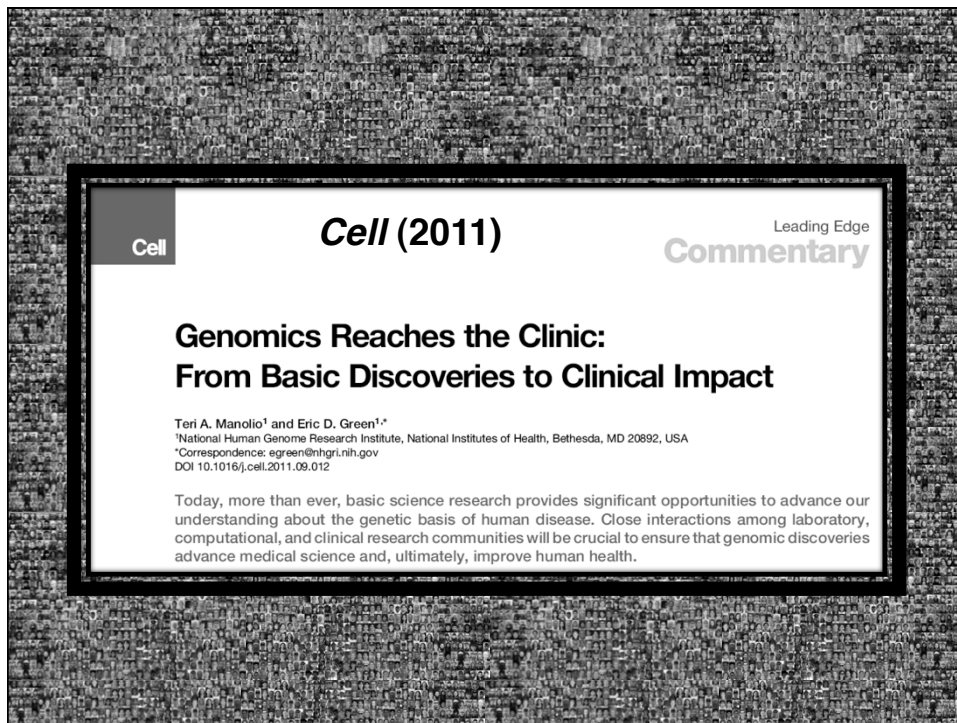
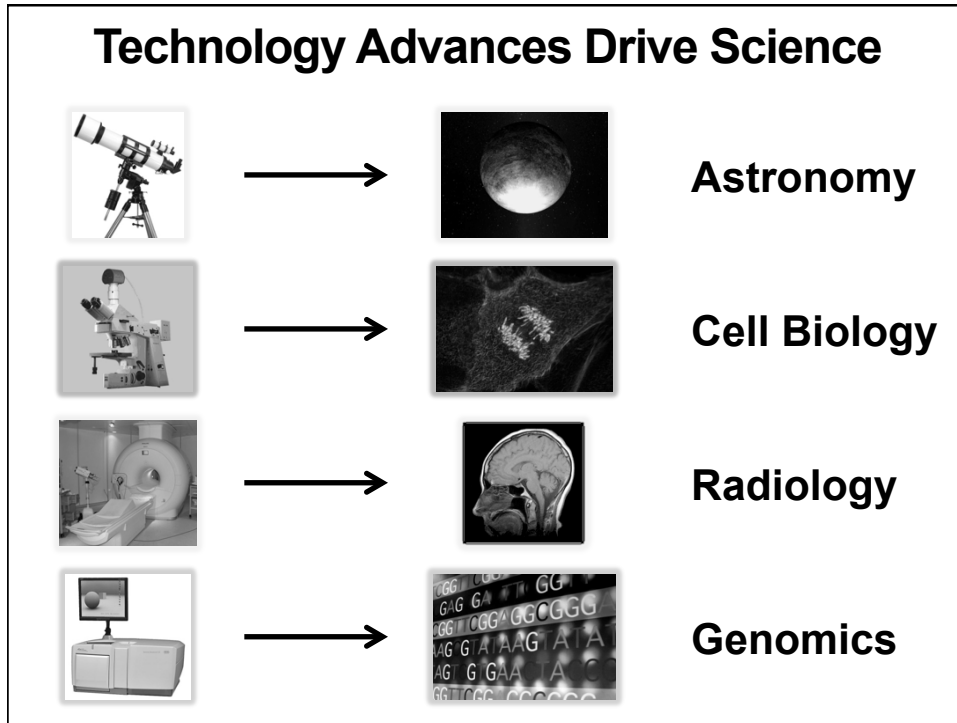
Defining the genetic components of disease. All diseases involve a genetic component. Genome sequencing could be used to determine the genetic variation underlying the full spectrum of diseases, from rare Mendelian to common complex disorders, through the study of upwards of a million patients; efforts should begin now to organize the necessary sample collections.

Comprehensive characterization of cancer genomes. A comprehensive genomic view of all cancers⁴⁷ will reveal molecular taxonomies and altered pathways for each cancer subtype. Such information should lead to more robust diagnostic and therapeutic strategies and a roadmap for developing new treatments^{47,5}.

Practical systems for clinical genomic informatics. Thousands of genomic variants associated with disease risk and treatment response are known, and many more will be discovered. New models for capturing and displaying these variants and their phenotypic consequences should be developed and incorporated into practical systems that make information available to patients and their healthcare providers, so that they can interpret and reinterpret the data as knowledge evolves.

The role of the human microbiome in health and disease. Many diseases are influenced by the microbial communities that inhabit our bodies (the microbiome)¹⁰³. Recent initiatives^{102,104} (<http://www.human-microbiome.org>) are using new sequencing technologies to catalogue the resident microflora at distinct body sites, and studying correlations between specific diseases and the composition of the microbiome¹⁰⁴. More extensive studies are needed to build on these first revelations and to investigate approaches for manipulating the microbiome as a new therapeutic approach.





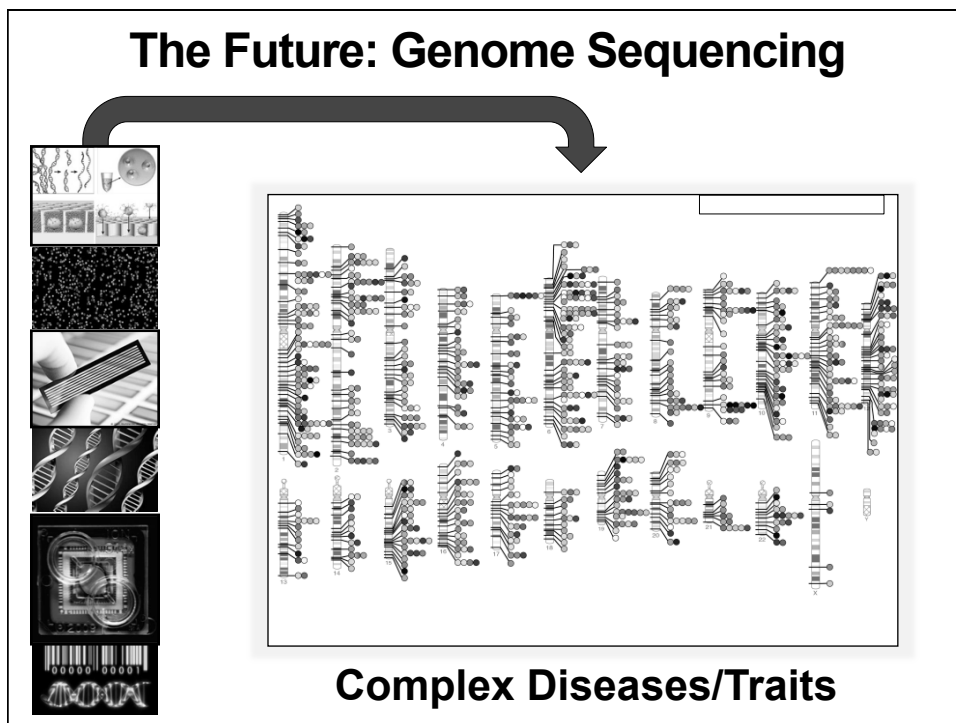
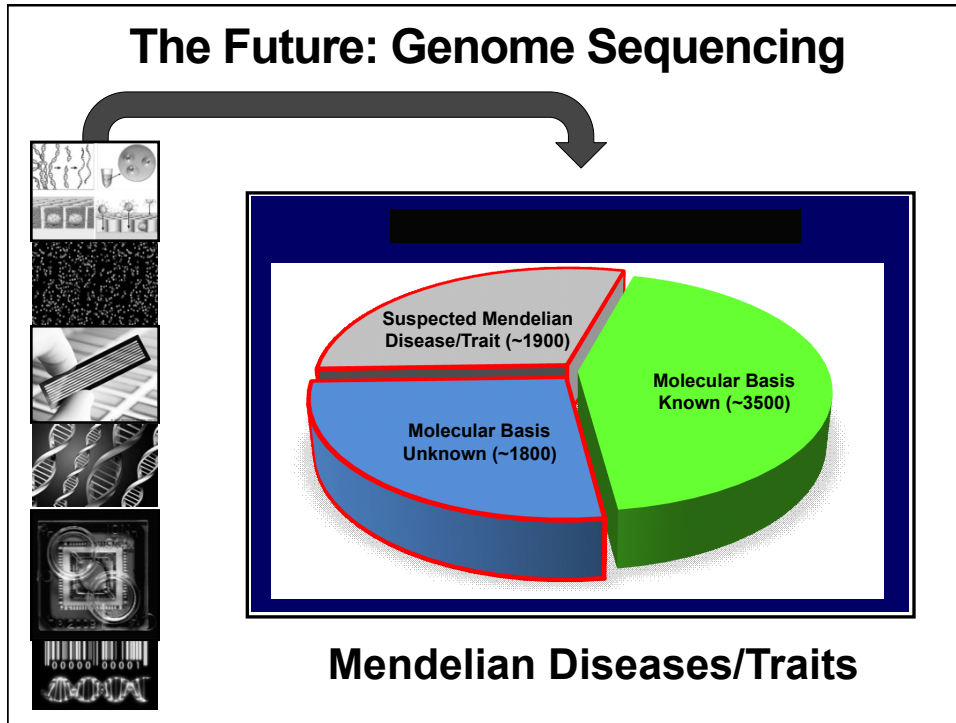
Cell Leading Edge
Commentary

Cell (2011)

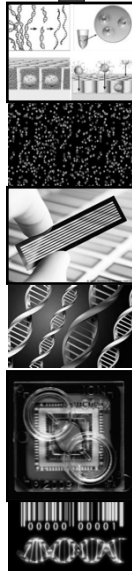
Genomics Reaches the Clinic: From Basic Discoveries to Clinical Impact

Teri A. Manolio¹ and Eric D. Green^{1,*}
¹National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892, USA
^{*}Correspondence: egreen@nhgri.nih.gov
DOI 10.1016/j.cell.2011.09.012

Today, more than ever, basic science research provides significant opportunities to advance our understanding about the genetic basis of human disease. Close interactions among laboratory, computational, and clinical research communities will be crucial to ensure that genomic discoveries advance medical science and, ultimately, improve human health.



The Future: Genome Sequencing



The Cancer Genome Atlas
Understanding genomics to improve cancer care

Launch Data Portal | Contact Us | For the Media

Search

Home About Cancer Genomics Cancers Selected for Study Research Highlights Publications News and Events About TCGA

About Cancer Genomics
Explore information and resources to improve your understanding of cancer genomics, the importance of tumor samples in genomic research and the role of cancer genomics in personalized medicine.
Learn More

Launch Data Portal
The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

Questions About Cancer
Visit www.cancer.gov
Call 1-800-4-CANCER
Use LiveHelp Online Chat

Multimedia Library
Images
Videos and Animations
Podcasts
Interactive

News Releases and Announcements
February 22, 2011
The Cancer Genome Atlas Announces Sessions at the AACR 2011 Annual Meeting

Leadership Update
February 2011
TCGA: A Future Arrived
Brad Ozenberger, Ph.D., TCGA Program Director for the National Human Genome Research Institute (NHGRI), talks about TCGA.

Cancer Genomics

The Cancer Genome Atlas
Understanding genomics to improve cancer care

Launch Data Portal | Contact Us | For the Media

Search

Home About Cancer Genomics Cancers Selected for Study Research Highlights Publications News and Events About TCGA

ICGC Data Portal Get Cancer Data Data Access Compliance Office Apply for Access to Controlled Data Contact Us Login | Create an ICGC account

International Cancer Genome Consortium

Home Cancer Genome Projects Committees Policies and Guidelines Media

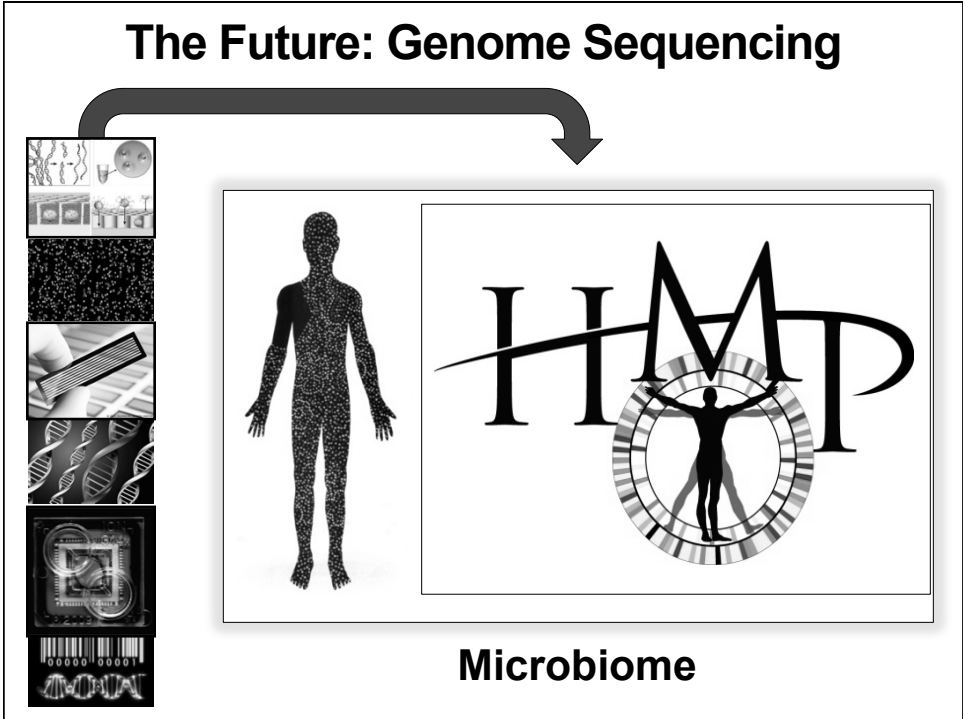
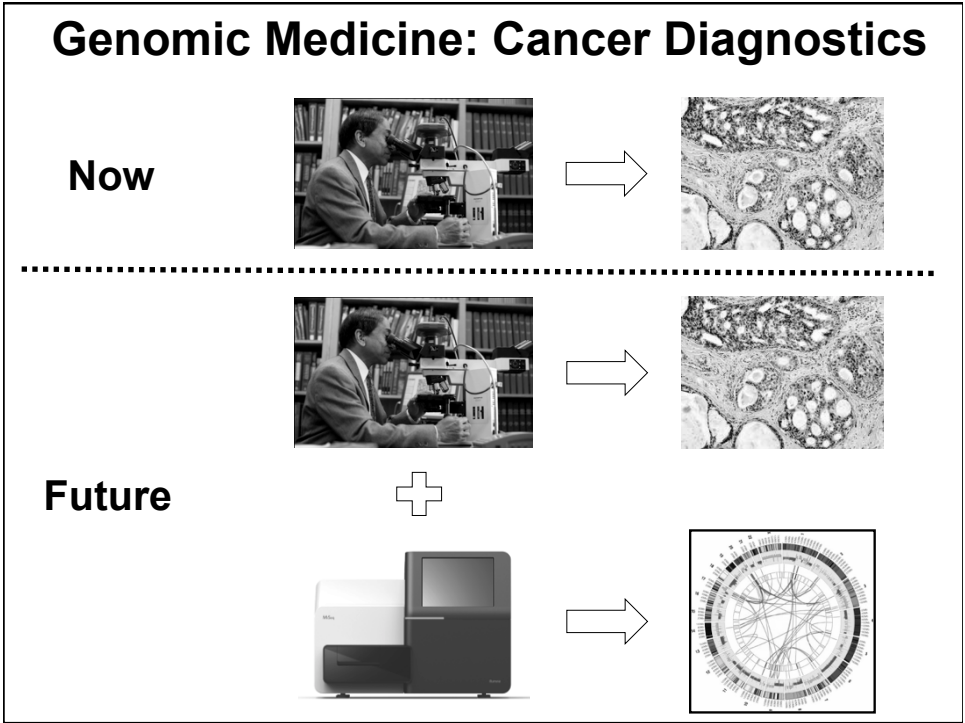
ICGC Cancer Genome Projects
Committed projects to date: 36

Sort by: Project

Bladder Cancer United States
Blood Cancer United States
Bone Cancer United Kingdom
Brain Cancer United States
Breast Cancer European Union / United Kingdom
Breast Cancer France

ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.
Read more

Launch Data Portal
Apply for Access to Controlled Data



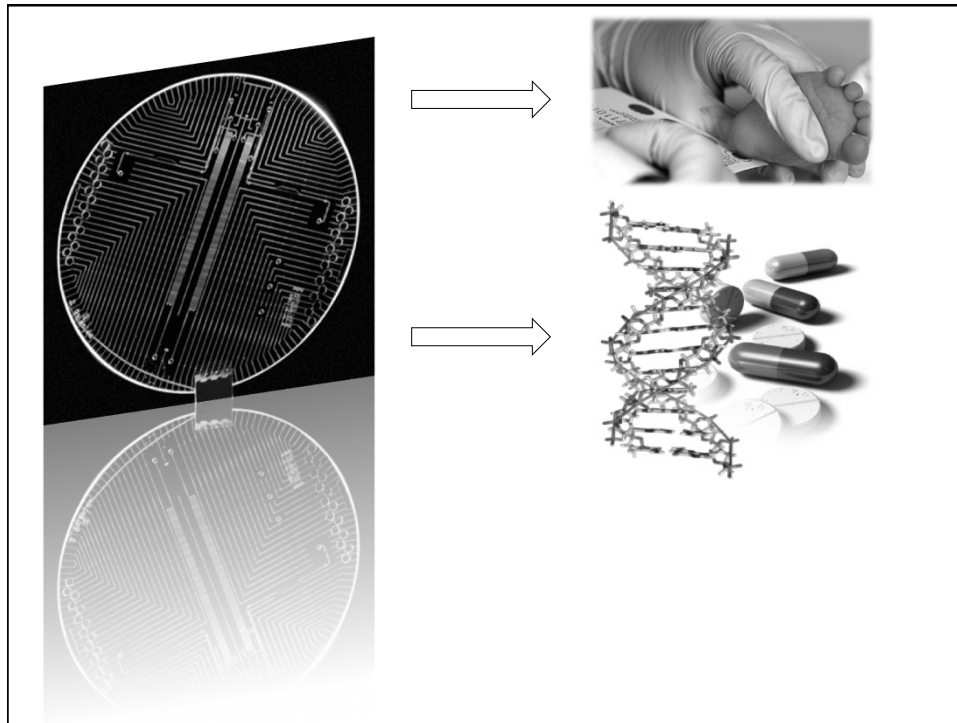
The screenshot shows the NIH Common Fund website for the Human Microbiome Project. At the top, it identifies the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) under the National Institutes of Health and U.S. Department of Health and Human Services. The main header reads 'The NIH Common Fund WE ACCELERATE DISCOVERY.' Below this is a navigation bar with links to HOME, COMMON FUND PROGRAMS, RESEARCH FUNDING, NEWS & EVENTS, HIGHLIGHTS, ABOUT, and CONTACTS. The page title is 'Human Microbiome Project'. The main content area features a large banner for the 'International Human Microbiome Consortium' with a navigation menu (Home, Organisation, Membership, 2012 Conference, Past meetings, Programs, Links) and a search bar. A 'Menu' sidebar lists various sections. The main text describes the consortium's goal: 'The goal of the IHMC is to work under a common set of principles and policies to study and understand the role of the human microbiome in the maintenance of health and causation of disease and to use that knowledge to improve the ability to prevent and treat disease.' It also lists past meetings from Paris 2005 to Shenzhen 2010. A 'Login' box is on the right.

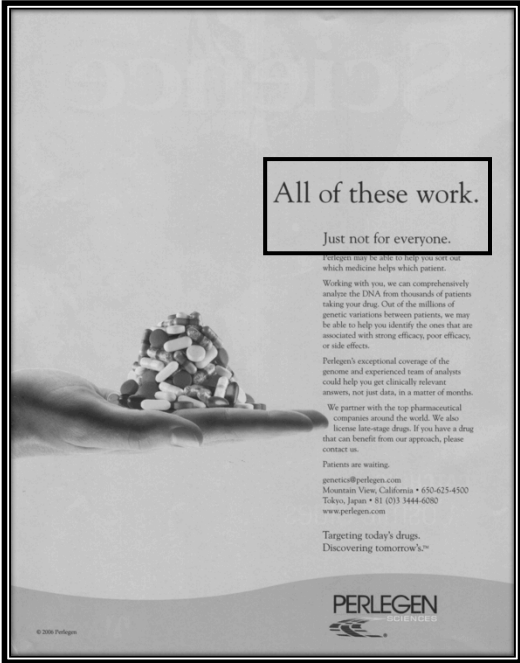
Genomic Medicine: Clinical Microbiology

Now

Future

The diagram illustrates the transition from current clinical microbiology to future genomic medicine. It shows a scientist working with petri dishes and a microscope, representing current methods. Below this, a flow diagram shows a laboratory instrument (likely a sequencer) leading to a microarray chip, which then leads to a circular genomic map, representing the future of genomic medicine in clinical microbiology.





All of these work.
Just not for everyone.

Perlegen can be able to help you sort out which medicine helps which patient.

Working with you, we can comprehensively analyze the DNA from thousands of patients taking your drug. Out of the millions of genetic variations between patients, we may be able to help you identify the ones that are associated with strong efficacy, poor efficacy, or side effects.

Perlegen's exceptional coverage of the genome and experienced team of analysts could help you get clinically relevant answers, not just data, in a matter of months.

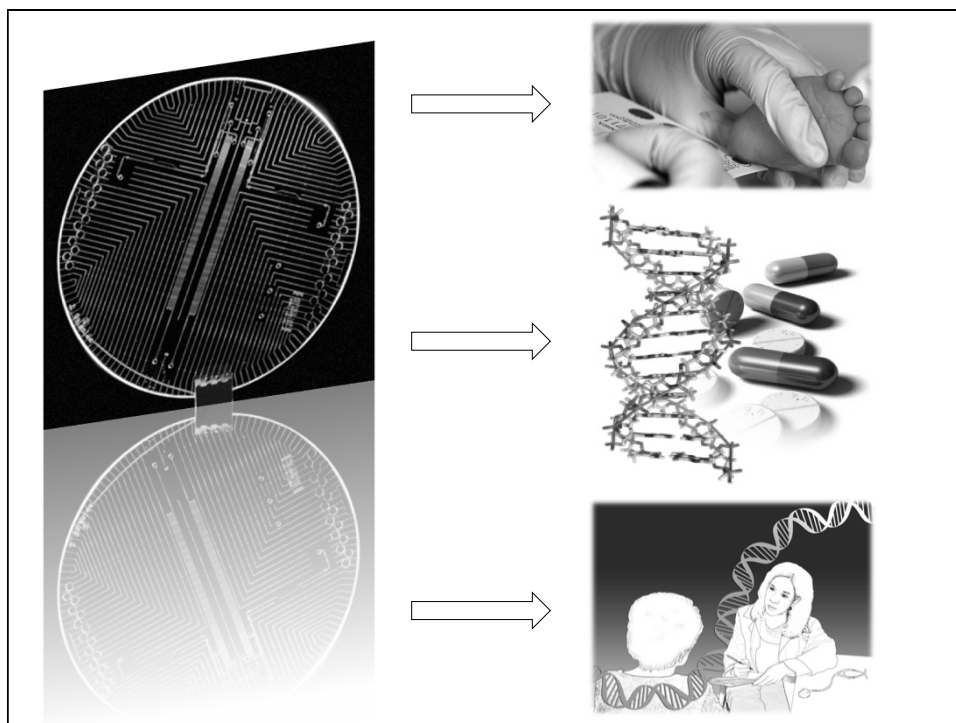
We partner with the top pharmaceutical companies around the world. We also license late-stage drugs. If you have a drug that can benefit from our approach, please contact us.

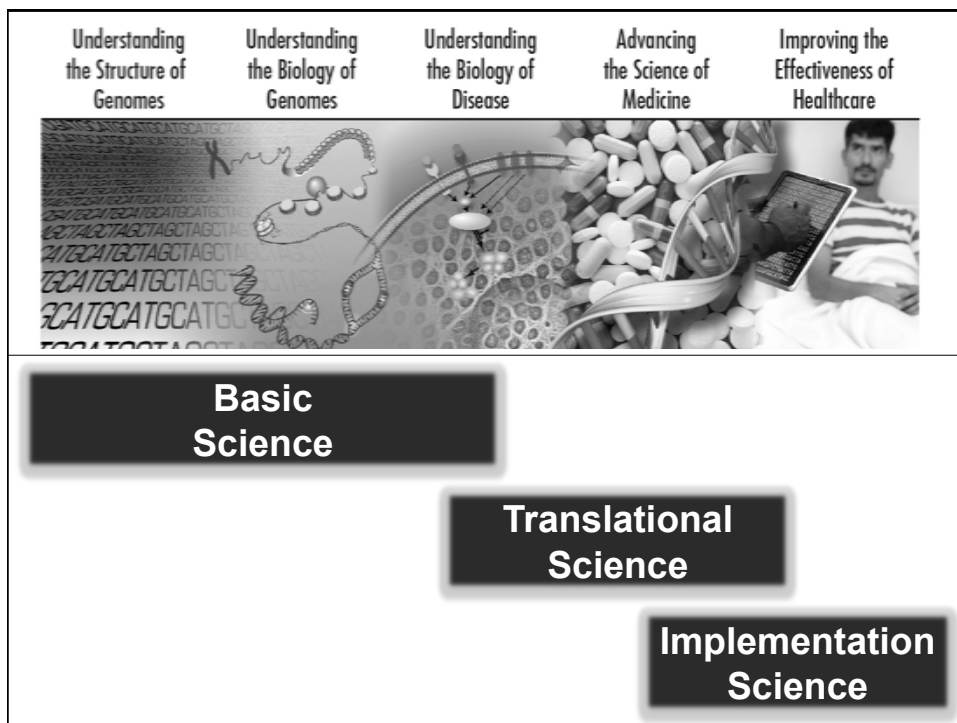
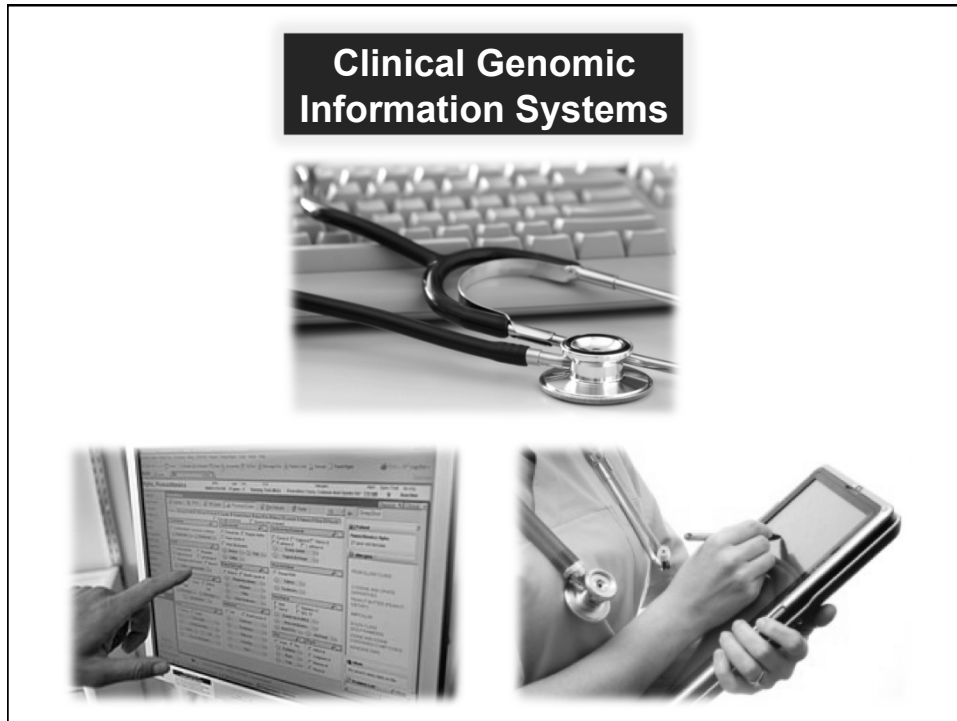
Patients are waiting.
genetics@perlegen.com
Mountain View, California • 650-625-4500
Tokyo, Japan • 81 (0)3 3444-6000
www.perlegen.com

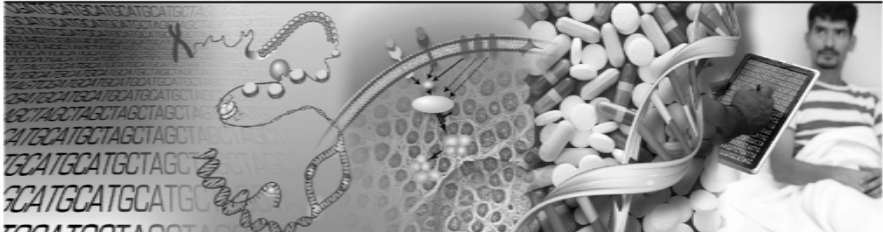
Targeting today's drugs.
Discovering tomorrow's.™

PERLEGEN
genetics

© 2009 Perlegen





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
				
<p>A pessimist sees the difficulty in every opportunity. An optimist sees the opportunity in every difficulty.</p> <p><i>--Winston Churchill</i></p>				

