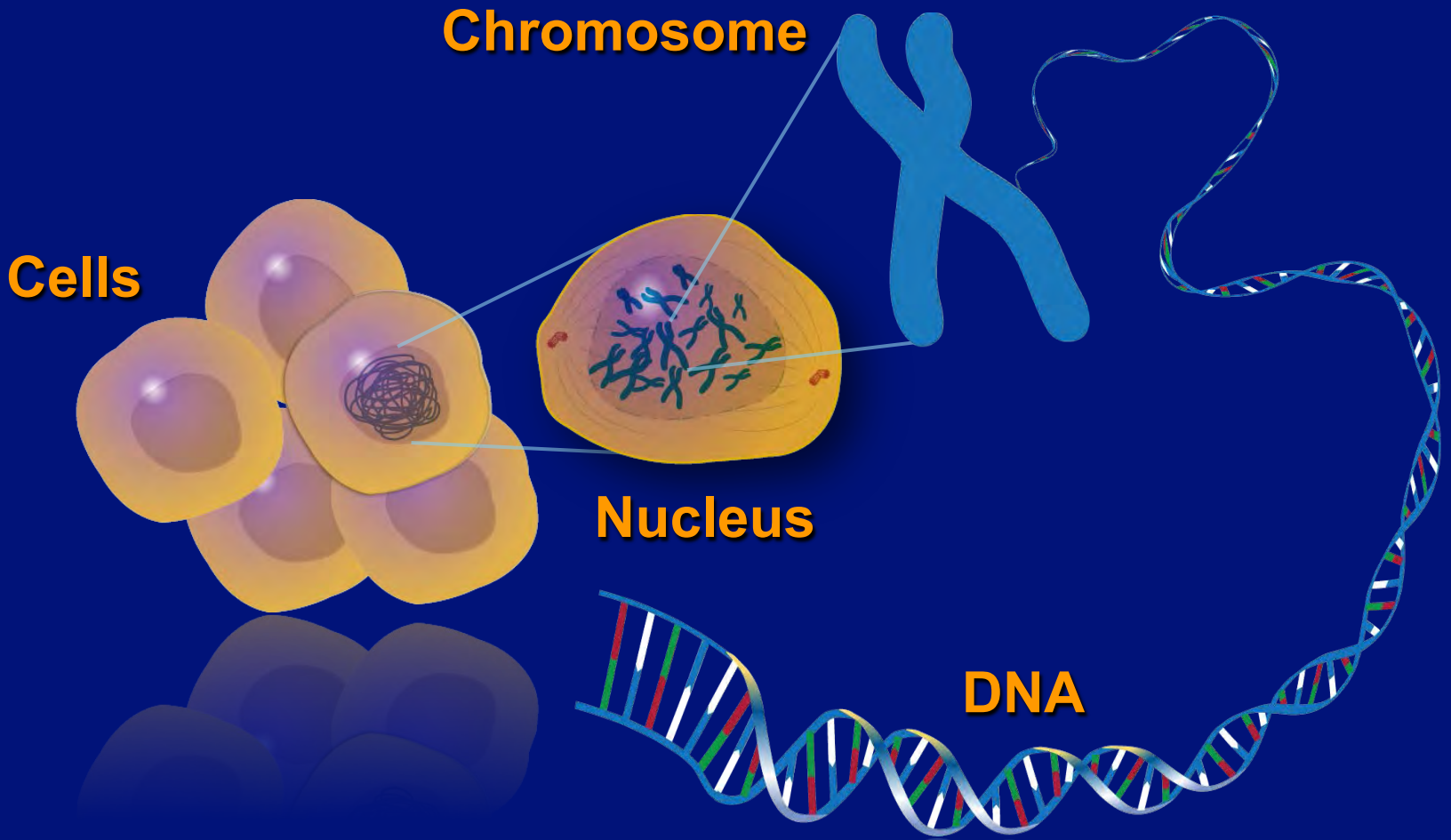
Human Genomics a Decade after the Human Genome Project: Opportunities and Challenges

Eric Green, M.D., Ph.D.

Director, NHGRI

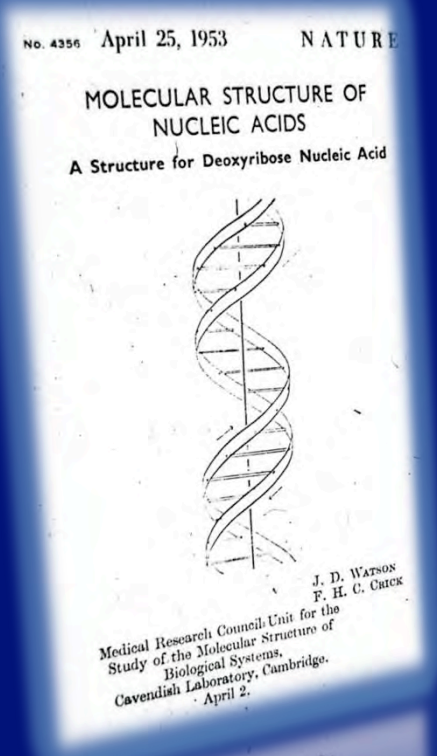
NIH National Human Genome Research Institute

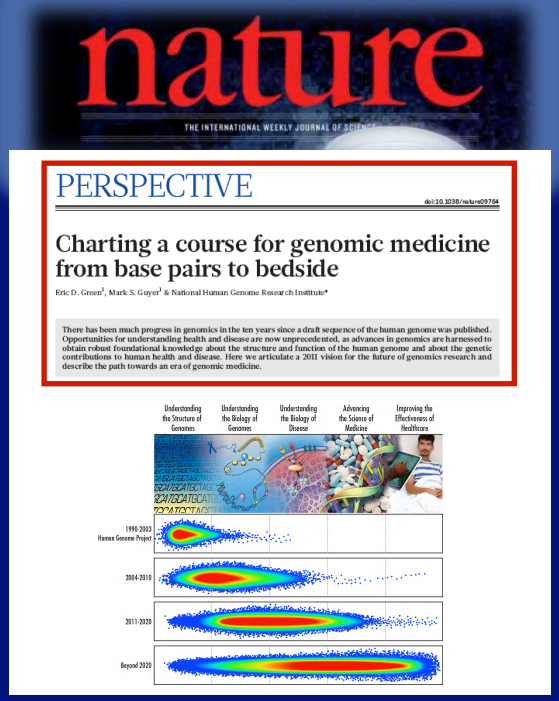
The Human Genome

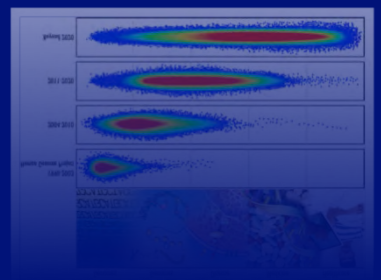


Human Genome:
~3 billion bases ('letters')

Human Genomics Landscape







Past → **Present** → **Future**

The Origin of "Genomics": 1987

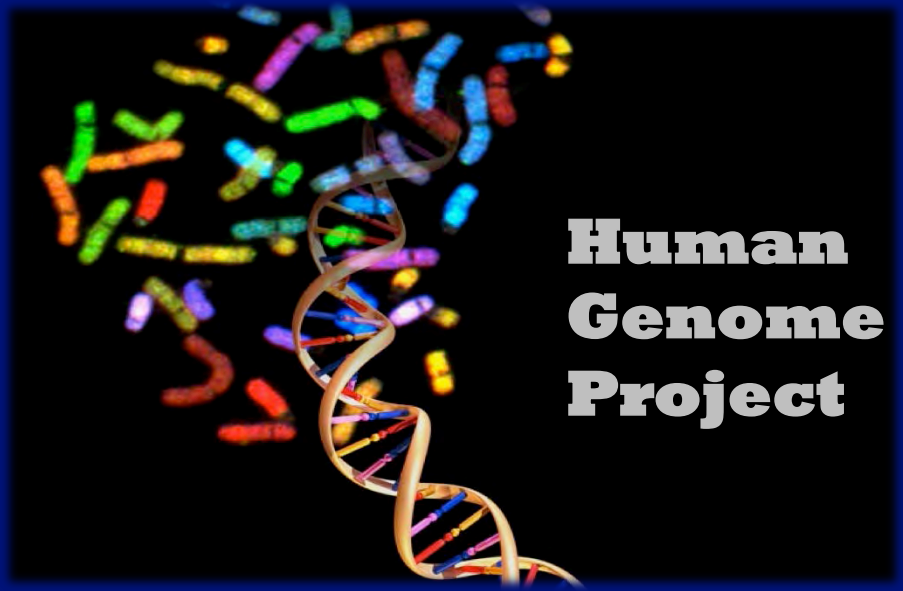
EDITORIAL

A New Discipline, A New Name, A New Journal

Genomics (1987)

"For the newly developing discipline of [genome] mapping/sequencing (including the analysis of the information), we have adopted the term GENOMICS… The new discipline is born from a marriage of molecular and cell biology with classical genetics and is fostered by computational science."

October, 1990



Human Genome Project Begins

April, 2003

Human Genome Project Ends

Myriad Applications of Genomics

Health, Disease, & Medicine

NIH

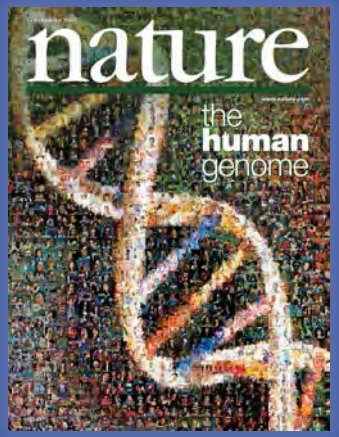
Turning discovery into health

Advancing human health through genomics research

Genomic Medicine

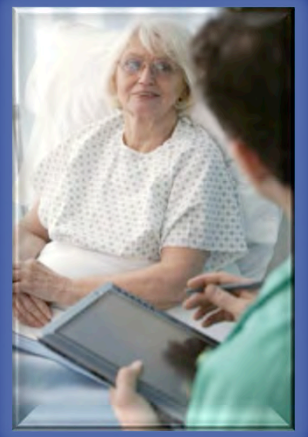
An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the other implications of that clinical use

The Path to Genomic Medicine



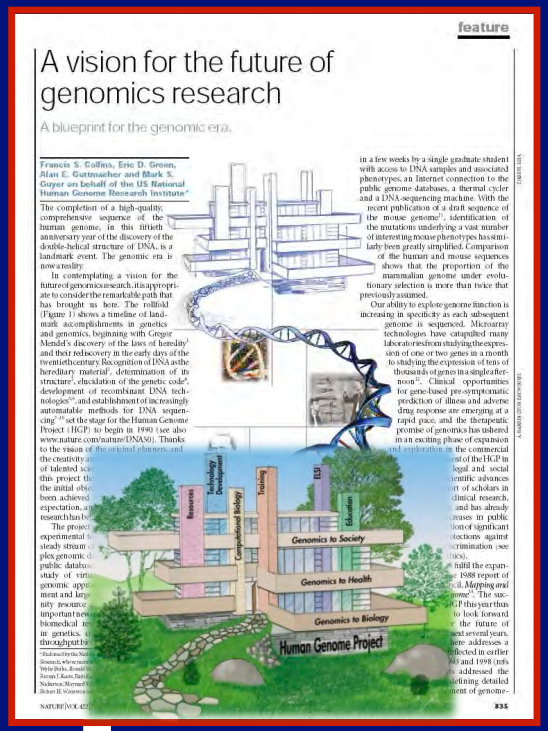
Human Genome Project

→ → ? → →



Realization of Genomic Medicine

✓ *"Fulfilling the Promise"* ?



feature

A vision for the future of genomics research

A blueprint for the genomic era.

Francis S. Collins, Eric D. Green, Alan E. Guttmacher and Mark S. Guyer on behalf of the US National Human Genome Research Institute*

The completion of a high-quality, comprehensive sequence of the human genome, in this fiftieth anniversary year of the discovery of the double-helical structure of DNA, is a landmark event. The genomic era is now a reality.

In contemplating a vision for the future of genomics research, it is appropriate to consider the remarkable path that has brought us here. The rollfold (Figure 1) shows a timeline of landmark accomplishments in genetics and genomics, beginning with Gregor Mendel's discovery of the laws of heredity[1] and their rediscovery in the early days of the twentieth century. Recognition of DNA as the hereditary material[2], determination of its structure[3], elucidation of the genetic code[4], development of recombinant DNA technologies[5,6], and establishment of increasingly automatable methods for DNA sequencing[7–10] set the stage for the Human Genome Project (HGP) to begin in 1990 (see also www.nature.com/nature/DNA50). Thanks to the vision of the original planners, and the creativity a… of talented sci… this project th… the initial obje… been achieved… expectation, a… research has be…

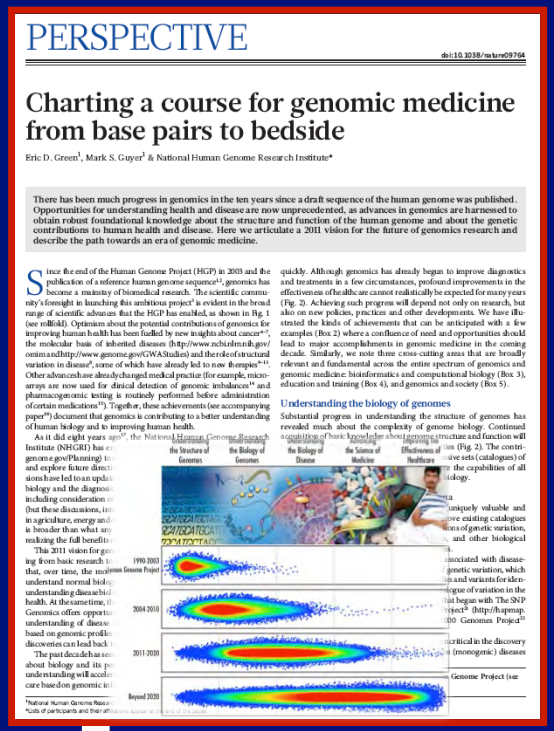
The project … experimental … steady stream … plex genomic … public databas… study of virtu… genomic appr… ment and larg… nity resource… important new… biomedical re… in genetics, … throughput bi…

in a few weeks by a single graduate student with access to DNA samples and associated phenotypes, an Internet connection to the public genome databases, a thermal cycler and a DNA-sequencing machine. With the recent publication of a draft sequence of the mouse genome[11], identification of the mutations underlying a vast number of interesting mouse phenotypes has similarly been greatly simplified. Comparison of the human and mouse sequences shows that the proportion of the mammalian genome under evolutionary selection is more than twice that previously assumed.

Our ability to explore genome function is increasing in specificity as each subsequent genome is sequenced. Microarray technologies have catapulted many laboratories from studying the expression of one or two genes in a month to studying the expression of tens of thousands of genes in a single afternoon[12]. Clinical opportunities for gene-based pre-symptomatic prediction of illness and adverse drug response are emerging at a rapid pace, and the therapeutic promise of genomics has unbreid in an exciting phase of expansion and exploration in the commercial …ent of the HGP in …legal and social …ientific advances …ort of scholars in …clinical research, …and has already …reases in public …tion of significant …tections against …crimination (see …ucts).

…fulfil the expan… …e 1988 report of …cal, *Mapping and …quence*[13]. The suc… …GP this year thus … to look forward … the future of … next several years, …here addresses a …flected in earlier …03 and 1998 (refs … addressed the …defining detailed …ment of genome-

Nature



PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], 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[9–12]. 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 e… genome.gov/Planning) to… and explore future direct… sions have led to an upda… biology and the diagnosi… including consideration … (but these discussions, int… in agriculture, energy and … is broader than what any … realizing the full benefits …

This 2011 vision for ge… ing from basic research t… that, over time, the mo… understand normal biolo… understanding disease biol… health. At the same time, t… Genomics offers opportu… understanding of disease … based on genomic profile… discoveries can lead back …

The past decade has see… about biology and its po… understanding will accele… care based on genomic in…

quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of the 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 …ies (Fig. 2). The contri… …ive sets (catalogues) of … the capabilities of all …iology.

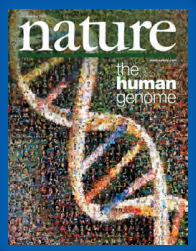
…a … …uniquely valuable and … …ove existing catalogues … …es of genetic variation, … and other biological …

…associated with disease- … …genetic variation, which … …s and variants for iden… …logue of variation in the … …at began with The SNP … …roject[18] (http://hapmap. … …00 Genomes Project[19] …

…critical in the discovery … …n (monogenic) diseases …

… Genome Project (see …

Nature



Base Pairs to Bedside

2003

2011

Health

NHGRI Strategic Vision for Genomics

PERSPECTIVE

doi:10.1038/nature09764

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], 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). ▶

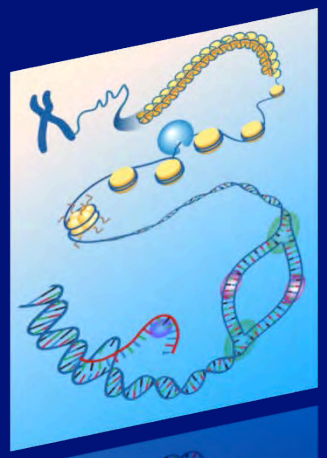
[1]National Human Genome Research Institute, National Institutes of Health, 31 Center Dr., Bethesda, Maryland 20892-2152, USA.
*Lists of participants and their affiliations appear at the end of the paper.

February 2011

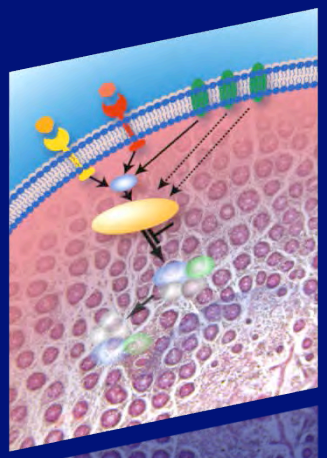
Five Domains of Genomics Research

Understanding the Structure of Genomes

Understanding the Biology of Genomes

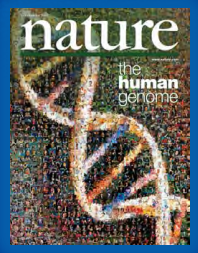


Understanding the Biology of Disease



Advancing the Science of Medicine

Improving the Effectiveness of Healthcare



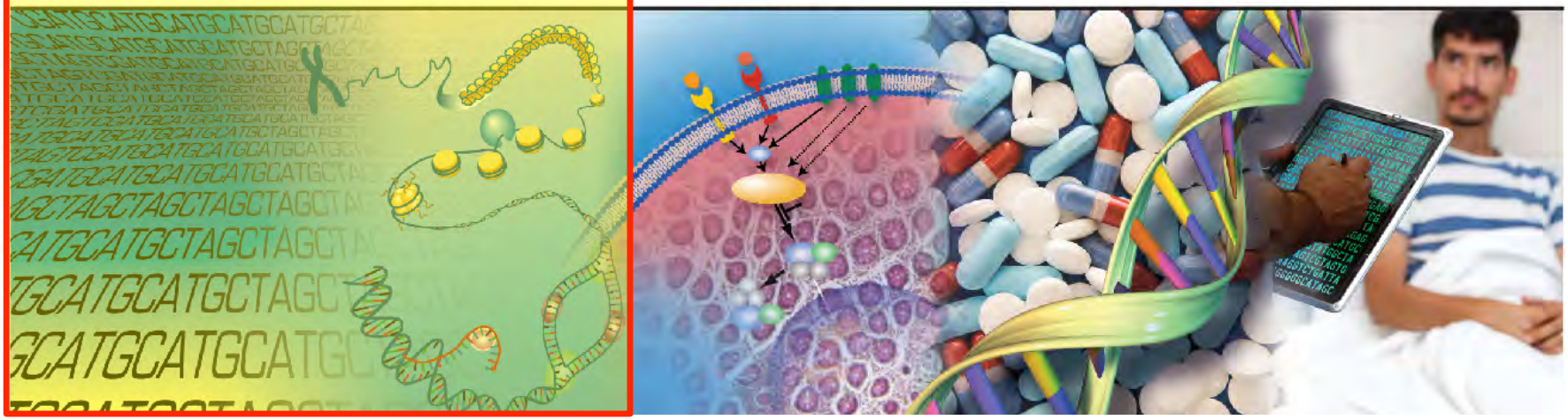
Understanding the Structure of Genomes

Understanding the Biology of Genomes

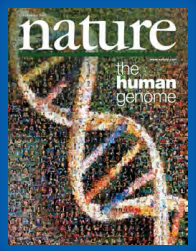
Understanding the Biology of Disease

Advancing the Science of Medicine

Improving the Effectiveness of Healthcare



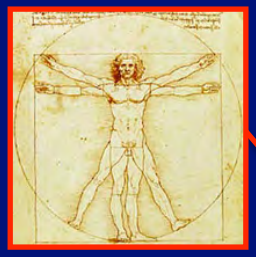
Function of the Human Genome Sequence

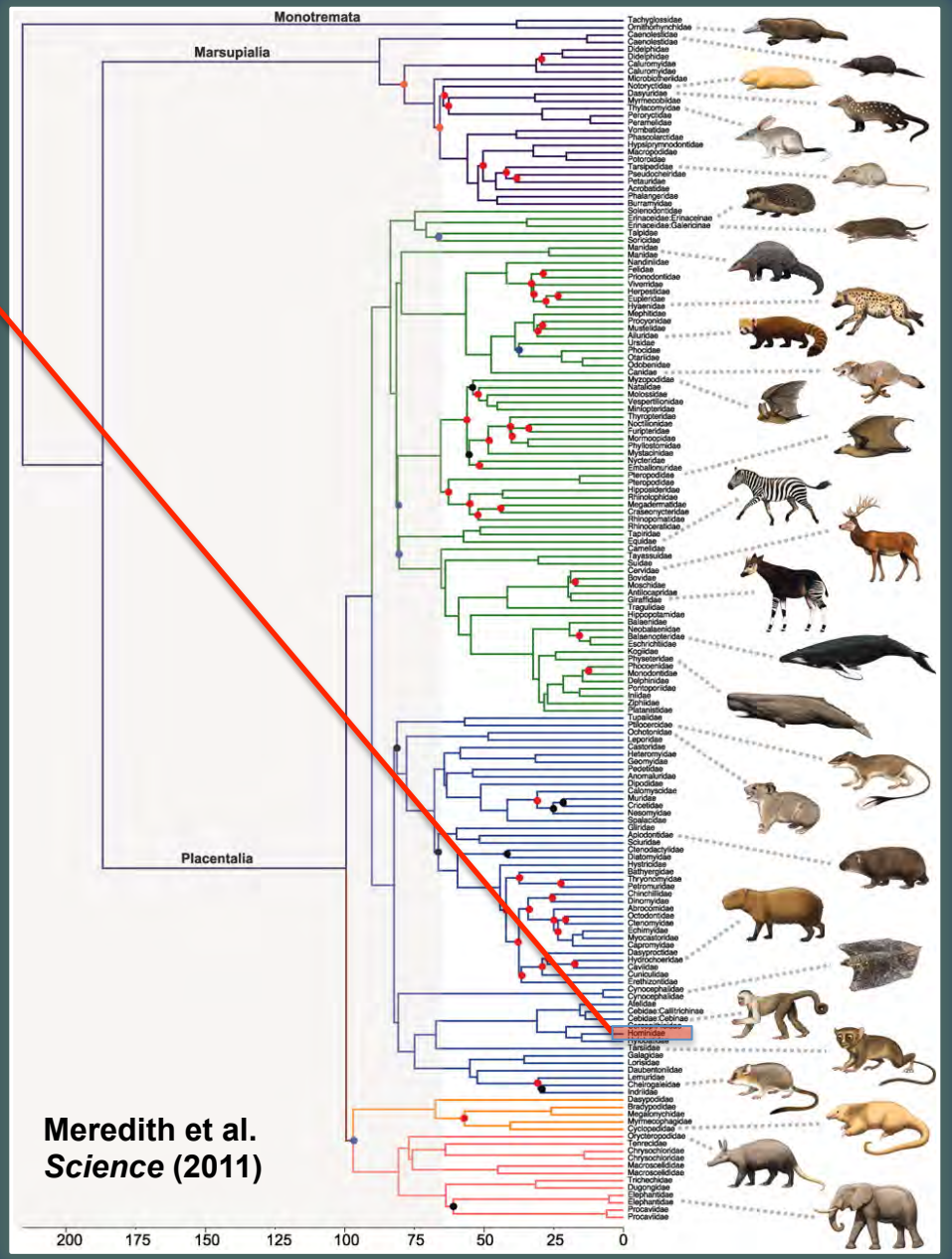


~3,000 bp (0.0001%) of Human Genome Sequence

TGCCGCGGAACTTTTCGGCTCTCTAAGGCTGTATTTTGATATACGAAAGGCACATTTTCCTTCCCTTTTCAAAATGCACCTTGCAAACGTAACAG
GAACCCGACTAGGATCATCGGGAAAAGGAGGAGGAGGAGGAAGGCAGGCTCCGGGGAAGCTGGTGGCAGCGGGTCCTGGGTCTGGCGGACCCTGA
CGCGAAGGAGGGTCTAGGAAGCTCTCCGGGGAGCCGGTTCTCCCGCCGGTGGCTTCTTCTGTCCTCCAGCGTTGCCAACTGGACCTAAAGAGAGG
CCGCGACTGTCGCCCACCTGCGGGATGGGCCTGGTGCTGGGCGGTAAGGACACGGACCTGGAAGGAGCGCGCGCGAGGGAGGGAGGCTGGGAGTC
AGAATCGGGAAAGGGAGGTGCGGGGCGGCGAGGGAGCGAAGGAGGAGAGGAGGAAGGAGCGGGAGGGGTGCTGGCGGGGGTGCGTAGTGGGTGGA
GAAAGCCGCTAGAGCAAATTTGGGGCCGGACCAGGCAGCACTCGGCTTTTAACCTGGGCAGTGAAGGCGGGGGAAAGAGCAAAAGGAAGGGGTGG
TGTGCGGAGTAGGGGTGGGTGGGGGGAATTGGAAGCAAATGACATCACAGCAGGTCAGAGAAAAAGGGTTGAGCGGCAGGCACCCAGAGTAGTAG
GTCTTTGGCATTAGGAGCTTGAGCCCAGACGGCCCTAGCAGGGACCCCAGCGCCCGAGAGACCATGCAGAGGTCGCCTCTGGAAAAGGCCAGCGT
TGTCTCCAAACTTTTTTTCAGGTGAGAAGGTGGCCAACCGAGCTTCGGAAAGACACGTGCCCACGAAAGAGGAGGGCGTGTGTATGGGTTGGGTT
TGGGGTAAAGGAATAAGCAGTTTTTAAAAAGATGCGCTATCATTCATTGTTTTGAAAGAAAATGTGGGTATTGTAGAATAAAACAGAAAGCATTA
AGAAGAGATGGAAGAATGAACTGAAGCTGATTGAATAGAGAGCCACATCTACTTGCAACTGAAAAGTTAGAATCTCAAGACTCAAGTACGCTACT
ATGCACTTGTTTTATTTCATTTTTCTAAGAAACTAAAAATACTTGTTAATAAGTACCTAAGTATGGTTTATTGGTTTTCCCCCTTCATGCCTTGG
ACACTTGATTGTCTTCTTGGCACATACAGGTGCCATGCCTGCATATAGTAAGTGCTCAGAAAACATTTCTTGACTGAATTCAGCCAACAAAAATT
TTGGGGTAGGTAGAAAATATATGCTTAAAGTATTTATTGTTATGAGACTGGATATATCTAGTATTTGTCACAGGTAAATGATTCTTCAAAAATTG
AAAGCAAATTTGTTGAAATATTTATTTTGAAAAAAGTTACTTCACAAGCTATAAATTTTAAAAGCCATAGGAATAGATACCGAAGTTATATCCAA
CTGACATTTAATAAATTGTATTCATAGCCTAATGTGATGAGCCACAGAAGCTTGCAAACTTTAATGAGATTTTTTAAAATAGCATCTAAGTTCGG
AATCTTAGGCAAAGTGTTGTTAGATGTAGCACTTCATATTTGAAGTGTTCTTTGGATATTGCATCTACTTTGTTCCTGTTATTATACTGGTGTGA
ATGAATGAATAGGTACTGCTCTCTCTTGGGACATTACTTGACACATAATTACCCAATGAATAAGCATACTGAGGTATCAAAAAAGTCAAATATGT
TATAAATAGCTCATATATGTGTGTAGGGGGGAAGGAATTTAGCTTTCACATCTCTCTTATGTTTAGTTCTCTGCATGTGCAGTTAATCCTGGAAC
TCCGGTGCTAAGGAGAGACTGTTGGCCCTTGAAGGAGAGCTCCTCCCTGTGGATGAGAGAGAAGGACTTTACTCTTTGGAATTATCTTTTTGTGT
TGATGTTATCCACCTTTTGTTACTCCACCTATAAAATCGGCTTATCTATTGATCTGTTTTCCTAGTCCTTATAAAGTCAAAATGTTAATTGGCAT
AAATTATAGACTTTTTTTAGCAGAGAACTTTGAGGAACCTAAATGCCAACCAGTCTAAAAATGCAGTTTTCAGAAGAATGAATATTTCATGGATA
GTTCTAAATACTAATGAACTTTAAAATAGCTTACTATTGATCTGTCAAAGTGGGTTTTTATATAATTTTCTTTTTACAAATCACCTGACACATTT
AATATAGGTTAAAAAATGCTATCAGGCTGGTTTGCAAAGAAAATGTATTACAAAGGCTGCTAAGTGTGTTAAGAGCATACTCATTTCTGTTCTCC
AAAATATTTCATAAGGTGCTTTAAGAATAGGTATGTTTTTAAAAGTTAAGTTCCTACTATTTATAGGAACTGACAATCACCTAAAATACCAATGA
TTACAAACTTCCTTCTGGCCTTCTGGACTGCAATTCTAAAAGTGTAAAAAACATATTTTCTGCATTAAGTTAGGCAGTATTGCTTAGTTTTCAAA
GTGGTAGGCTTTGGAGTCAGATTATTTTGATTCAGATCCTACATCTACTGTTTAGTAGCTCTGTTGCCTGAGGCAGGTCCCTTAACATCTCTGTG
TGTGACTTGACCTTTAAAATTTGGAGACTGTCATAGGGGTTAATCCCTTGAGAAAATGAATGTGAAAAGTTAGCCTAATGTTAACTGCTATTATT
ATGGATTACCATATTTTCACATTCATCACAGTACATGCACCTTGTTAATATAAGATGCTCAATTCATCTTTGAGTATAATTTTGTGACTCTCAAT
CTGGATATGCAATGAGTGGGCCTGTATGAGAATTTAATTTATGAAAAATTGTGTTTCACATGGCCTTACCAGATATACAGGAAACACGTCACATG
TTTCTATTGTATGTTGTTAAATGCCTTAGAATTTAACTTTCTGAATAGGATCCCTTCAGTTTGAGAGTCATAAAAGAGTAAAATTATTATGGTAT

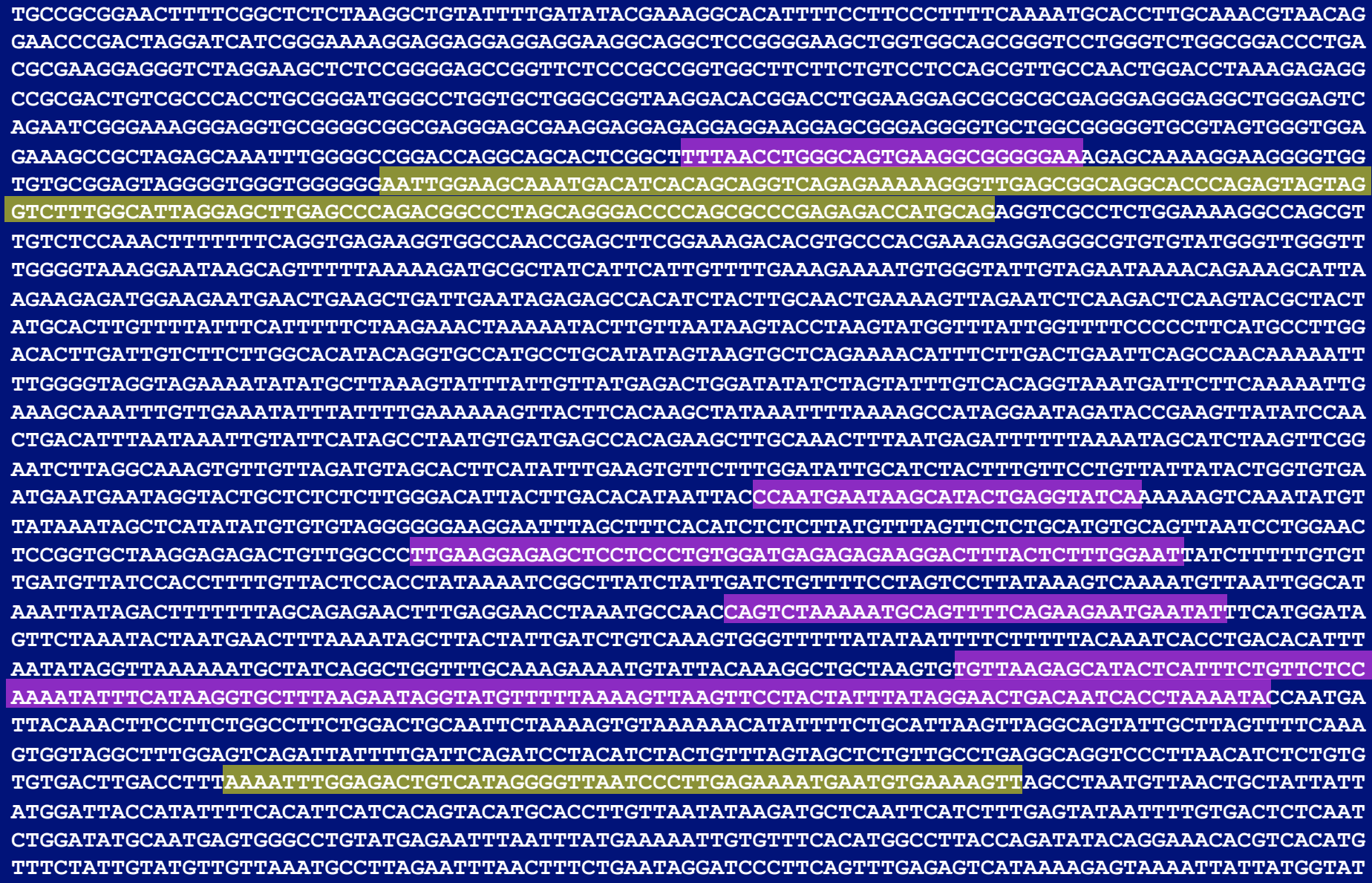
Comparative Genome Sequencing



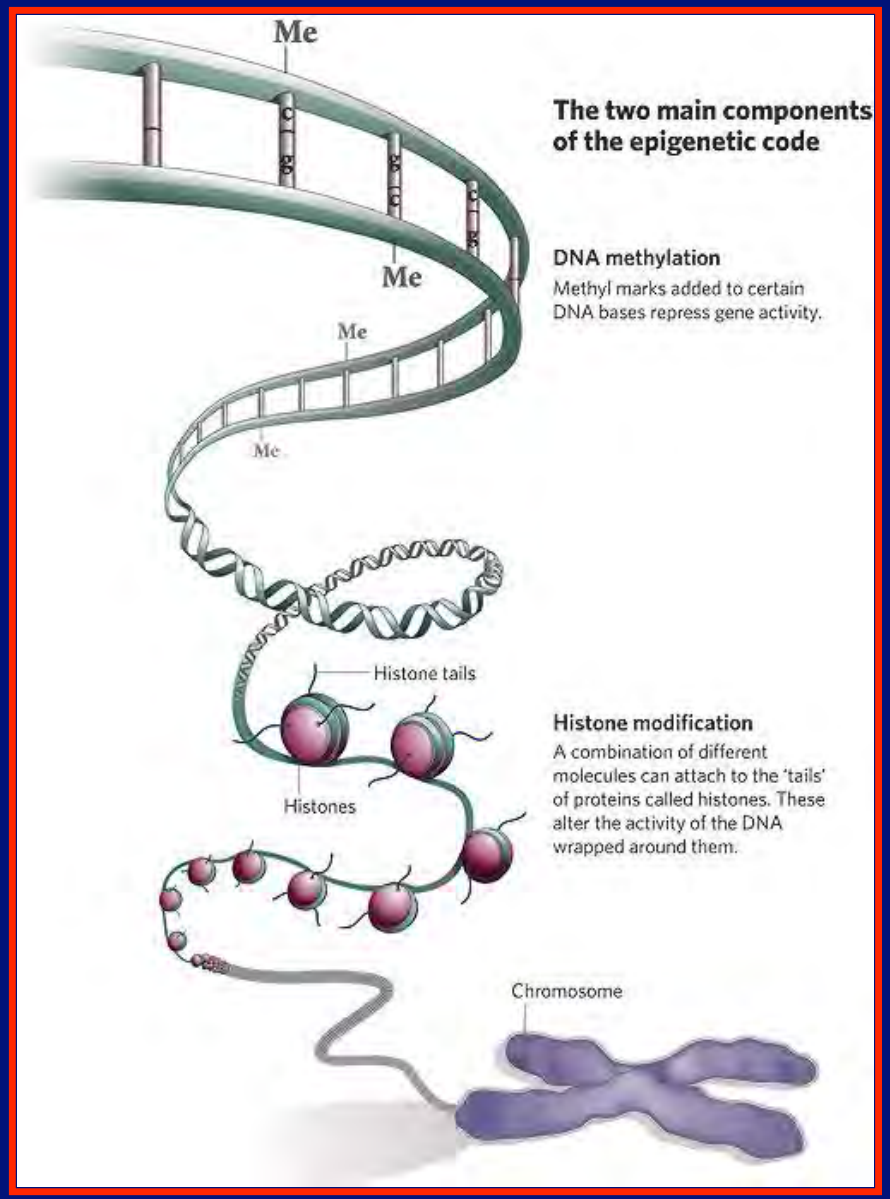


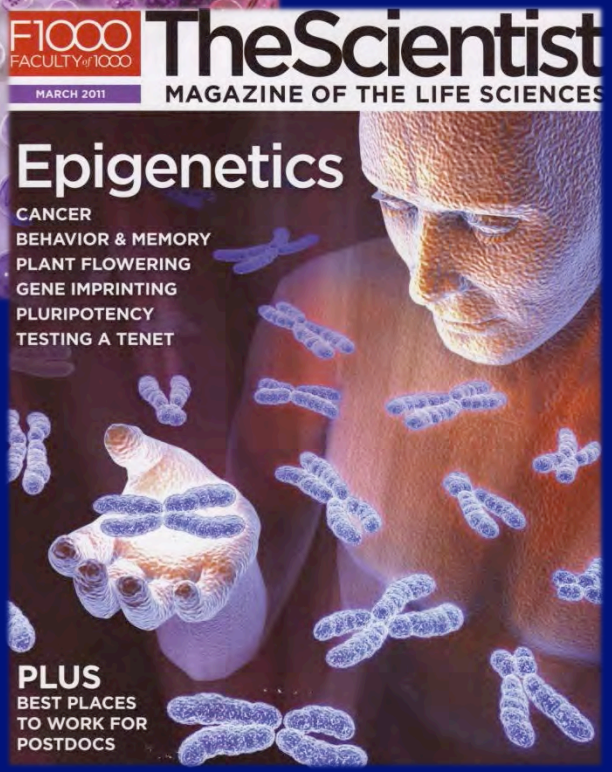
Meredith et al.
Science (2011)

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

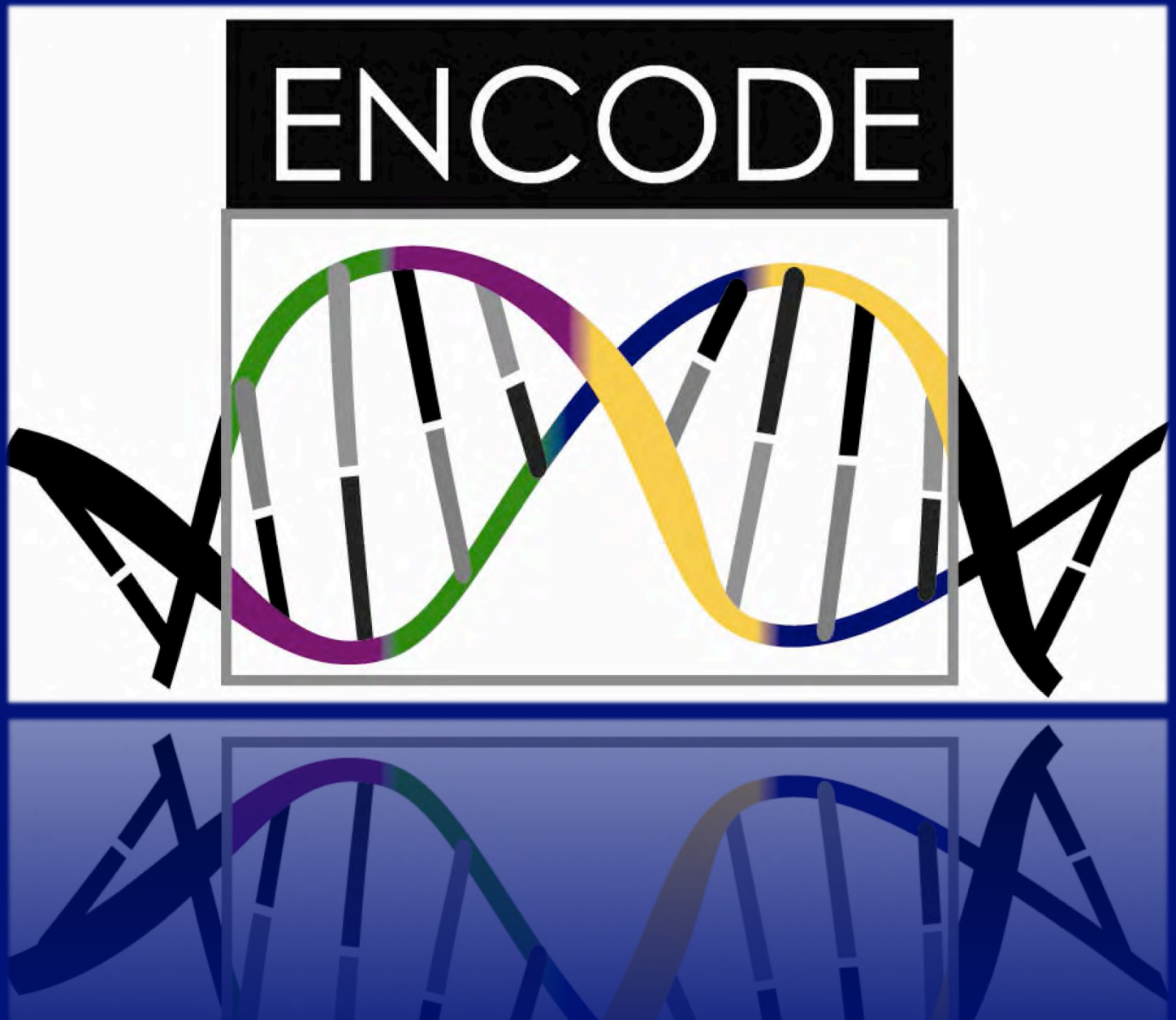


The Epigenomic Landscape

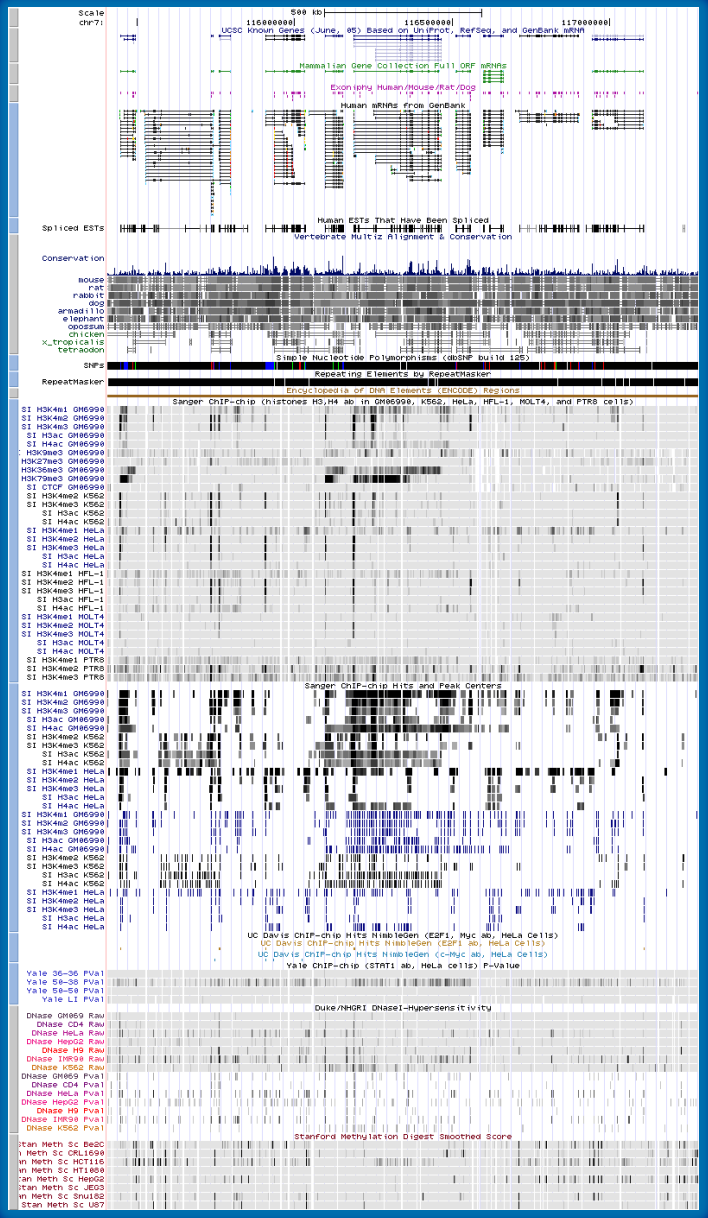




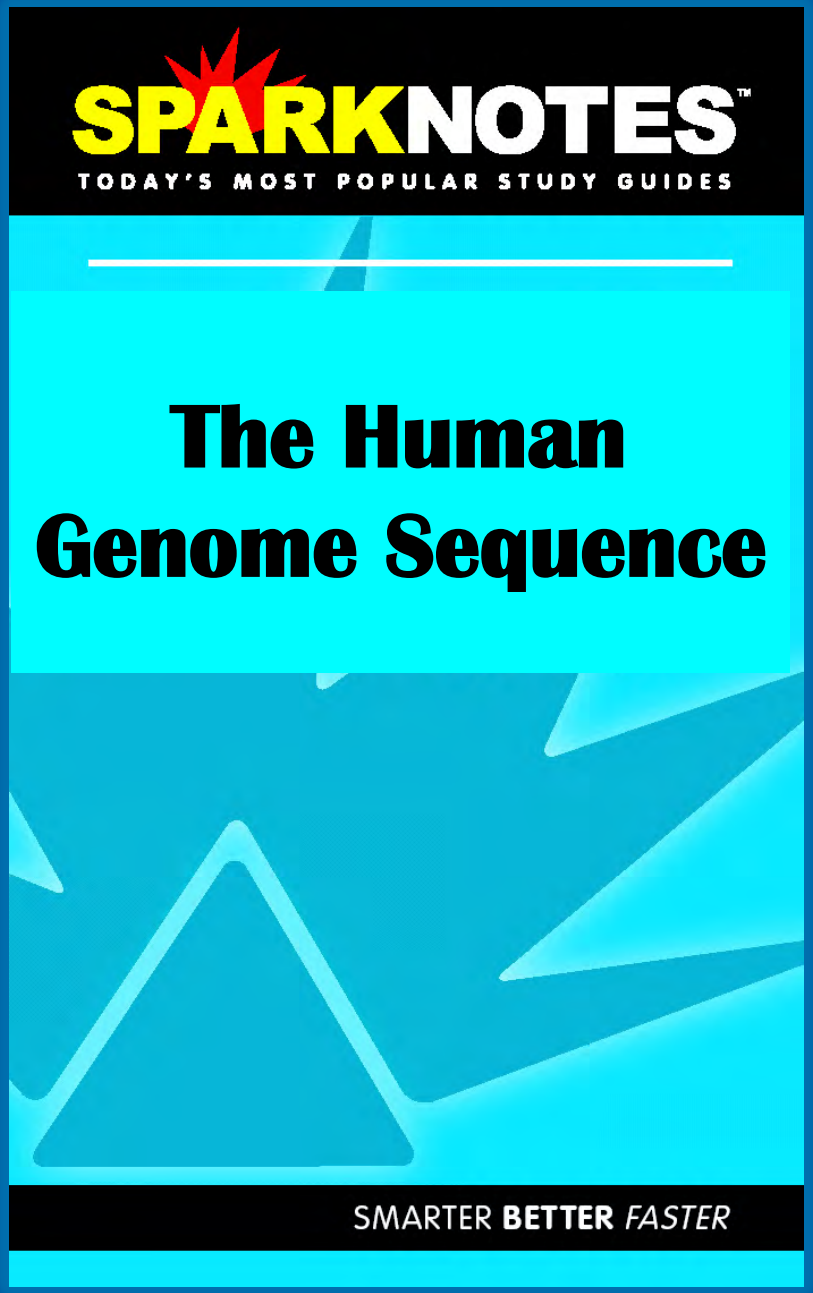
ENCyclopedia Of DNA Elements



A ‘GPS’ View of the Human Genome



TGCCGCGGAACTTTTCGGCTCTCTAAGGCTGTATTTTGATAT
ACGAAAGGCACATTTTCCTTCCCTTTTCAAAATGCACCTTGC
AAACGTAACAGGAACCCGACTAGGATCATCGGGAAAAGGAGG
AGGAGGAGGAAGGCAGGCTCCGGGGAAGCTGGTGGCAGCGGG
TCCTGGGTCTGGCGGACCCTGACGCGAAGGAGGGTCTAGGAA
GCTCTCCGGGGAGCCGGTTCTCCCGCCGGTGGCTTCTTCTGT
CCTCCAGCGTTGCCAACTGGACCTAAAGAGAGGCCGCGACTG
TCGCCCACCTGCGGGATGGGCCTGGTGCTGGGCGGTAAGGAC
ACGGACCTGGAAGGAGCGCGCGCGAGGGAGGGAGGCTGGGAG
TCAGAATCGGGAAAGGGAGGTGCGGGGCGGCGAGGGAGCGAA
GGAGGAGAGGAGGAAGGAGCGGGAGGGGTGCTGGCGGGGGTG
CGTAGTGGGTGGAGAAAGCCGCTAGAGCAAATTTGGGGCCGG
ACCAGGCAGCACTCGGCTTTTAACCTGGGCAGTGAAGGCGGG
GGAAAGAGCAAAAGGAAGGGGTGGTGTGCGGAGTAGGGGTGG
GTGGGGGGAATTGGAAGCAAATGACATCACAGCAGGTCAGAG
AAAAAGGGTTGAGCGGCAGGCACCCAGAGTAGTAGGTCTTTG
GCATTAGGAGCTTGAGCCCAGACGGCCCTAGCAGGGACCCCA
GCGCCCGAGAGACCATGCAGAGGTCGCCTCTGGAAAAGGCCA
GCGTTGTCTCCAAACTTTTTTTCAGGTGAGAAGGTGGCCAAC
CGAGCTTCGGAAAGACACGTGCCCACGAAAGAGGAGGGCGTG
TGTATGGGTTGGGTTTGGGGTAAAGGAATAAGCAGTTTTTAA
AAAGATGCGCTATCATTCATTGTTTTGAAAGAAAATGTGGGT
ATTGTAGAATAAAACAGAAAGCATTAAGAAGAGATGGAAGAA
TGAACTGAAGCTGATTGAATAGAGAGCCACATCTACTTGCAA
CTGAAAAGTTAGAATCTCAAGACTCAAGTACGCTACTATGCA
CTTGTTTTATTTCATTTTTCTAAGAAACTAAAAATACTTGTT
AATAAGTACCTAAGTATGGTTTATTGGTTTTCCCCCTTCATG
CCTTGGACACTTGATTGTCTTCTTGGCACATACAGGTGCCAT
GCCTGCATATAGTAAGTGCTCAGAAAACATTTCTTGACTGAA
TTCAGCCAACAAAAATTTTGGGGTAGGTAGAAAATATATGCT
TAAAGTATTTATTGTTATGAGACTGGATATATCTAGTATTTG
TCACAGGTAAATGATTCTTCAAAAATTGAAAGCAAATTTGTT
GAAATATTTATTTTGAAAAAAGTTACTTCACAAGCTATAAAT
TTTAAAAGCCATAGGAATAGATACCGAAGTTATATCCAACTG
ACATTTA



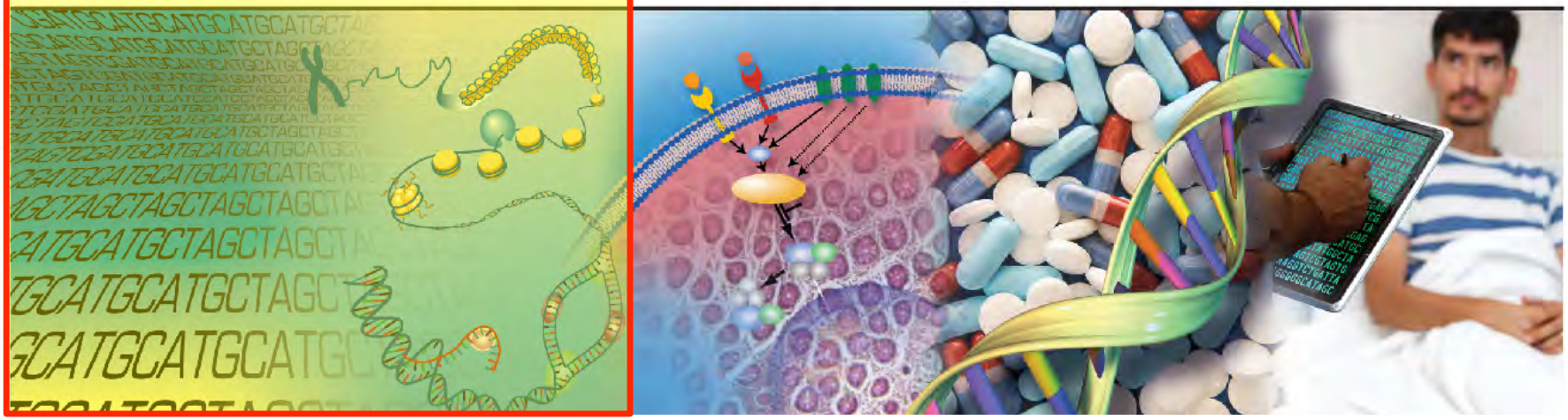
Understanding the Structure of Genomes

Understanding the Biology of Genomes

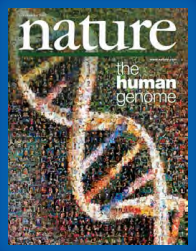
Understanding the Biology of Disease

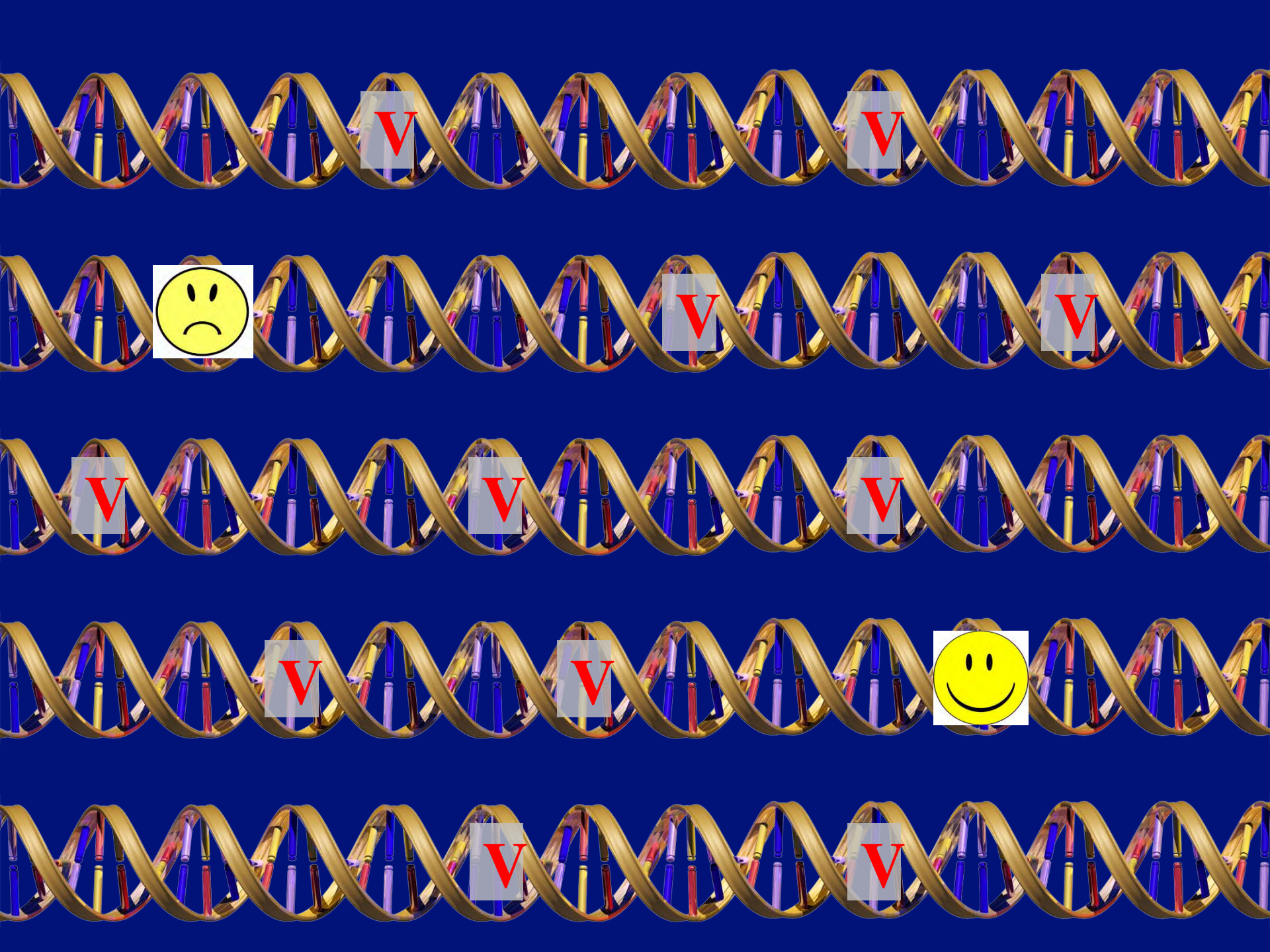
Advancing the Science of Medicine

Improving the Effectiveness of Healthcare



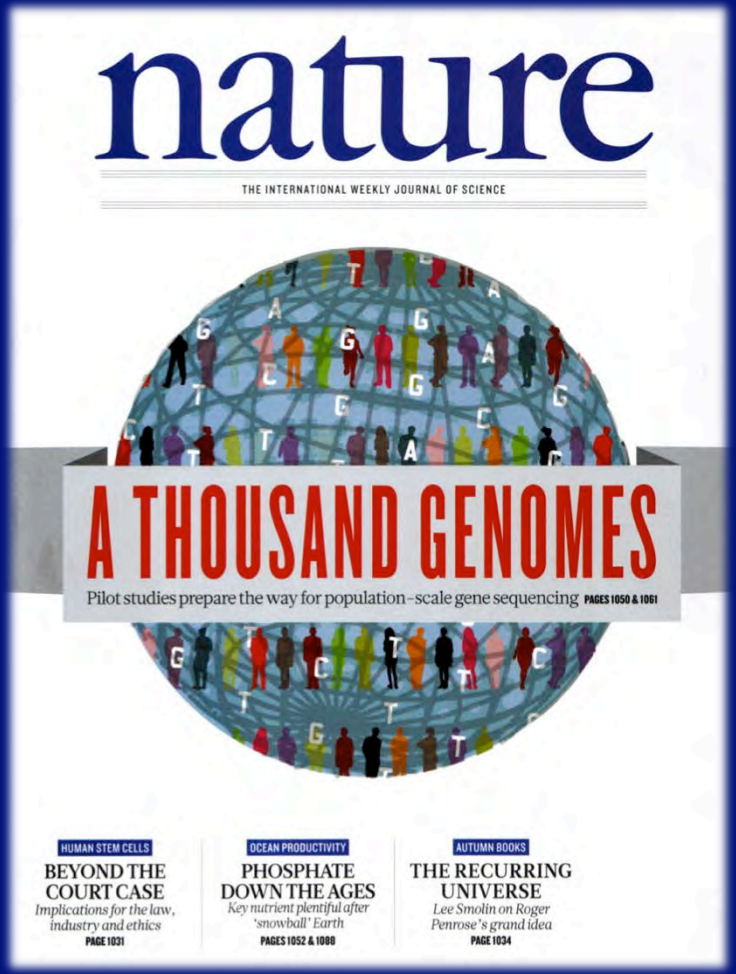
Human Genomic Variation



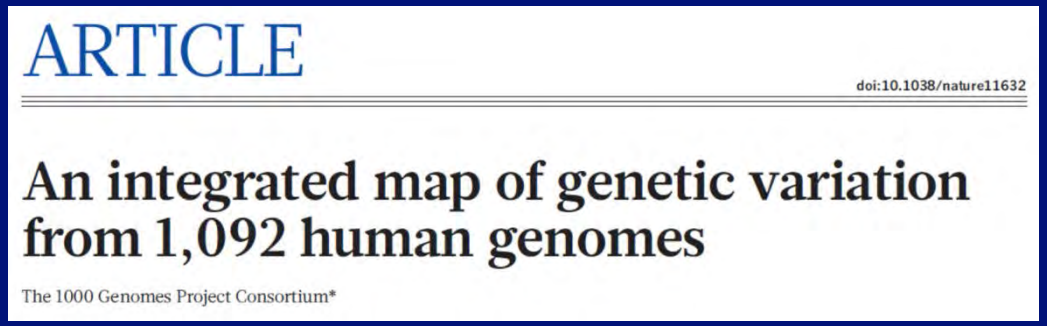

V
V
V
V
V
V
V
V
V
V
V
V
V
V

1000 Genomes

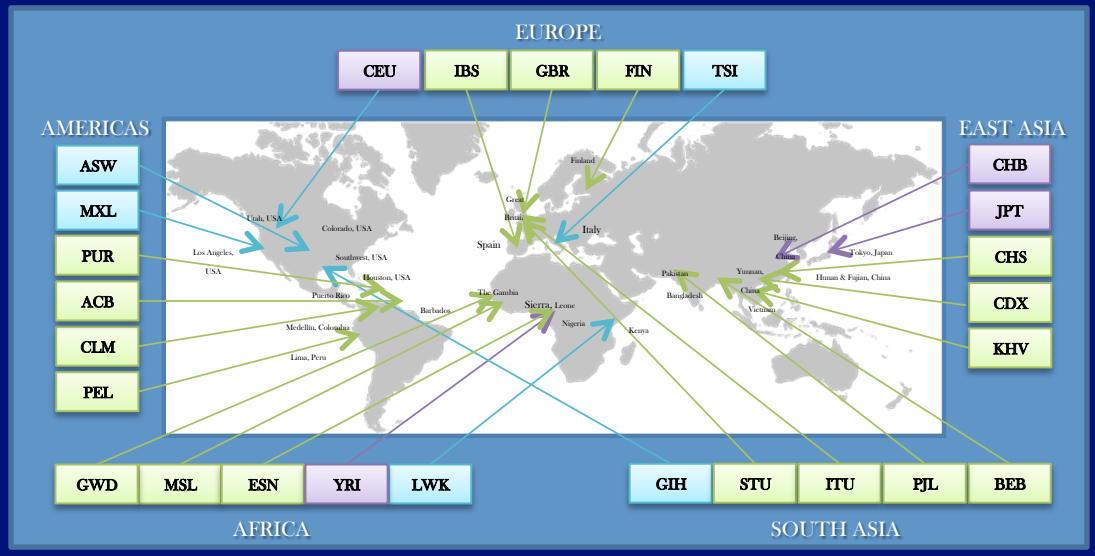
A Deep Catalog of Human Genetic Variation



Nature (2010)

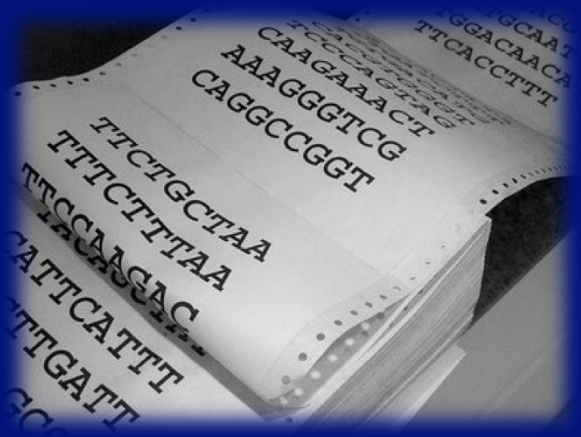


Nature (2012)



2535 Humans, 26 Populations

Your Genome: By the Numbers



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

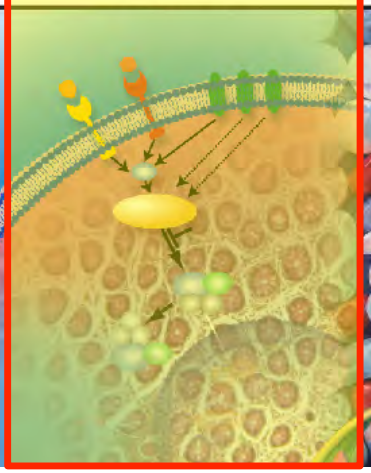
Understanding the Structure of Genomes

Understanding the Biology of Genomes

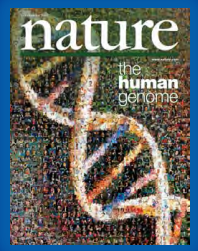
Understanding the Biology of Disease

Advancing the Science of Medicine

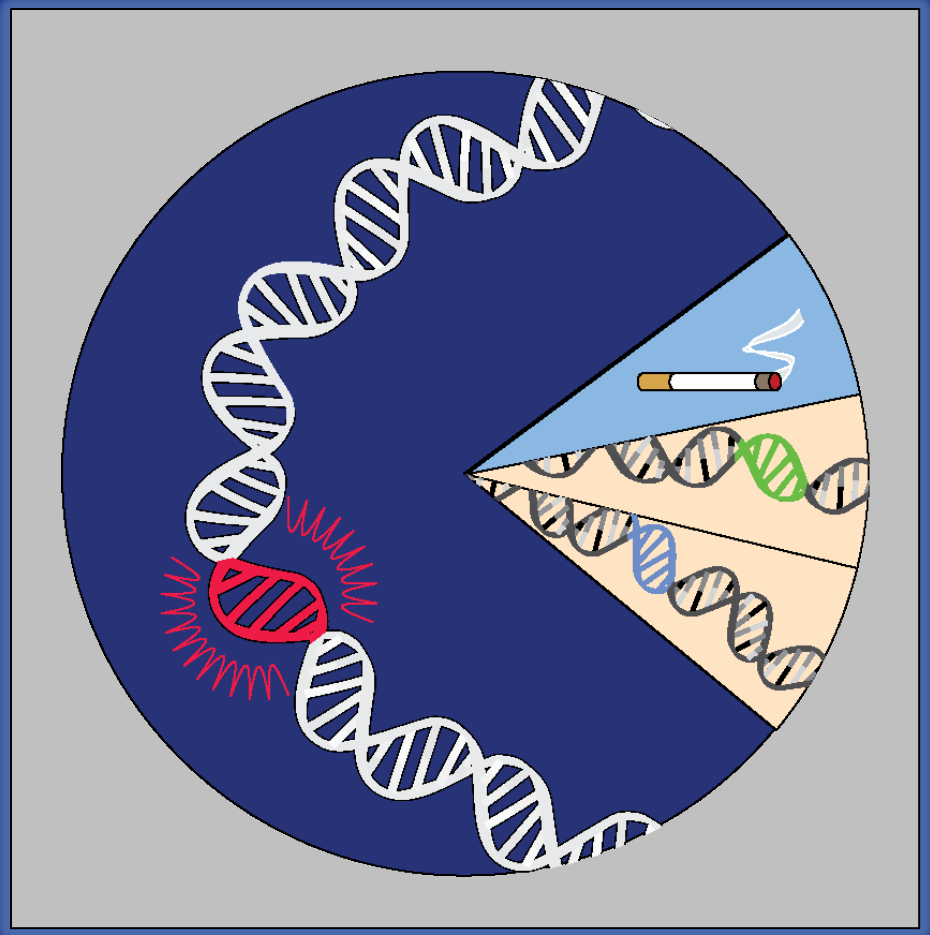
Improving the Effectiveness of Healthcare



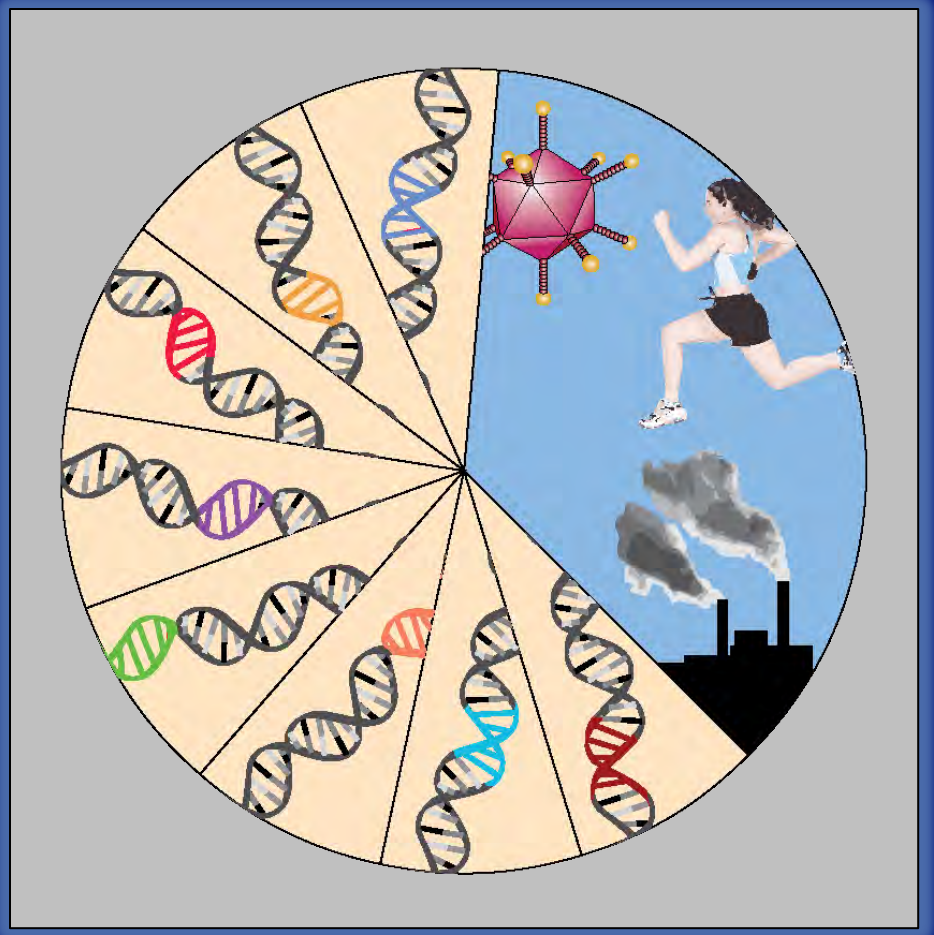
Genomic Basis for Human Diseases



Genomic Architecture of Genetic Diseases



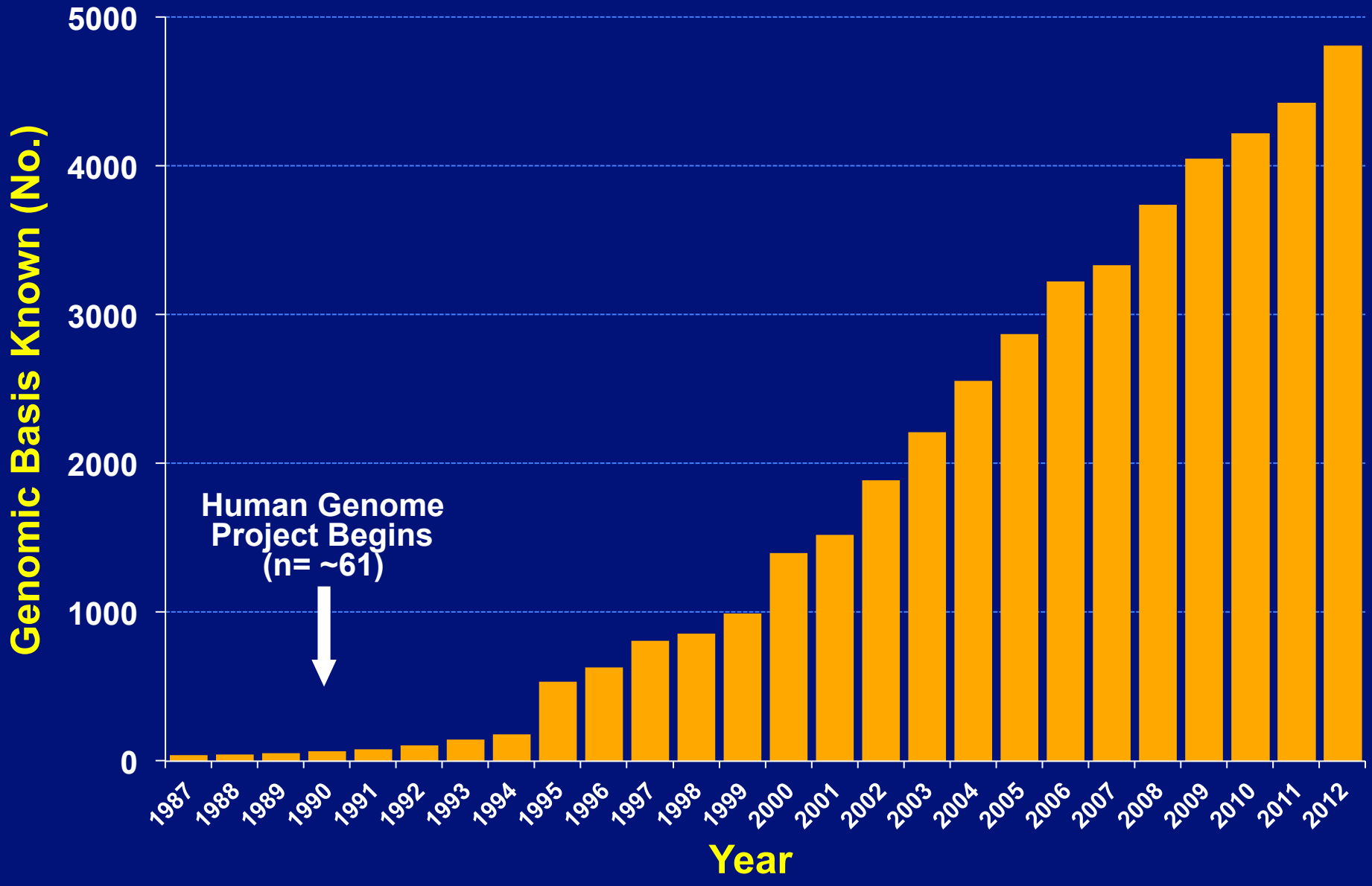
Rare, Simple, Monogenic, Mendelian…



Common, Complex, Multigenic, Non-Mendelian…

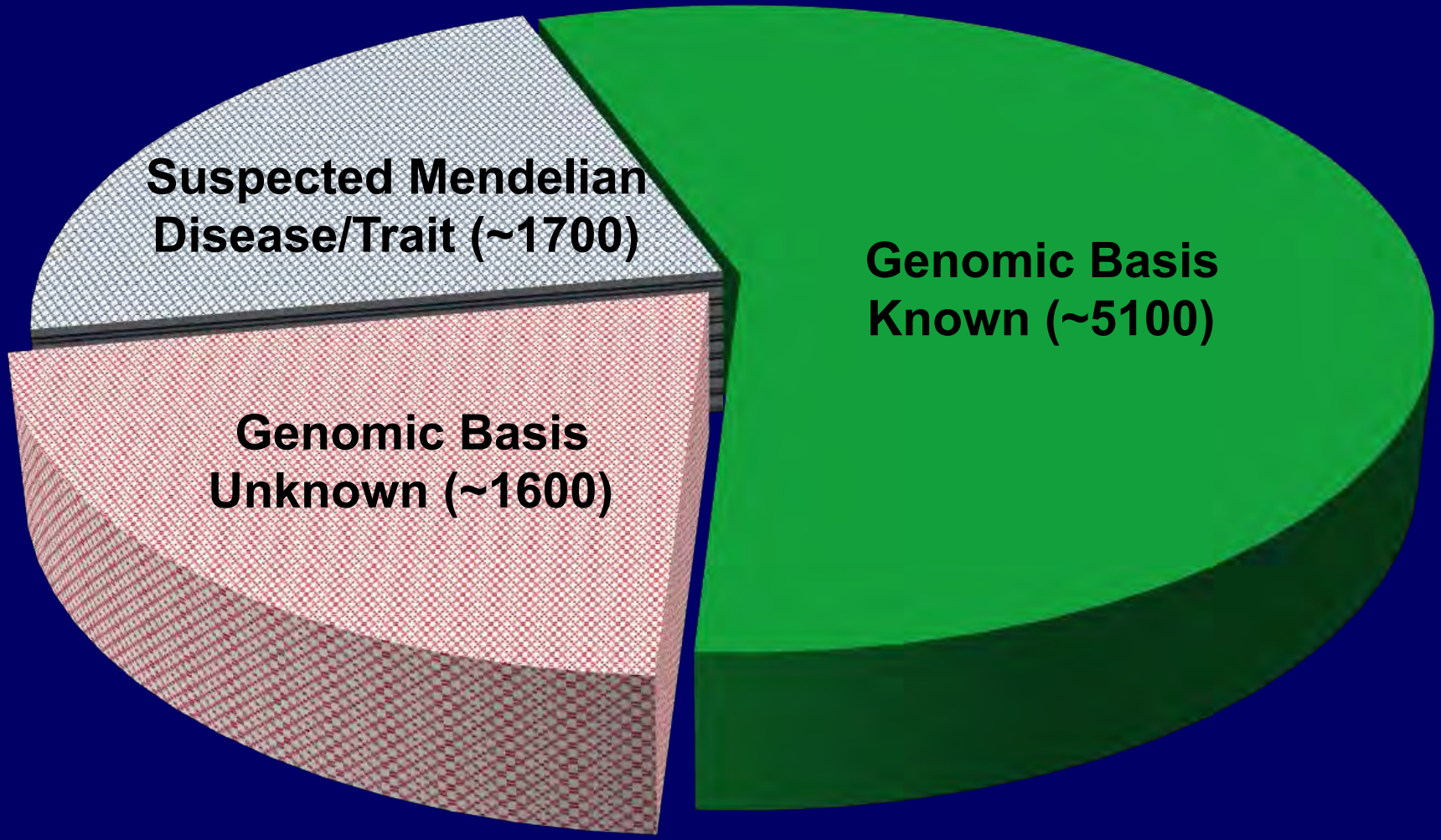
Manolio et al., J Clin Invest (2008)

Monogenic Diseases/Traits



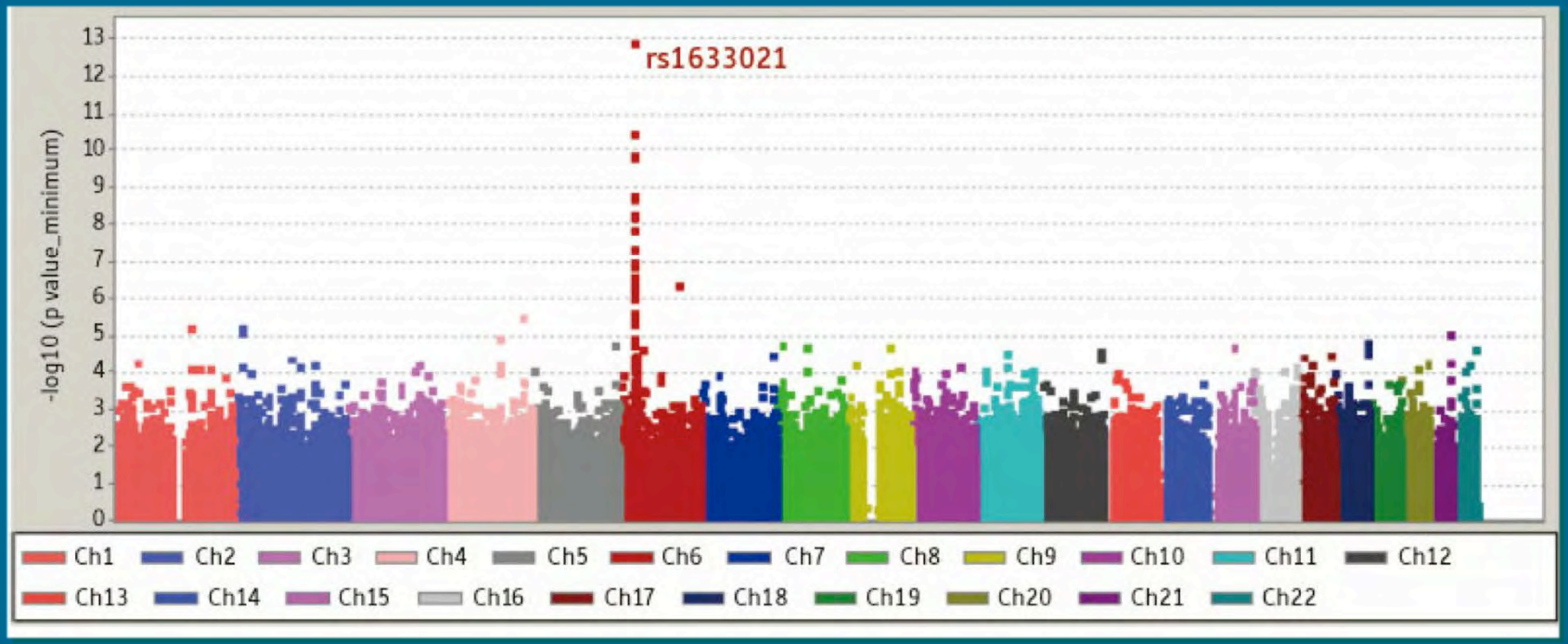
Source: *Online Mendelian Inheritance in Man* (www.omim.org)

Monogenic Diseases/Traits



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

Genome-Wide Association Studies (GWAS)

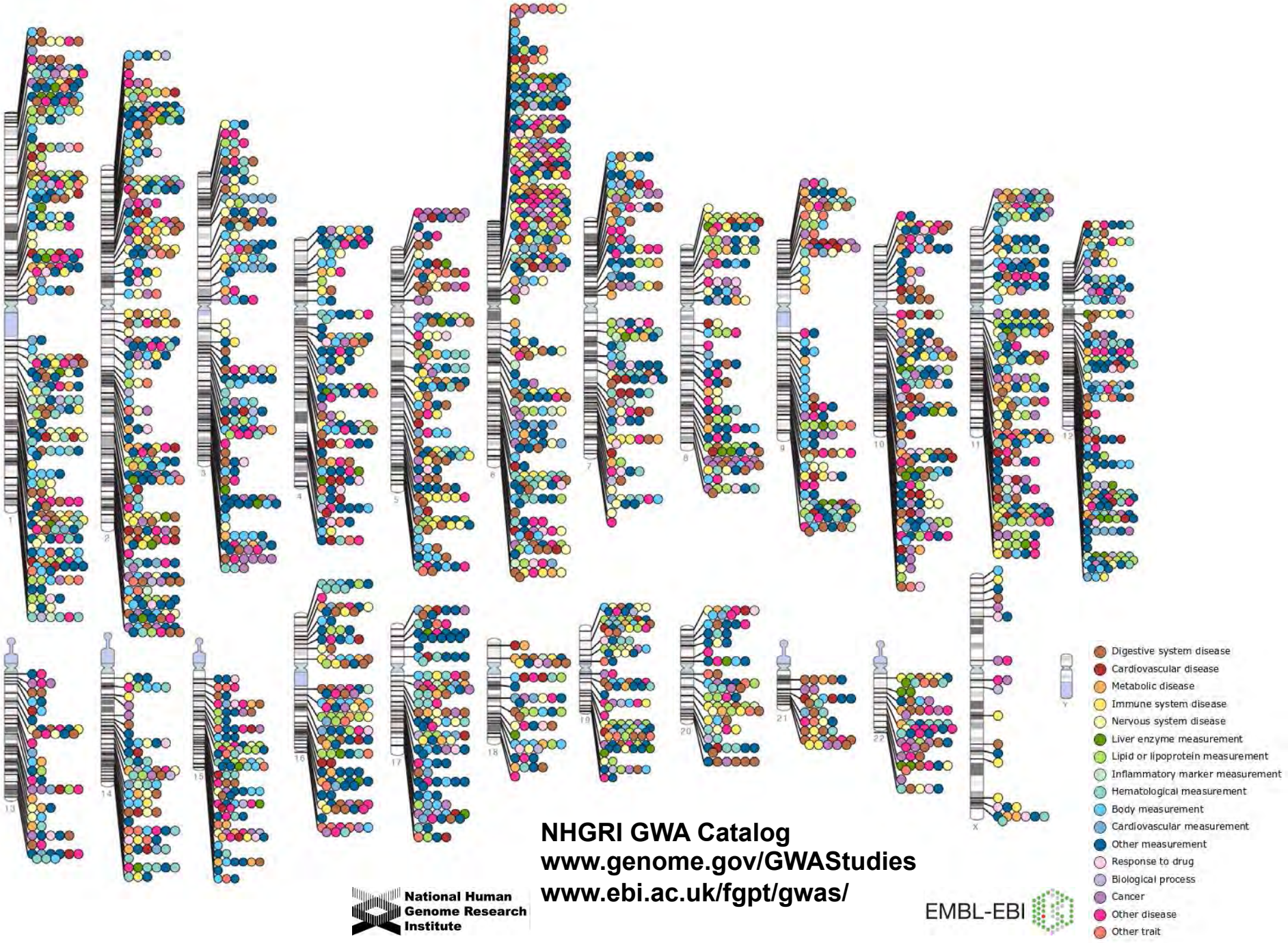


The First GWAS Success Story: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration

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)**



NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

Understanding the Structure of Genomes

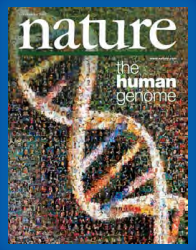
Understanding the Biology of Genomes

Understanding the Biology of Disease

Advancing the Science of Medicine

Improving the Effectiveness of Healthcare

Routine Whole-Genome Sequencing



feature

A vision for the future of genomics research

A blueprint for the genomic era.

Francis S. Collins, Eric D. Green, Alan E. Guttmacher and Mark S. Guyer on behalf of the US National Human Genome Research Institute*

The completion of a high-quality, comprehensive sequence of the human genome, in this fiftieth anniversary year of the discovery of the double-helical structure of DNA, is a landmark event. The genomic era is now a reality.

In contemplating a vision for the

in a few weeks by a single graduate student with access to DNA samples and associated phenotypes, an Internet connection to the public genome databases, a thermal cycler and a DNA-sequencing machine. With the recent publication of a draft sequence of the mouse genome[1], identification of the mutations underlying a vast number of interesting mouse phenotypes has similarly been greatly simplified. Comparison of the human and mouse sequences shows that the proportion of the mammalian genome under evolu-

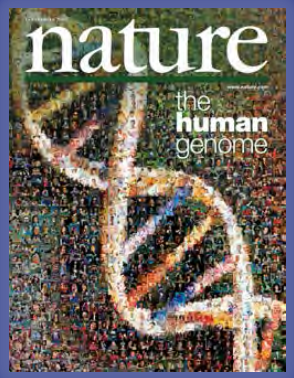
"…'technological leaps' that seem so far off as to be almost fictional but which, if they could be achieved, would revolutionize biomedical research and clinical practice.

[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

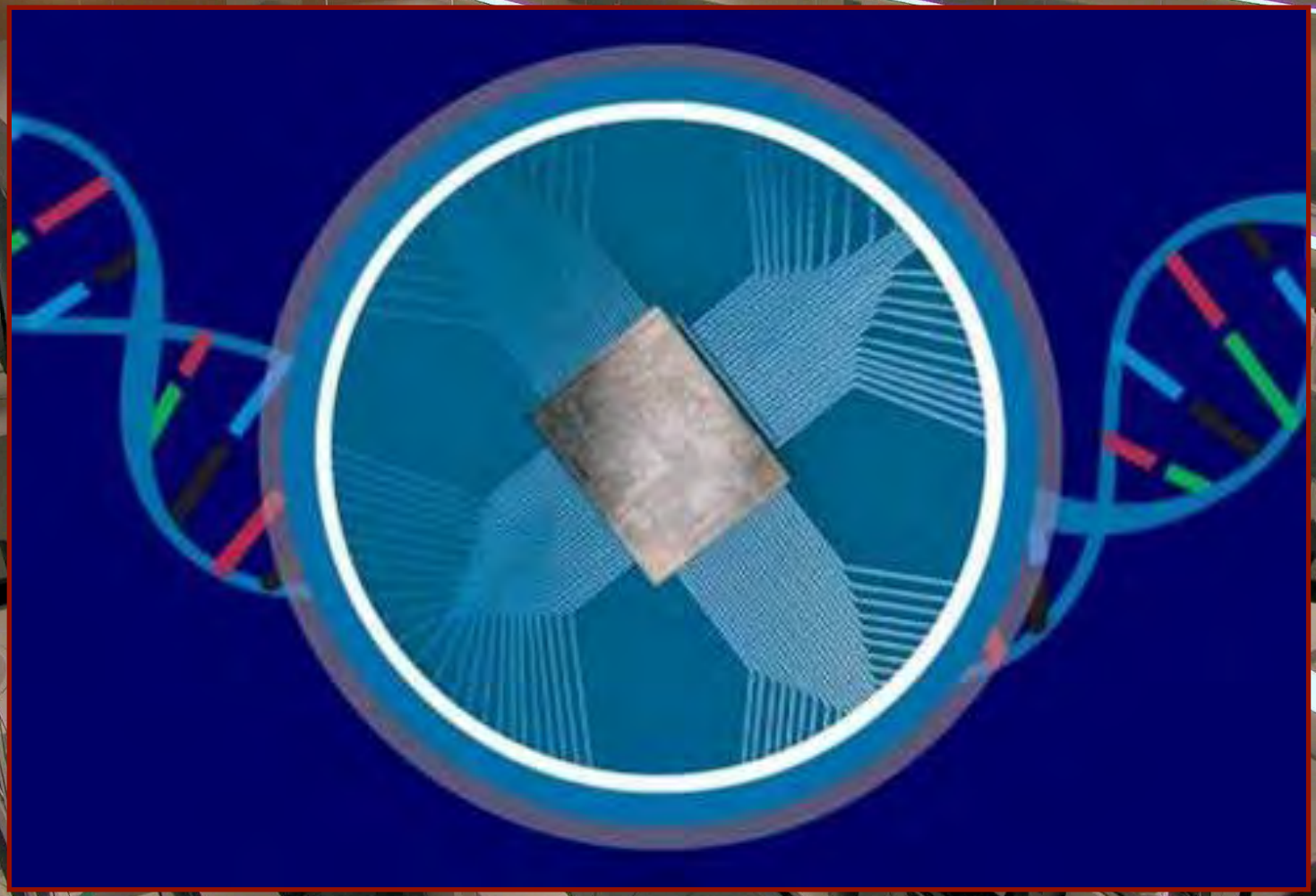
Human Genome Sequence

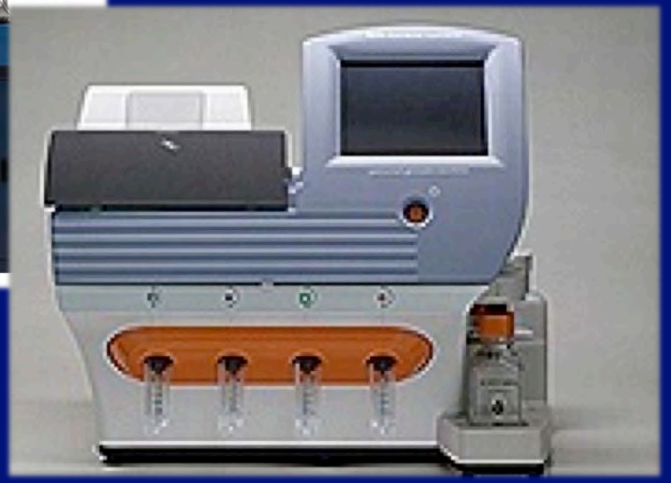
~$1,000,000,000



~$1,000

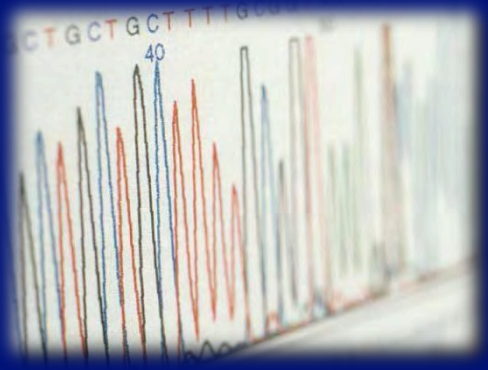
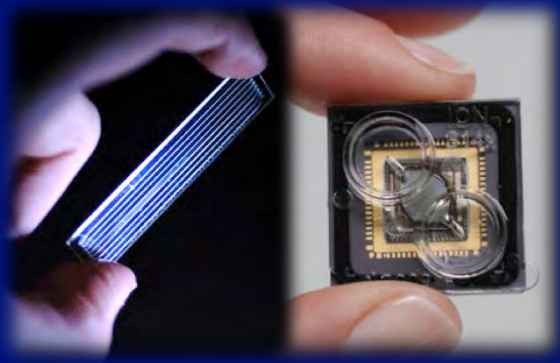
"The $1000 Genome"



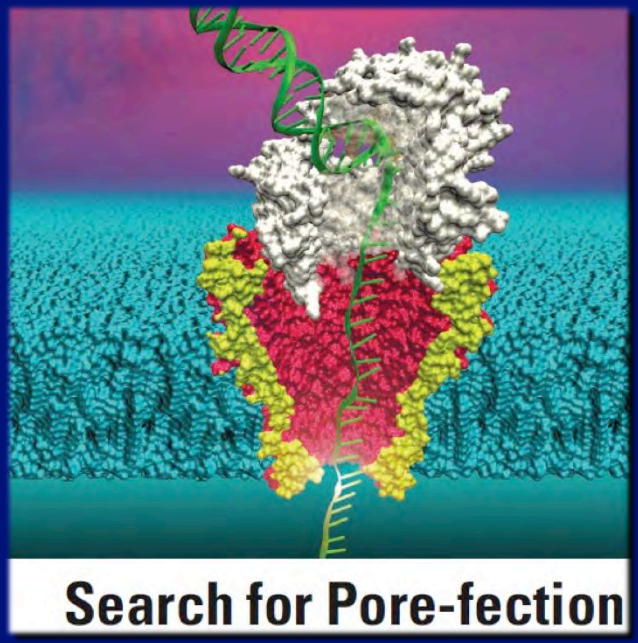



POLONATOR G.007

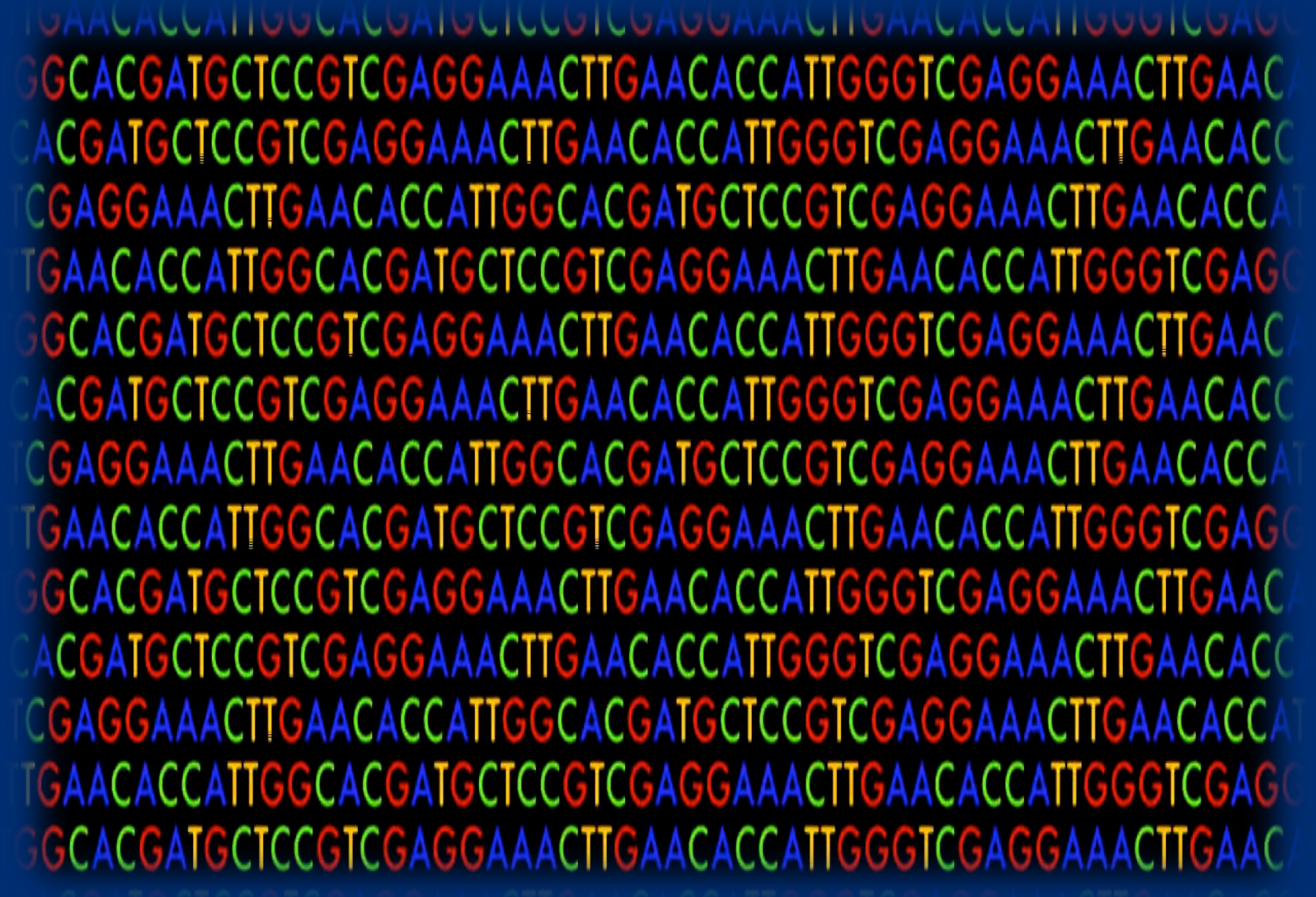
Sequencing a Human Genome

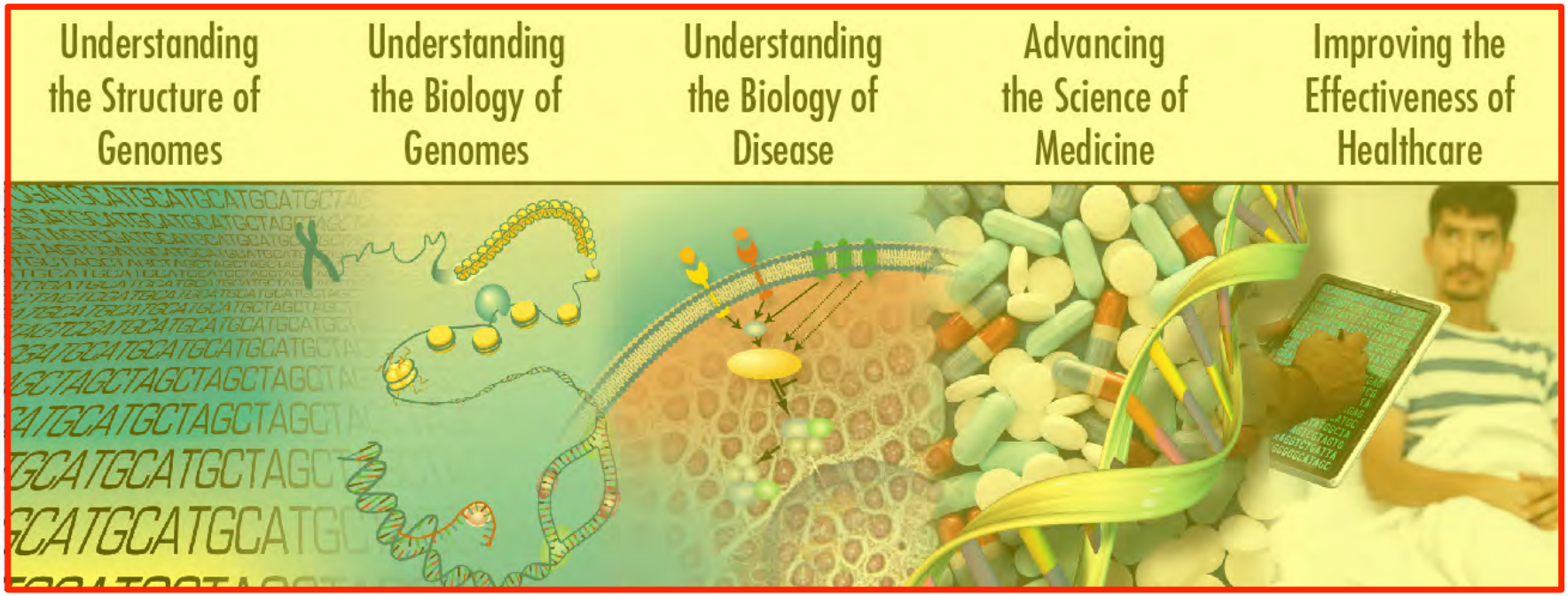
HGP (1st Sequence)	*Immediate Post-HGP*	*Today*
		
~6-8 years	~3-4 months	~1-3 days
~$1B	~$10-50M	~$3-5K

And Yet Newer Technologies…

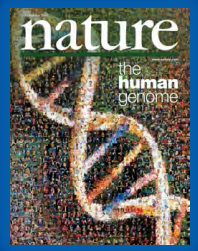


Genome Sequencing as a ‘Commodity’





Routine Analysis of Genome Sequences



The Largest Current Bottleneck in Genomics…


4 September 2008 | www.nature.com/nature | $10
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
nature
THE BITER BIT
Viral infections for viruses
TROPICAL CYCLONES
The strong get stronger
BLACK HOLE PHYSICS
A new window on the Galactic Centre
BIG DATA
NATUREJOBS
Minnesota musings
SCIENCE IN THE PETABYTE ERA

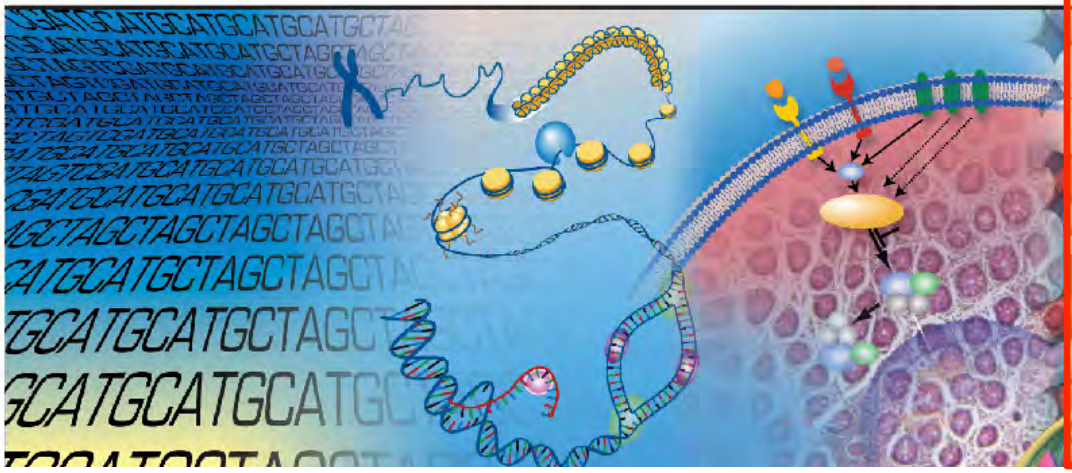

11 February 2011 | $10
Science
information
climate
science
research
new
analysis
visualization
access
researchers
many
human
challenges
sharing
data
AAAS

The Data Analysis Bottleneck

Understanding the Structure of Genomes

Understanding the Biology of Genomes

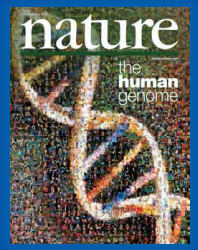
Understanding the Biology of Disease



Advancing the Science of Medicine

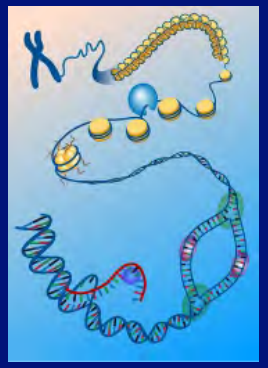
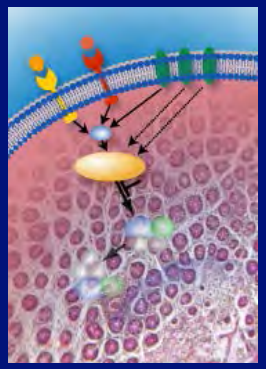
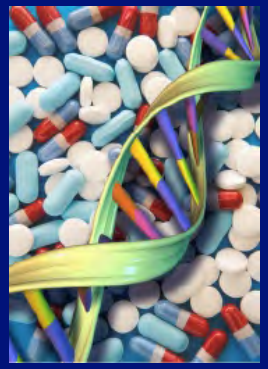
Improving the Effectiveness of Healthcare

New Diagnostics




The Future
NEXT EXIT

Genomic Accomplishments Across Domains

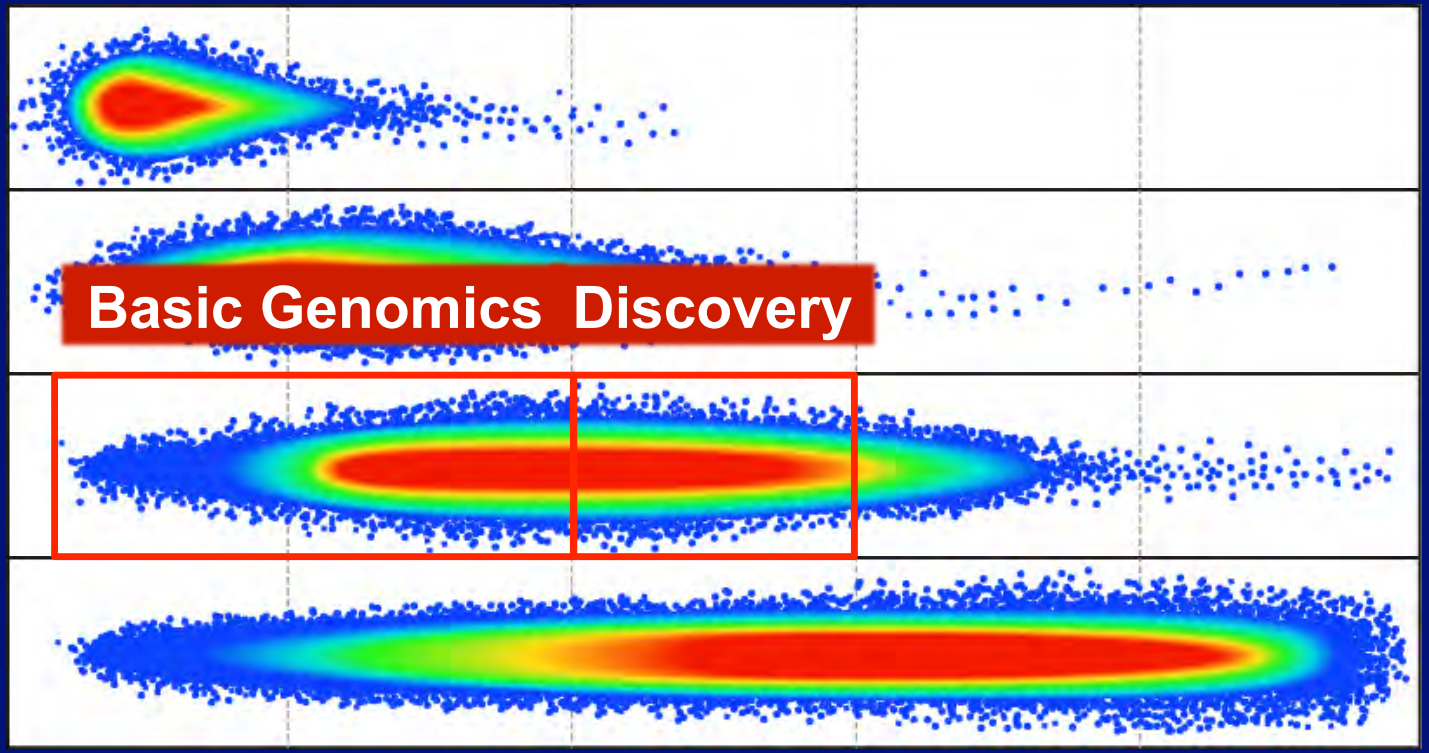
Understanding the Structure of Genomes	Understanding the Biology of Genomes	Understanding the Biology of Disease	Advancing the Science of Medicine	Improving the Effectiveness of Healthcare
				

1990-2003
Human Genome Project

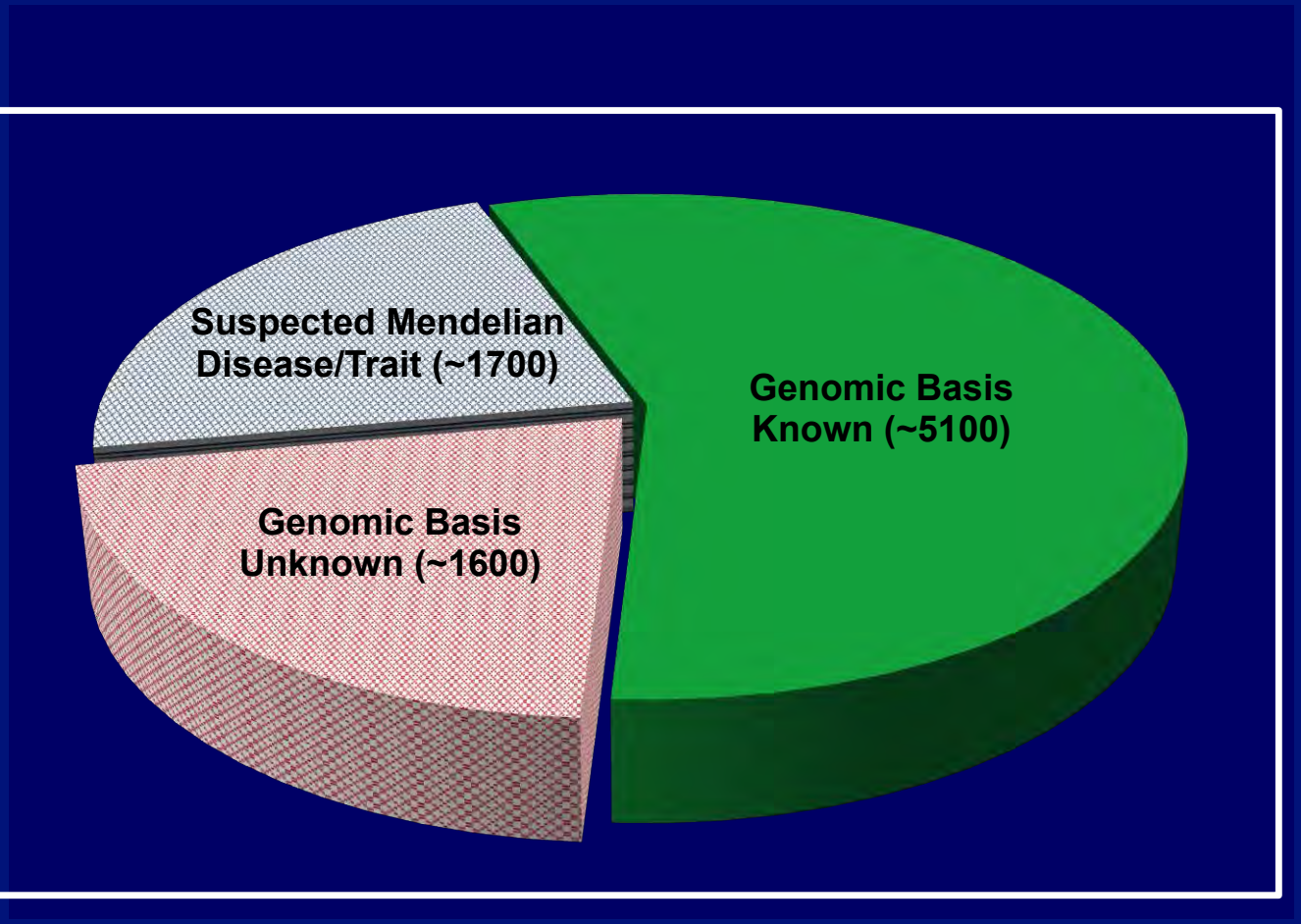
2004-2010

2011-2020

Beyond 2020

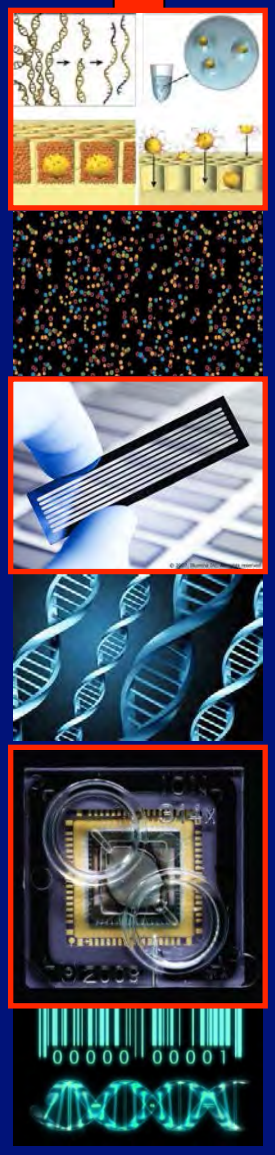


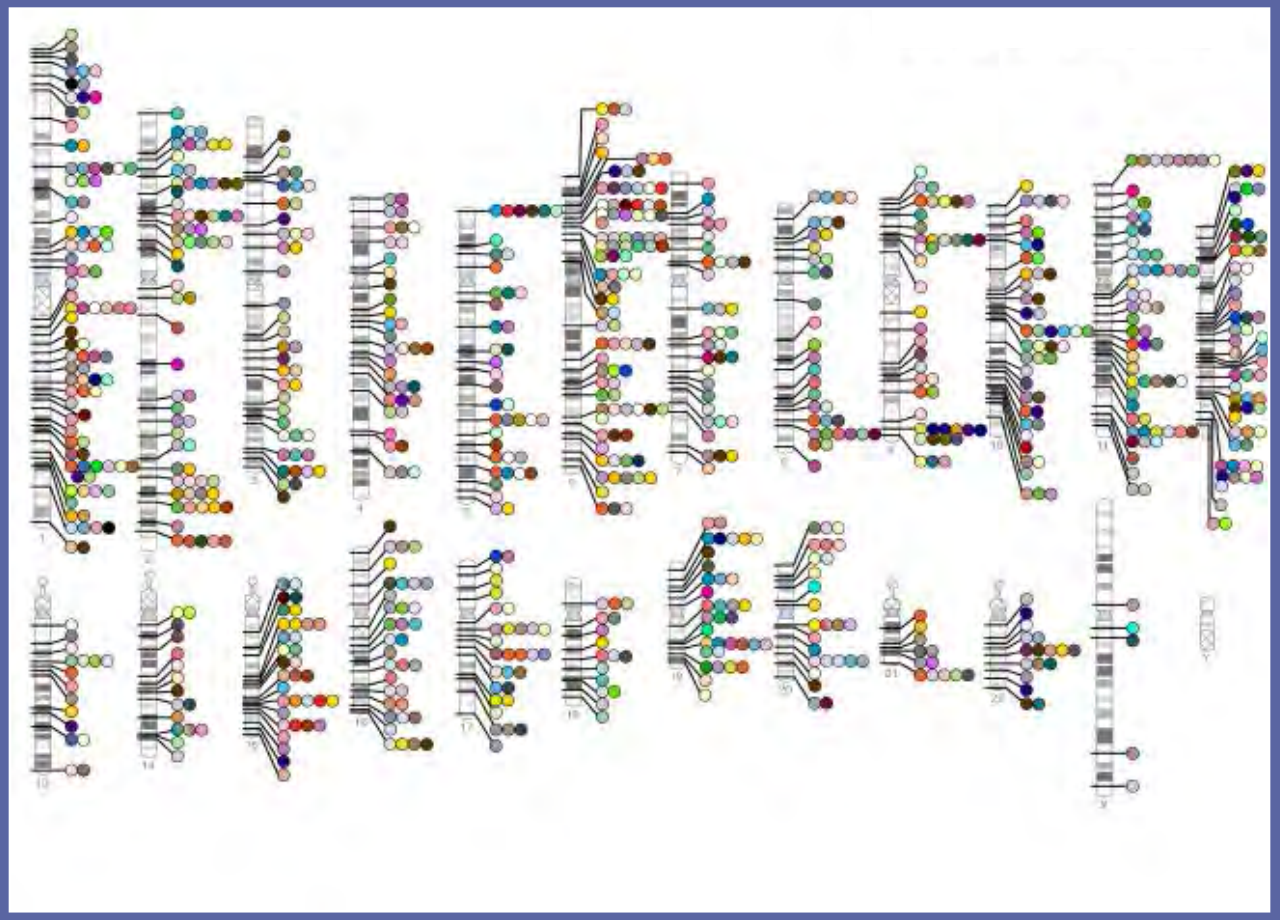
The Future: Genome Sequencing



Mendelian Diseases/Traits

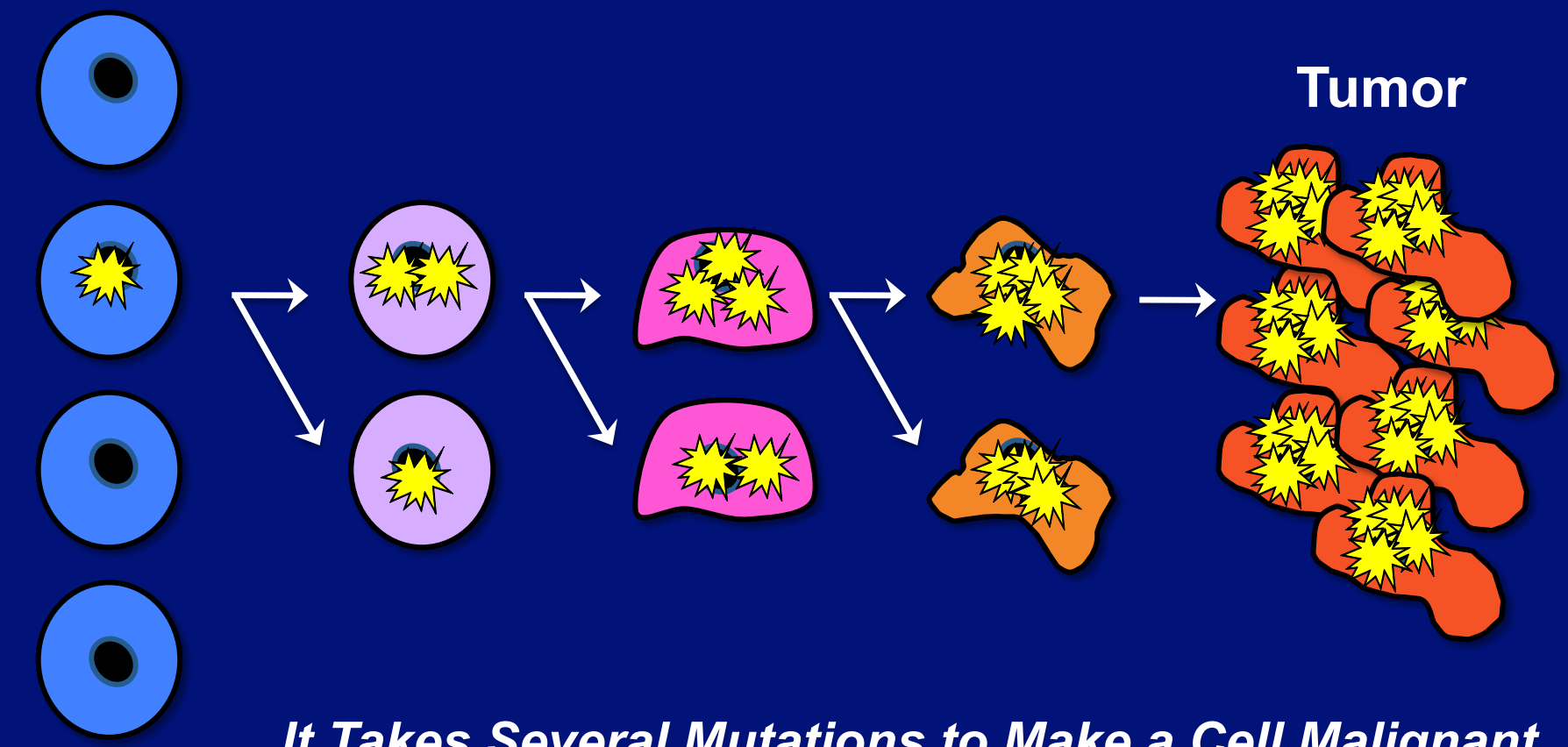
The Future: Genome Sequencing





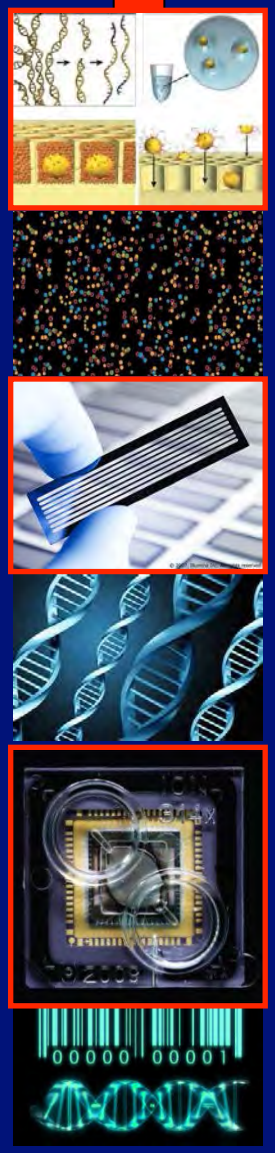
Complex Diseases/Traits

Cancer is a Disease of the Genome



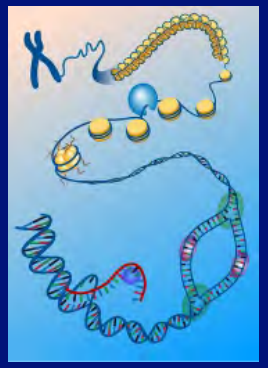
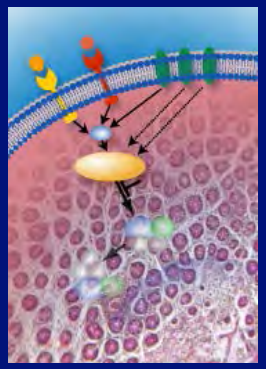
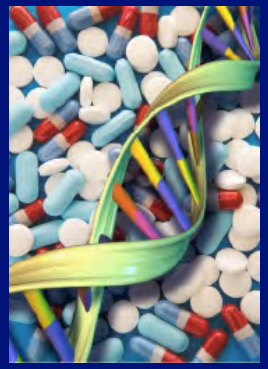
It Takes Several Mutations to Make a Cell Malignant

The Future: Genome Sequencing



Cancer Genomics

Genomic Accomplishments Across Domains

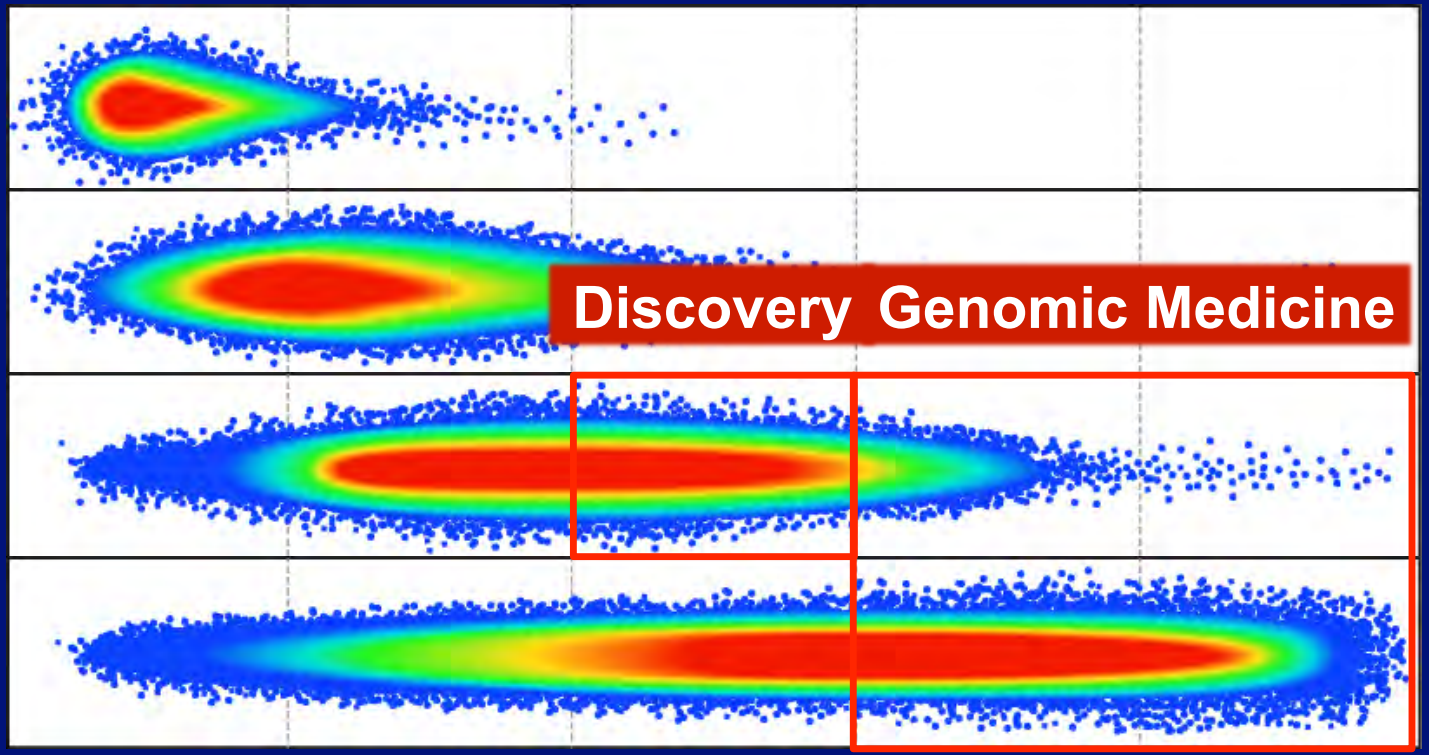
Understanding the Structure of Genomes	Understanding the Biology of Genomes	Understanding the Biology of Disease	Advancing the Science of Medicine	Improving the Effectiveness of Healthcare
				

1990-2003
Human Genome Project

2004-2010

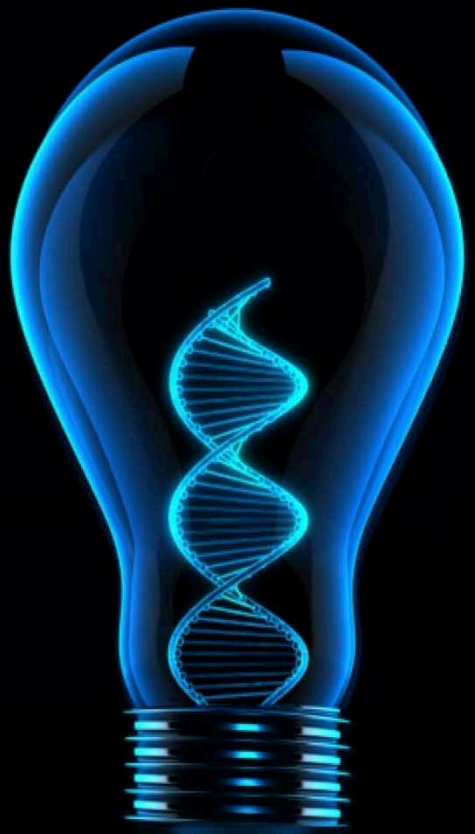
2011-2020

Beyond 2020

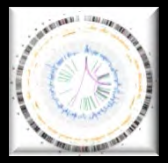


Bringing Genomic Medicine Into Focus

‘Hot Areas’ in Genomic Medicine

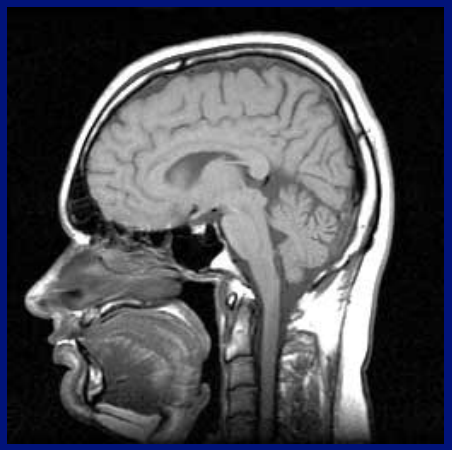


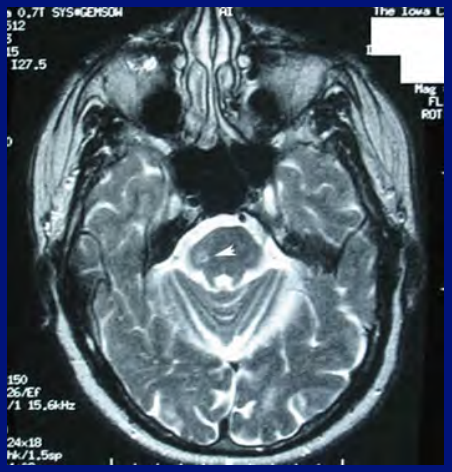
Cancer Genomics



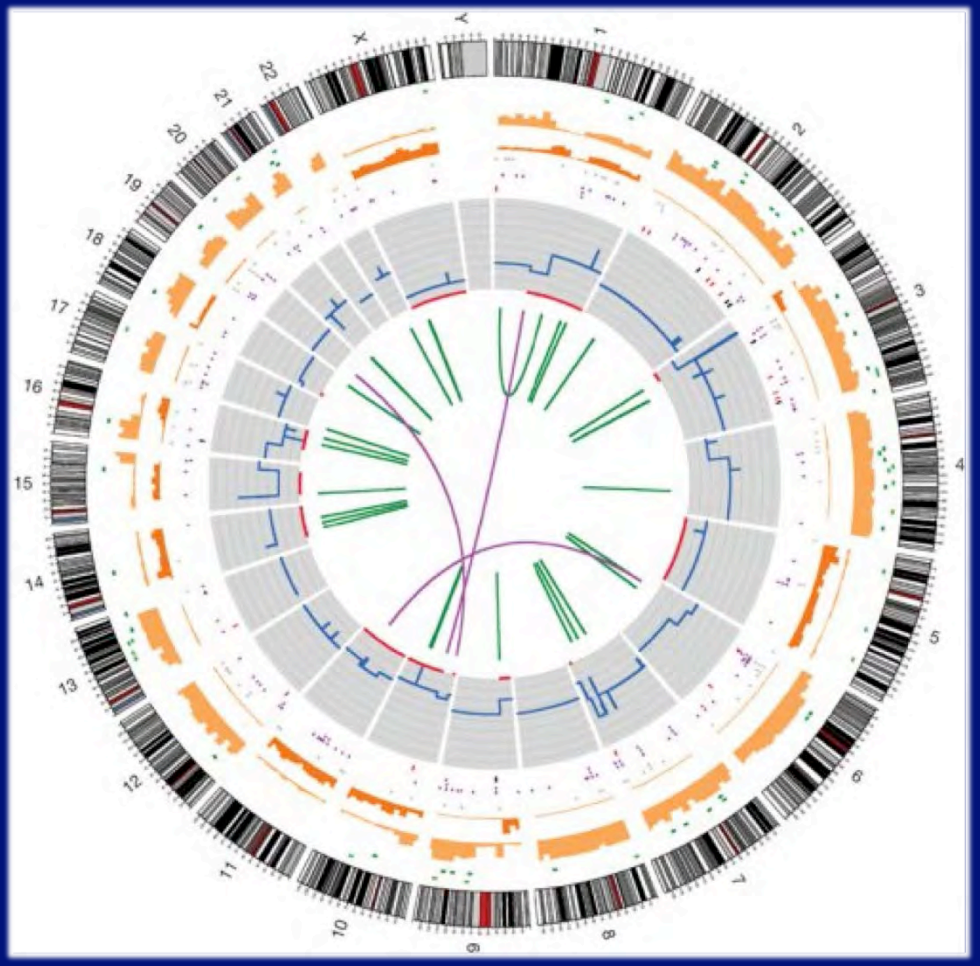
Routine Clinical Diagnostic Tools

Radiographic Imaging

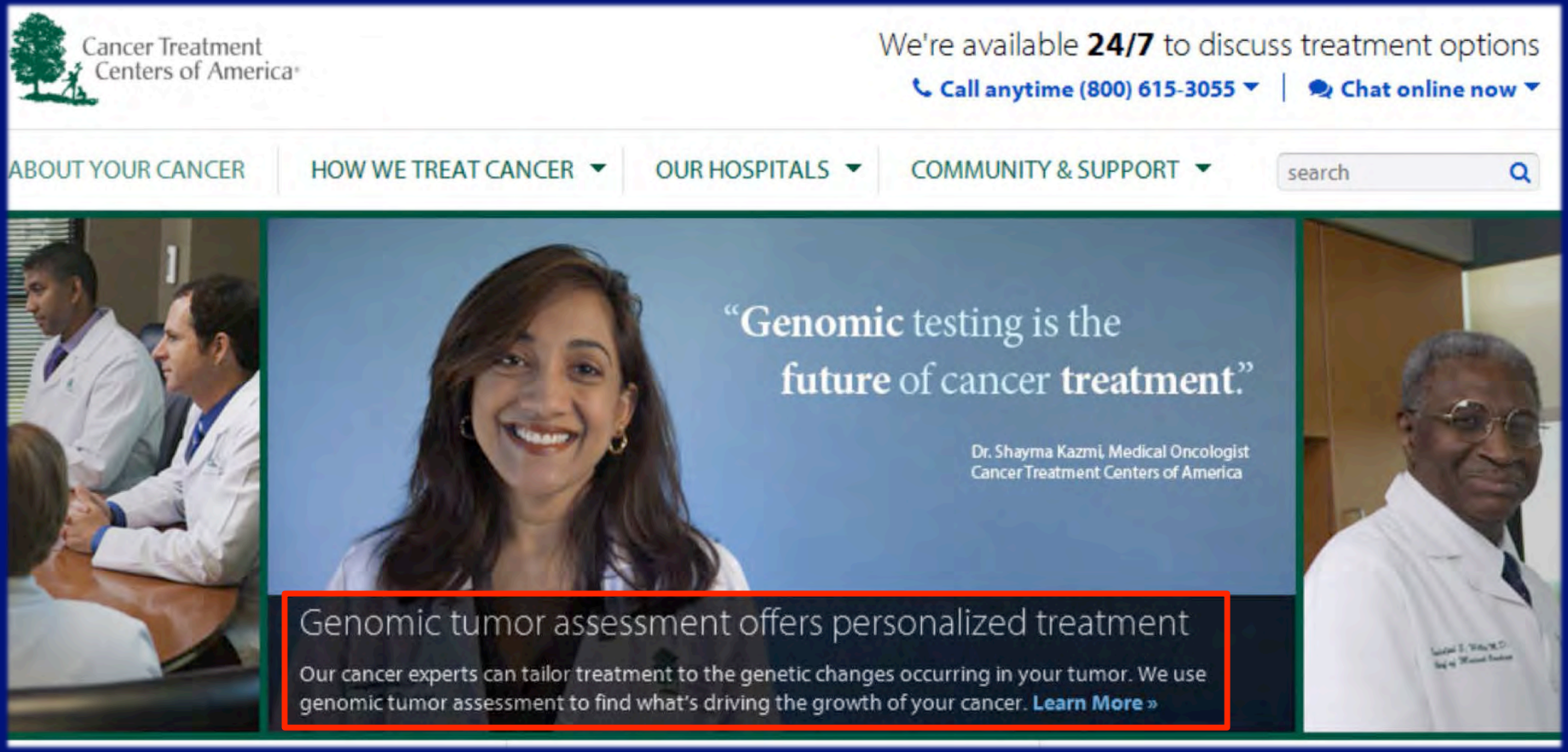




Cancer Genome Sequencing

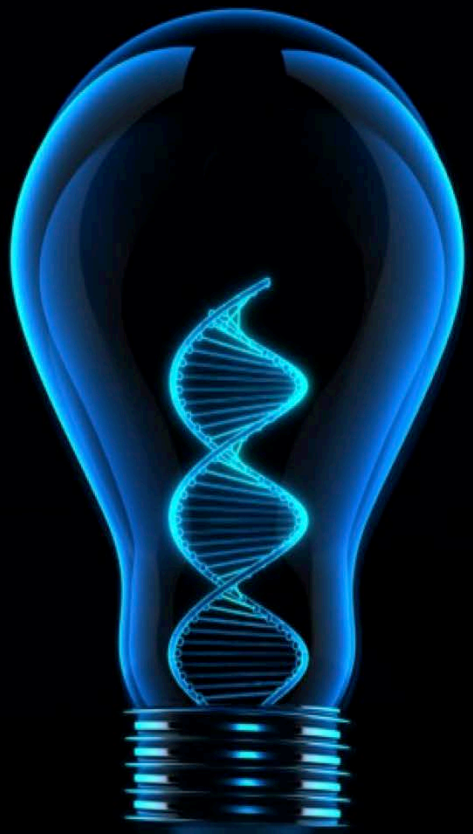


Cancer Genomics: Here and Now

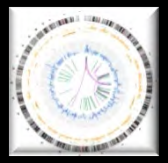


www.cancercenter.com

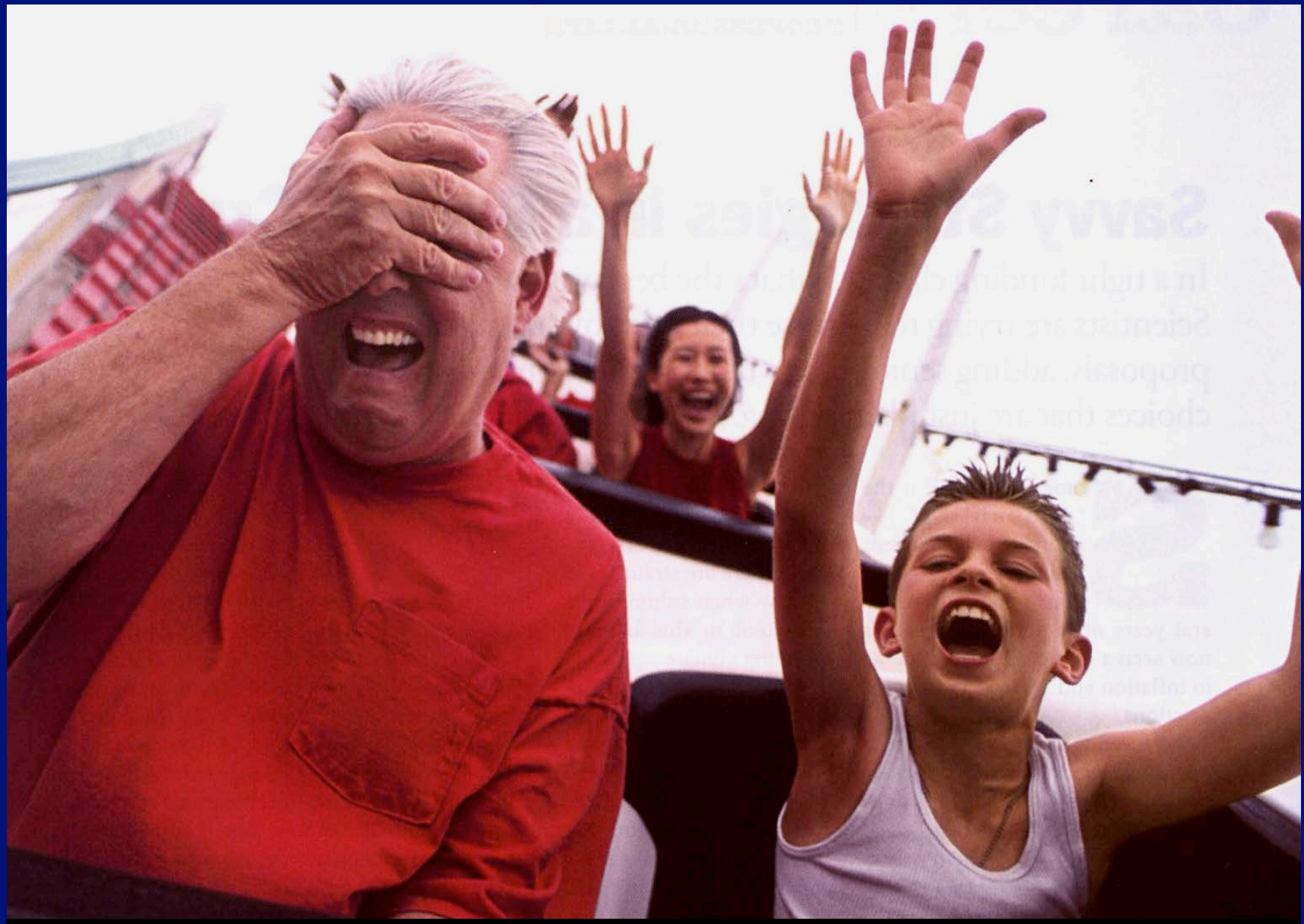
‘Hot Areas’ in Genomic Medicine



Cancer Genomics



Pharmacogenomics



Because Everyone Responds Differently.

All of these work.

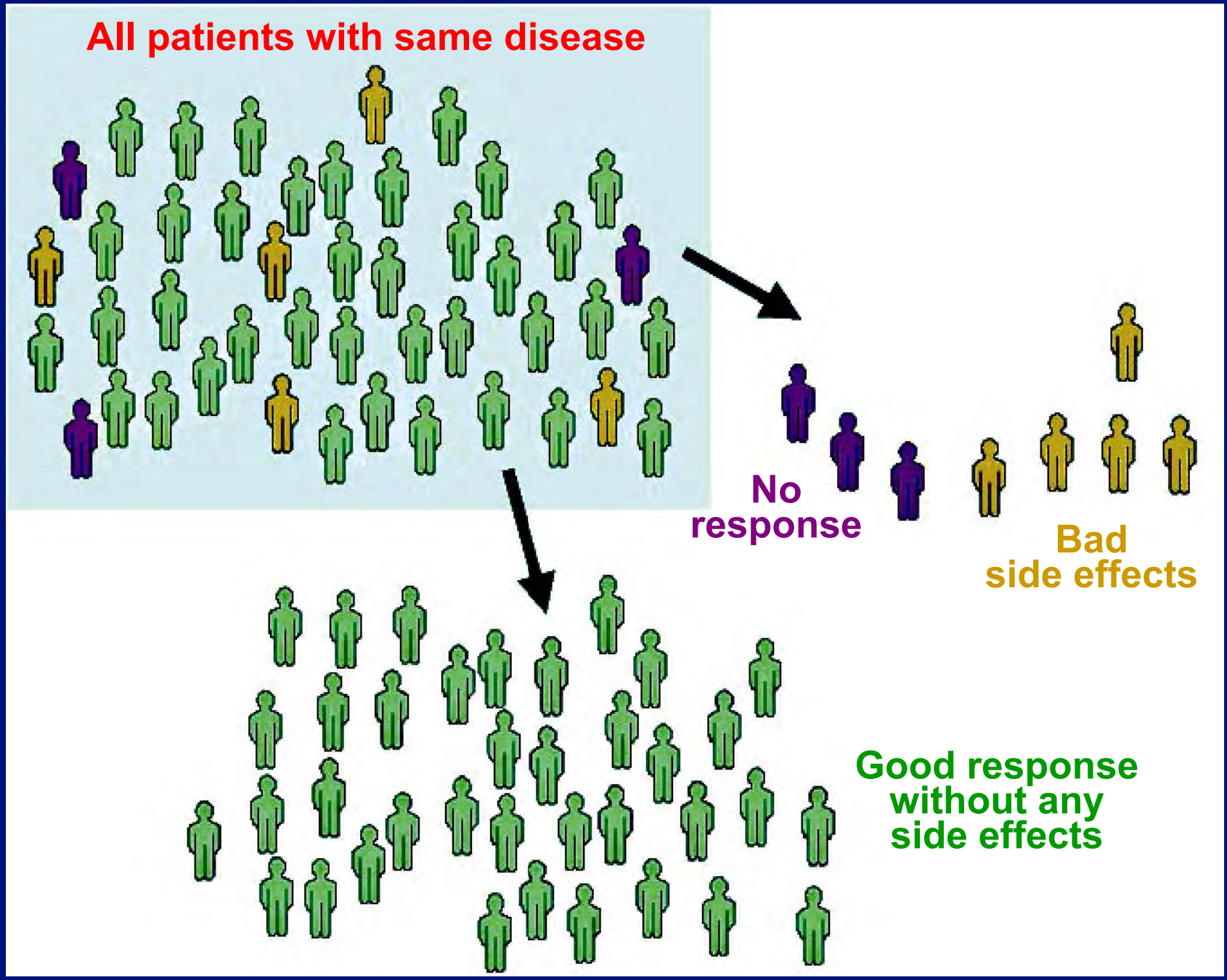
Just not for everyone.

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

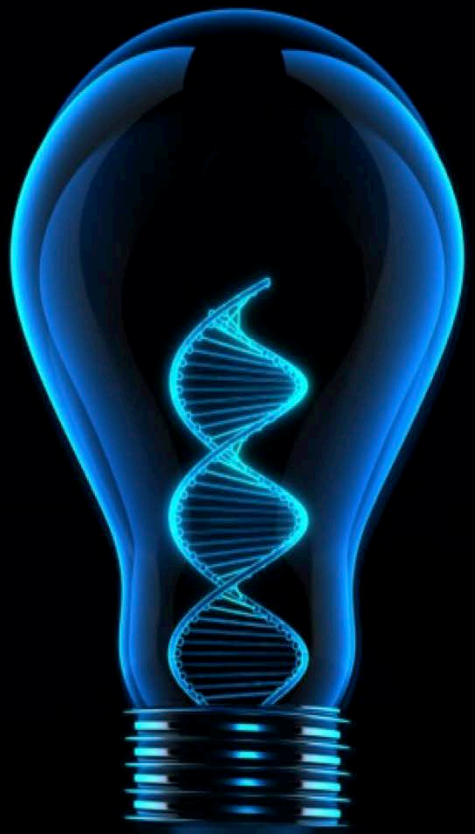
Working with you, we can comprehensively analyze the DNA from thousands of patients taking your drug. Out of the millions of genetic variations between patients, we may be able to help you identify the ones that are associated with strong efficacy, poor efficacy, or side effects.

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.

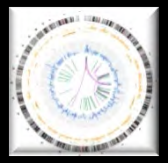
We partner with the top pharmaceutical companies around the world. We also license late-stage drugs. If you have a drug that can benefit from our approach, please contact us.


All patients with same disease
No response
Bad side effects
Good response without any side effects

‘Hot Areas’ in Genomic Medicine



Cancer Genomics



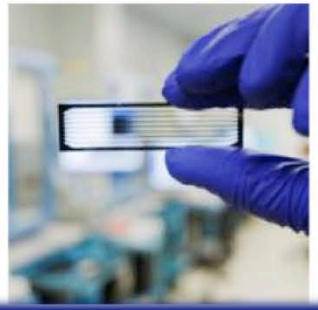
Pharmacogenomics

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)

Implementing Genomics in Practice (IGNITE)

Share Print

Overview

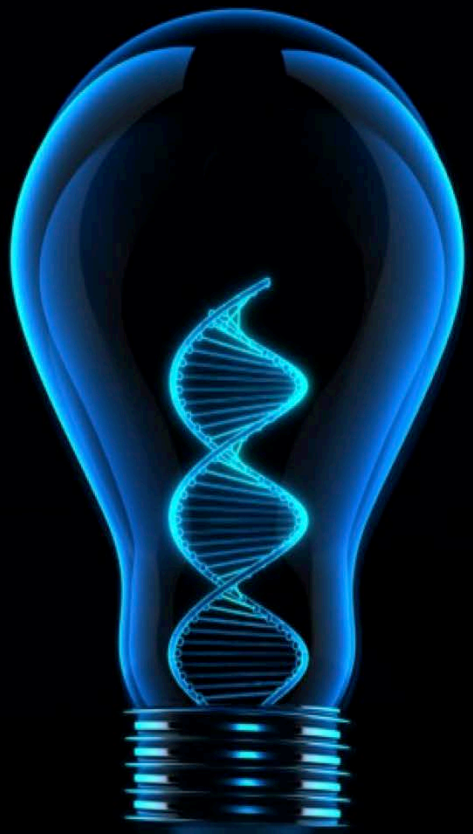
Findings from the genomics field have slowly started to find applications in clinical care. The field of "genomic medicine" could potentially improve patient health and treatment strategies or better predict the likelihood of disease.

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.

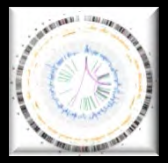
These demonstration projects will incorporate genomic information into the electronic medical record (EMR) and provide clinical decision support (CDS) for implementation of appropriate interventions or clinical advice. The sites will work together to develop new methods and projects and disseminate their 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

‘Hot Areas’ in Genomic Medicine



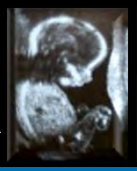
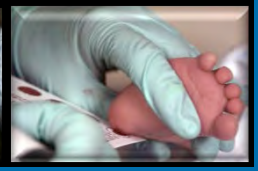
- Cancer Genomics



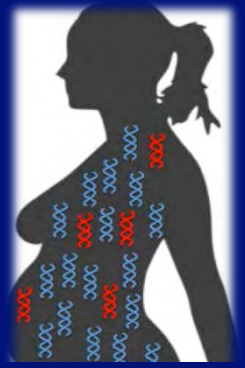
- Pharmacogenomics

- Genomic Medicine ‘Test Drive’ Programs

- Prenatal & Newborn Genomic Analysis

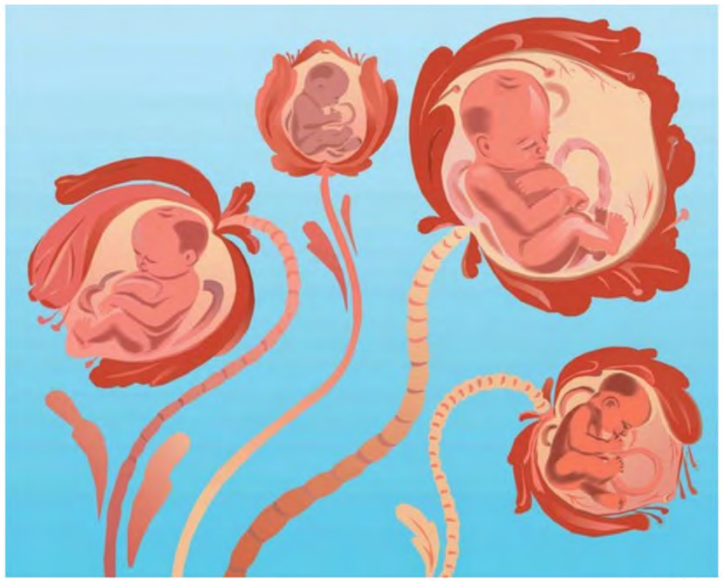
Noninvasive Prenatal Genome Sequencing



PERSONAL HEALTH | OCTOBER 7, 2013, 12:01 AM | 110 Comments

Breakthroughs in Prenatal Screening

By JANE E. BRODY



Yvetta Fedorova

***New York Times* (2013)**

Genome Sequencing in Newborns (NSIGHT)

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.

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

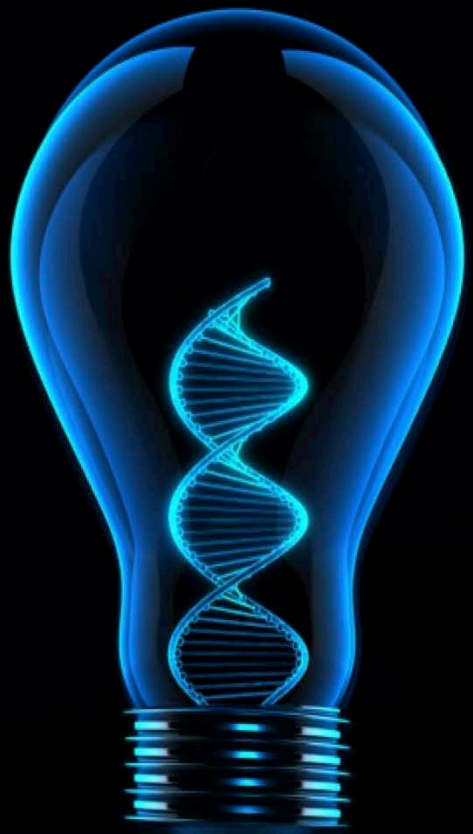
plans to give the raw genetic data to the children's families, even though that could allow the children to benefit from it throughout their lives.

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.

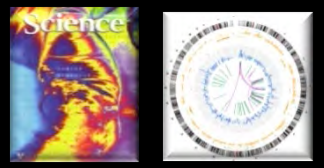
As researchers explore these questions, sequencing costs continue

***Nature* (2013)**

‘Hot Areas’ in Genomic Medicine



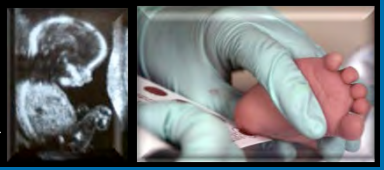
- Cancer Genomics



- Pharmacogenomics

- Genomic Medicine ‘Test Drive’ Programs

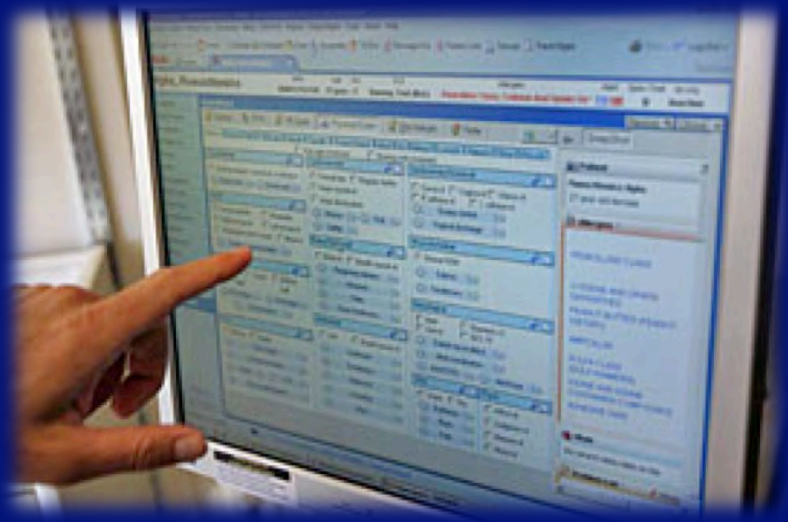
- Prenatal & Newborn Genomic Analysis



- 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

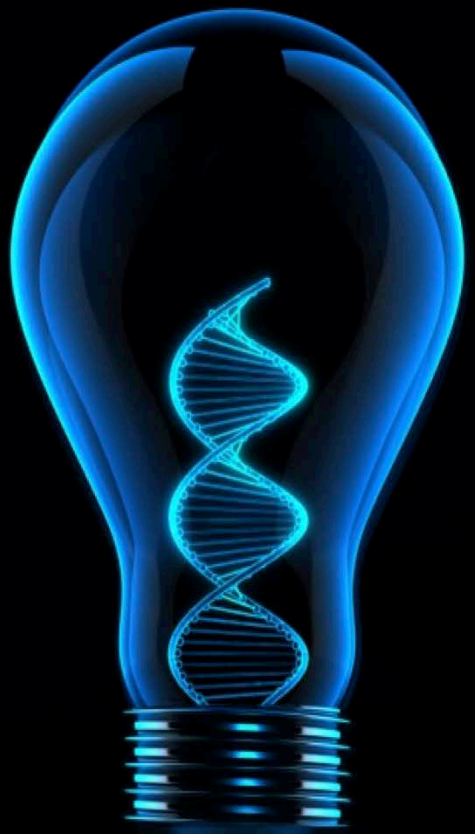
Bethesda, Md., Wed., Sept. 25, 2013 - Three grants totaling more than $25 million over four years will help three research groups to develop authoritative information on the millions of genomic variants relevant to human disease and the hundreds that are expected to be useful for clinical practice. The 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.

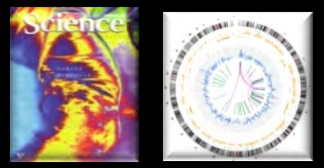
The grants will support a consortium of research groups to develop the Clinical Genome Resource (ClinGen). The investigators will design and implement a framework for evaluating which variants play a role in disease and those that are relevant to patient care, and will work closely with the National 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

‘Hot Areas’ in Genomic Medicine



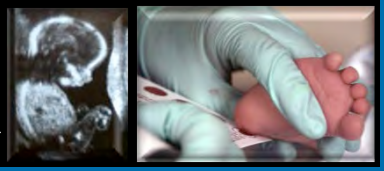
- Cancer Genomics



- Pharmacogenomics

- Genomic Medicine ‘Test Drive’ Programs

- Prenatal & 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

Ya
Matt
Alici
Matth
Magalie

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)

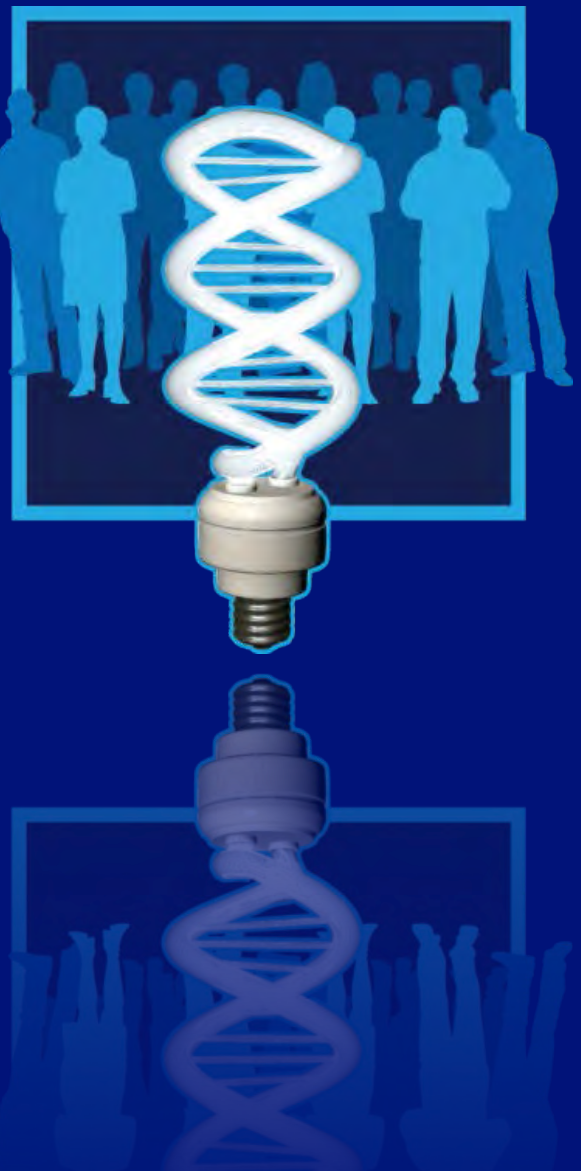
The Relevance of Genomics

Biomedical Researchers

Healthcare Professionals

Patients (and Friends & Relatives of Patients)

Genomics and Society




NATIONAL HUMAN GENOME
RESEARCH INSTITUTE
Advancing human health
through genomics research