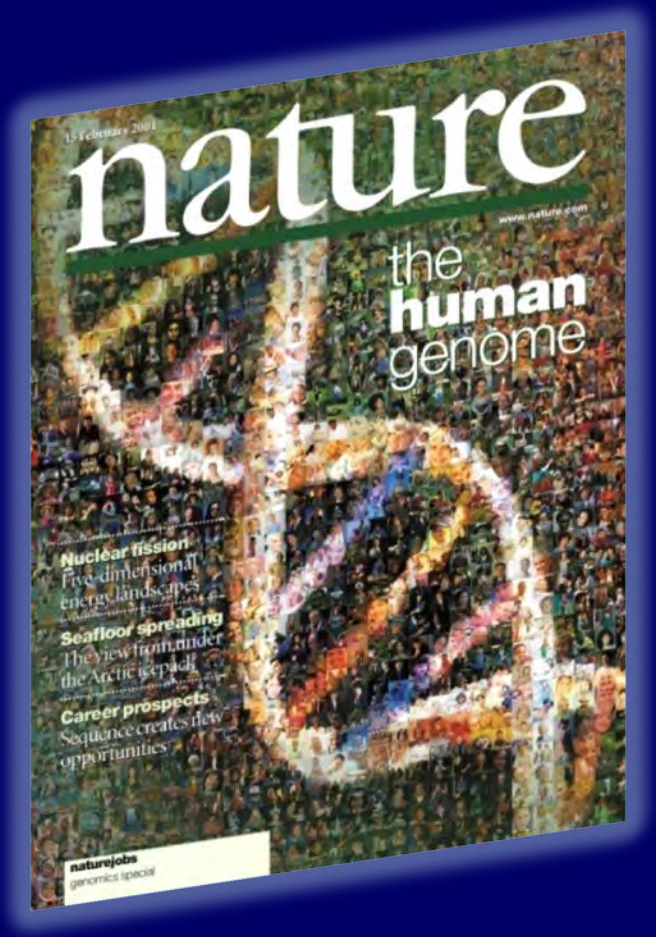
Next-Gen 101: The Changing Landscape of Genome Sequencing

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

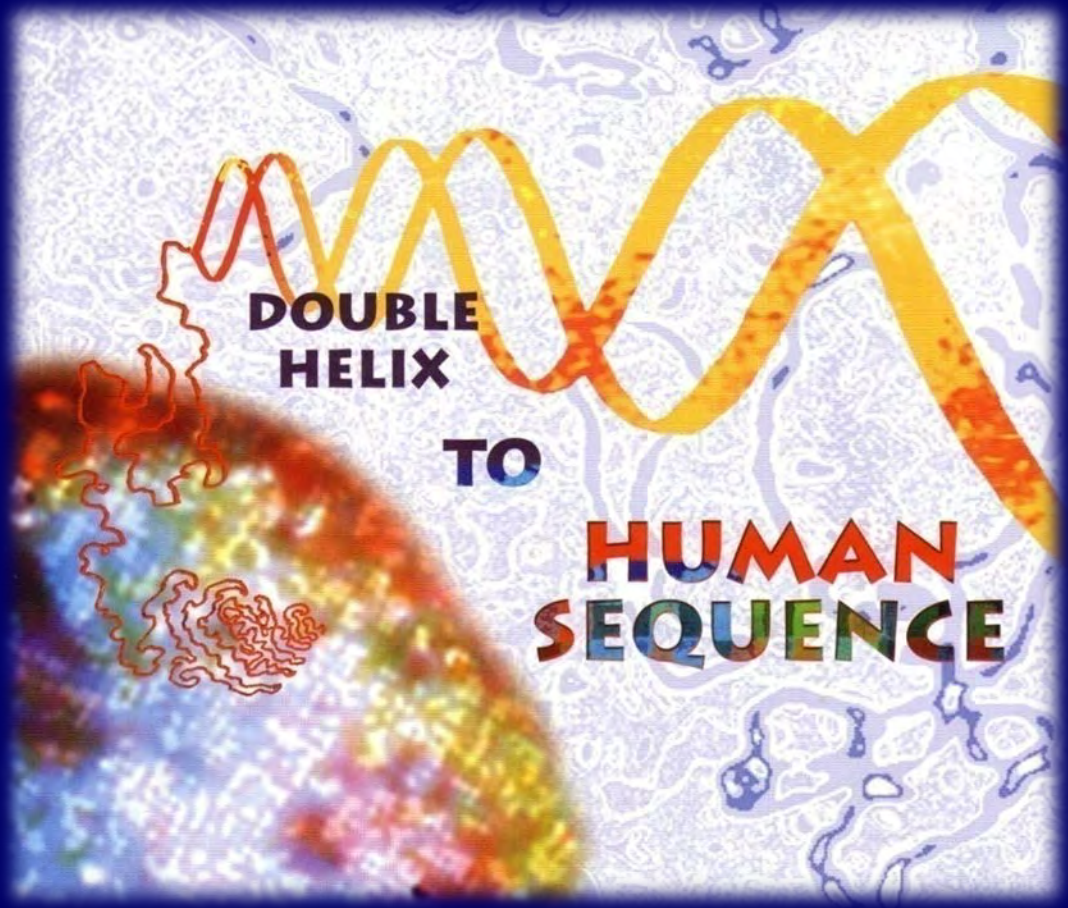
~10 Years and ~7 Months Ago



February 2001

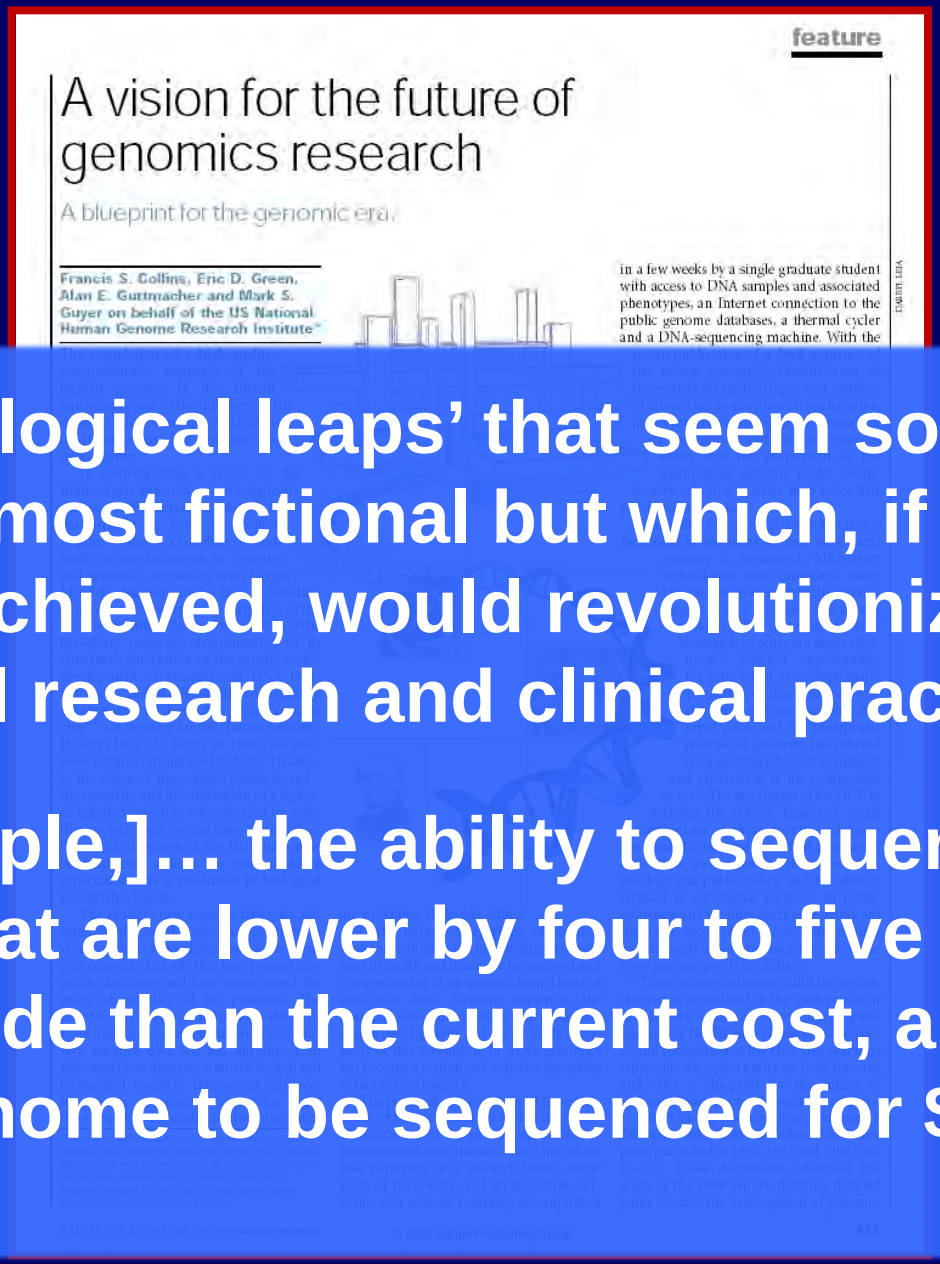
Draft Human Genome Sequence Published

~8 Years Ago



April 2003

Human Genome Project Ends


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*

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

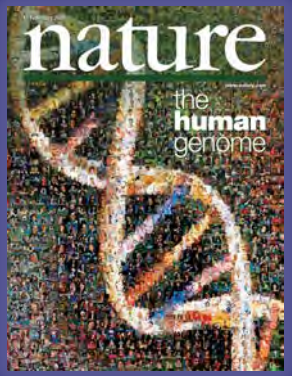
"…'technological leaps' that seem so far off as to be almost fictional but which, if they could be achieved, would revolutionize biomedical research and clinical practice.

[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**

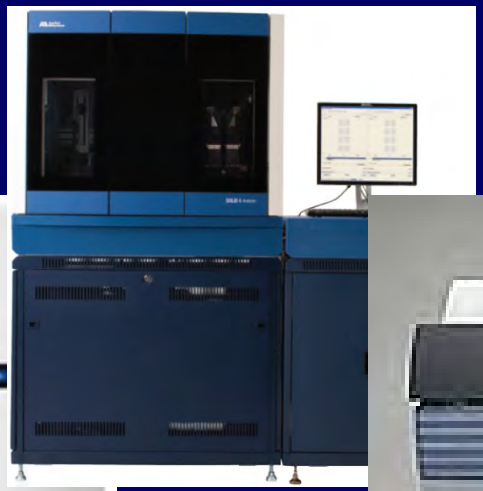
Human Genome Sequence

~$1,000,000,000

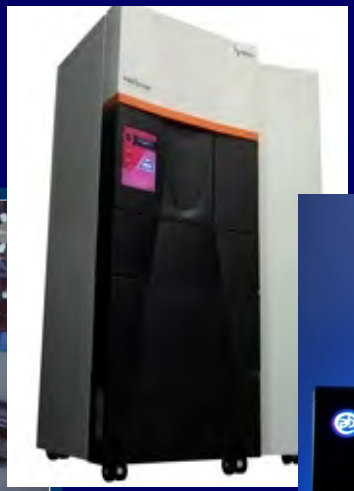


~$1,000

“The $1000 Genome”

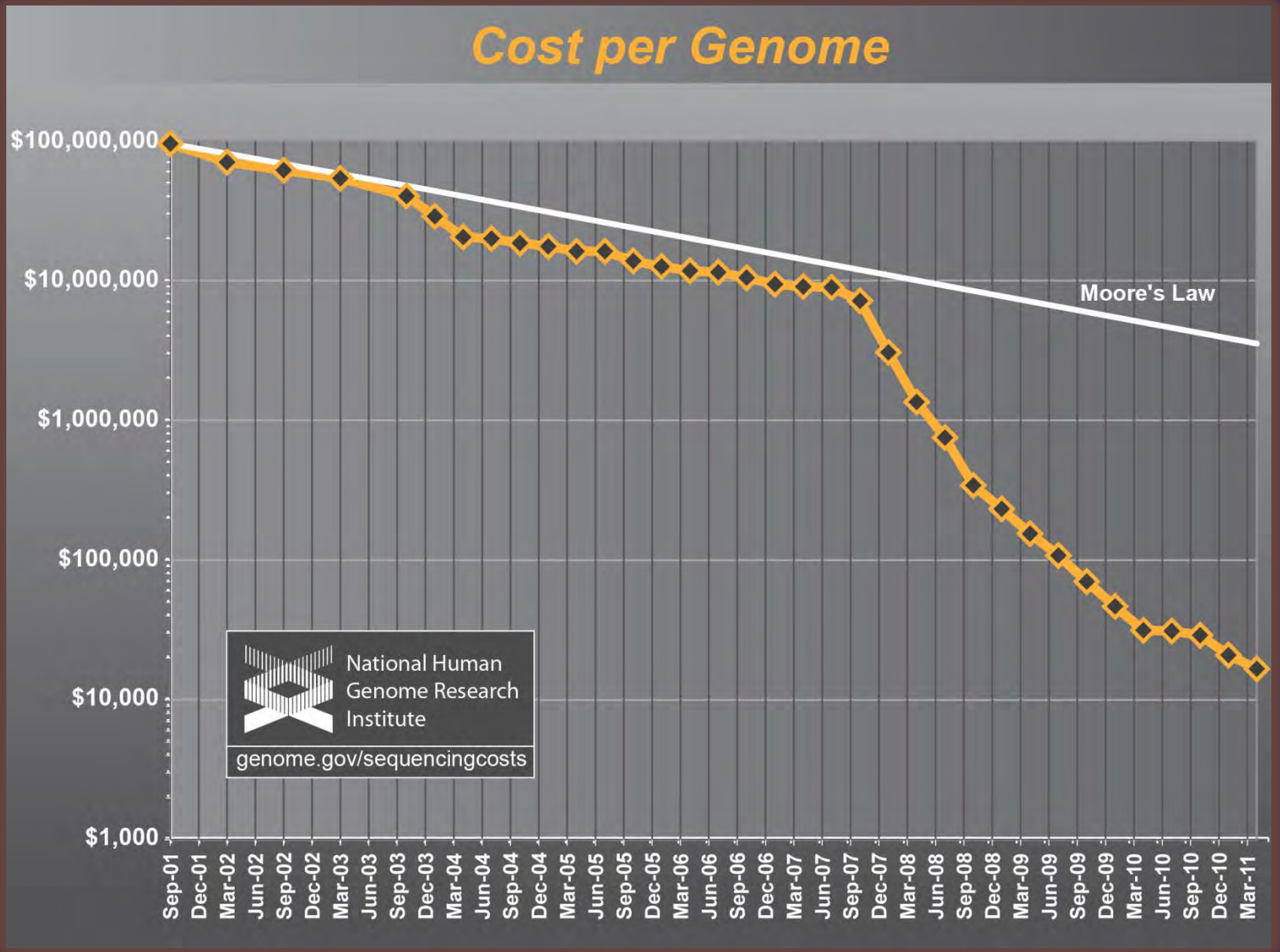



POLONATOR G.007

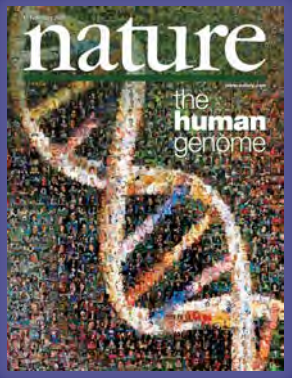



9 September 2010 | www.nature.com/nature | $10
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
nature
DNA SEQUENCING
Enter the graphene nanopore
BIOLOGICAL NOISE
Taking the good with the bad
THE NEW TAXONOMY
Automation rules
DINOSAUR MORPHOLOGY
The hunchback of Las Hoyas
NATUREJOBS
Project management
TGCATTGCTAGCAATGCATTGC
ATGCATGGCTAGCAAAAAGCATGGT
AATGCACCCTGCTAAAGGGATACAG

Cost per Sequenced Human Genome



Human Genome Sequence



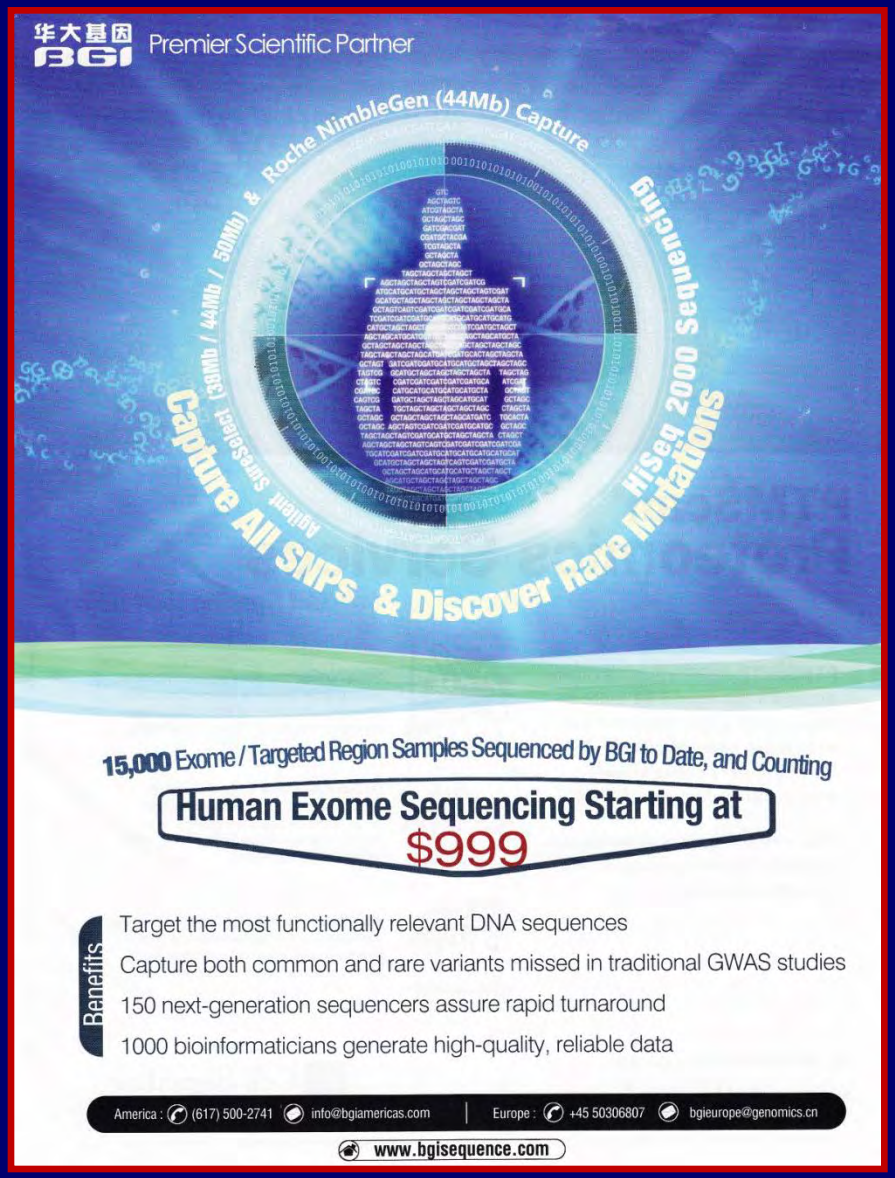
~$1,000,000,000

Current Cost

~$1,000

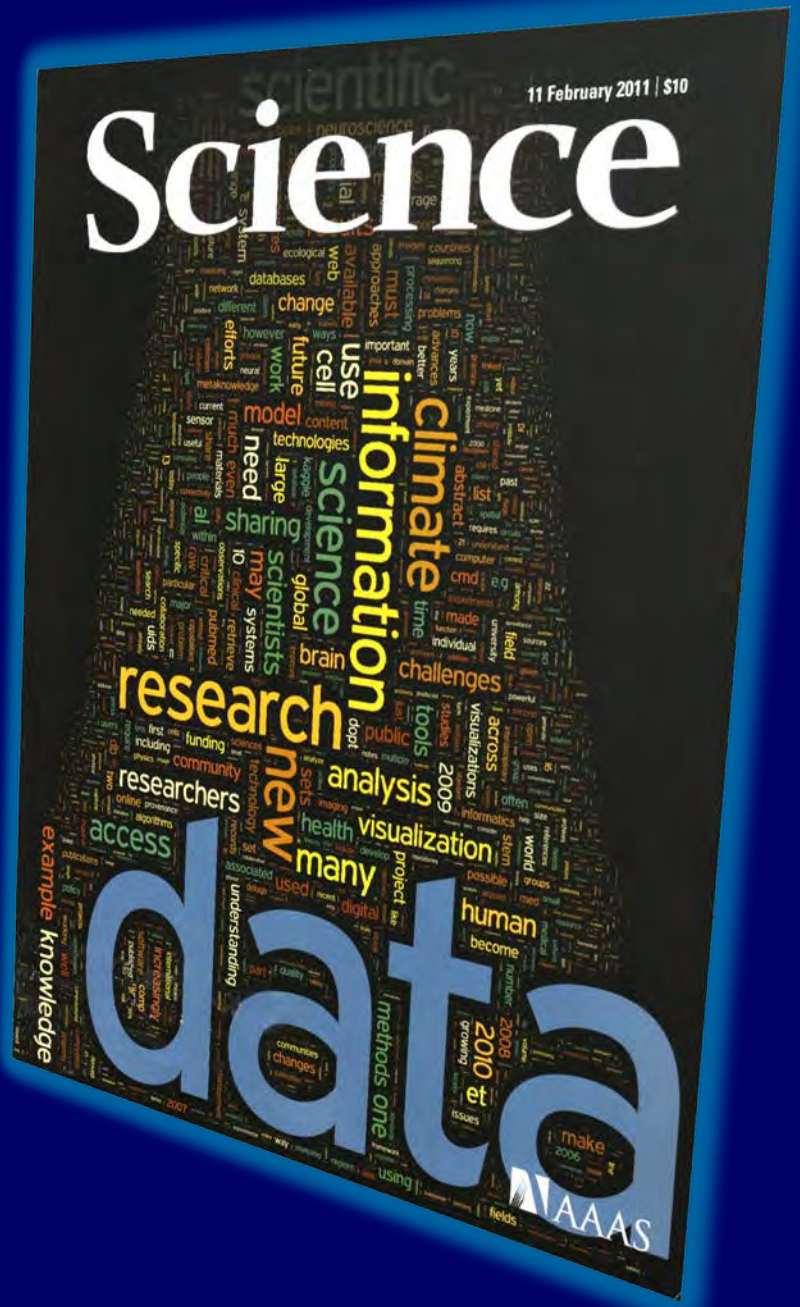
"The $1000 Genome"

Genome Sequencing as a ‘Commodity’



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
data
climate
information
science
research
challenges
analysis
visualization
researchers
access
new
many
human
AAAS

The Informational Bottleneck

Ten Years On — The Human Genome and Medicine

Harold Varmus, M.D.

On a June day nearly 10 years ago, the leaders of the United States and the United Kingdom, accompanied by the leaders of the public and private teams deciphering the human genome, announced that a draft sequence had been completed. That occasion was rich with promises of new and more powerful ways to understand, diagnose, prevent,

Human Genome Project has not yet directly affected the health care of most individuals."[2]

In this issue, the *Journal* begins another series of articles on genomic medicine.[3] Is it appropriate for the *Journal* to be taking stock so soon? It is, and for the following reasons.

First, readers will want to know the state of

Physicians are still a long way from submitting their patients' full genomes for sequencing, not because the price is high, but because the data are difficult to interpret.

some strong genetic markers for assessing drug responsiveness, risk of disease, or risk of disease progression — have entered routine medical practice. And most of these can be traced to discoveries that preceded the unveiling of the human genome. As Francis Collins, formerly the leader of the publicly funded sequencing efforts, recently commented: "the consequences for clinical medicine . . . have thus far been modest . . . the

influential haplotypes, and in general, other implicated susceptibility haplotypes collectively account for only a small fraction of the apparent heritable risk. Clearly, more than one decade of genomics will be required to understand the inborn risks of most common disorders, such as diabetes and hypertension.

Second, readers will enjoy learning from these articles how rapidly the engines of genomics and

***NEJM* (2010)**

~7 Months Ago

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 update division 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[3] (http://hapmap.ncbi.nlm.nih.gov), and is ongoing with the 1000 Genomes Project[22] (http://www.1000genomes.org).

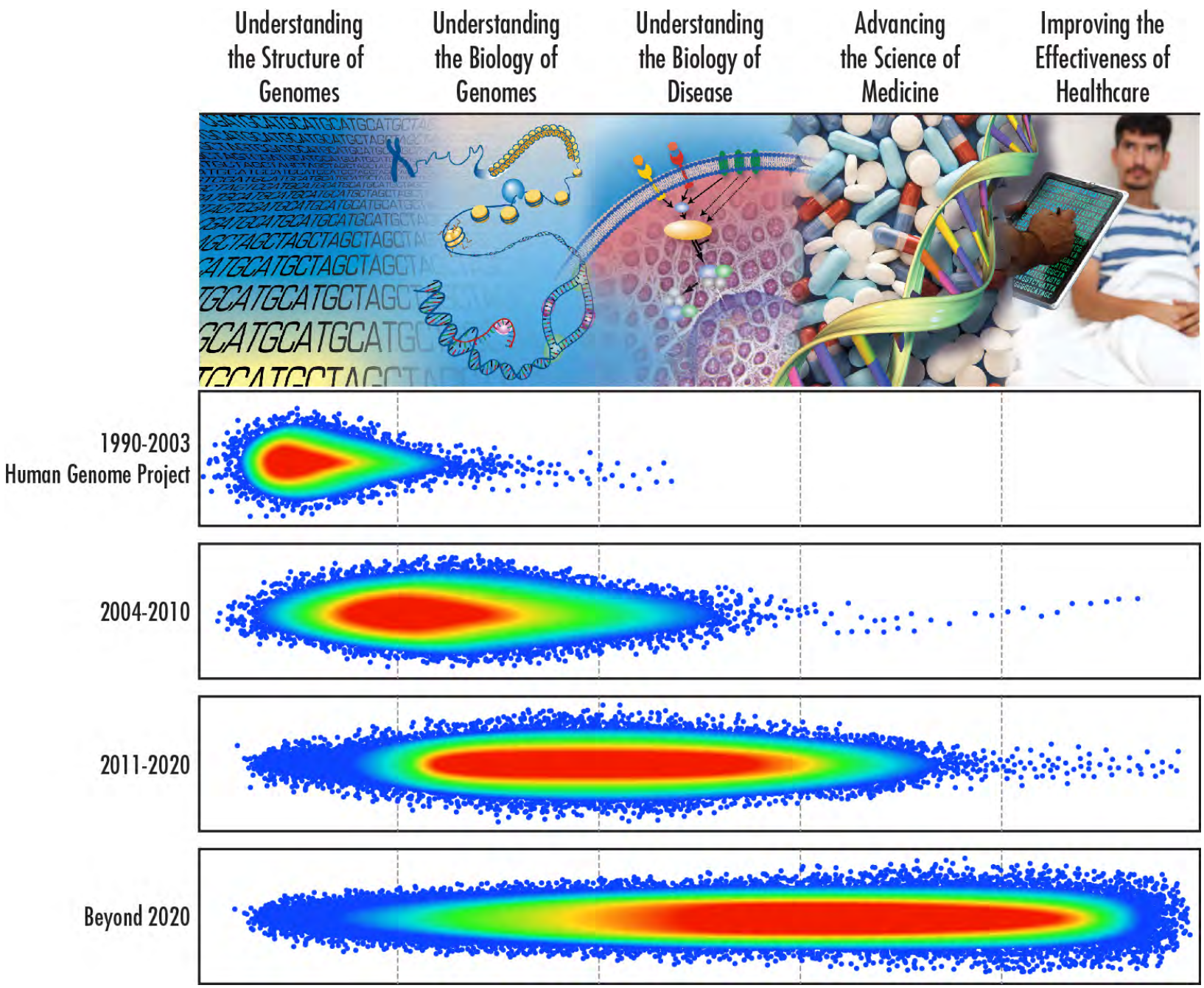
Over the past decade, these catalogues have been critical in the discovery of the specific genes for roughly 3,000 Mendelian (monogenic) diseases

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

NHGRI Published New Vision for Genomics



Green et al. 2011

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.

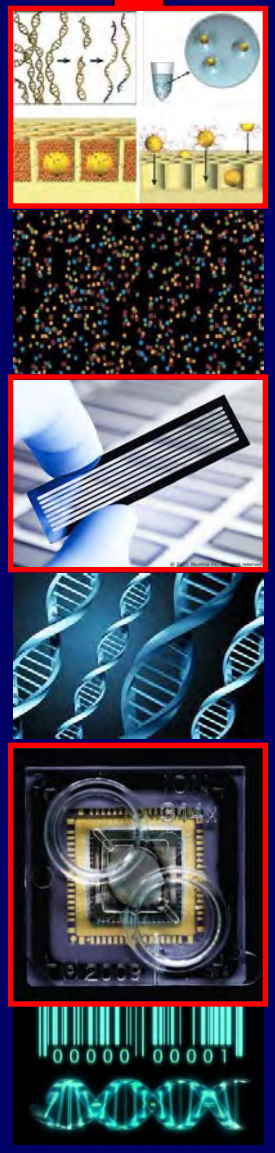
Defining the genetic components of disease. All diseases involve a genetic component. Genome sequencing could be used to determine the genetic variation underlying the full spectrum of diseases, from rare Mendelian to common complex disorders, through the study of upwards of a million patients; efforts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

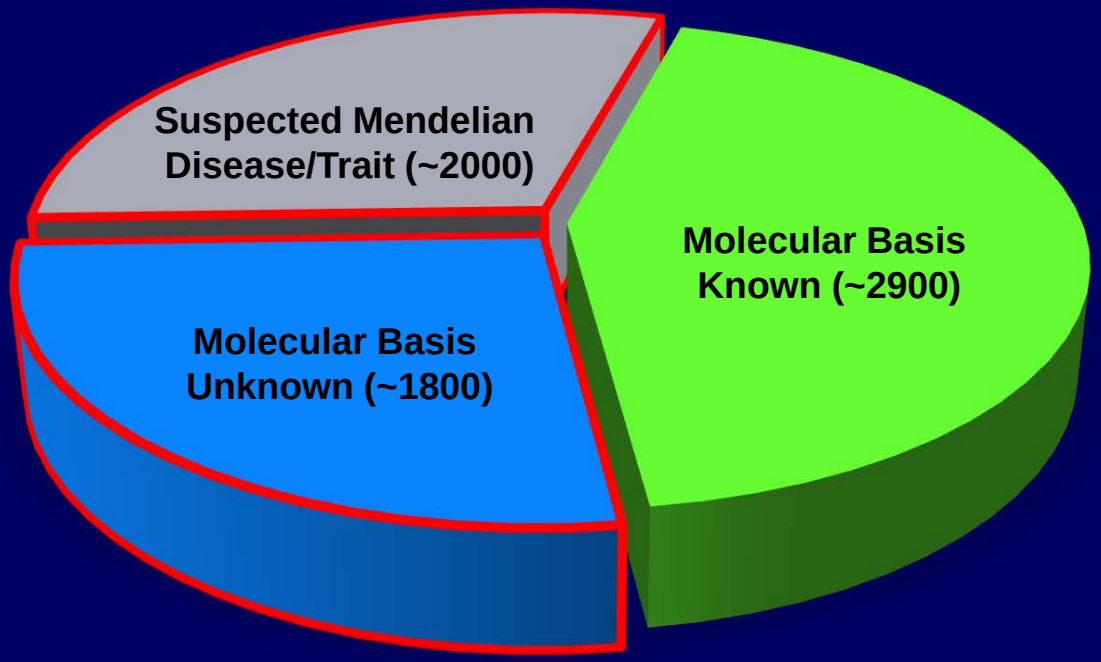
Comprehensive characterization of cancer genomes. A comprehensive genomic view of all cancers[4–7] will reveal molecular taxonomies and altered pathways for each cancer subtype. Such information should lead to more robust diagnostic and therapeutic strategies and a roadmap for developing new treatments[74,75].

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)[101]. Recent initiatives[102,103] (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 microbiome[104]. More extensive studies are needed to build on these first revelations and to investigate approaches for manipulating the microbiome as a new therapeutic approach.

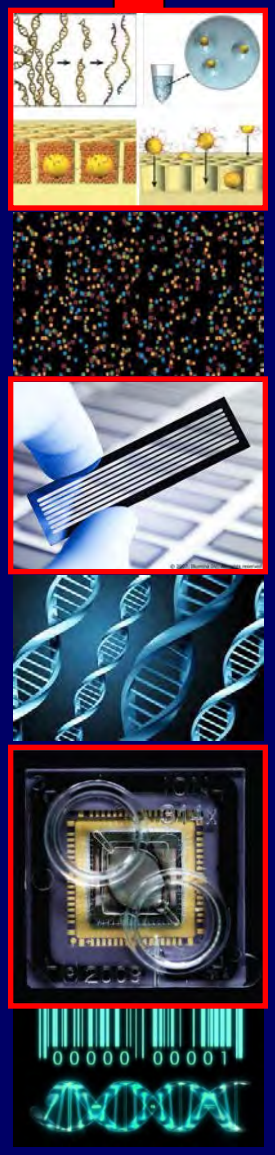
The Future: Genome Sequencing

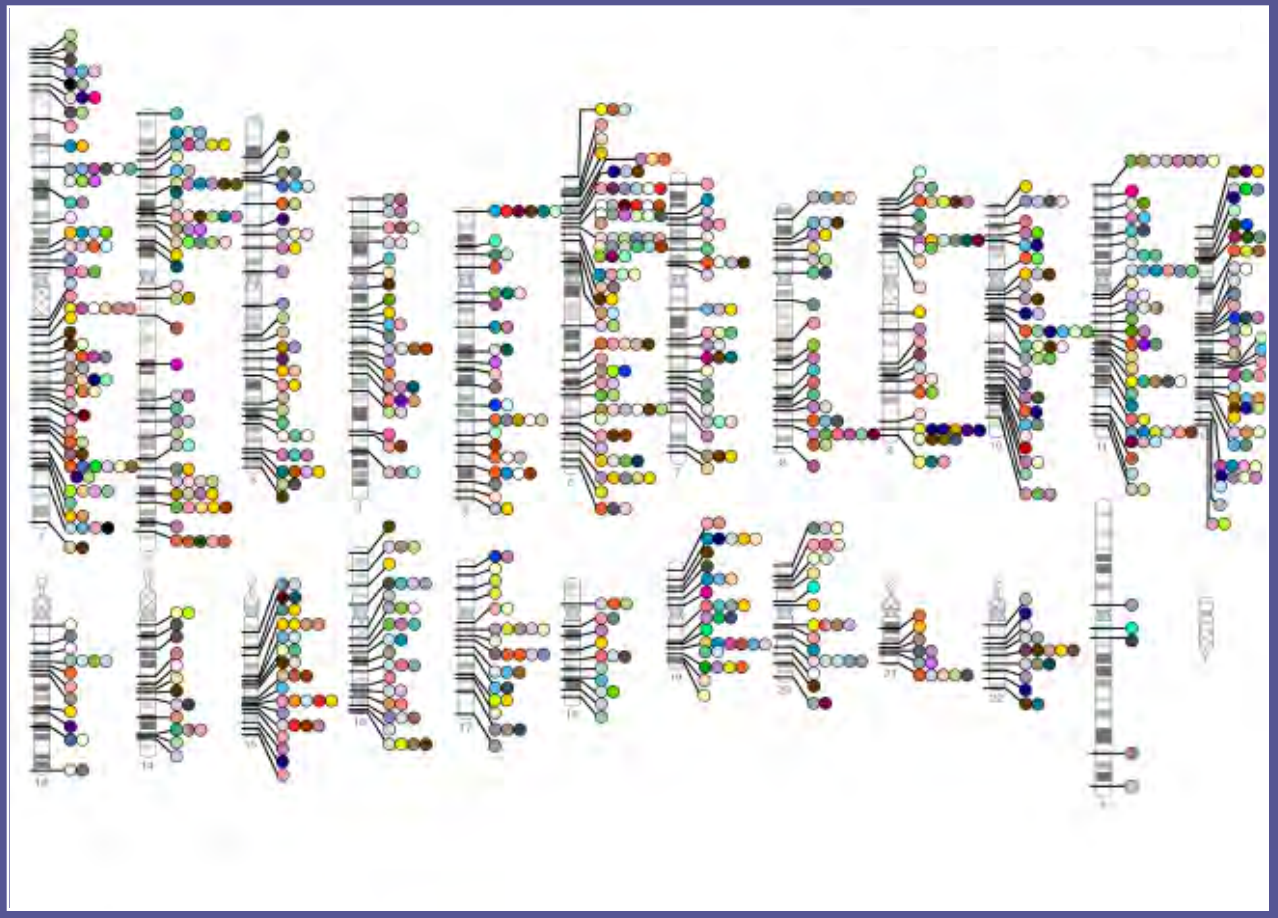




Mendelian Diseases/Traits

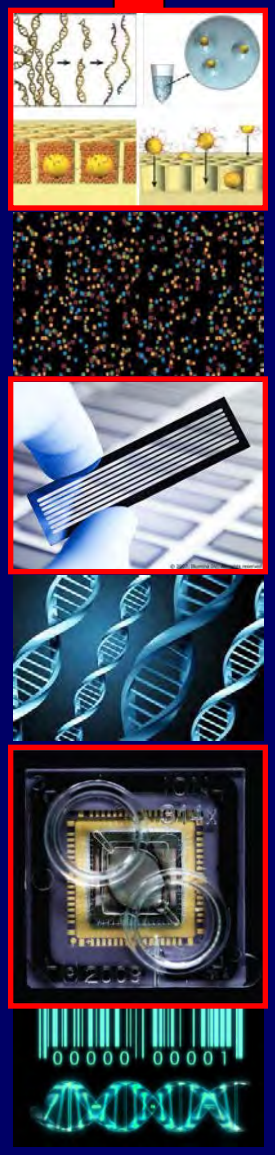
The Future: Genome Sequencing





Complex Diseases/Traits

The Future: Genome Sequencing



National Cancer Institute | National Human Genome Research Institute

The Cancer Genome Atlas — *Understanding genomics to improve cancer care*

Launch Data Portal | Contact Us | For the Media

Search | 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

About Cancer Genomics | TCGA in Action | Cancers Selected for Study | Perspectives

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.

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

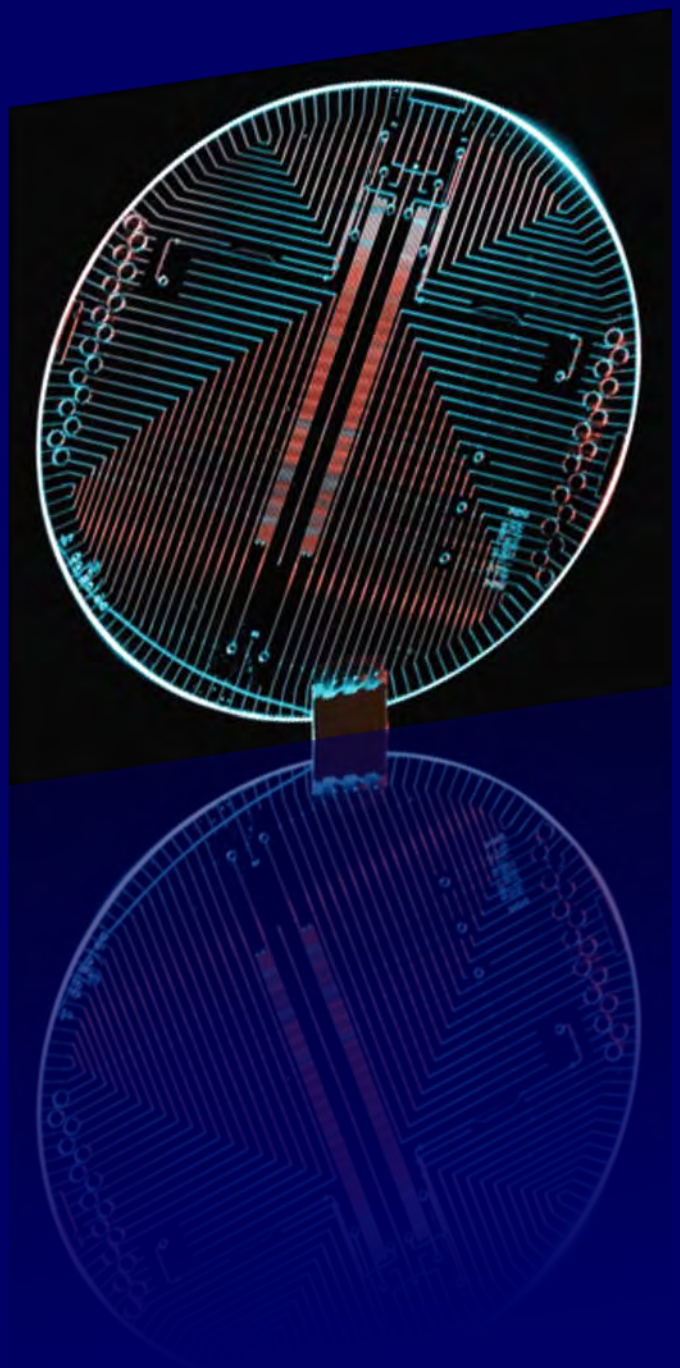
Call 1-800-4-CANCER

Use LiveHelp Online Chat

Multimedia Library

Images
Videos and Animations
Podcasts
Interactive

Cancer Genomics



Clinical Genomic Information Systems

Best is yet to come

Ten years after the human genome was sequenced, its promise is still to be fulfilled.

Former US president Bill Clinton called it the "most important, most wondrous map ever produced by humankind". To then UK prime minister Tony Blair, it was a "breakthrough that takes humankind across a frontier and into a new era". His science minister David Sainsbury said: "We now have the possibility of achieving all we ever hoped for from medicine." When *Nature* published a 62-page article on 15 February 2001 titled 'Initial sequencing and analysis of the human genome' it is not difficult to see why the world got excited. Perhaps, even, a little overexcited. One of our editors, Henry Gee, penned a newspaper piece at the time that promised, by 2099, "genomics will allow us to alter entire organisms out of all recognition, to suit our needs and tastes… [and] will allow us to fashion the human form into any conceivable shape. We will have extra limbs, if we want them — maybe even wings to fly."

As Eric Lander, director of the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, and the first author on that 2001 paper, writes on page 187 of this issue: "The human genome has had a certain tendency to incite passion and excess." A decade on, Lander notes, the pattern continues, with "a front-page news story on the tenth anniversary of the announcement that chided genome scientists for not yet having cured most diseases". The 2001 sequence was always a milestone on the journey to better medical care, rather than a destination. The ten-year anniversary of the publication in *Nature* and *Science* of sequences prepared respectively by the international Human Genome Project and Celera Genomics, now of Alameda, California, provides another — as well as an opportunity to reflect on progress.

Some things have undoubtedly changed. *Nature*'s Editorial page in the 15 February 2001 issue examined not the scientific and medical promise of the genome sequence, but the challenge of public access to information gathered by the commercial genomics sector. Acrimony over the differing public and private approaches has since faded; concerns over access to genomic data now centre on privacy issues.

Has medical progress been slower than was expected at the time? In an article on page 204, Eric Green and Mark Guyer of the US National Human Genome Research Institute in Bethesda, Maryland, offer an "updated vision" of the prospects for genomic medicine. "Significant change rarely comes quickly," they write. "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." Research is not enough, they say, and new policies and practices as part of an expanded global effort are needed too.

The sequencing of the human genome was in many ways a triumph for technology as much as it was for science. That technology has continued to develop over the past decade, which Elaine Mardis of the Genome Center at Washington University in St Louis describes in an article starting on page 198 as a "remarkable sequencing technology explosion".

Massively parallel sequencing technology allows questions to be asked and answered with "unprecedented speed and resolution", she says. "The continuing upward trajectory of sequencing technology development is enabling clinical applications that are aimed at improving medical diagnosis and treatment." A useful example is the development of genome-wide association studies to probe the underlying genetic landscape of some common diseases.

More than a decade ago, Michael Dexter, then head of the UK Wellcome Trust, which took part in the Human Genome Project, branded the genome sequence as the outstanding achievement of human history, eclipsing the significance both of the Moon landings and of the invention of the wheel. It is too early for that history to be written. For the genome sequence to be a true success, we must yet ensure that greater achievements are built on it. ■

NATURE.COM
To comment online, click on Editorials at:
go.nature.com/xhuuqv

"The 2001 [human genome] sequence was always a milestone on the journey to better medical care, rather than a destination."


NHGRI
genome.gov