Thalassemia Research Center

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หนึ่งทศวรรษ(หลังโครงการ)จีโนมมนุษย์ กับการวิจัยทางการแพทย์

Suthat Fucharoen, M.D.

Thalssemia Research Center
Institute of Molecular Biosciences
Mahidol University

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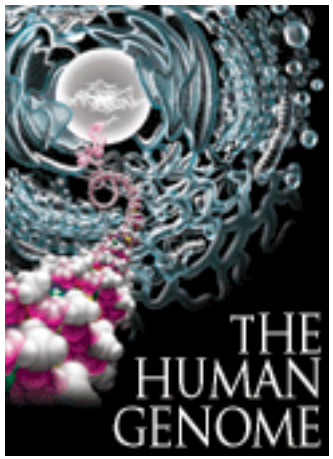
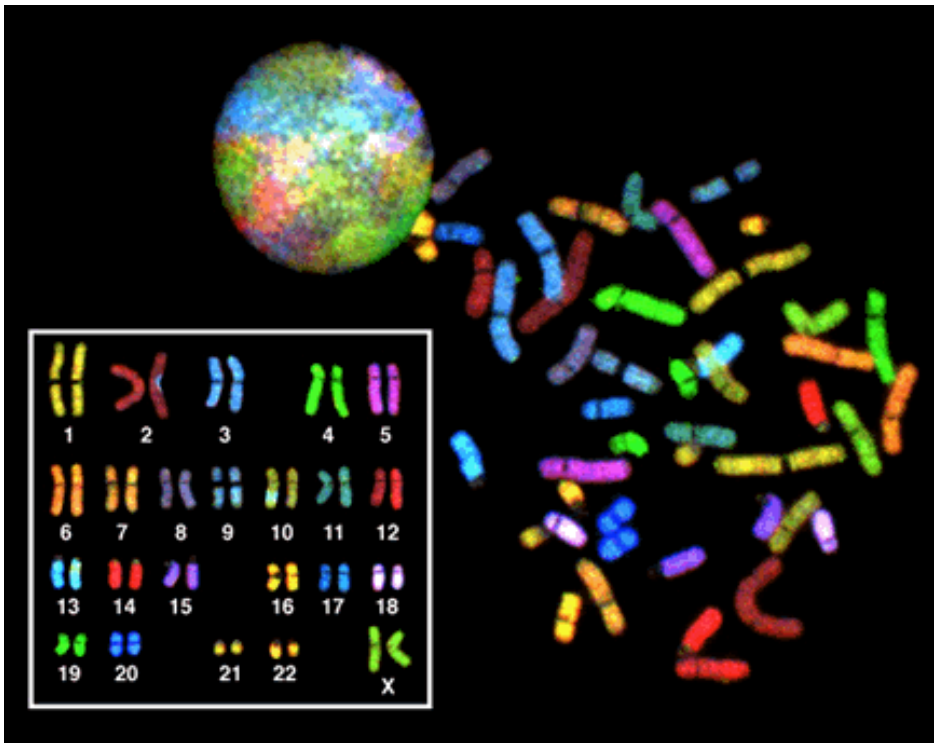
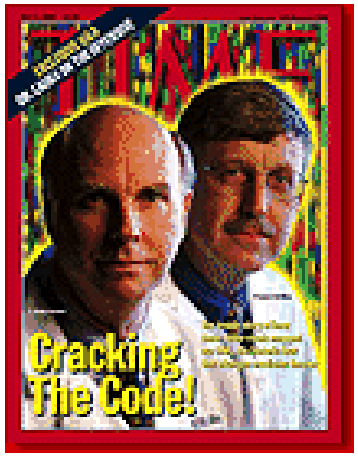
The Human Genome Project

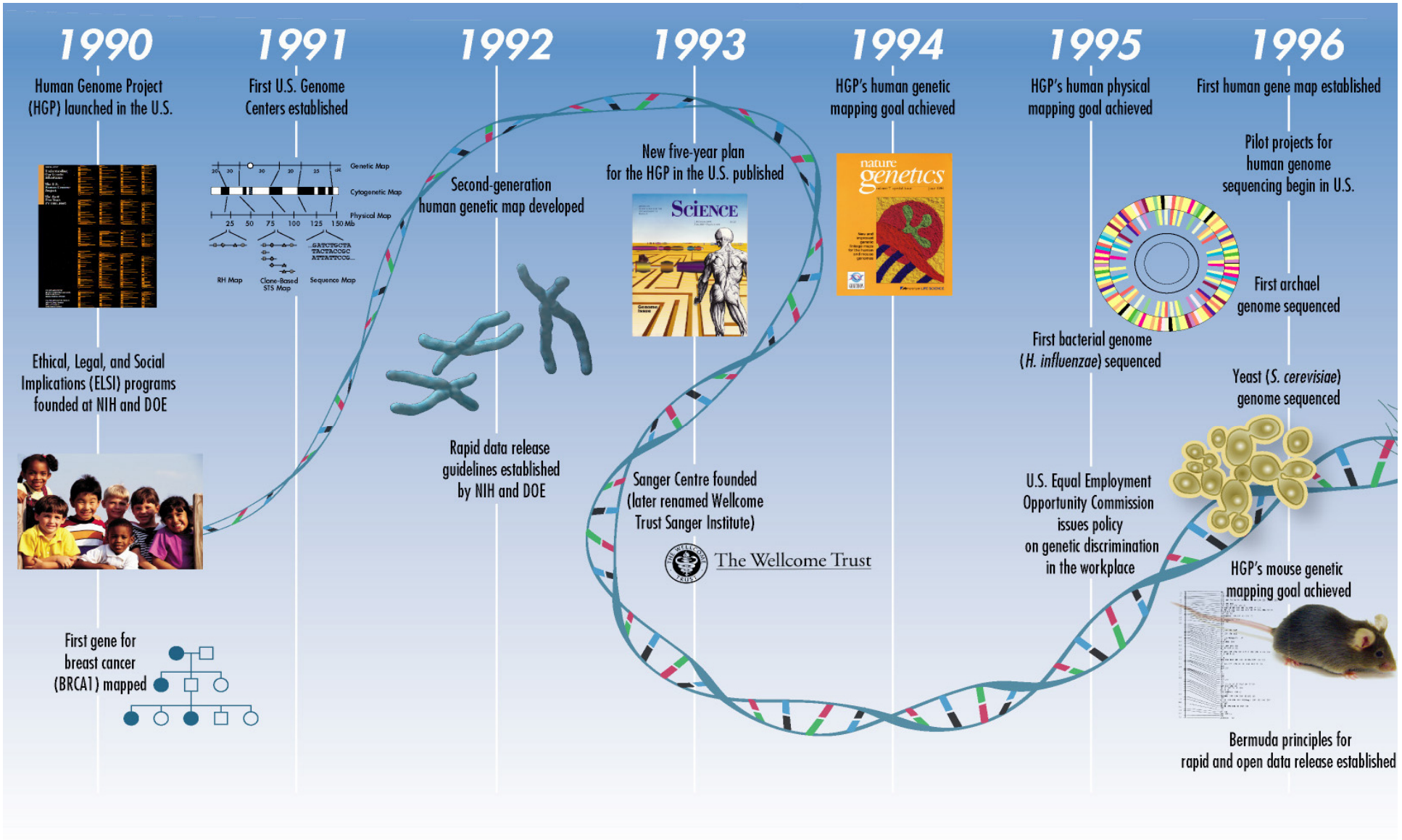






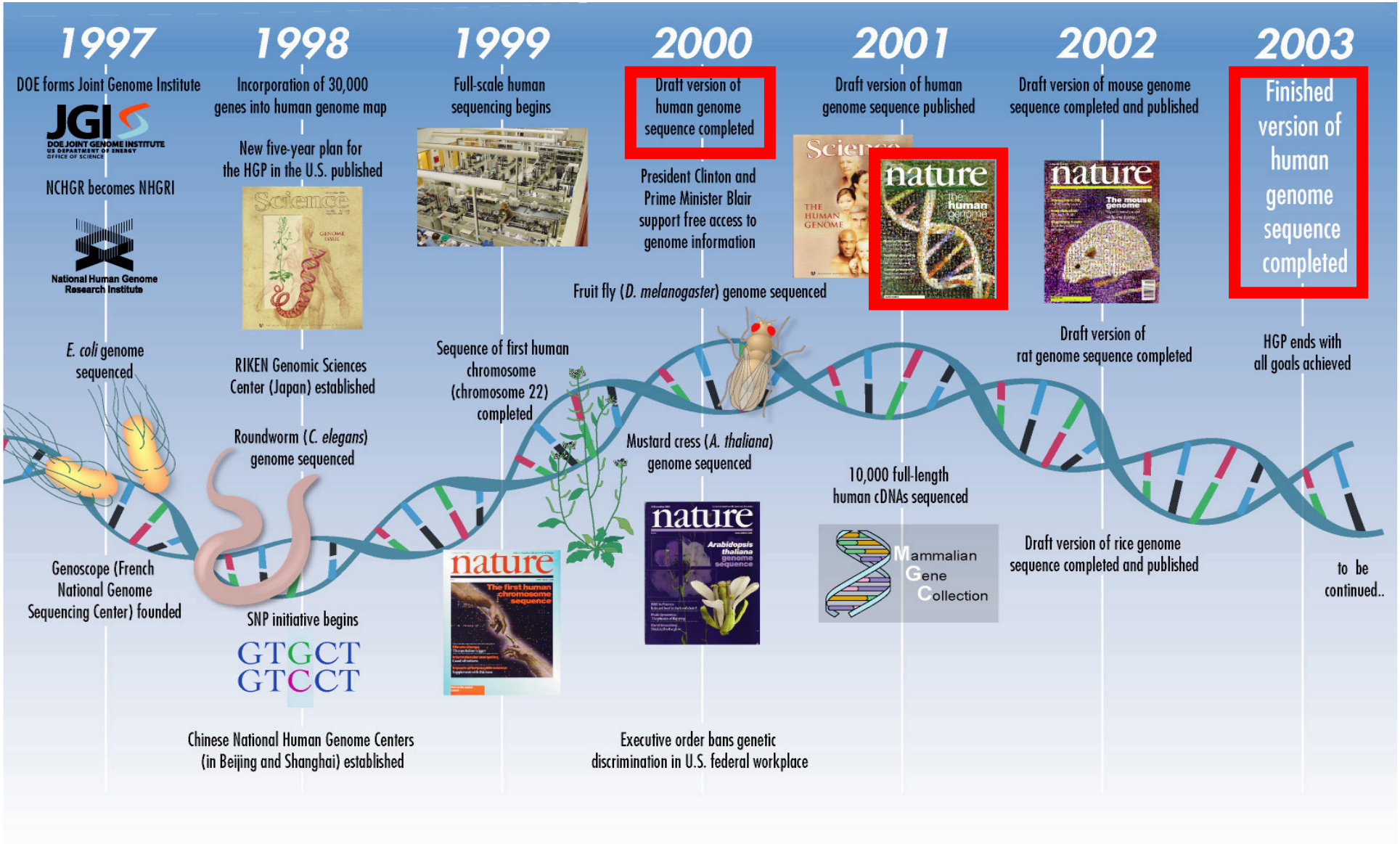
3 billion bases **30,000 genes**

http://www.genome.gov/



Human Genome Project Timeline

www.gonome.gov



Human Genome Project Timeline

www.gonome.gov

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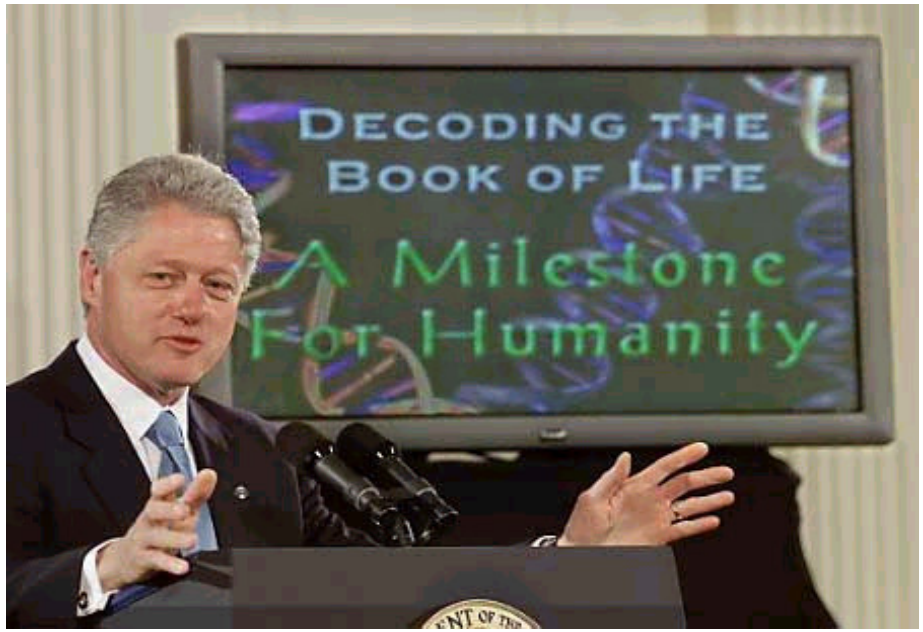
President Bill Clinton, J Craig Venter (left) and Dr. Francis Collins

Venter's company Celera Genomics Corporation participated in a publicly financed Human Genome Project with private efforts



1st Human Genome Draft Sequence

June 26, 2000

President Clinton announced,
``Today, we are learning the
language that allowed God to create life.``

USA	54%
UK	33%
Japan	7%
France	3%
Germany	2%
China	1%

"China has become the latest contributor to the worldwide sequencing effort alongside France, Germany, Japan, UK and USA."

International Human Genome Sequencining Consortium
1 Sept. 1999

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HGP

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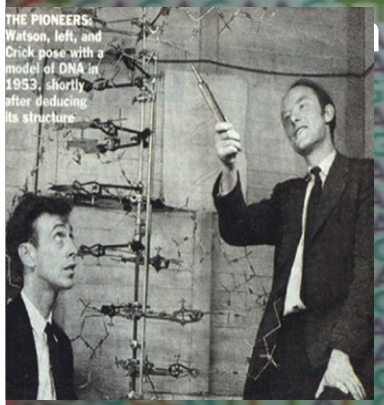
"Life is of sequence"

"The precise sequence of the bases is the code which carries the genetic

."

Watson & Crick
May 30, 1953

"GENETIC IMPLICATIONS OF THE STRU CTURE OF DE-OXYRIBONUCLEIC ACIDS"



"Life is digital!"

"the instructions for making a life from one generation to the next is digital, NOT analogue . "

John Sulston, 2001

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Two Platforms of Genomics

"Life is of sequence"

Sequencers

"Life is digital!"

Supercomputers

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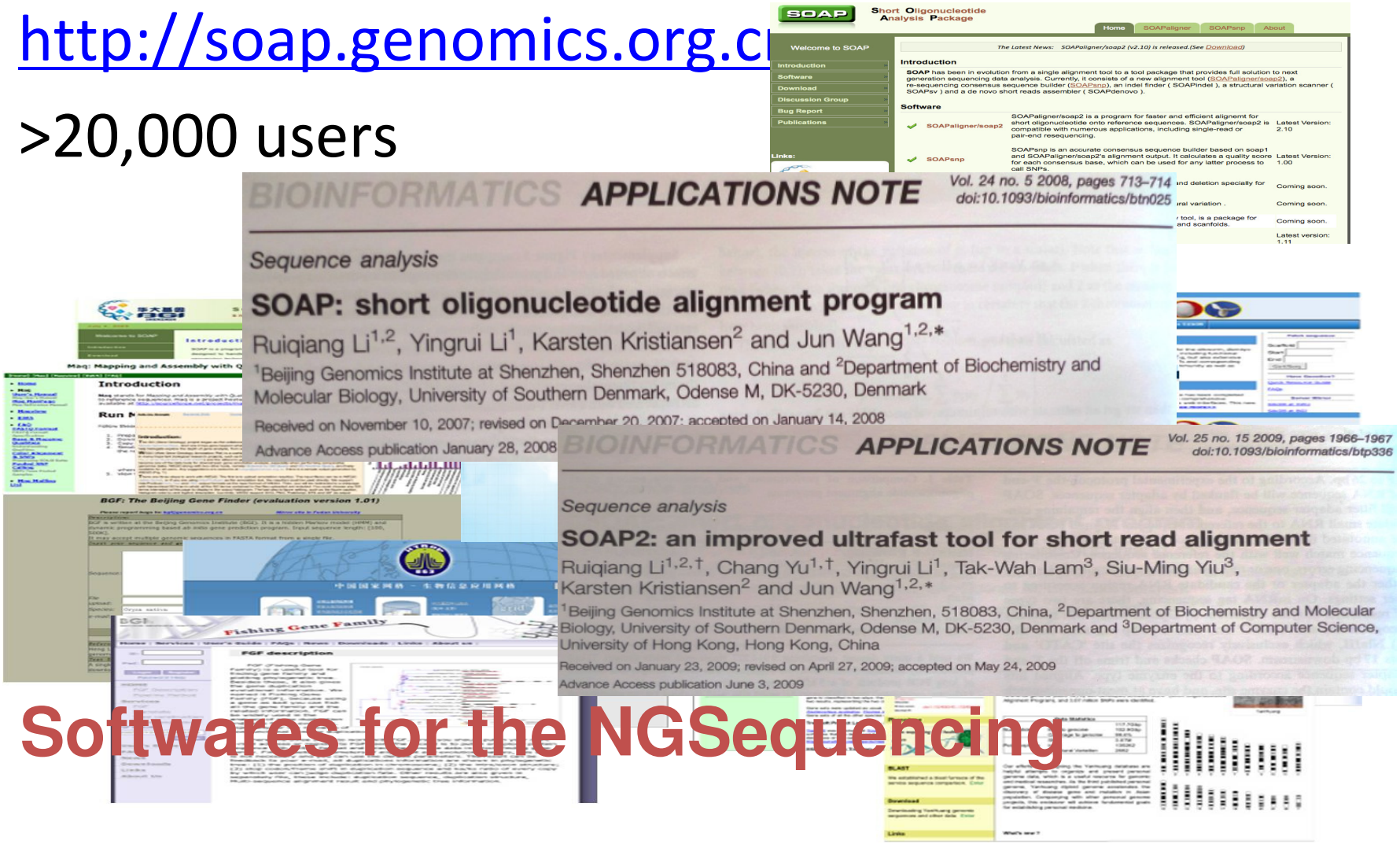
Bioinformatics: the core competiveness

SOAP: Short Oligonucleotide Alignment Program

http://soap.genomics.org.cn

>20,000 users



Softwares for the NGSequencing

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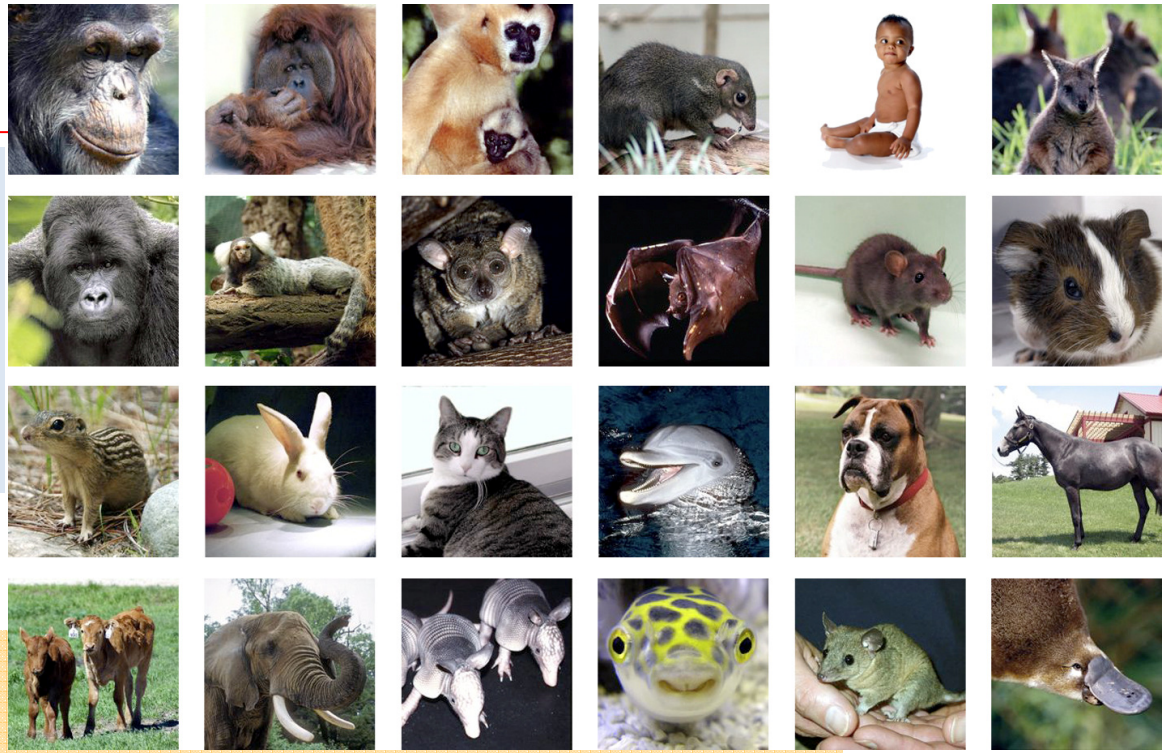
2003: The Complete Human Genome Sequence
All 3,000 million G, A, T, C letters
All 30,000 genes

View from 2000

4 eukaryotes (yeast, fly, nematode, Arabidopsis)

38 prokaryotes

Total < 500 Mb



View from 2010

Today

250 eukaryotes (~120 Gb)

4000 bacteria and viruses (~5 Gb)

Metagenomic samples (ocean, environment, gut, skin)

>500 human genomes resequenced, lots more in progress

10,000 vertebrates under discussion

(A courtesy by E. Lander)

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James Watson received a digital copy of his genome sequence from Jonathan Rothberg (Ion Torrent, Inc).

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Archbishop Tutu Gets Sequenced--And Finds a Surprise in His Ancestry

The richness of the African gene pool is demonstrated by decoding DNA from the antiapartheid activist and several Bushmen hunter-gatherers

From HGP to HapMap

from

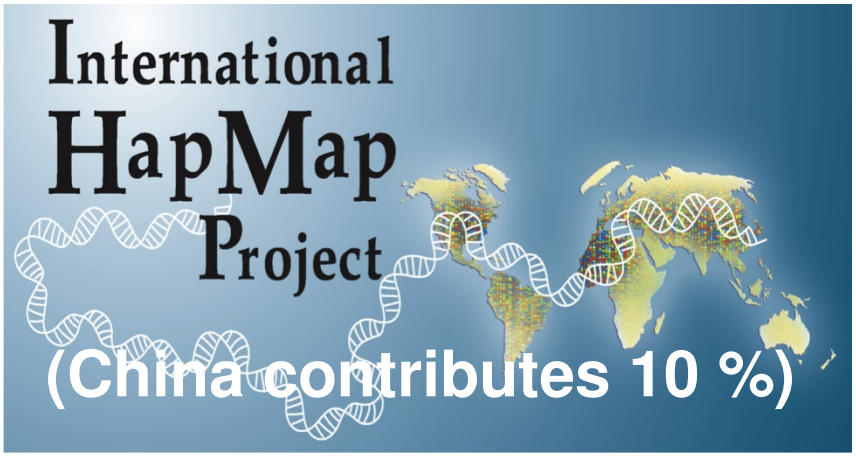
a *representative* genome

of a single Caucasian individual

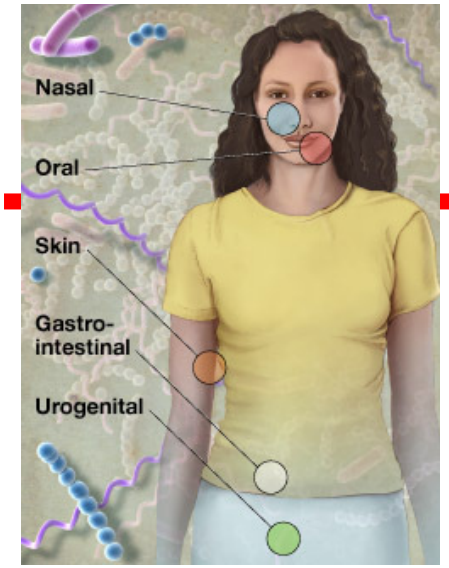
to

population variations (>4m SNPs)

of 270 individuals from 3 major populations



Human Metagenomes



SEVENTH FRAMEWORK PROGRAMME

MetaHIT

ARTICLES

A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin[1]
Chaysavar
Junhua Li[1]
Yinlong Xi
Paslier[10], A
Keith Turn
Songgang
Karsten Kr
S. Dusko E

R. Mende[2],
ong Zheng[1],
Denis Le
en[9],
hang[1],
[5],
Peer Bork[2],

> 2000 species

> 3 m ORFs

To understa
we describ
microbial g
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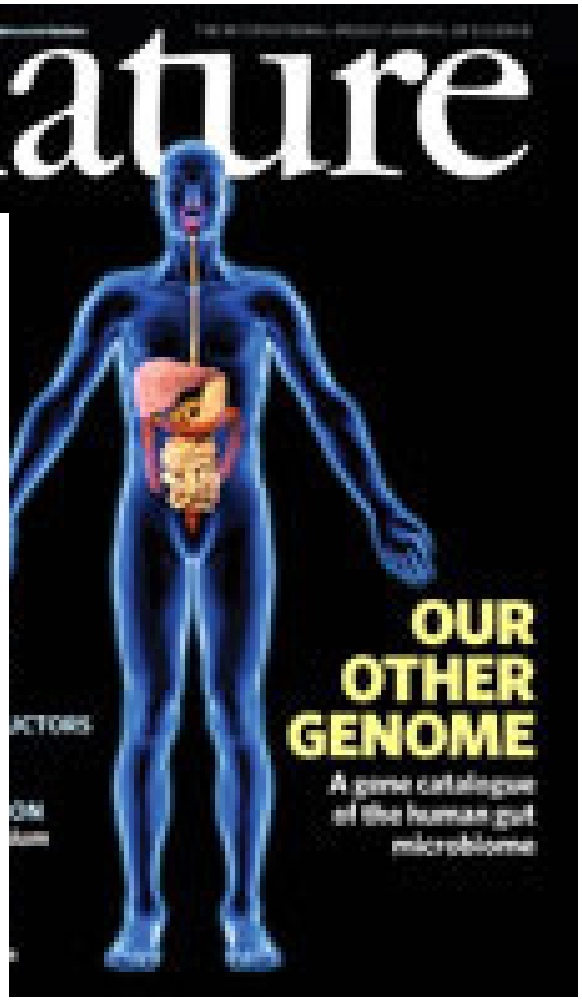
otential. Here
edundant
The gene set,
ore frequent)
ial genes. The

genes are largely shared among individuals of the cohort. Over 99% of the genes are bacterial, indicating that the entire cohort harbours between 1,000 and 1,150 prevalent bacterial species and each individual at least 160 such species, which are also largely shared. We define and describe the minimal gut metagenome and the minimal gut bacterial genome in terms of functions present in all individuals and most bacteria, respectively.



March 4, 2010

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Ethical issues in medical genetics

ETHICS

LEGAL

SOCIAL

IMPACT

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"Life Sciences for All" in the 21st Century

Humanitarian
Ethical
Legal
Cultural
Responsibility
Economic
Safety/Security
Social

HELCRESS Issues

(from ELSI to HELCRESS issues)

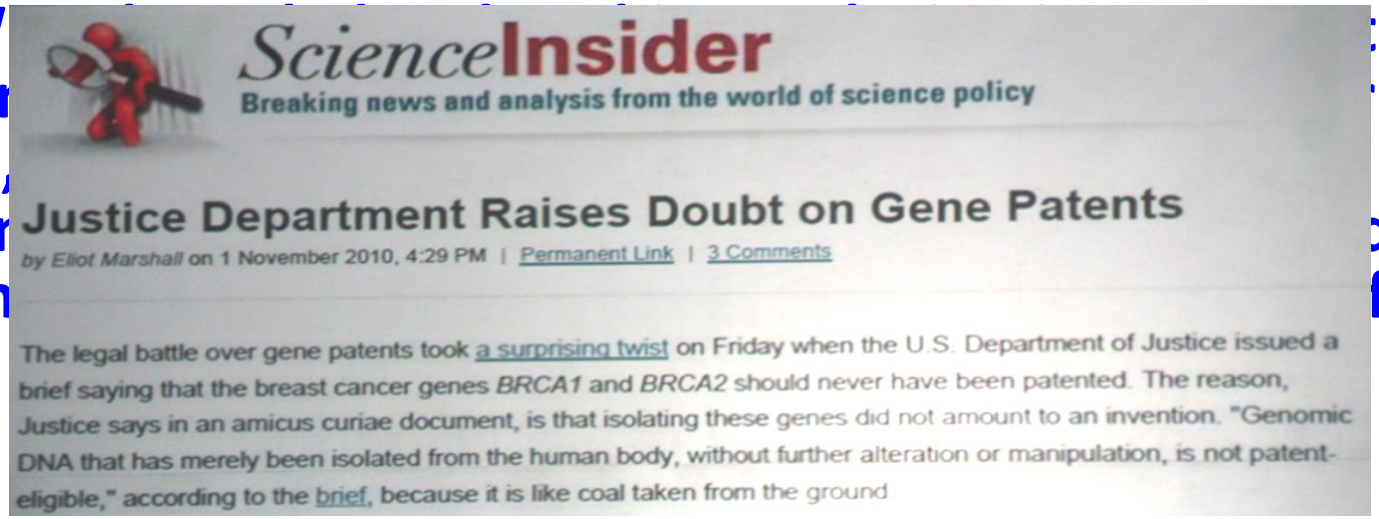
U.S. Says Genes Should Not Be Patented

New York Times By ANDREW POLLACK, October 29, 2010

The federal government said on Friday that human and other genes should not be eligible for patents because they are part of nature.

The new position could have a huge impact on medicine and on the biotechnology industry. The new position was declared in a friend-of-the-court brief filed by the Department of Justice late Friday in a case involving two human genes linked to breast and ovarian cancer.

"W…o the lo…k Office, gover…d obtain…f said.



ScienceInsider

Breaking news and analysis from the world of science policy

Justice Department Raises Doubt on Gene Patents

by Eliot Marshall on 1 November 2010, 4:29 PM | Permanent Link | 3 Comments

The legal battle over gene patents took a surprising twist on Friday when the U.S. Department of Justice issued a brief saying that the breast cancer genes *BRCA1* and *BRCA2* should never have been patented. The reason, Justice says in an amicus curiae document, is that isolating these genes did not amount to an invention. "Genomic DNA that has merely been isolated from the human body, without further alteration or manipulation, is not patent-eligible," according to the brief, because it is like coal taken from the ground

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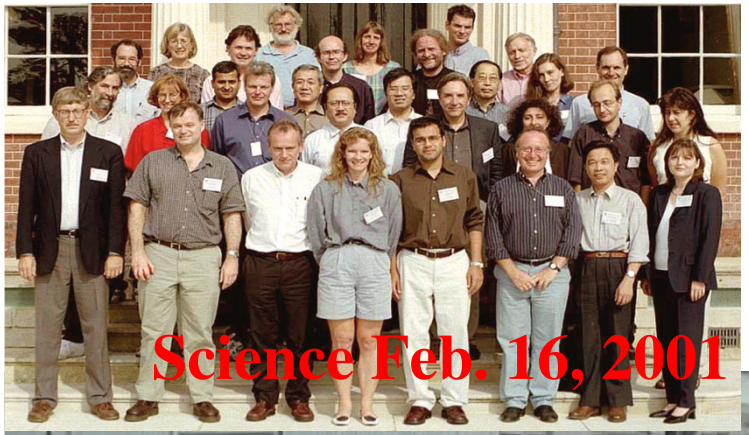
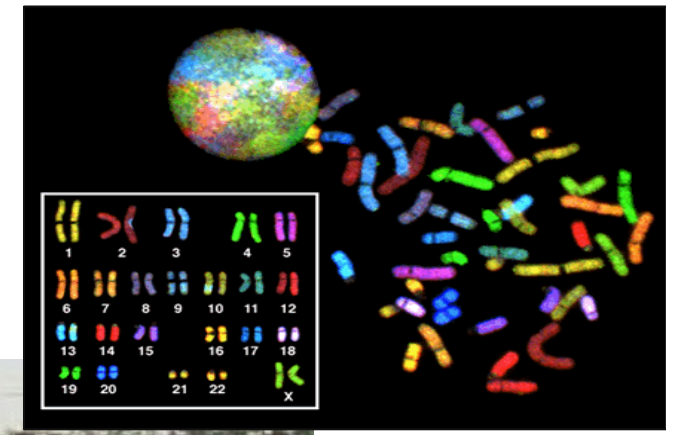
"The HGP Spirit"

"Owned by all, done by all, shared by all!"

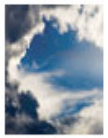




nature International weekly journal of science

FEATURES OF THE YEAR









Chinese bioscience: The sequence factory

The bold ambitions of one institute could make China the world leader in genome sequencing. David Cyranoski asks if its science will survive the industrial ramp-up.

David Cyranoski


THE SEQUENCE FACTORY

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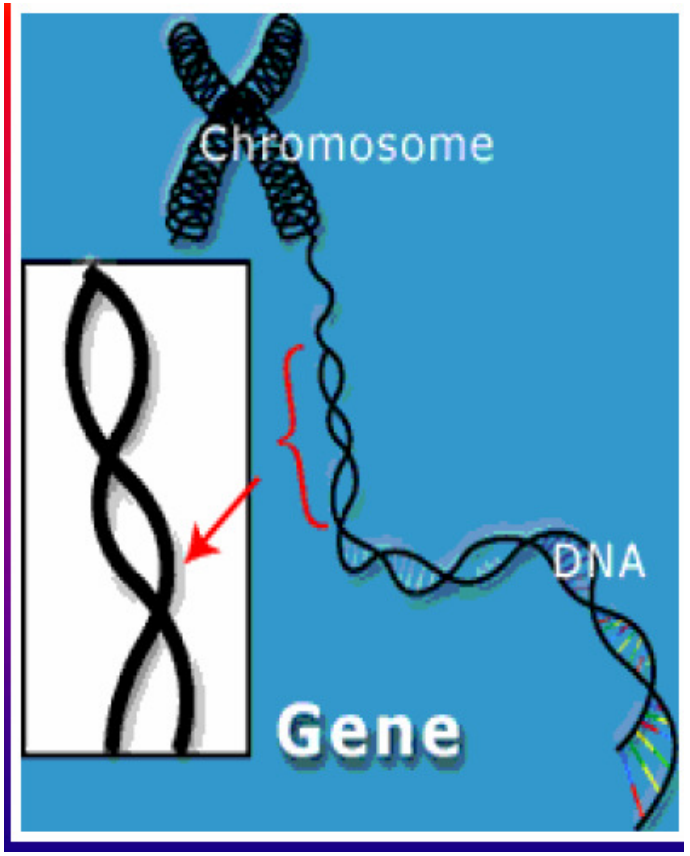
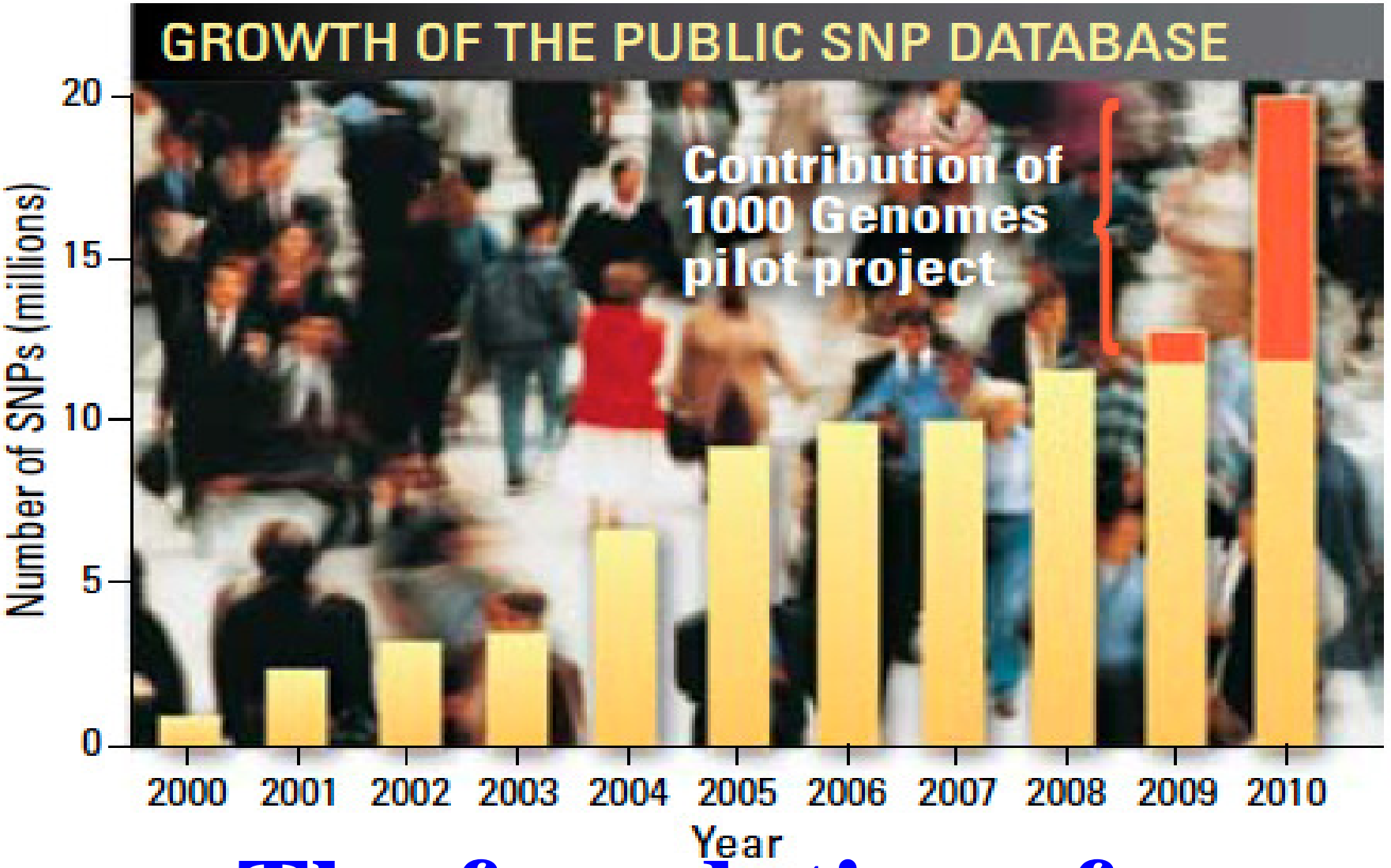
- The success of the last 10 years have mainly been in the identification of monogenic “Mendelian” diseases.
- Little progress has occurred in understanding the genetic contribution to common complex disease.
- Shift in strategies to find multiple genes which contribute small to modest effects.



➢ *Genome-wide association studies*



Pinning down differences. The 1000 Genomes Project has greatly increased the number of known single-base differences that can exist among people.

The foundation of a new wave of GWAS

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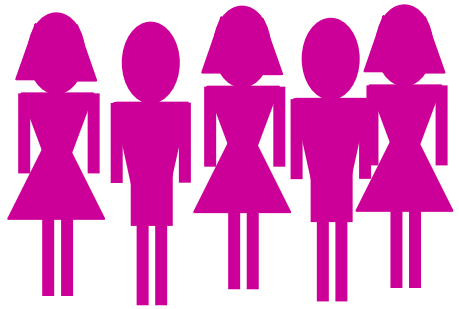
Principle of GWAS

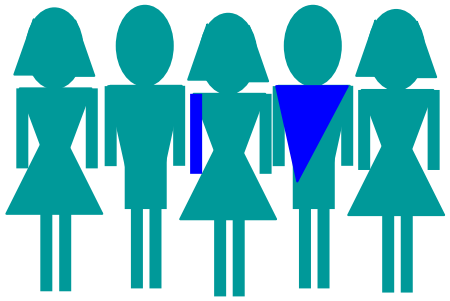


Principle

The frequency of Allele A is obviously higher in case than in control, which suggested that allele A was associated with the disease.

ATGCAAGCTGATCGATCGATCGCGACCATGCAGCACCTGACTGC

ATGCAAGCTGTTCGATCGATCGCGACCATGCAGCACCTGACTGC



	Alllele	
	A	T
Cases	55%	45%
Controls	30%	70%

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Thalassemia in Thailand

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α-Thalassemia (α-thal1 and α-thal2)	20 - 30%
Hb Constant Spring (□-thal 2 like effect)	1 - 8%
□-Thalassemia	3 - 9%
Hemoglobin E	10 - 53%

Total number of thalassemic patients and the number of births per year (total births = 800,000/year)

Diseases	Couple at risk (per year)	Birth (per year)	Living patients
Homozygous □-thalassemia	828	207	2,070
□-Thalassemia/Hb E	12,852	3,213	96,390
Hb Bart's hydrops fetalis	3332	833	0
Hb H disease	22,400	5,600	336,000
Total	39,412	9,853	434,460

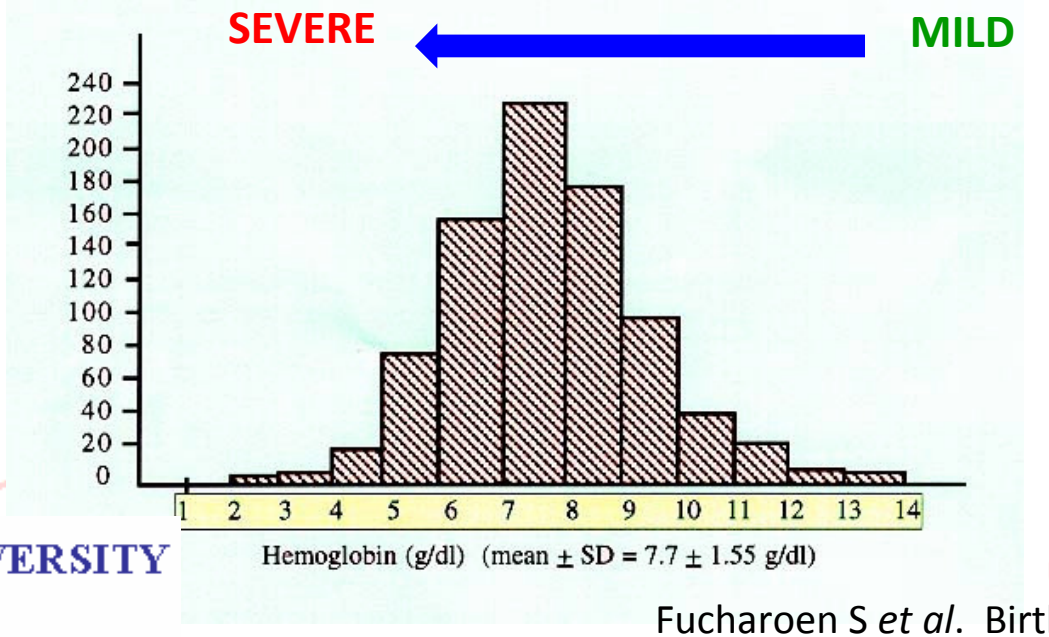
Fucharoen S. and Winichagoon P., 1988

PHENOTYPIC HETEROGENEITY IN β-THALASSEMIA

~1985

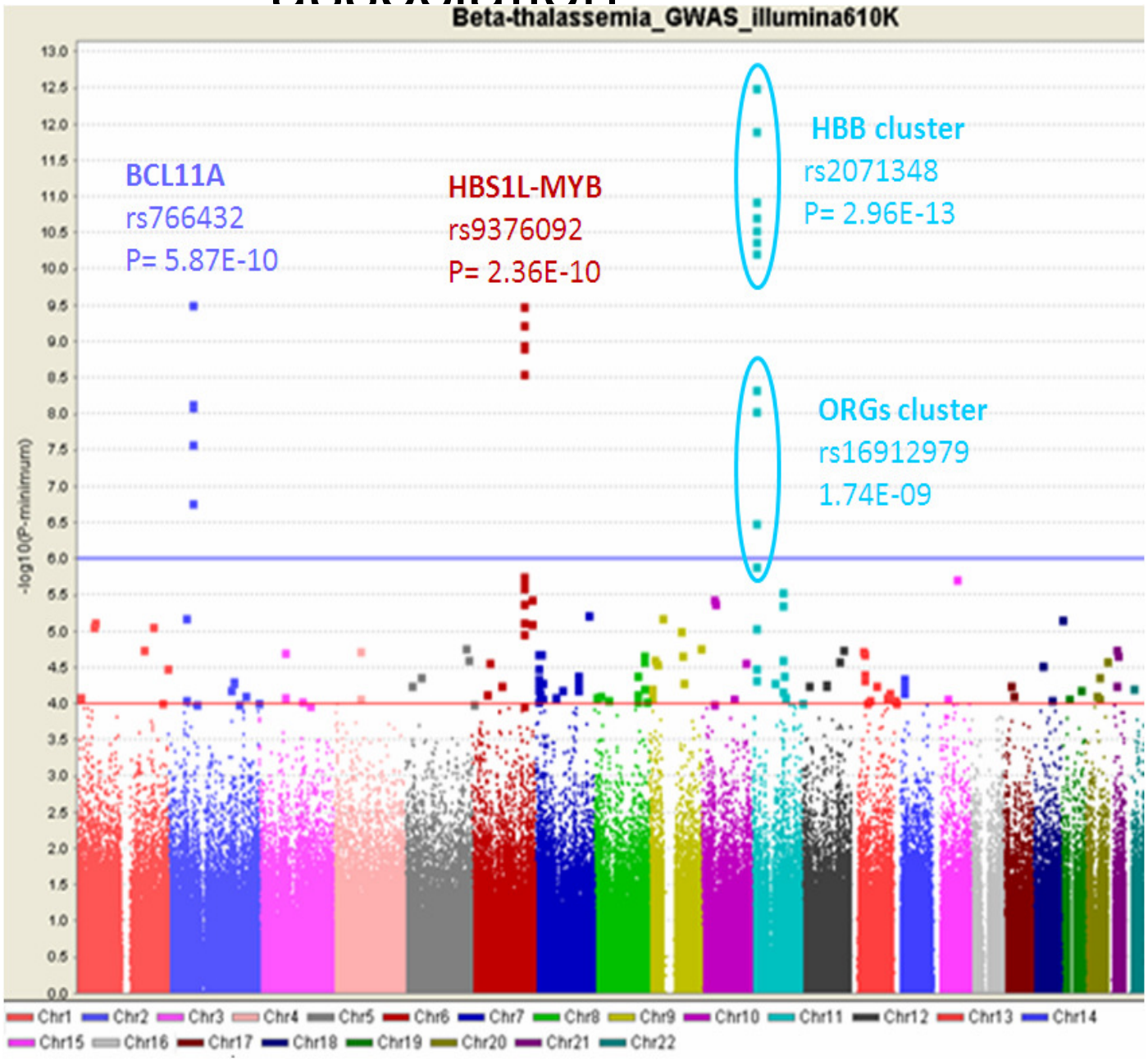
2005

SEVERE ← MILD



Fucharoen S *et al*. Birth Defects, 1988.

Results of genome-wide association



Nuinoon et al. Hum Genetics 125: 303-14, 2010

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The Human Genome Project Still Fails to Deliver its Promised Cures

by M.Thornley, citizen journalist

NaturalNews.com, August 30, 2010

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Mapping the human genome would lead to ``the diagnosis, prevention and treatment of most, if not all, human diseases.``

Francis Collins, director of the genome agency at the National Institutes of Health, concurred, saying at a news conference that

the genome project would lead to a ``complete transformation in therapeutic medicine.`` Ten years later, this promise has not been realized.

HGP suffers from a ``genetic determinist paradigm`` or a belief that all illness is caused by genes. There is, they argue, no way to connect a gene to a trait. There are too many other environmental and genetic influences. A connection between a particular gene and a condition can only be considered a predisposition, or susceptibility, rather than an isolated, definitive cause.

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Eric Lander

Broad Institute Director

Annual American Society of Human Genetics (ASHG) Convention in Washington, D.C.,

November 2010

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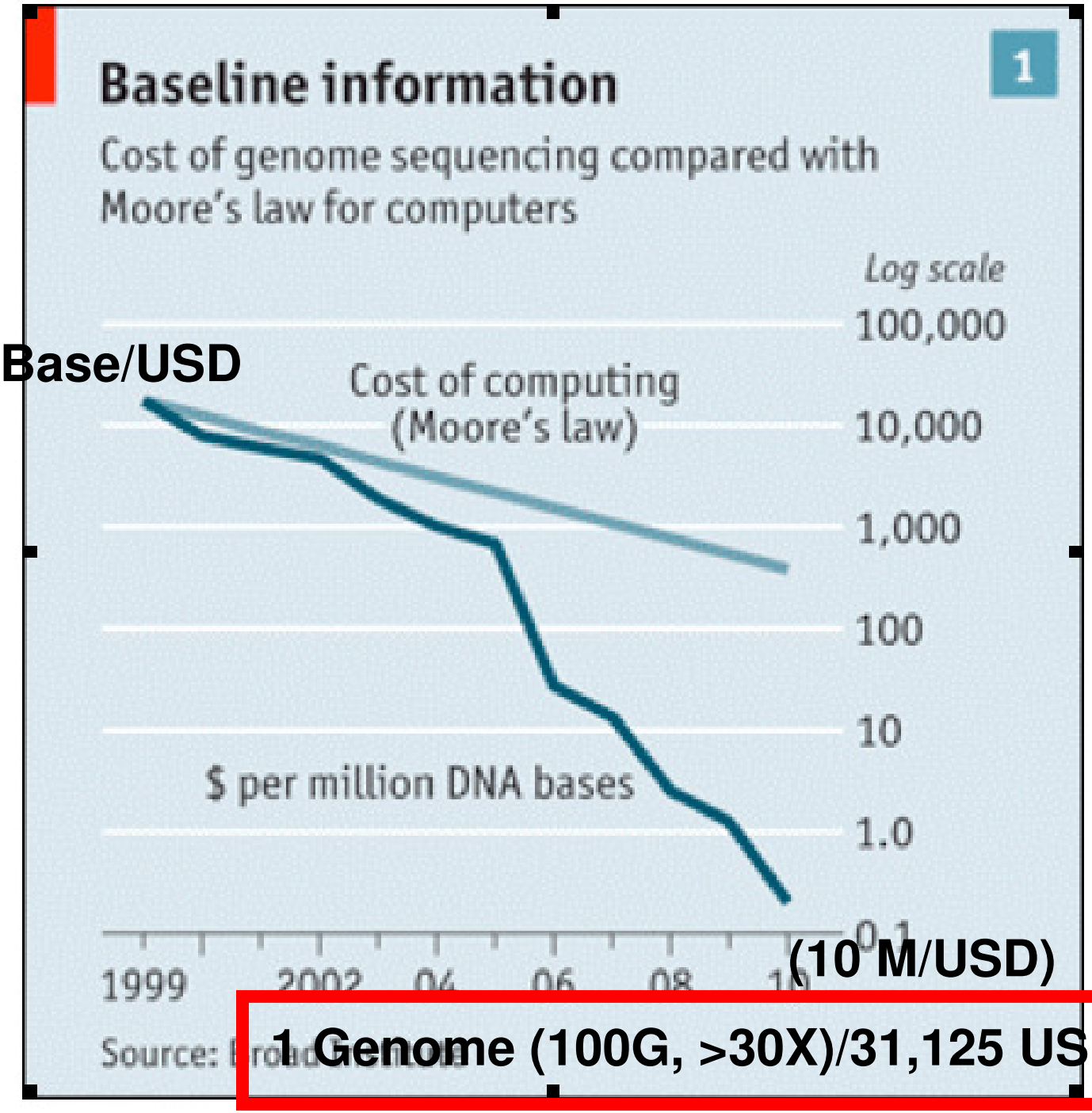
Cost [of sequencing] has fallen 100,000 fold in past decade, vastly faster than Moore's Law,"



1 Base/USD

(10 M/USD)

1 Genome (100G, >30X)/31,125 USD

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Technical Perspective:

HGP produced “a scaffold onto which information can be put,” including cancer genes, epigenomics, evolutionary selection, disease association, 3-D folding

2000: only four eukaryotic genomes (yeast fly, worm, and Arabidopsis) had been sequenced, as well as a few dozen bacteria.

Today, those numbers stand at 250 eukaryotic genomes, 4,000 bacteria and viruses, metagenomic projects and many hundreds of human genomes. By the end of this year, Lander expects Broad Institute generate 100,000 Gigabases (Gb) of sequence.

29 mammalian genomes shows some 3 million conserved non-coding elements in the genome, covering about 4.7% of the genome. Some of these have regulatory functions.
Another exciting area was the generation of genome-wide 3-D maps, which has revealed that the genome resides in ‘open’ and ‘closed’ compartments.

2000: the genes for about 1,300 Mendelian genetic disorders had been identified. Today, that number is about 2,900, leaving “another 1,800 Mendelian disorders to go,”
Some whole-genome sequencing projects identify rare Mendelian disease genes

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"GWAS"

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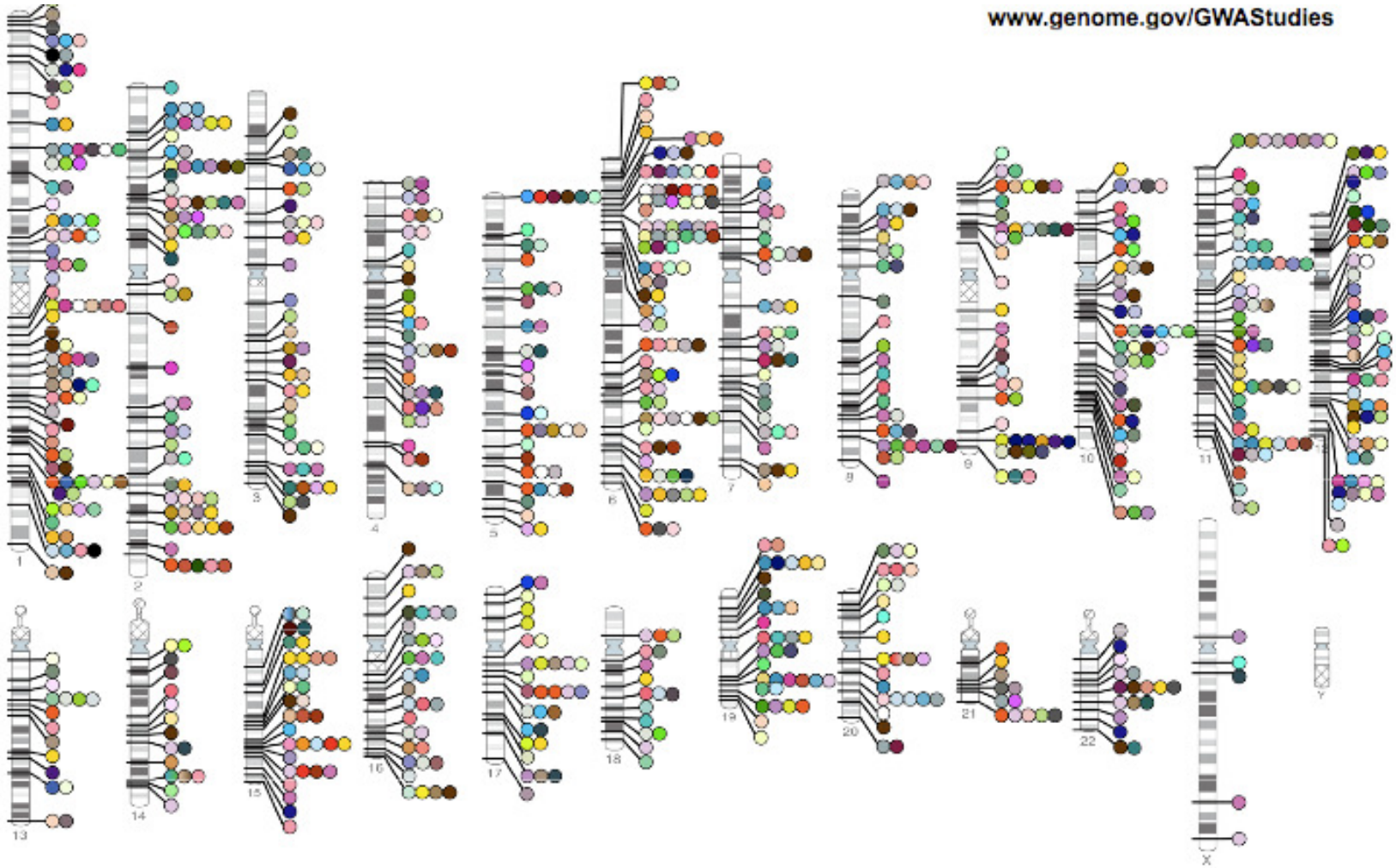
>1100 loci associated with >165 common diseases and traits



(A courtesy by E. Lander)

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The path to the promise

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In 2000, Lander said some 80 cancer-related genes were known. The tally is now 240 genes, with genome sequencing studies revealing mutational hotspots in colon, lung, and skin cancers with therapeutic implications.

If the HGP provided the raw tools, scientists were still translating basic genome discoveries into more medically directed research. That's how far we've progressed in ten years. But that still leaves the daunting tasks of clinical interventions, clinical testing, regulatory approval and widespread adoption.

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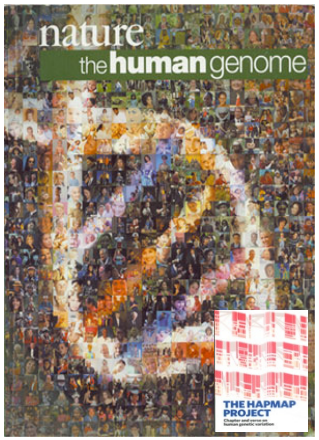
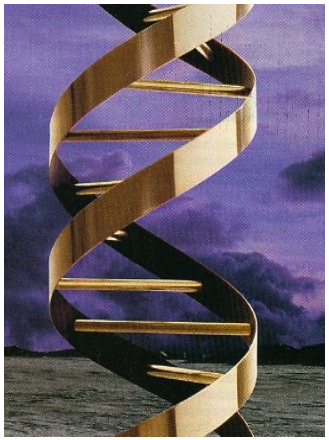
Genomics:
The Door to Personalized Medicine





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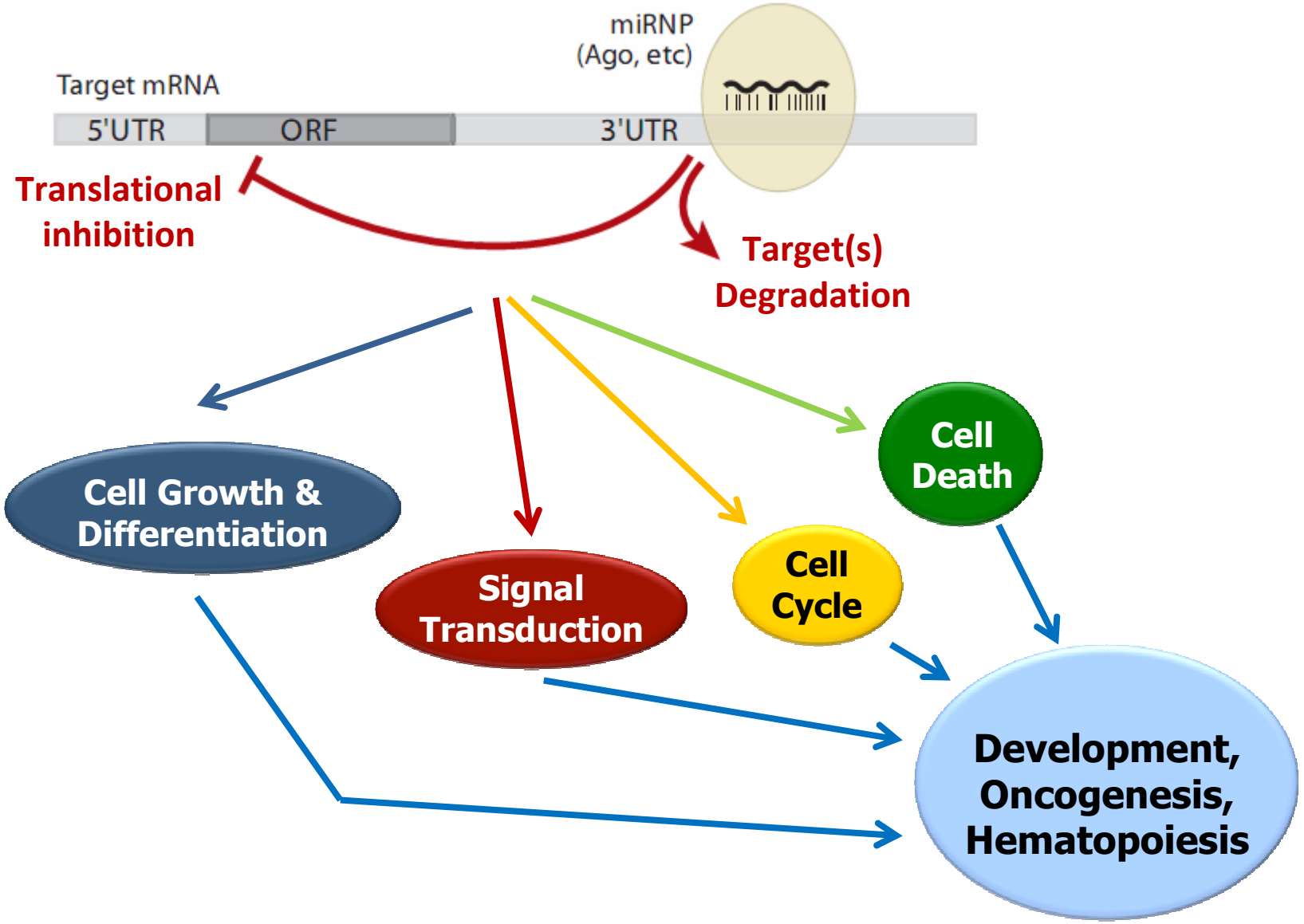
Roles of MicroRNAs



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A Gene-miRNA Interaction Map for Parkinson Disease

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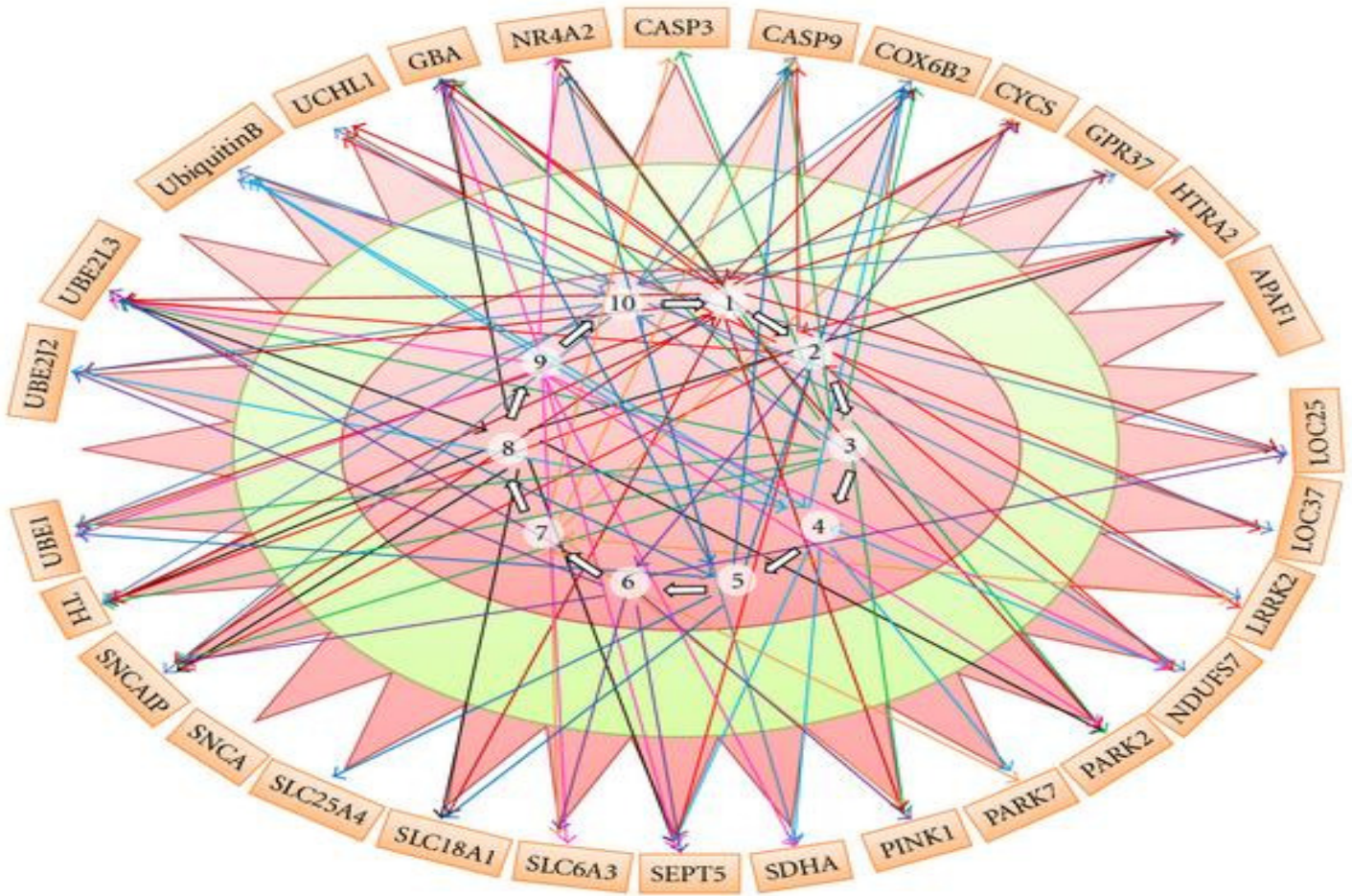

1: miR-1226*
2: miR-638
3: miR-608
4: miR-1469
5: miR-658
6: miR-939
7: miR-1301
8: miR-1207-5p
9: miR-1183
10: miR-612

Santosh S., et.al. J Biomed Biotechnol. 2009

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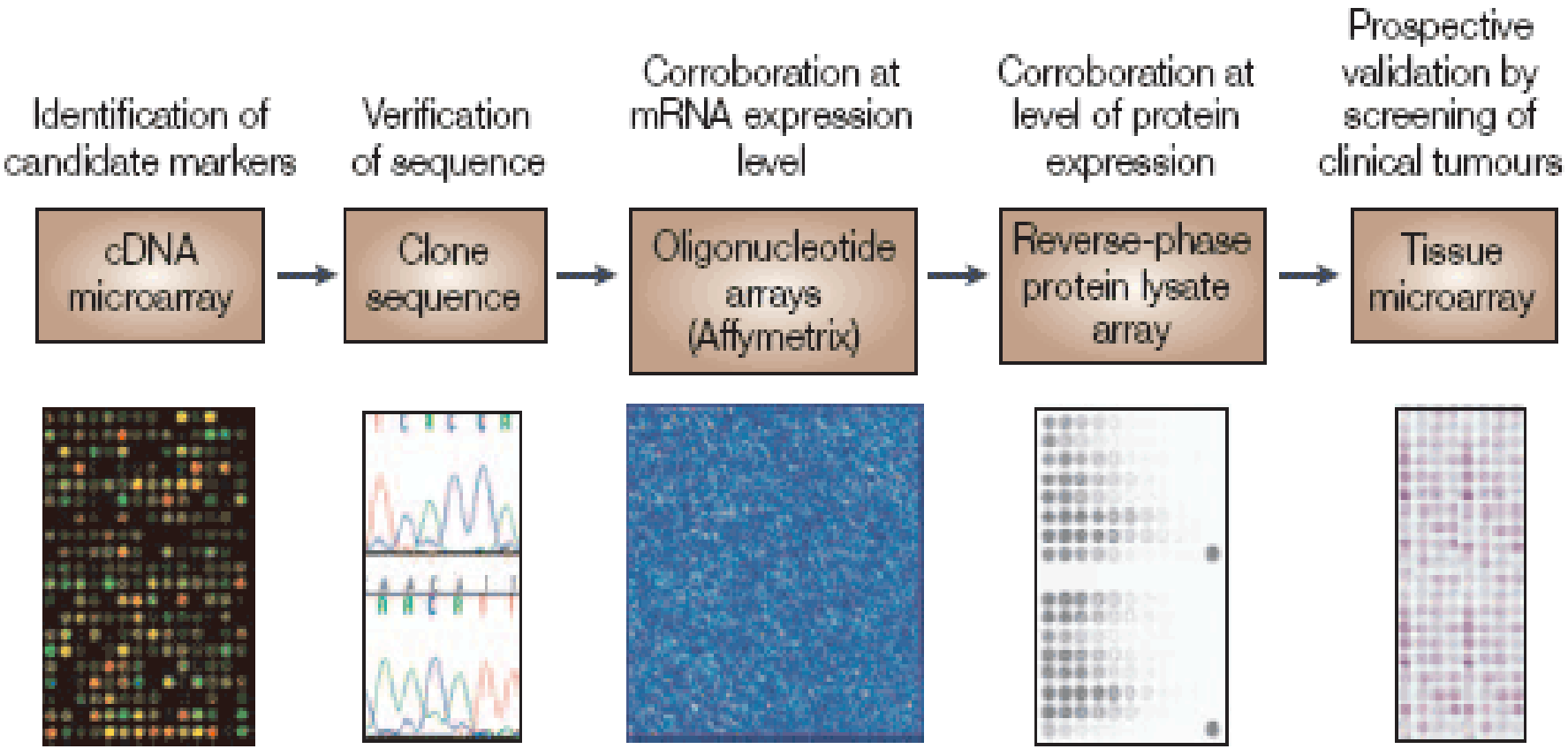
Biomarkers in Cancers

Medscape® www.medscape.com



Source: Nat Rev Cancer © 2005 Nature Publishing Group

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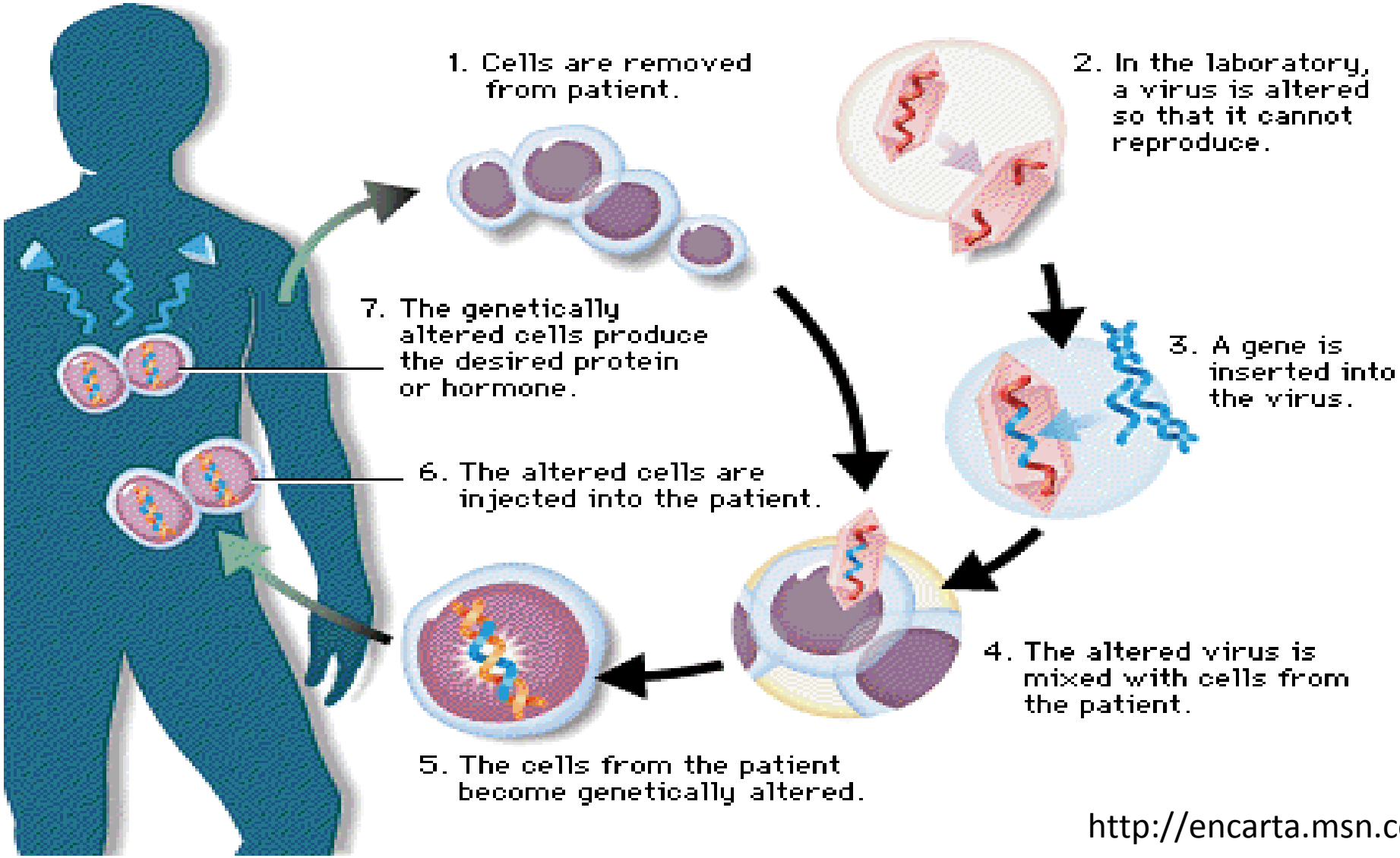
Gene Therapy



http://encarta.msn.com

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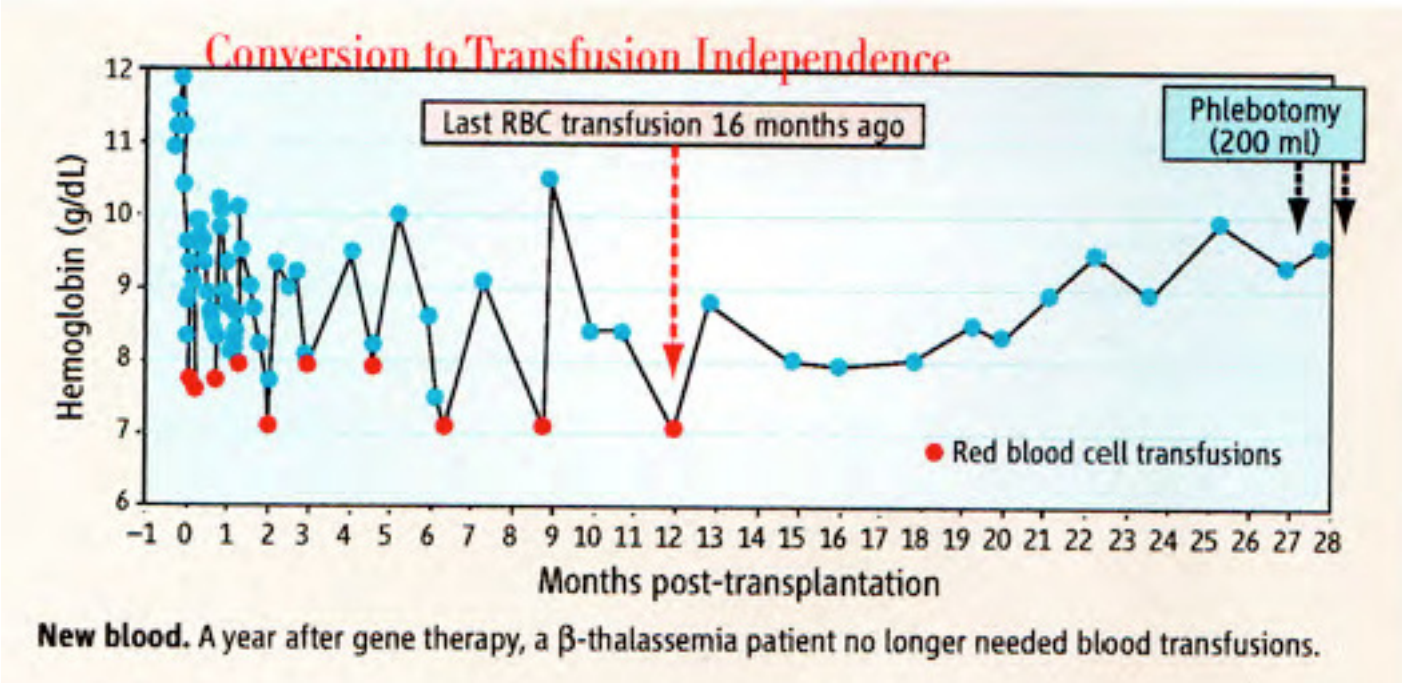
Gene Therapy for Thalassemia

Conversion to transfusion independence (I)

Last RBC transfusion 11.5 months ago



New blood. A year after gene therapy, a β-thalassemia patient no longer needed blood transfusions.

Months post-transplantation

11 DECEMBER 2009 VOL 326 **SCIENCE** www.sciencemag.org
Published by AAAS

Marina Cavazzana-Calvo, ….Philippe Leboulch. Nature 467: 318-23, September 16, 2010

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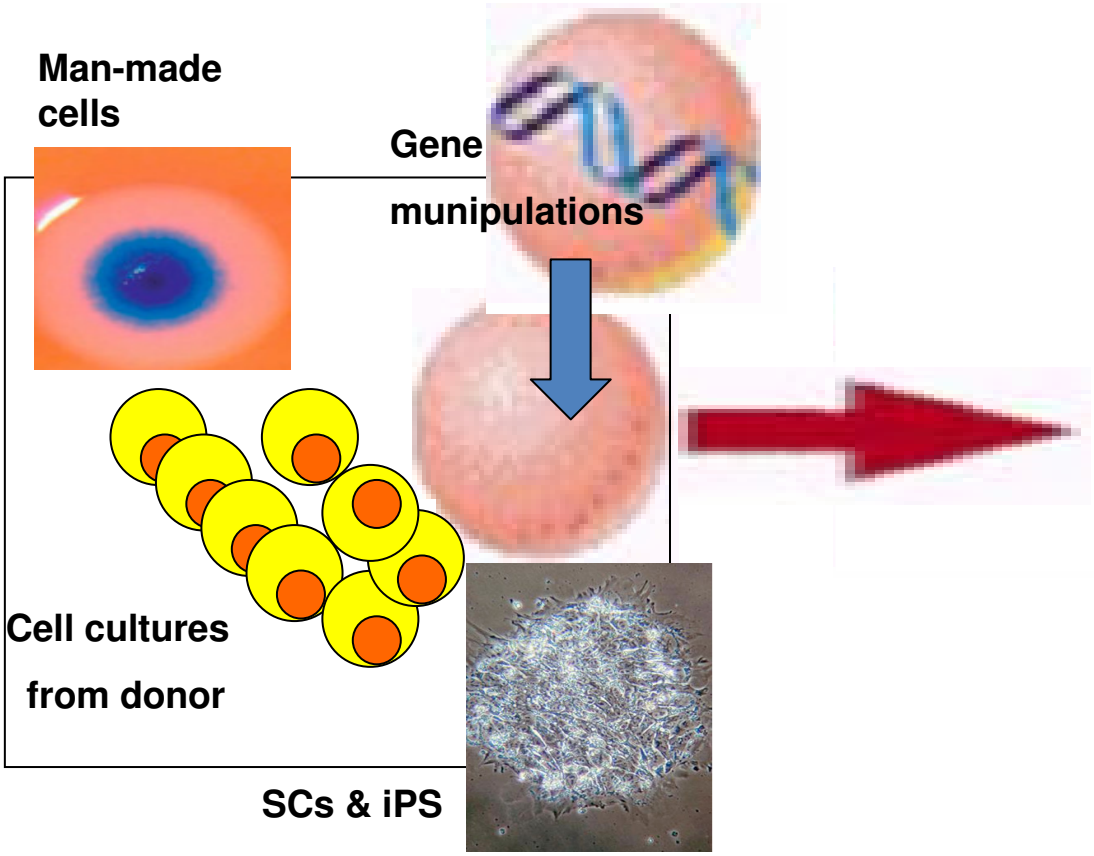
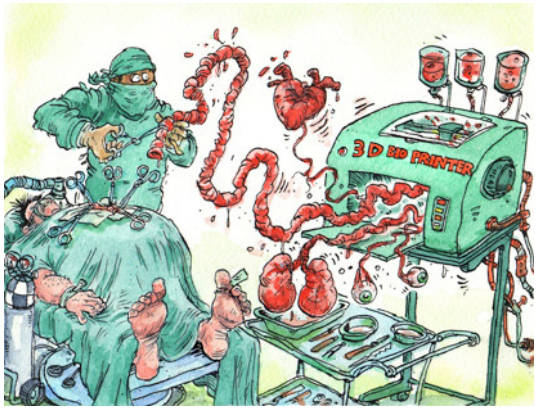
The Century of Biology





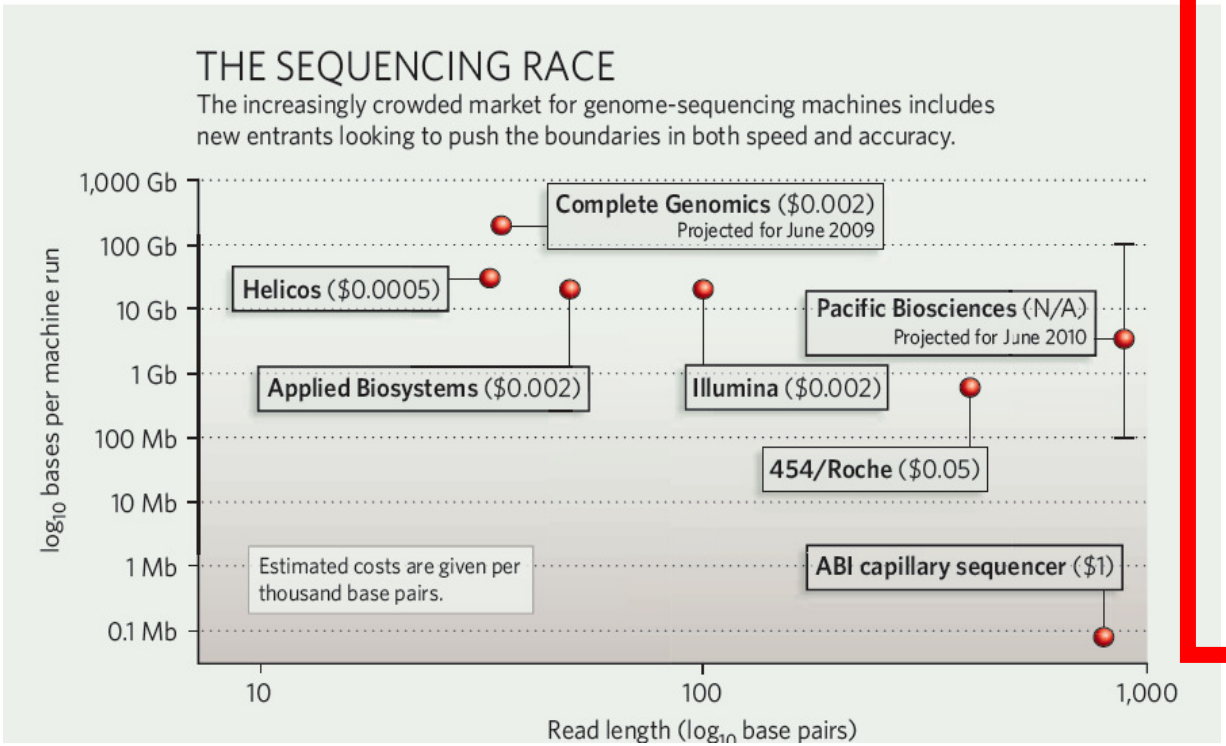
GM /SynBio + SC/iPS + Cloning

nature

NEWS

Genome sequencing: the third generation

Companies unveil data from their latest technologies.



Rule I:

Nobody would care so much what make a sequence is.

R. Michelmore

Thalassemia Research Center

MAHIDOL UNIVERSITY
Wisdom of the Land

Personalized Medicine is Coming True

Personalized Medicine

requires more knowledge about

population-specific differences and

more knowledge about evolution

and adaptation/selection

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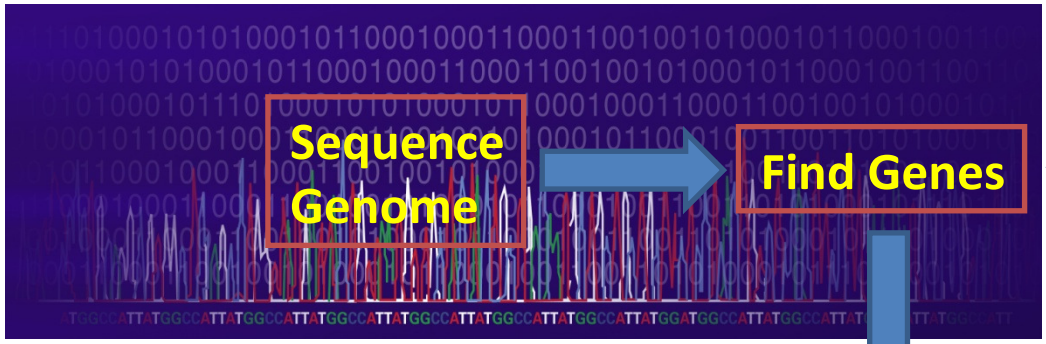
Molecular Biology to Medicine



Genetic Mapping, Mutation Detection

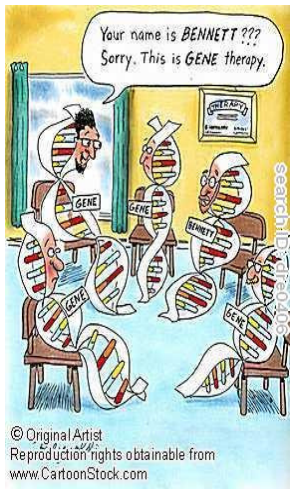
Establish Function and Disease Mechanism

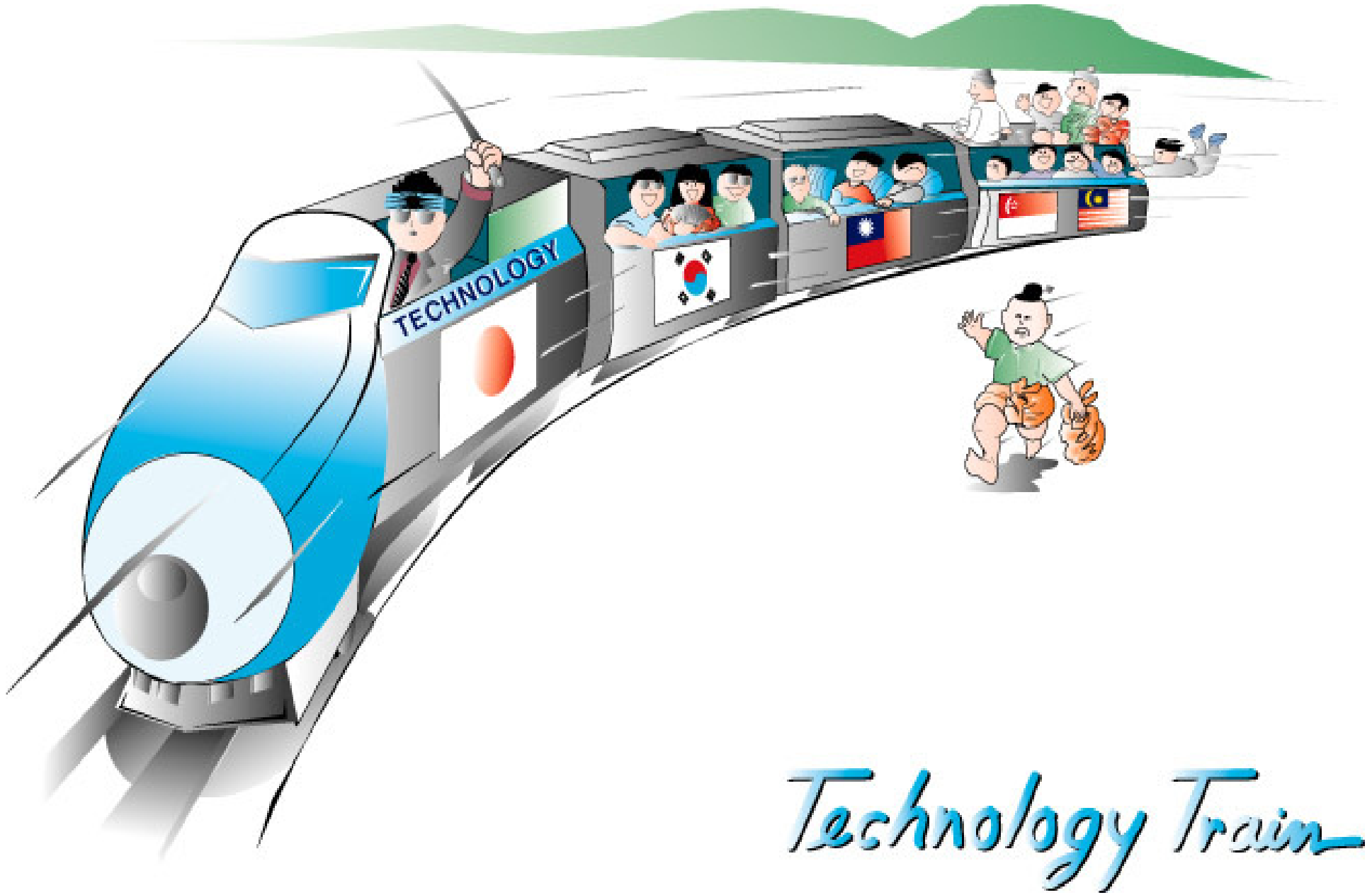
Diagnostics/ Prognostics

Drug Candidates

Cure

Gene Therapy





Technology Train