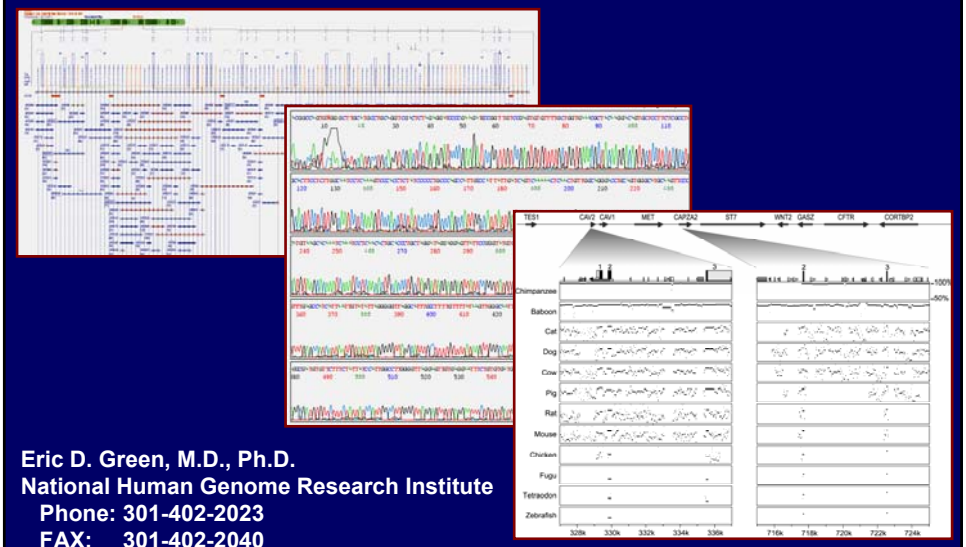
Techniques for Genome Mapping & Sequencing

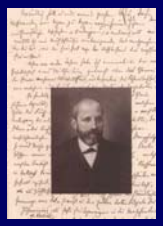


Eric D. Green, M.D., Ph.D.
National Human Genome Research Institute
Phone: 301-402-2023
FAX: 301-402-2040
E-Mail: egreen@nhgri.nih.gov

Foundational Milestones in Genetics & Genomics

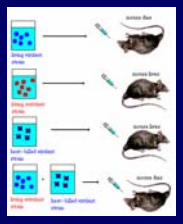
Mendel

1865



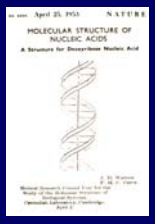
Miescher

1871



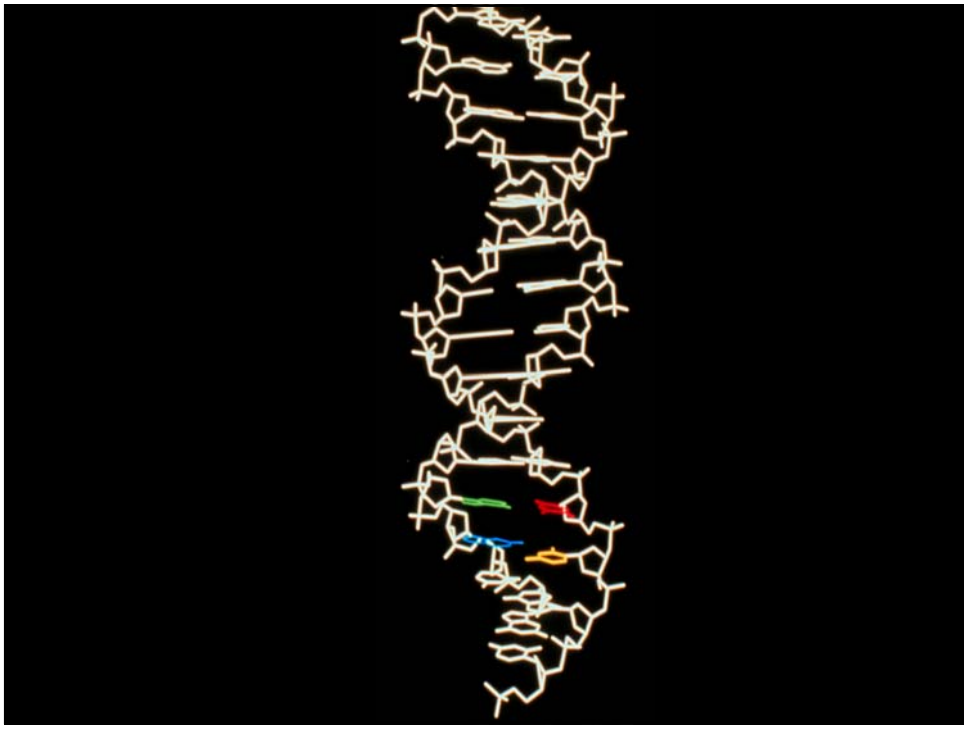
Avery

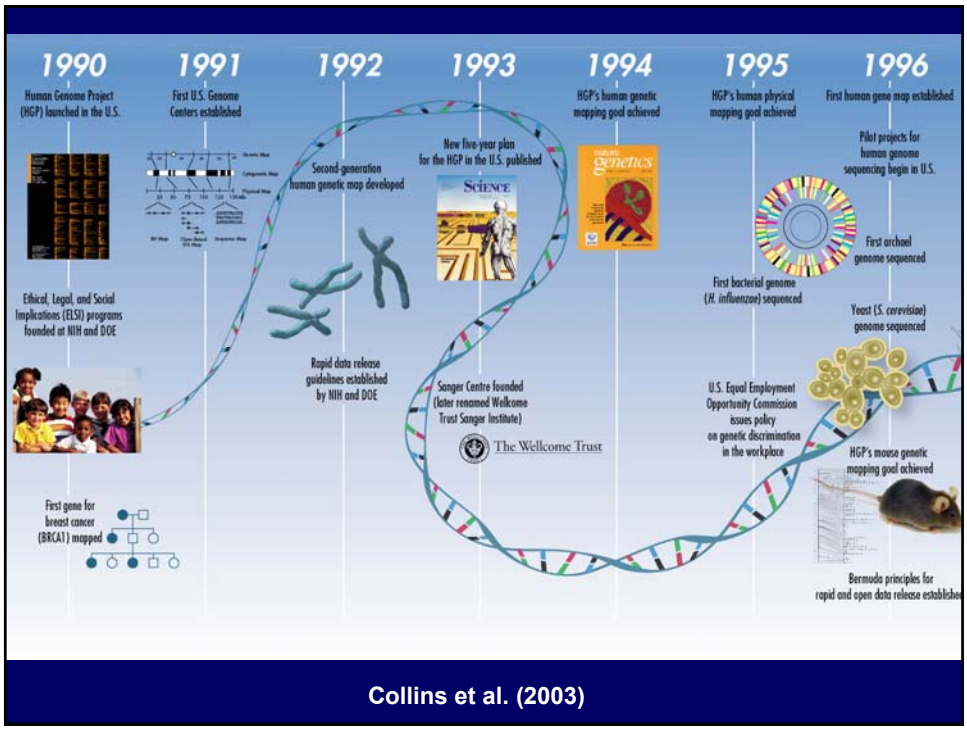
1944



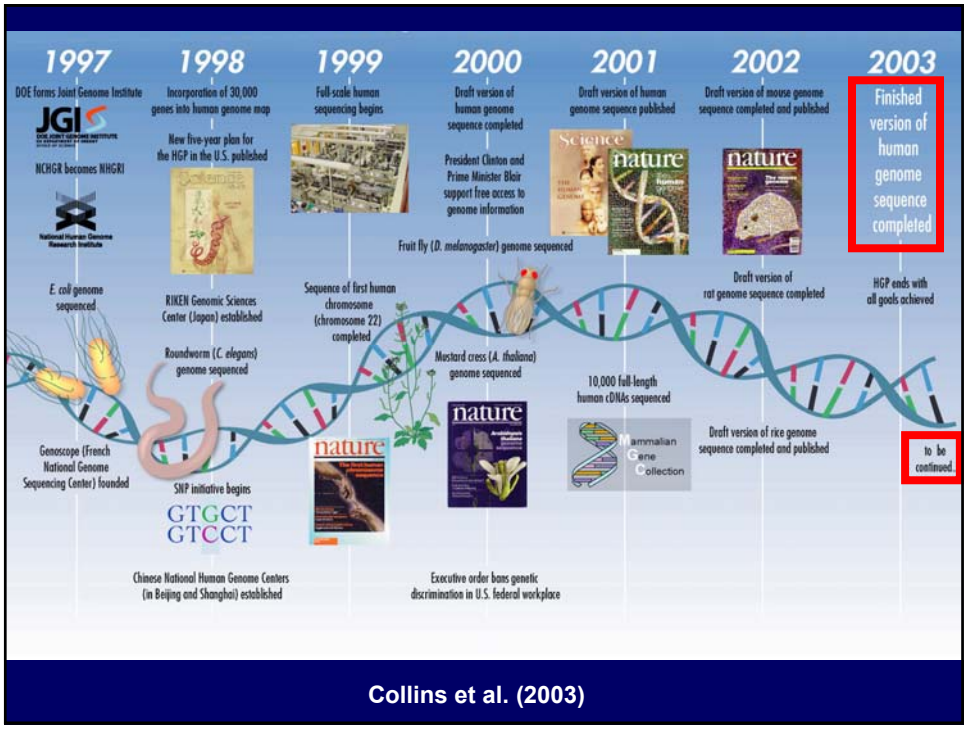
Watson & Crick

1953





Collins et al. (2003)



Collins et al. (2003)

Outline

I. Fundamentals of Genome Mapping

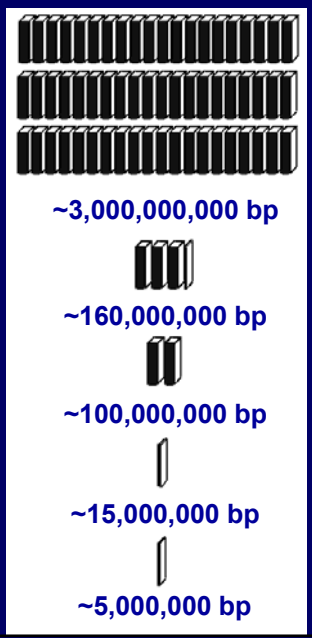
II. Fundamentals of Genome Sequencing

III. Mapping & Sequencing in the Human Genome Project

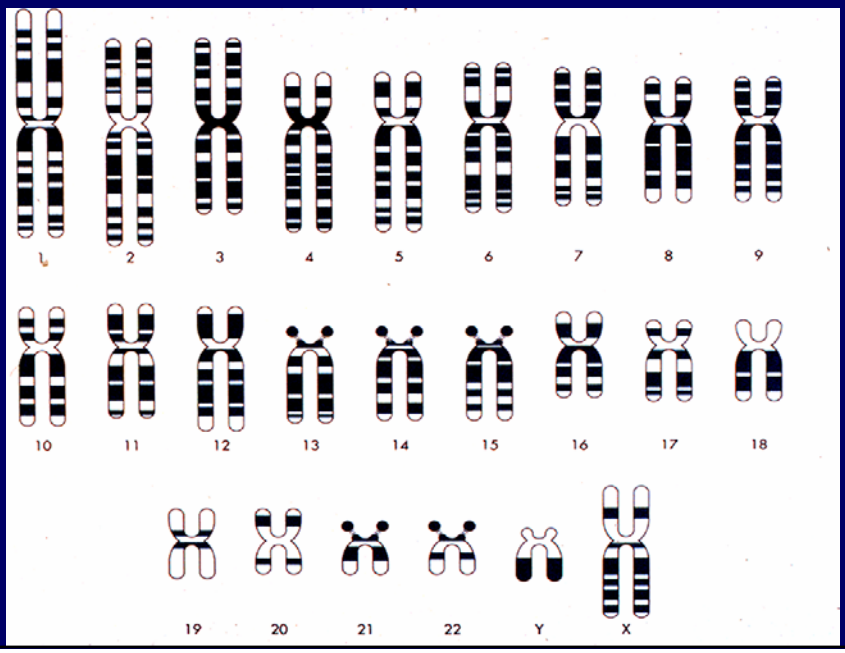
IV. Comparative Sequencing

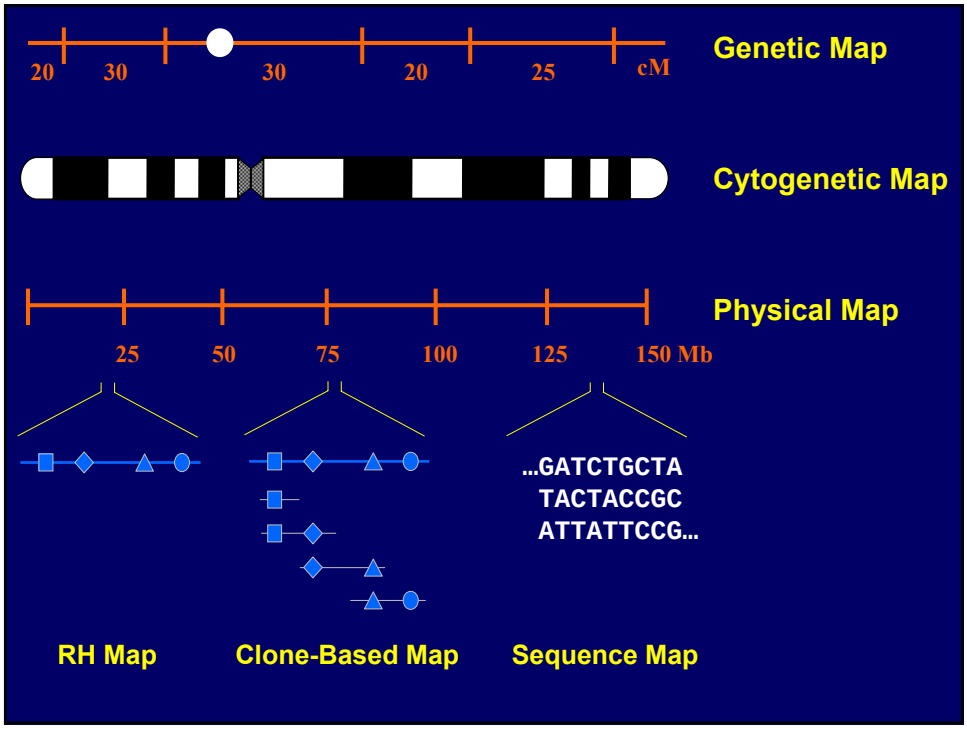
V. New DNA Sequencing Technologies

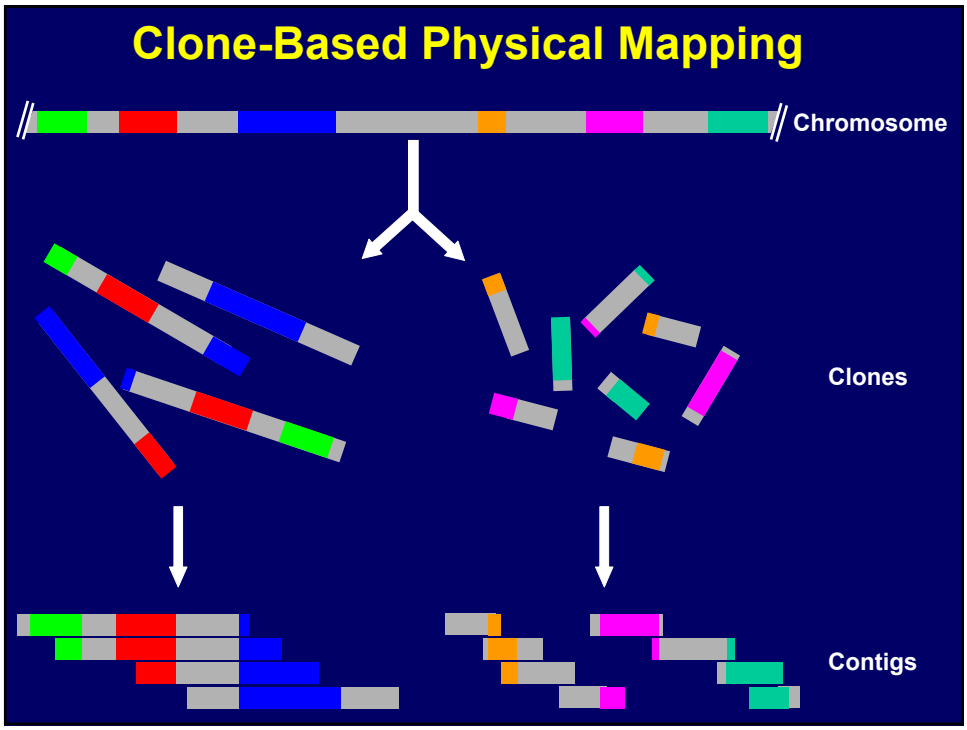
Genome Sizes



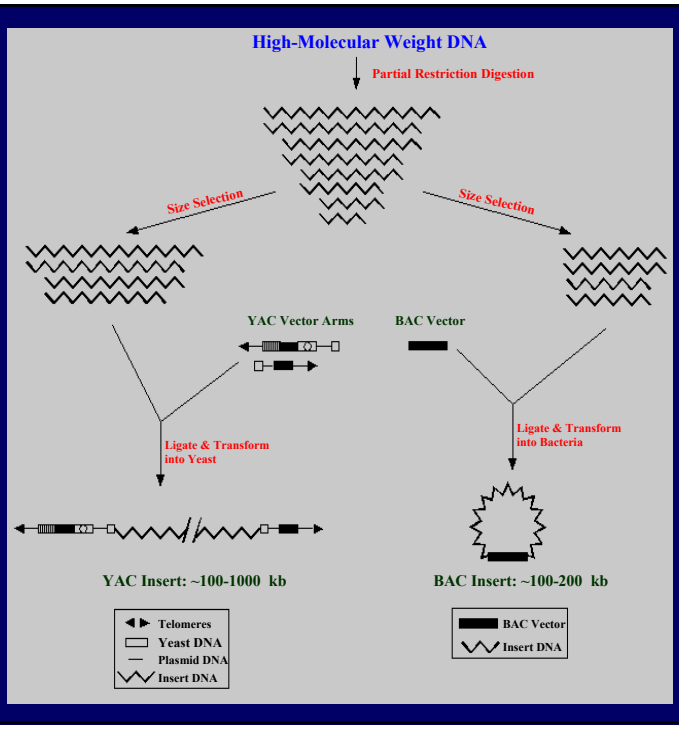
The Human Cytogenetic Map




Genetic Map
20
30
30
20
25
cM
Cytogenetic Map
Physical Map
25
50
75
100
125
150 Mb
...GATCTGCTA
TACTACCGC
ATTATTCCG...
RH Map
Clone-Based Map
Sequence Map


Clone-Based Physical Mapping
Chromosome
Clones
Contigs

Construction of YACs and BACs



Green et al. (1998)
Birren et al. (1998)

Genome Sizes

Human
Mouse
~3,000,000,000 bp

Fruit Fly
~160,000,000 bp

Nematode
~100,000,000 bp

Yeast
~15,000,000 bp

E. coli
~5,000,000 bp

Cloning Capacity

YAC
~1,000,000 bp

BAC
~100,000 bp

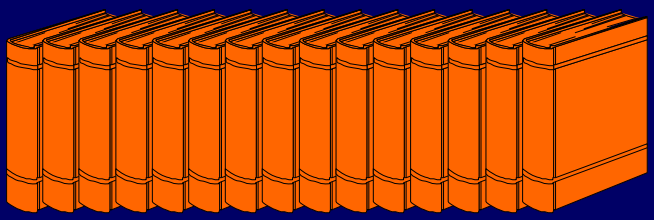
Cosmid
~45,000 bp

Bacteriophage
~25,000 bp

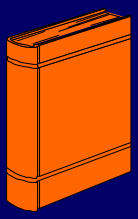
Bacterial Artificial Chromosomes (BACs)

- Bacterial-Based Cloning System
- Based on the *E. coli* F Factor (Fertility Plasmid): Replication Control
- Cloned Inserts: 100-200 kb, Circular DNA
- Low Copy Number

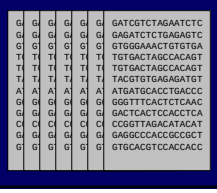
  Low Yields of DNA by Standard Methods
  Reasonably Stable
- BAC Libraries from Many Different Species Available
  (e.g., www.chori.org/bacpac)
- See Birren et al. (1998)



Genome
(~3000 Mb)



Chromosome
(~130 Mb)

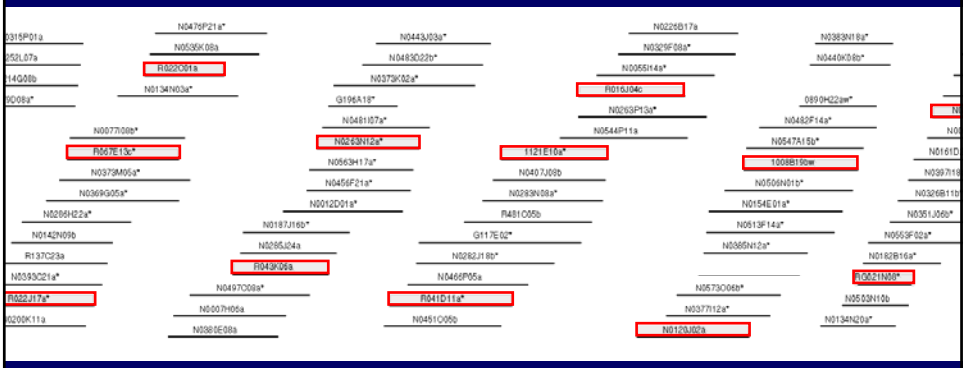


YAC
(~0.5-1.0 Mb)

BAC
(~0.1-0.2 Mb)

Sequence-Ready Contig Map

Marra et al. (1997) and Gregory et al. (1997)

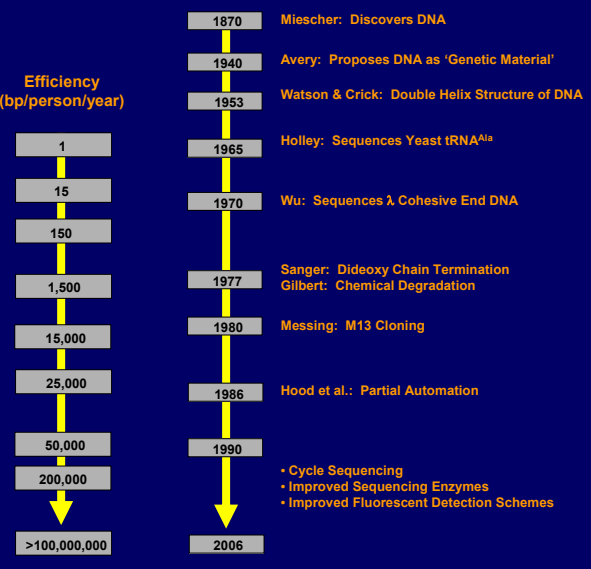


Physical Mapping: Future Prospects

- Strategies for Physical Mapping have Advanced Greatly in the Sequence-Based Era
- Close Interplay of Mapping and Sequencing in the Exploration of Genomes
- Availability of Many BAC Libraries is Allowing Physical Mapping of More Species' Genomes

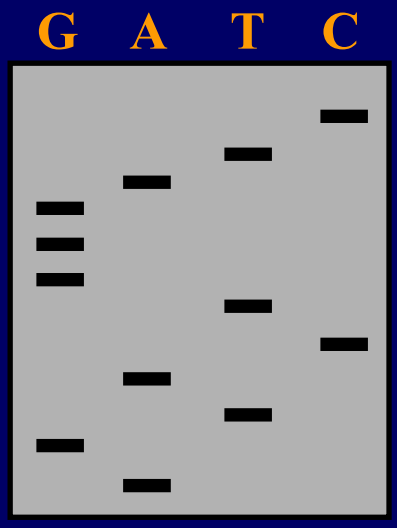
DNA Sequencing

History of DNA Sequencing



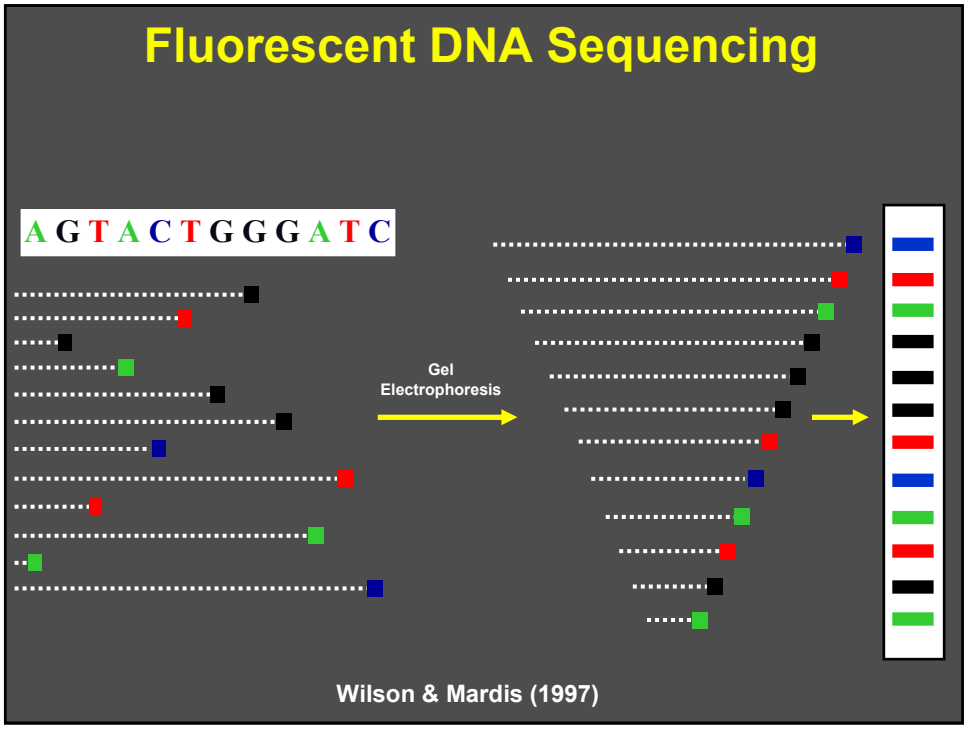
Adapted from Messing & Llaca, *PNAS* (1998)

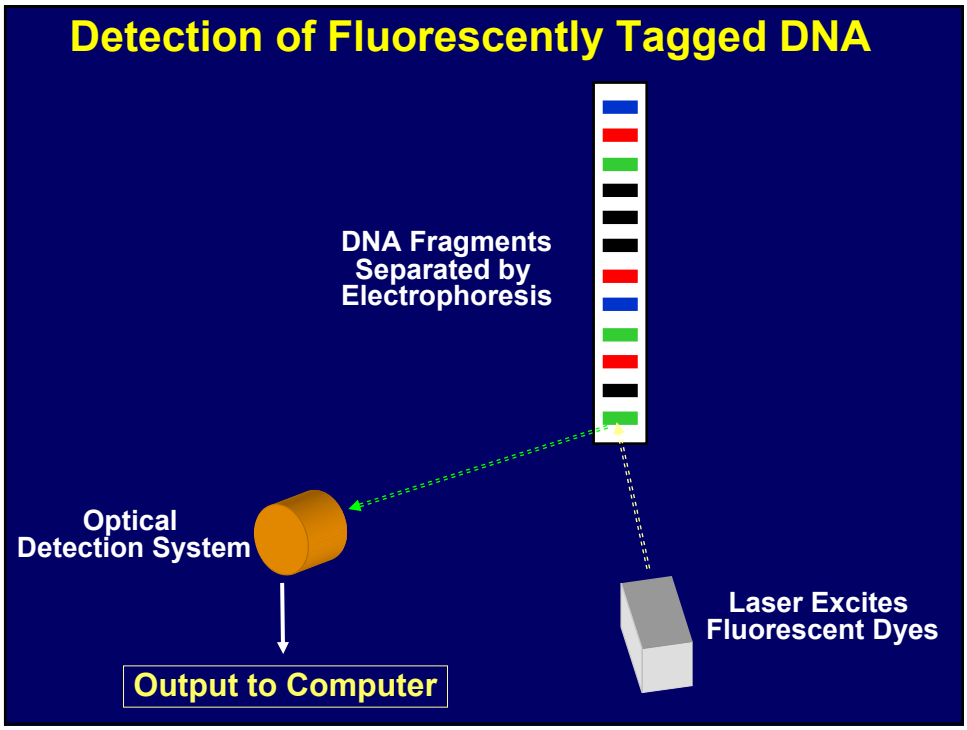
DNA Tagged with Radioactivity



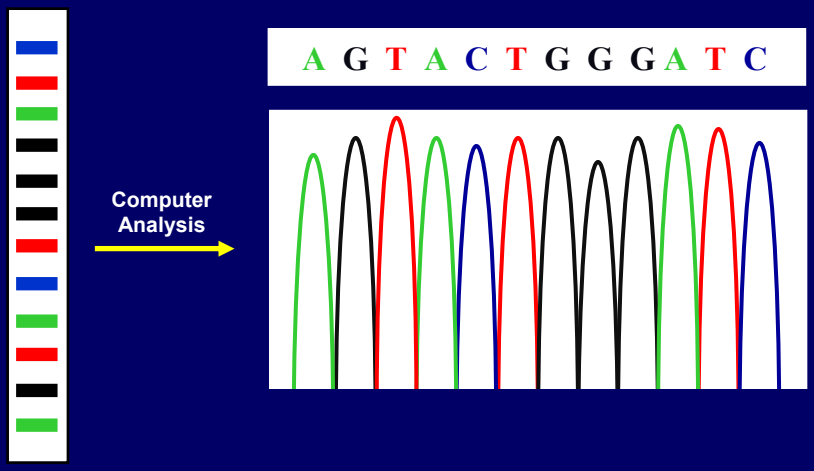
G: G Reaction
A: A Reaction
T: T Reaction
C: C Reaction

Radioactive Sequencing

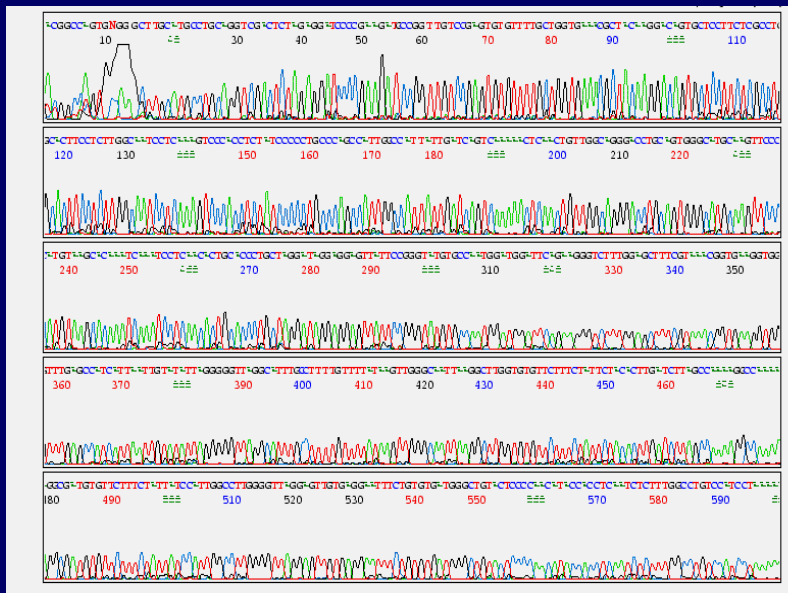

Fluorescent DNA Sequencing
A G T A C T G G G A T C
Gel
Electrophoresis
Wilson & Mardis (1997)


Detection of Fluorescently Tagged DNA
DNA Fragments
Separated by
Electrophoresis
Optical
Detection System
Output to Computer
Laser Excites
Fluorescent Dyes

Analyzing Fluorescent DNA Sequencing Data



Fluorescent DNA Sequencing Results



Slab Gel-Based DNA Sequencing Instruments

Capillary-Based DNA Sequencing Instruments

Large-Scale cDNA Sequencing

- ESTs: Expressed-Sequence Tags
- SAGE: Serial Analysis of Gene Expression
- Full-Insert (Full-Length) cDNA Sequencing

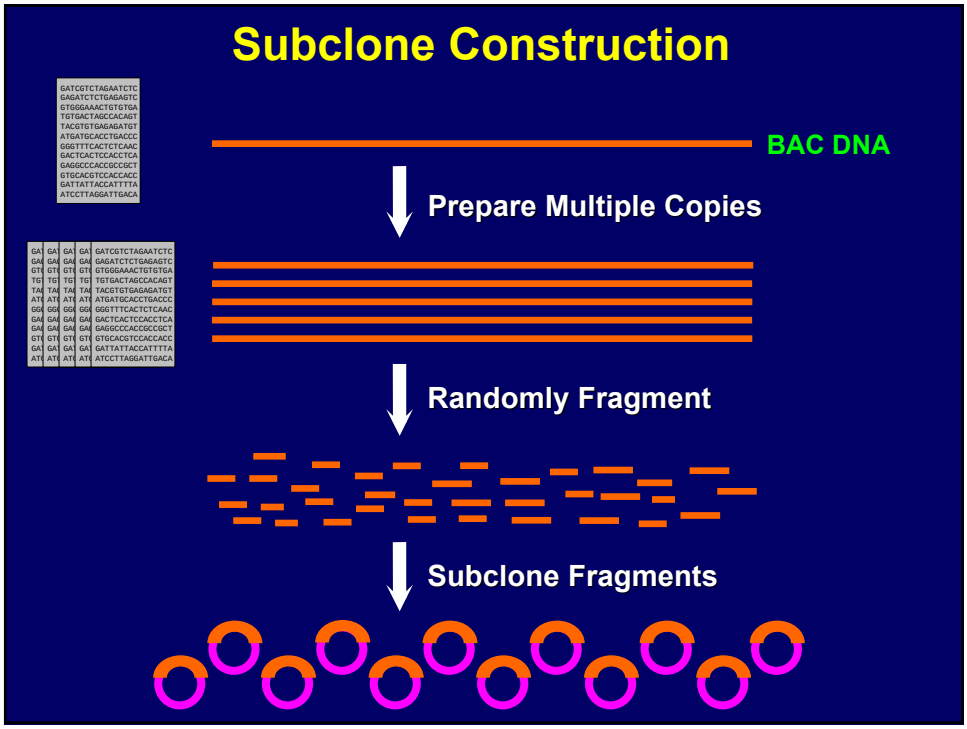
mgc.nci.nih.gov

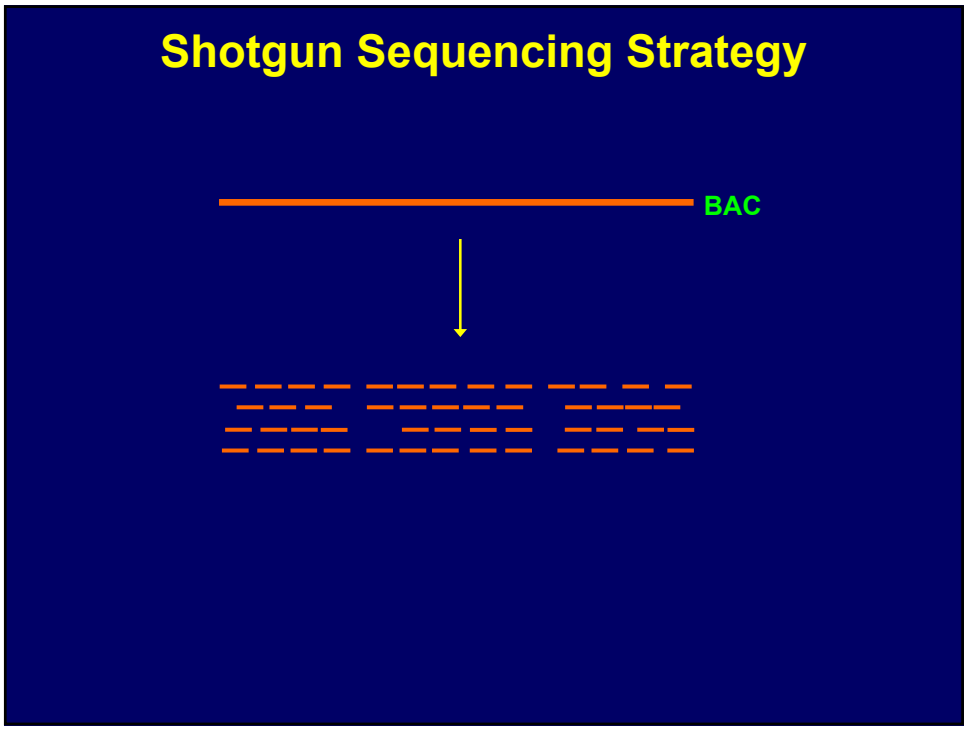
Gerhard et al. (2004)

Large-Scale Genome Sequencing

Shotgun Sequencing

Wilson & Mardis (1997)
Green (2001)


Subclone Construction
BAC DNA
Prepare Multiple Copies
Randomly Fragment
Subclone Fragments


Shotgun Sequencing Strategy
BAC

Poisson Calculations

The sequencing strategy for the shotgun approach follows the Lander and Waterman application of the Poisson distribution

The probability a base is not sequenced is given by:

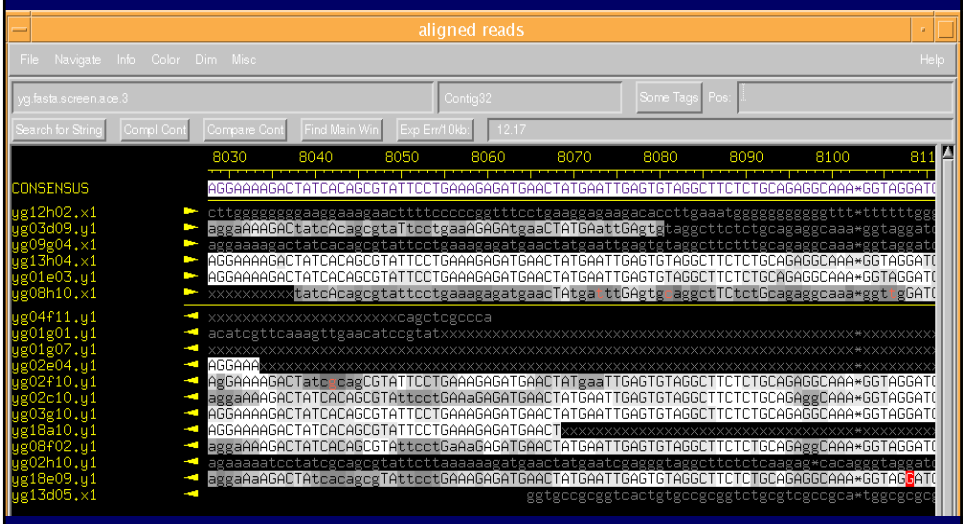
$$P_0 = e^{-c}$$

Where:

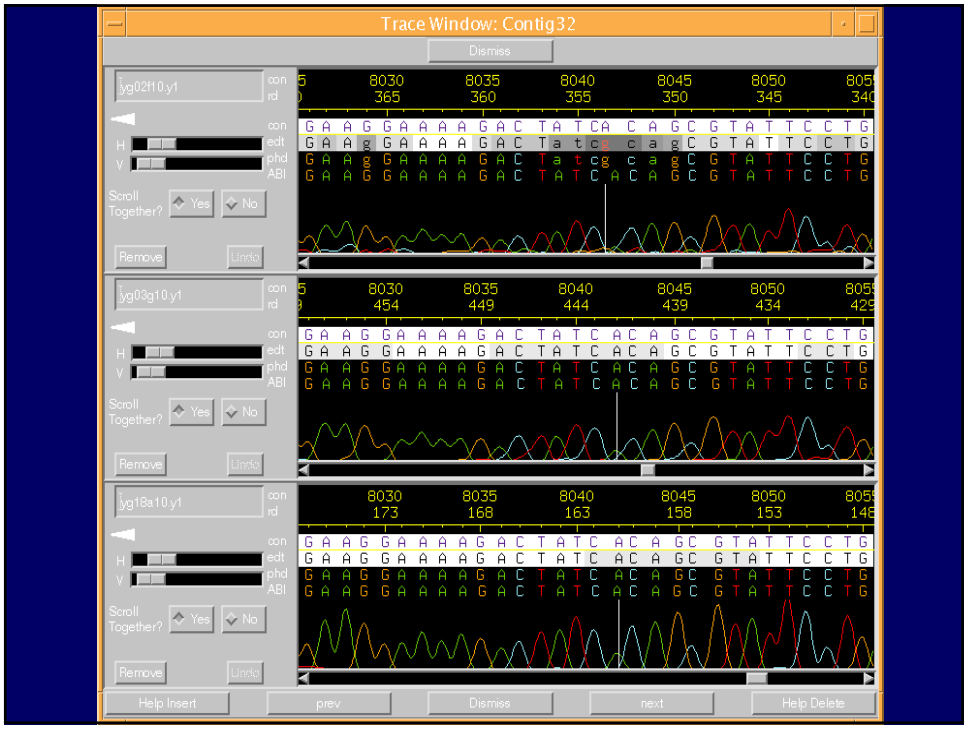
- c = fold sequence coverage (c=LN/G),
- LN = # bases sequenced, i.e. L = average sequencing read length and N = # reads
- G = target sequence length
- e = 2.718 (e=2.718281828459)

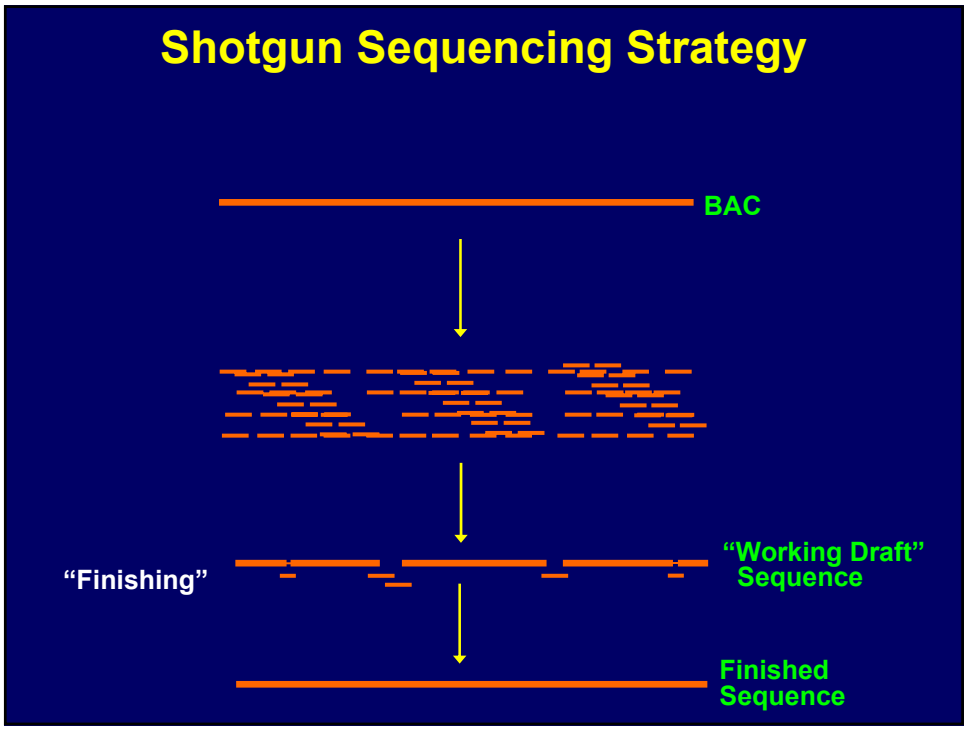
Fold Coverage	$P_0=e^{-c}$	% not sequenced	% sequenced
1	0.37	37%	63%
2	0.135	13.5%	87.5%
3	0.05	5%	95%
4	0.018	1.8%	98.2%
5	0.0067	0.6%	99.4%
6	0.0025	0.25%	99.75%
7	0.0009	0.09%	99.91%
8	0.0003	0.03%	99.97
9	0.0001	0.01%	99.99%
10	0.000045	0.005%	99.995%

Shotgun Sequence Assembly

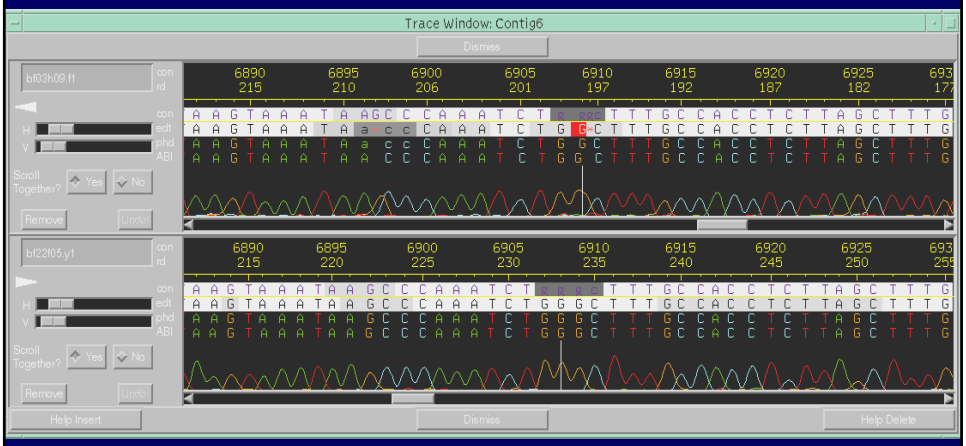


"Consed" (Gordon et al., 1998)


Trace Window: Contig32
Dismiss
Help Insert
prev
Dismiss
next
Help Delete


Shotgun Sequencing Strategy
BAC
"Finishing"
"Working Draft" Sequence
Finished Sequence

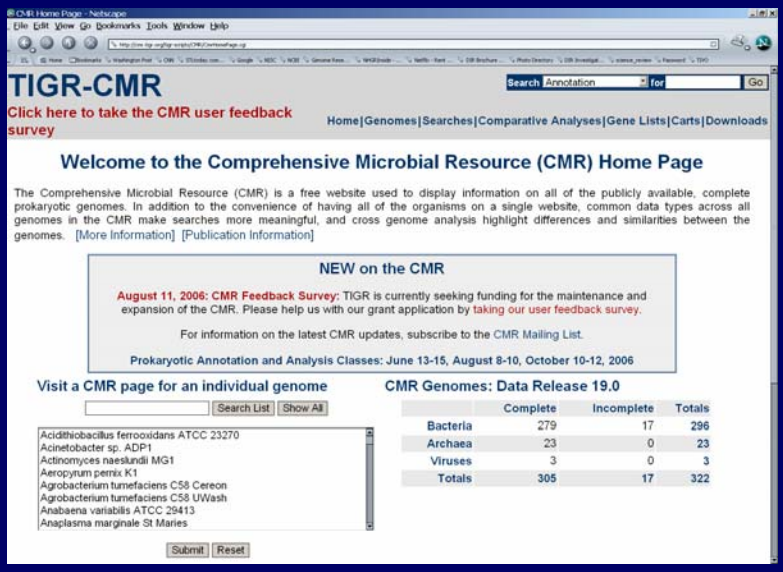
Sequence Finishing: Resolving Ambiguities



*** Sequence Finishing: Remains Relatively Expensive ***

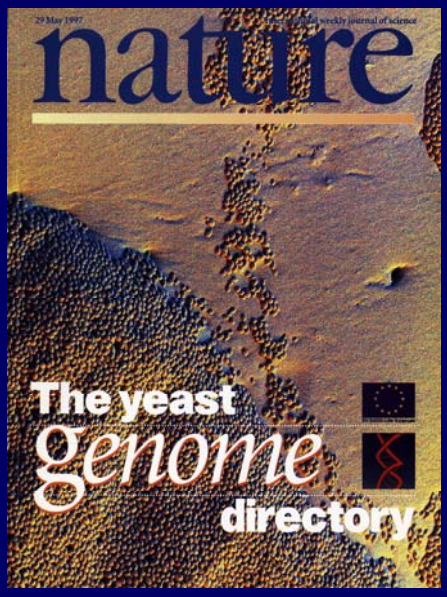
Historically Significant Genome Sequencing Projects

Microbial Genome Sequences



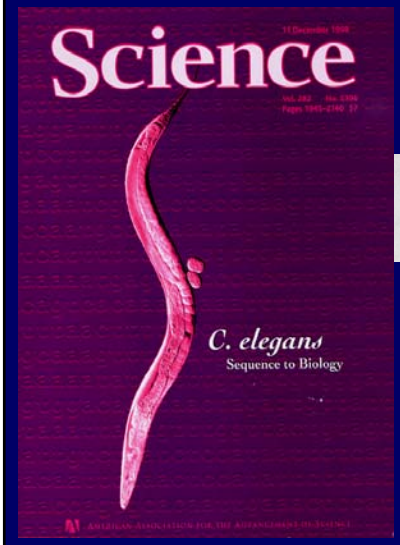
www.tigr.org

First Eukaryotic Genome Sequence



Goffeau et al. (1997)

First Animal Genome Sequence

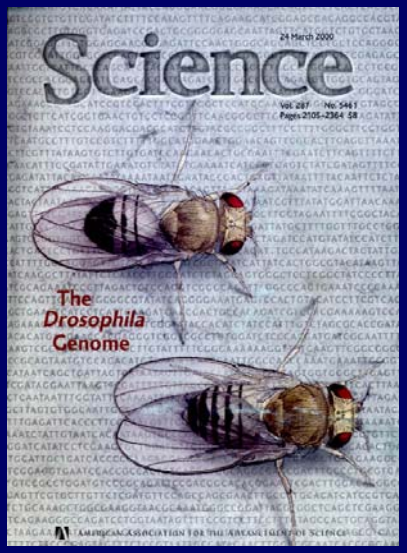


Genome Sequence of the Nematode *C. elegans*: A Platform for Investigating Biology

The *C. elegans* Sequencing Consortium*

***C. elegans* Sequencing Consortium (1998)**

Second Animal Genome Sequence



THE *DROSOPHILA* GENOME

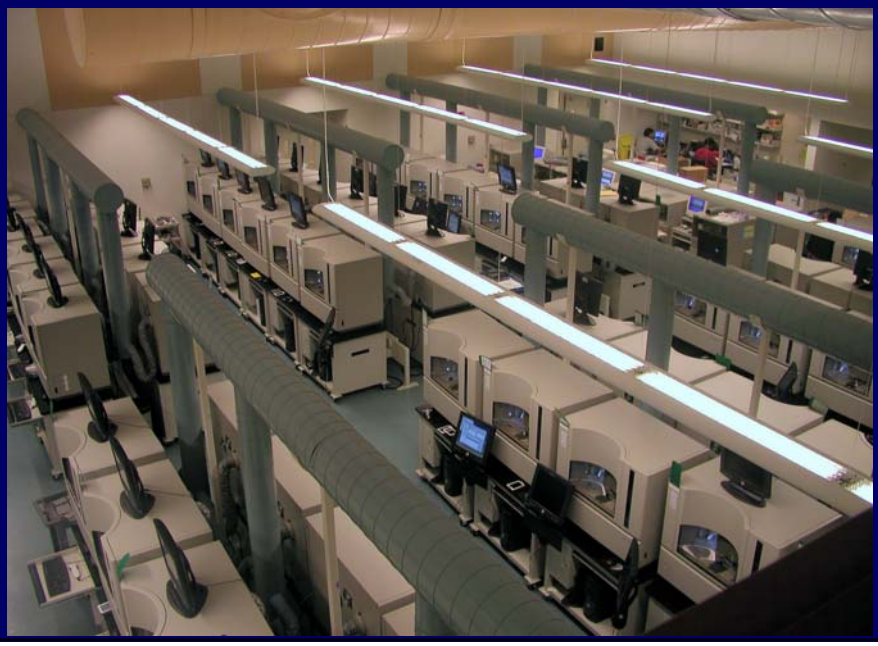
REVIEW

The Genome Sequence of *Drosophila melanogaster*

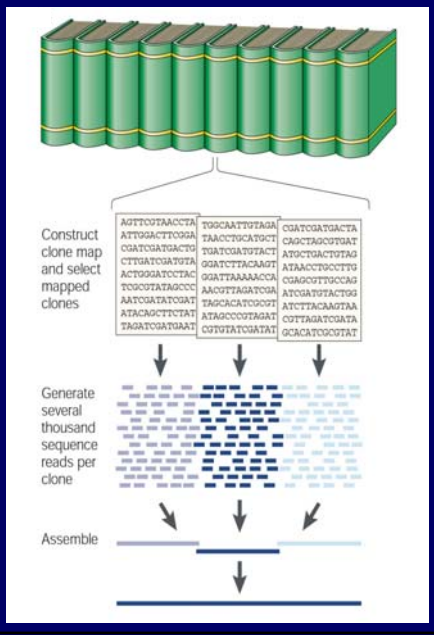
Mark D. Adams,[1*] Susan E. Celniker,[2] Robert A. Holt,[1] Cheryl A. Evans,[1] Jeannine D. Gocayne,[1] Peter G. Amanatides,[1] Steven E. Scherer,[3] Peter W. Li,[1] Roger A. Hoskins,[2] Richard F. Galle,[4] Reed A. George,[2] Suzanna E. Lewis,[4] Stephen Richards,[2] Michael Ashburner,[5] Scott N. Henderson,[1] Granger G. Sutton,[1] Jennifer R. Wortman,[1] Mark D. Yandell,[1] Qing Zhang,[1] Lin X. Chen,[1] Rhonda C. Brandon,[1] Yu-Hui C. Rogers,[1] Robert G. Blazej,[3] Mark Champe,[2] Barret D. Pfeiffer,[2] Kenneth H. Wan,[2] Clare Doyle,[2] Evan G. Baxter,[2] Gregg Helt,[4] Catherine R. Nelson,[4] George L. Gabor Miklos,[7] Josep F. Abril,[8] Anna Agbayani,[2] Hui-Jin An,[1] Cynthia Andrews-Pfannkoch,[1] Danita Baldwin,[1] Richard M. Ballew,[1] Anand Basu,[1] James Baxendale,[1] Leyla Bayraktaroglu,[9] Ellen M. Beasley,[1] Karen Y. Beeson,[1] P. V. Benos,[10] Benjamin P. Berman,[4] Deepali Bhandari,[1] Slava Bolshakov,[11] Dana Borkova,[12] Michael R. Botchan,[13] John Bouck,[2] Peter Brokstein,[4] Phillipe Brottier,[14] Kenneth C. Burtis,[15] Dana A. Busam,[1] Heather Butler,[16] Edouard Cadieu,[17] Angela Center,[1] Ishwar Chandra,[1] J. Michael Cherry,[18] Simon Cawley,[19] Carl Dahlke,[1] Lionel B. Davenport,[1] Peter Davies,[1] Beatriz de Pablos,[20] Arthur Delcher,[1] Zuoming Deng,[1] Anne Deslattes Mays,[1] Ian Dew,[1] Suzanne M. Dietz,[1] Kristina Dodson,[1] Lisa E. Doup,[1] Michael Downes,[21] Shannon Dugan-Rocha,[2] Boris C. Dunkov,[22] Patrick Dunn,[1] Kenneth J. Durbin,[1] Carlos C. Evangelista,[1] Concepcion Ferraz,[23] Steven Ferriera,[1] Wolfgang Fleischmann,[5] Carl Fosler,[1] Andrei E. Gabrielian,[1] Neha S. Garg,[1] William M. Gelbart,[2] Kan Glasser,[1] Anna Glodek,[1] Fangcheng Gong,[1] J. Harley Gorrell,[2] Zhiping Gu,[1] Ping Guan,[1] Michael Harris,[1] Nomi L. Harris,[2] Damon Harvey,[4] Thomas J. Heiman,[1] Judith R. Hernandez,[3] Jarrett Houck,[1] Damon Hostin,[1] Kathryn A. Houston,[2] Timothy J. Howland,[1] Ming-Hui Wei,[1] Chinyere Ibegwam,[1] Mena Jalali,[1] Francis Kalush,[1] Gary H. Karpen,[21] Zhaoxi Ke,[1] James A. Kennison,[24] Karen A. Ketchum,[1] Bruce E. Kimmel,[2] Chinnappa D. Kodira,[1] Cheryl Kraft,[1] Saul Kravitz,[1] David Kulp,[4] Zhongwu Lai,[1] Paul Lasko,[25] Yiding Lei,[1] Alexander A. Levitsky,[1] Jiayin Li,[1] Zhenya Li,[1] Yong Liang,[1] Xiaoying Lin,[26] Xiangjun Liu,[1] Bettina Mattei,[1] Tina C. McIntosh,[1] Michael P. McLeod,[3] Duncan McPherson,[1] Gennady Merkulov,[1] Natalia V. Milshina,[1] Clark Mobarry,[1] Joe Morris,[4] Ali Moshrefi,[2] Stephen M. Mount,[27] Mee Moy,[1] Brian Murphy,[1] Lee Murphy,[28] Donna M. Muzny,[2] David L. Nelson,[2] David R. Nelson,[29] Keith A. Nelson,[1] Katherine Nixon,[2] Deborah R. Nusskern,[1] Joanne M. Pacleb,[2] Michael Palazzolo,[2] Gjange S. Pittman,[1] Sue Pan,[1] John Pollard,[1] Vinita Puri,[1] Martin G. Reese,[4] Knut Reinert,[1] Karin Remington,[1] Robert D. C. Saunders,[30] Frederick Scheeler,[1] Hua Shen,[2] Bixiang Christopher Shue,[1] Inga Sidén-Kiamos,[11] Michael Simpson,[1] Marian P. Skupski,[1] Tom Smith,[1] Eugene Spier,[1] Allan C. Spradling,[31] Mark Stapleton,[2] Renee Strong,[1] Eric Sun,[1] Robert Svirskas,[32] Cyndee Tector,[1] Russell Turner,[1] Eli Venter,[1] Alhui H. Wang,[1] Xin Wang,[1] Zhen-Yuan Wang,[1] David A. Wassarman,[33] George M. Weinstock,[2] Jean Weissenbach,[14] Sherita M. Williams,[1] Trevor Woodage,[1] Kim C. Worley,[2] David Wu,[1] Song Yang,[2] Q. Alison Yao,[1] Jane Ye,[1] Ru-Fang Yeh,[10] Jayshree S. Zaveri,[1] Ming Zhan,[1] Guangren Zhang,[1] Qi Zhao,[1] Liansheng Zheng,[1] Xiangqun H. Zheng,[1] Fei N. Zhong,[1] Wenyan Zhong,[1] Xiaojun Zhou,[2] Shiaoping Zhu,[1] Xiaohong Zhu,[1] Hamilton O. Smith,[1] Richard A. Gibbs,[2] Eugene W. Myers,[1] Gerald M. Rubin,[34] J. Craig Venter[1]

Adams et al. (2000)

Human Genome Sequencing Centers

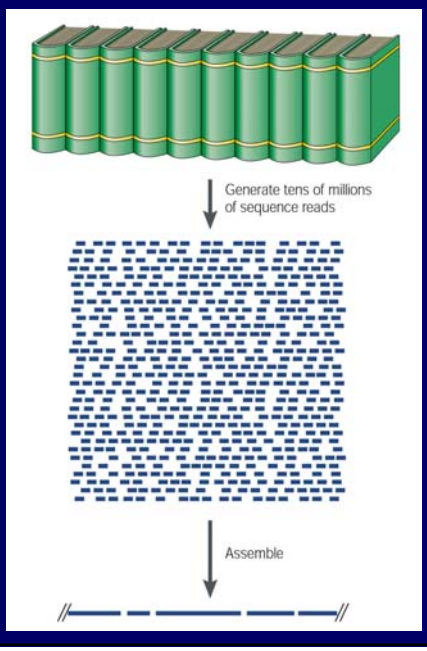


Clone-Based Shotgun Sequencing



Green (2001)

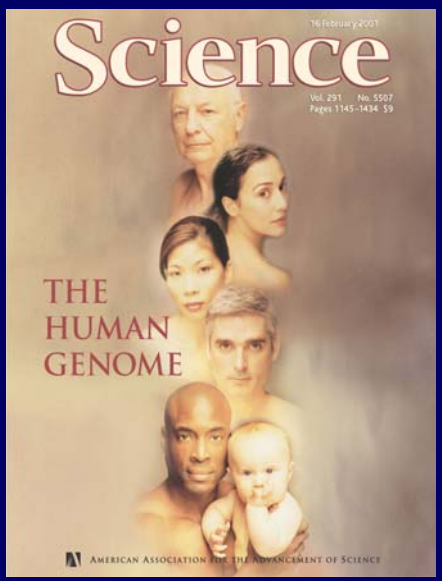
Whole-Genome Shotgun Sequencing



Green (2001)

February, 2001 Draft Sequence

International Human Genome Sequencing Consortium (2001)



Venter et al. (2001)

April, 2003 Completion

October, 2004 Publication


articles

Finishing the euchromatic sequence of the human genome

International Human Genome Sequencing Consortium*

International Human Genome Sequencing Consortium (2004)

CNN's #1 Medical Story of Past 25 Years

CNN.com

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Top 25: Medical stories

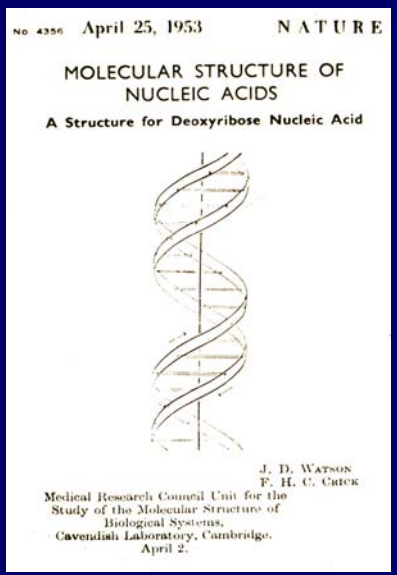
Human genome mapping ranks No. 1 in health news

Tuesday, March 29, 2005 Posted: 4:24 PM EST (2124 GMT)

(CNN) -- Much of the marvel of medicine has to do with discovery. Mapping the human genome, the complete sequence of DNA, gave scientists a blueprint for building a person, making it the No. 1 medical story, according to a distinguished panel CNN gathered to rank the top 25 medical stories of the past quarter-century.

Two men from two separate groups -- Francis Collins of the National Institutes of Health and Craig Venter of Celera Genomics Inc., a pharmaceutical-development company -- worked independently to discover the sequence of the human genome and identify the genes that it contains. This

April, 1953 → April, 2003



No 4356 April 25, 1953 NATURE

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

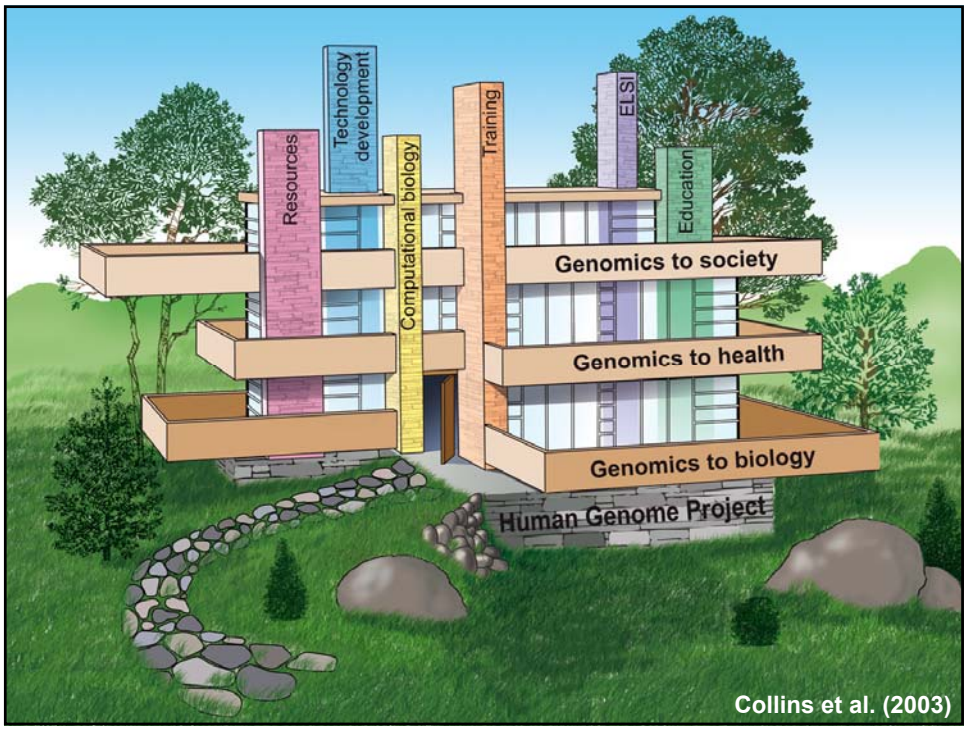
J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

All of the original goals of the Human Genome Project have been accomplished!

What's Next?

Collins et al. (2003)



Collins et al. (2003)

Mapping the Human Genome	~1990 to ~2000	The Human Genome Project
Sequencing the Human Genome	~1998 to ~2003	
Interpreting the Human Genome Sequence	~2003 to ???	*Beyond* The Human Genome Project

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

TGCCGCGGAACTTTTCGGCTCTCTAAGGCTGTATTTTGATATACGAAAGGCACATTTTCCTTCCCTTTTCAAAATGCACCTTGCAAACGTAACAG
GAACCCGACTAGGATCATCGGGAAAAGGAGGAGGAGGAGGAAGGCAGGCTCCGGGGAAGCTGGTGGCAGCGGGTCCTGGGTCTGGCGGACCCTGA
CGCGAAGGAGGGTCTAGGAAGCTCTCCGGGGAGCCGGTTCTCCCGCCGGTGGCTTCTTCTGTCCTCCAGCGTTGCCAACTGGACCTAAAGAGAGG
CCGCGACTGTCGCCCACCTGCGGGATGGGCCTGGTGCTGGGCGGTAAGGACACGGACCTGGAAGGAGCGCGCGCGAGGGAGGGAGGCTGGGAGTC
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TTTCTATTGTATGTTGTTAAATGCCTTAGAATTTAACTTTCTGAATAGGATCCCTTCAGTTTGAGAGTCATAAAAGAGTAAAATTATTATGGTAT

The Human Genome… by the Numbers

~5% of Human Genome is Functionally Important

- 5% of 3B Bases = ~150M Bases
- Do NOT Yet Know the Position of these ~150M Functional Bases

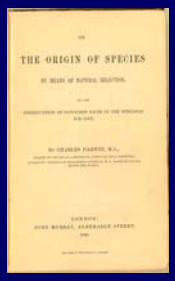
~1.5% Encodes for Protein (Genes)

- Corresponds to ~18-22K Genes
- Many More than ~22K Different Proteins
- Good Inventory at Present

~3.5% Functional But Non-Coding

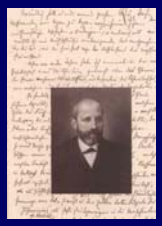
- Gene Regulatory Elements
- Chromosomal Functional Elements
- Undiscovered Functional Elements (NOT Yet in Textbooks!)
- Poor Inventory at Present

Foundational Milestones in Genetics & Genomics

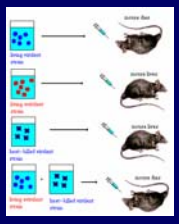


Darwin *1859*

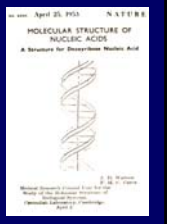
Mendel *1865*



Miescher *1871*

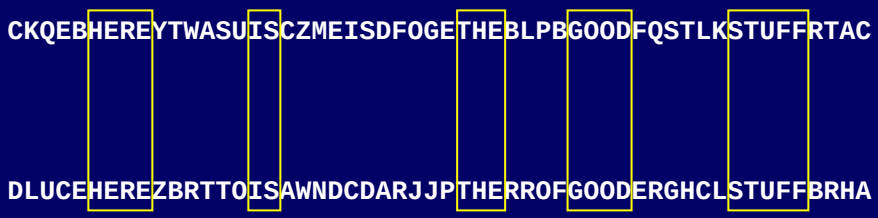


Avery *1944*



Watson & Crick *1953*

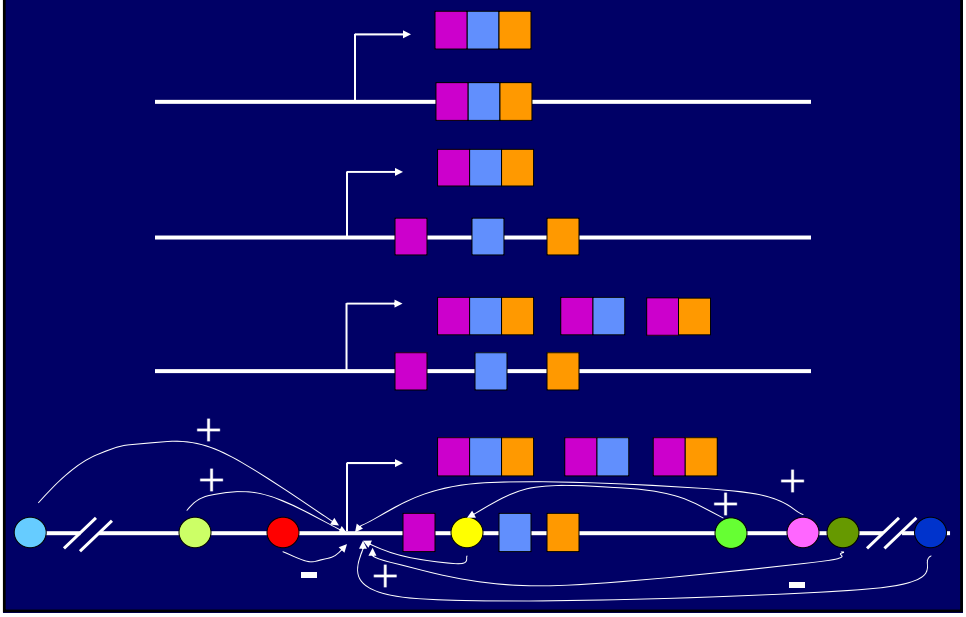
Comparing Genomes is Like Cryptography



Functional Elements: Coding vs. Non-Coding

- Coding Sequences (i.e., Genes)
  - Relatively EASY to Identify
  - Mostly Know What to Look For
  - Complementary Data Sets Available (ESTs, cDNAs)
  - Ever-Improving Computational Gene Predictions
- Non-Coding Functional Sequences
  - HARD to Identify
  - Very Little Known About What to Look For
  - Virtually No Complementary Data Sets Available
  - Poor Computational Predictions

The Language of the Genome



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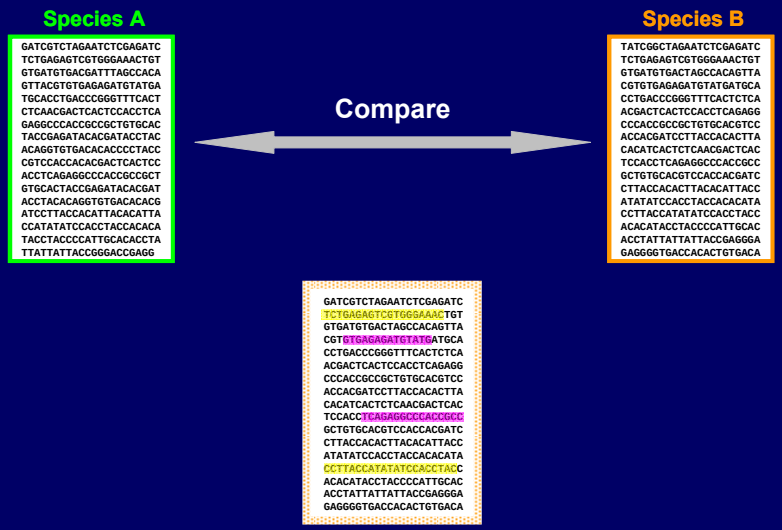
Major role for comparative sequence analysis will be the identification of functionally important, non-coding sequences

Comparative Sequence Analysis

Using the Experiments of Evolution to Decode the Human Genome



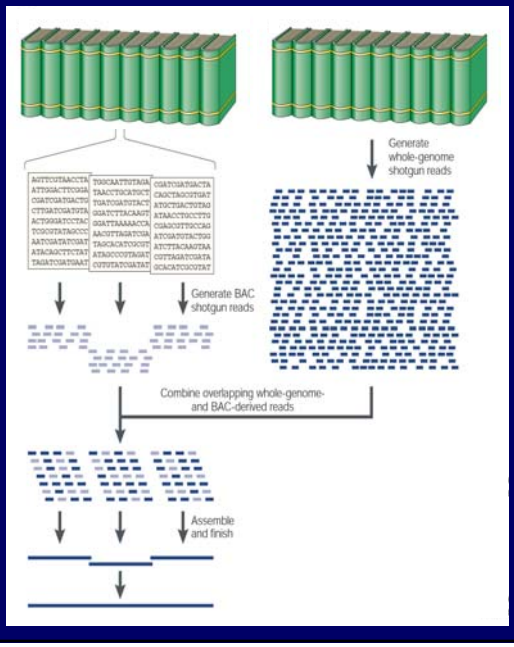
Vertebrate Genome Sequences

Mouse Rat Chicken Chimpanzee Dog

Macaque Orangutan Marmoset Cow Monodelphis Platypus

Xenopus Zebrafish Pufferfish

Hybrid Shotgun Sequencing



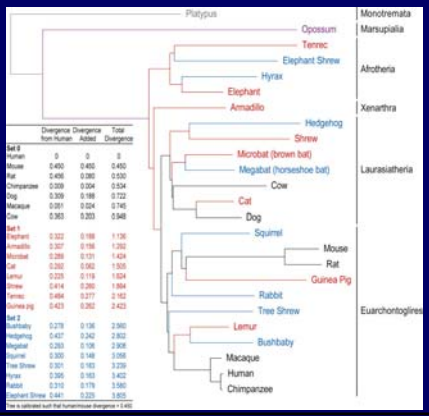
Green (2001)

Low-Redundancy, Whole-Genome Shotgun Sequencing

An initial strategy for the systematic identification of functional elements in the human genome by low-redundancy comparative sequencing

Elliott H. Margulies*[†], Jade Vinson[†§], NISC Comparative Sequencing Program*[¶‖], Webb Miller[‖], David B. Jaffe[#], Kerstin Lindblad-Toh[#], Jean Chang[#], Eric D. Green*[‖], Eric S. Lander[#], James C. Mullikin*[‖**], and Michele Clamp[†**]

Margulies EM et al. (2005)

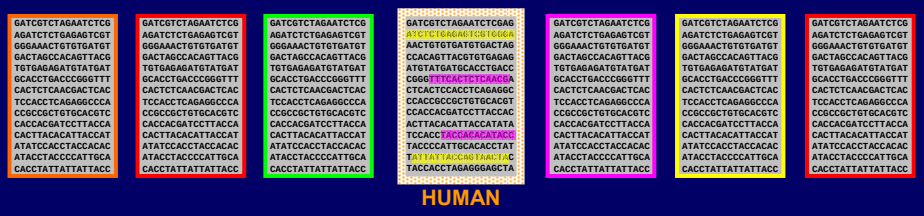


Landscape of Vertebrate Genome Sequencing

- Human
- Mouse
- Rat
- Pufferfish
- Zebrafish
- Chicken
- Chimpanzee
- Dog
- Cow
- Xenopus
- Monodelphis
- Macaque
- Platypus
- Marmoset
- Orangutan
- Armadillo
- Elephant
- Tenrec
- Rabbit
- Cat
- Shrew
- Guinea Pig
- Hedgehog

(and others…)

Multi-Species Sequence Comparisons

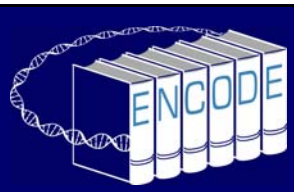


Multi-Species Conserved Sequences (MCSs)

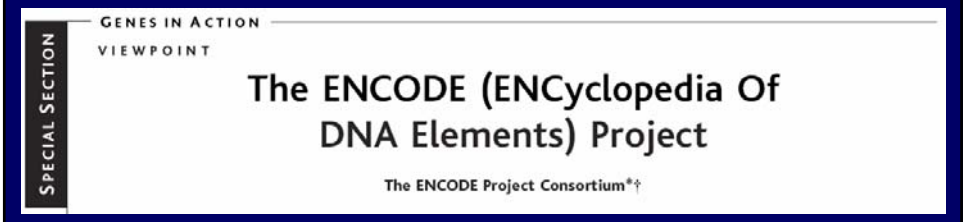
Margulies et al. (2003)

Future Genomes to Sequence???

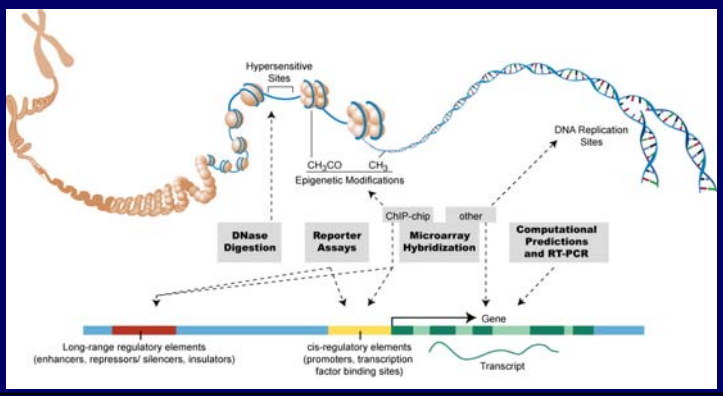
ENCODE Project



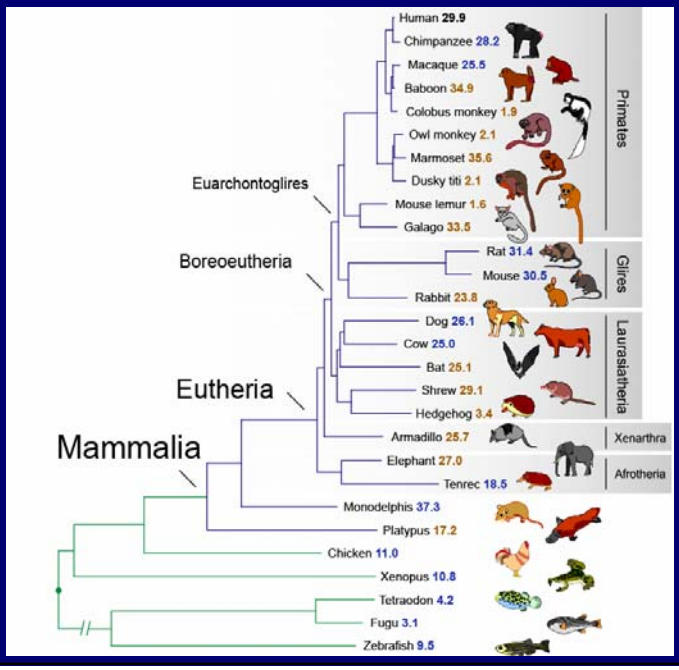
- ENCODE: ENCyclopedia Of DNA Elements
- Goal: Compile a *Comprehensive Encyclopedia* of All Functional Elements in the Human Genome
- Initial Pilot Project: 1% of Human Genome
- Apply Multiple, Diverse Approaches to Study and Analyze that 1% in a Consortium Fashion



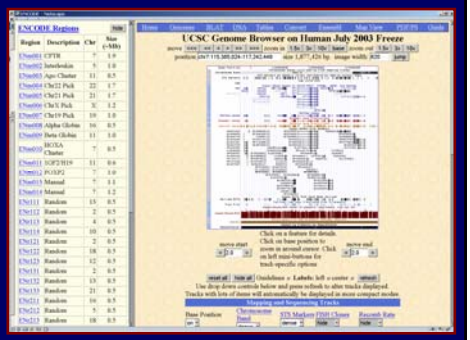
ENCODE Project Consortium (2004)



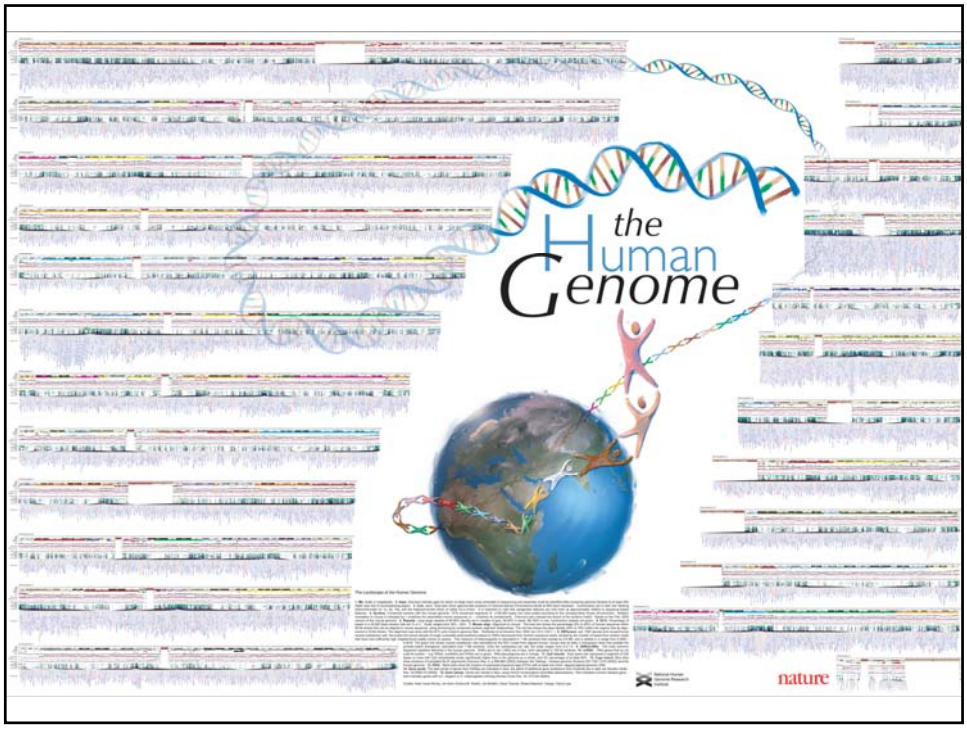
ENCODE Project: Comparative Sequencing



ENCODE Project: Web Sites



genome.gov/ENCODE genome.ucsc.edu/ENCODE

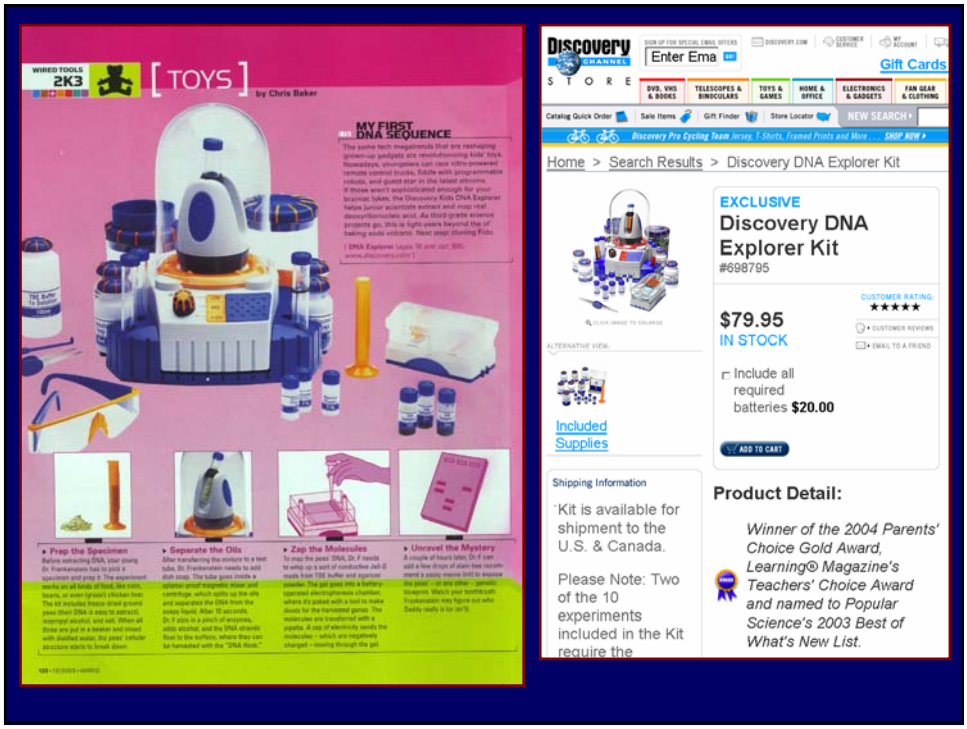


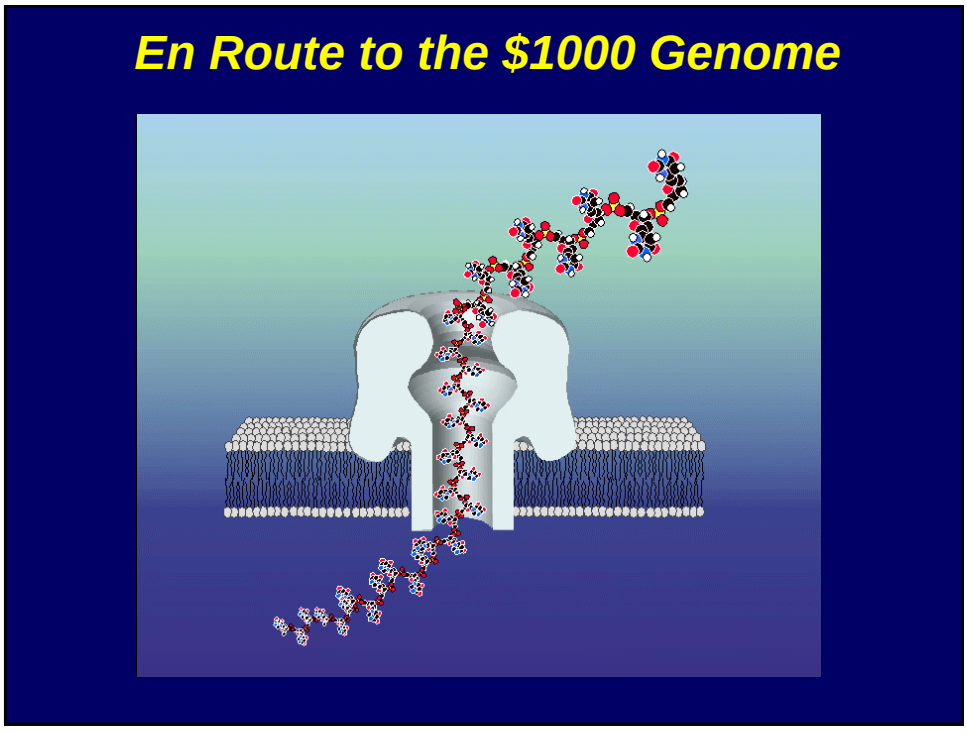
Human Genome Sequence

>$1,000,000,000

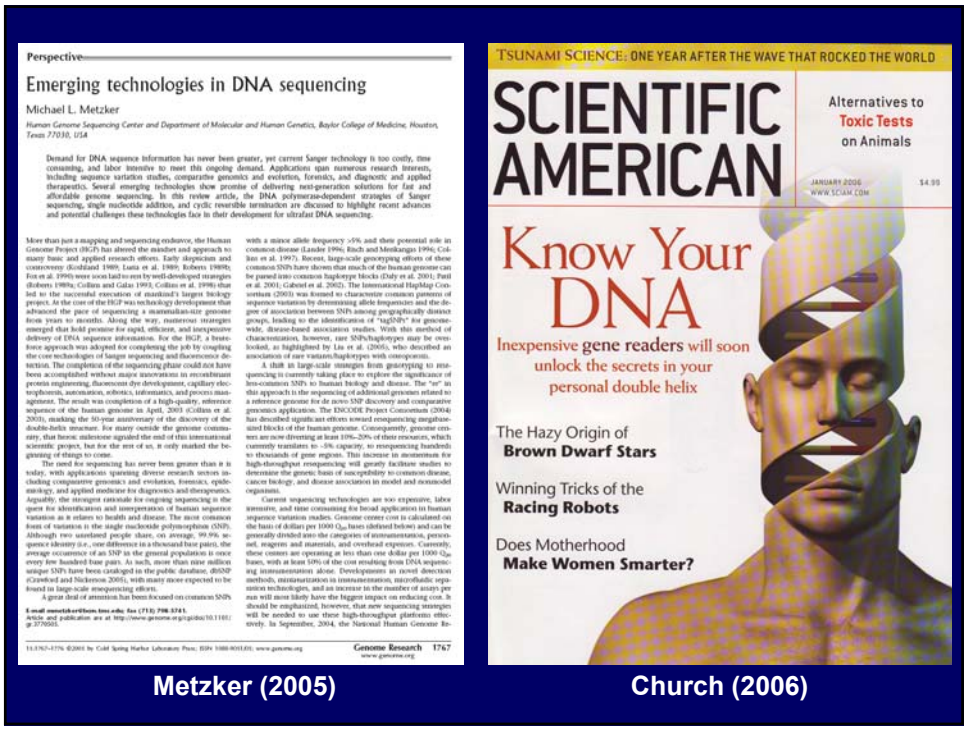
~$100,000

~$1,000


WIRED TOOLS
2K3
[TOYS]
by Chris Baker
MY FIRST DNA SEQUENCE
Prep the Specimen
Separate the Oils
Zap the Molecules
Unravel the Mystery
Discovery CHANNEL STORE
Enter Ema
Gift Cards
Home > Search Results > Discovery DNA Explorer Kit
EXCLUSIVE
Discovery DNA Explorer Kit
#698795
$79.95
IN STOCK
Include all required batteries $20.00
ADD TO CART
Included Supplies
Shipping Information
'Kit is available for shipment to the U.S. & Canada.
Please Note: Two of the 10 experiments included in the Kit require the
Product Detail:
Winner of the 2004 Parents' Choice Gold Award, Learning® Magazine's Teachers' Choice Award and named to Popular Science's 2003 Best of What's New List.


En Route to the $1000 Genome


Genome sequencing in microfabricated high-density picolitre reactors
Marcel Margulies, Michael Egholm, William E. Altman, Said Attiya, Joel S. Bader, Lisa A. Bemben, Jan Berka, Michael S. Braverman, Yi-Ju Chen, Zhoutao Chen, Scott B. Dewell, Lei Du, Joseph M. Fierro, Xavier V. Gomes, Brian C. Godwin, Wen He, Scott Helgesen, Chun He Ho, Gerard P. Irzyk, Szilveszter C. Jando, Maria L. I. Alenquer, Thomas P. Jarvie, Kshama B. Jirage, Jong-Bum Kim, James R. Knight, Janna R. Lanza, John H. Leamon, Steven M. Lefkowitz, Ming Lei, Jing Li, Kenton L. Lohman, Hong Lu, Vinod B. Makhijani, Keith E. McDade, Michael P. McKenna, Eugene W. Myers, Elizabeth Nickerson, John R. Nobile, Ramona Plant, Bernard P. Puc, Michael T. Ronan, George T. Roth, Gary J. Sarkis, Jan Fredrik Simons, John W. Simpson, Maithreyan Srinivasan, Karrie R. Tartaro, Alexander Tomasz, Kari A. Vogt, Greg A. Volkmer, Shally H. Wang, Yong Wang, Michael P. Weiner, Pengguang Yu, Richard F. Begley & Jonathan M. Rothberg
Margulies M et al. (2005)
Solexa Ltd
Simon Bennett PhD
Business Development Director
Solexa Ltd is developing an integrated system, based on a breakthrough single molecule sequencing technology, to address a US$2 billion market that is expected to grow
Bennett (2004)
Toward the $1000 human genome
Simon T Bennett, Colin Barnes, Anthony Cox, Lisa Davies & Clive Brown
Revolutionary new technologies, capable of transforming the economics of sequencing, are providing an unparalleled opportunity to analyze human genetic variation comprehensively at the whole-genome level within a realistic timeframe and at affordable costs. Current estimates suggest that it would cost somewhere in the region of US$30 million to sequence
Bennett et al. (2005)
Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome
Jay Shendure, Gregory J. Porreca, Nikos B. Reppas, Xiaoxia Lin, John P. McCutcheon, Abraham M. Rosenbaum, Michael D. Wang, Kun Zhang, Robi D. Mitra, George M. Church
Shendure et al. (2005)

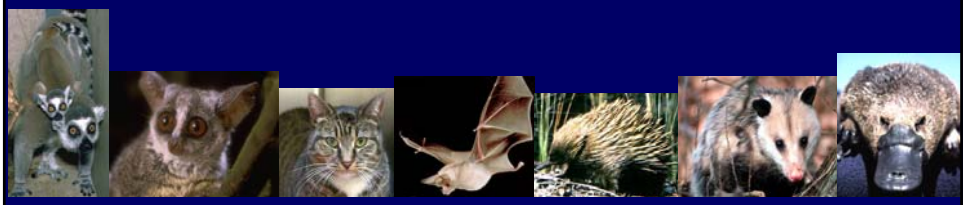

Perspective
Emerging technologies in DNA sequencing
Michael L. Metzker
Human Genome Sequencing Center and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, USA
Demand for DNA sequence information has never been greater, yet current Sanger technology is too costly, time consuming, and labor intensive to meet this ongoing demand. Applications span numerous research interests, including sequence variation studies, comparative genomics and evolution, forensics, and diagnostic and applied therapeutics. Several emerging technologies show promise of delivering next-generation solutions for fast and affordable genome sequencing. In this review article, the DNA polymerase-dependent strategies of Sanger sequencing, single nucleotide addition, and cyclic reversible termination are discussed to highlight recent advances and potential challenges these technologies face in their development for ultrafast DNA sequencing.
Genome Research 1767
Metzker (2005)
TSUNAMI SCIENCE: ONE YEAR AFTER THE WAVE THAT ROCKED THE WORLD
SCIENTIFIC AMERICAN
Alternatives to Toxic Tests on Animals
JANUARY 2006
WWW.SCIAM.COM
$4.99
Know Your DNA
Inexpensive gene readers will soon unlock the secrets in your personal double helix
The Hazy Origin of Brown Dwarf Stars
Winning Tricks of the Racing Robots
Does Motherhood Make Women Smarter?
Church (2006)

DNA Sequencing Technologies

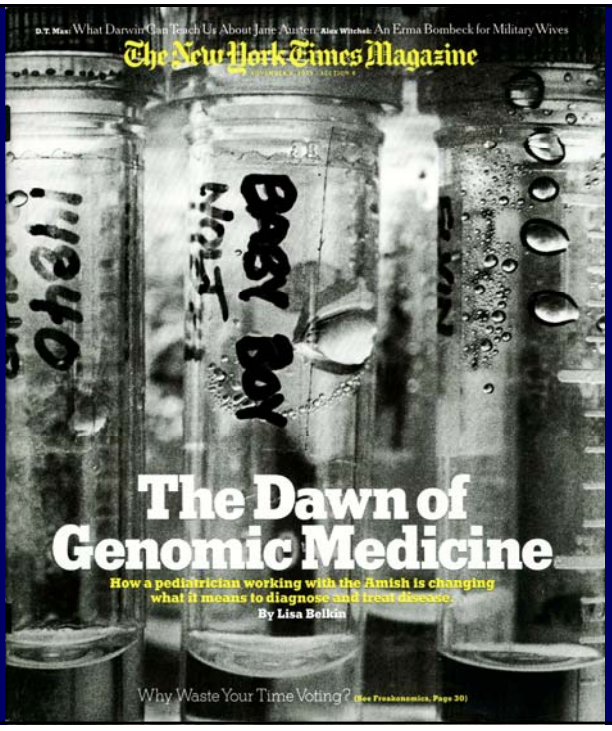
Method	Feasibility	Read Length	Data Quality	Raw Data Production
Sanger Sequencing	Well Established	Long (800-1200 bases)	+++	+
Stepwise Synthesis	Becoming Established	Short (25-100 bases)	+	+++++
Single Molecule	Far from Established	Long (>1000 bases ?)	???	+++++ ?

Realities of New DNA Sequencing Technologies…

"Inter-Species" Comparisons



"Intra-Species" Comparisons



The Pathway to Genomic Medicine

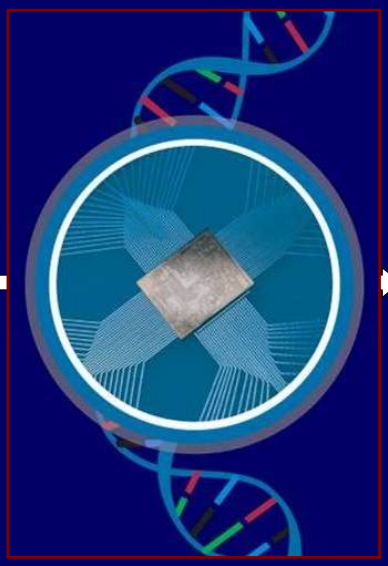
HGP

→ → ? → →

Realization of Genomic Medicine

The Pathway to Genomic Medicine

HGP



Realization of Genomic Medicine

The Current Big Challenges…

- Defining "Saturation Points" in Terms of Information Gained by Comparative Sequence Analyses
- Achieving the "$1000 Genome"
- Large-Scale Deployment of Medical Sequencing

The Human Genome Sequence to Genomic Medicine…

…from base pairs to bedside.

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