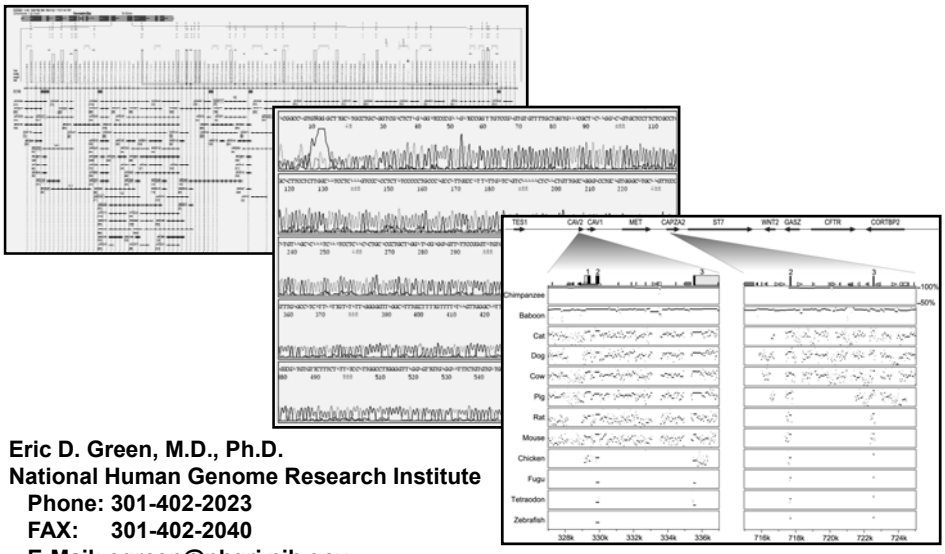
# Techniques for Analyzing Genomes I

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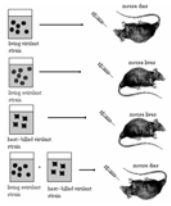
# Foundational Milestones in Genetics & Genomics

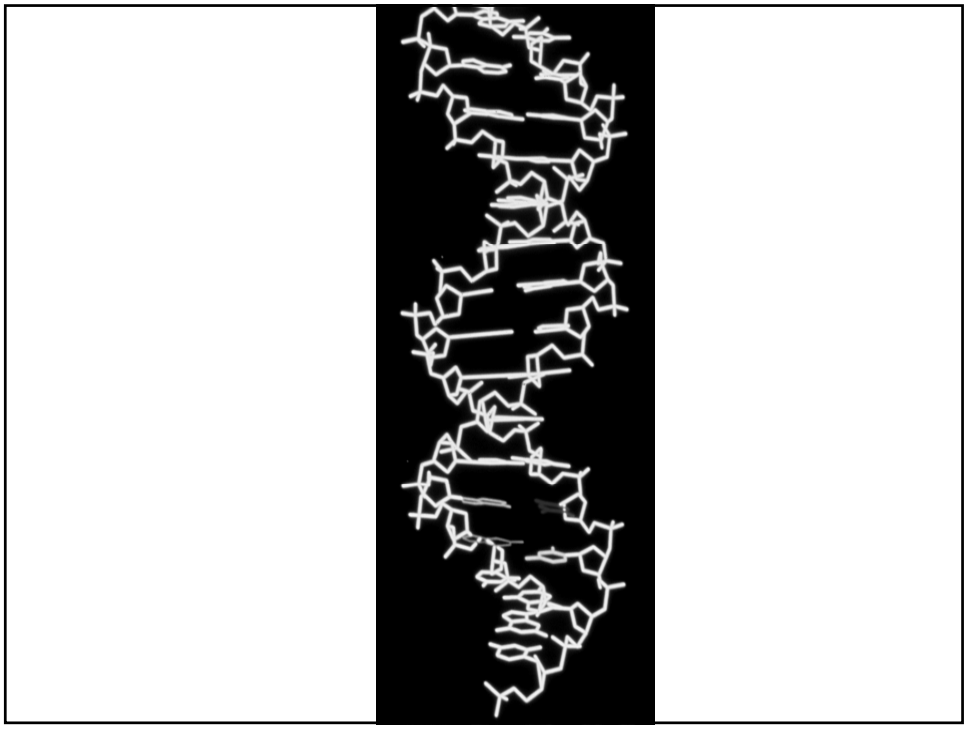
**Mendel** *1865*

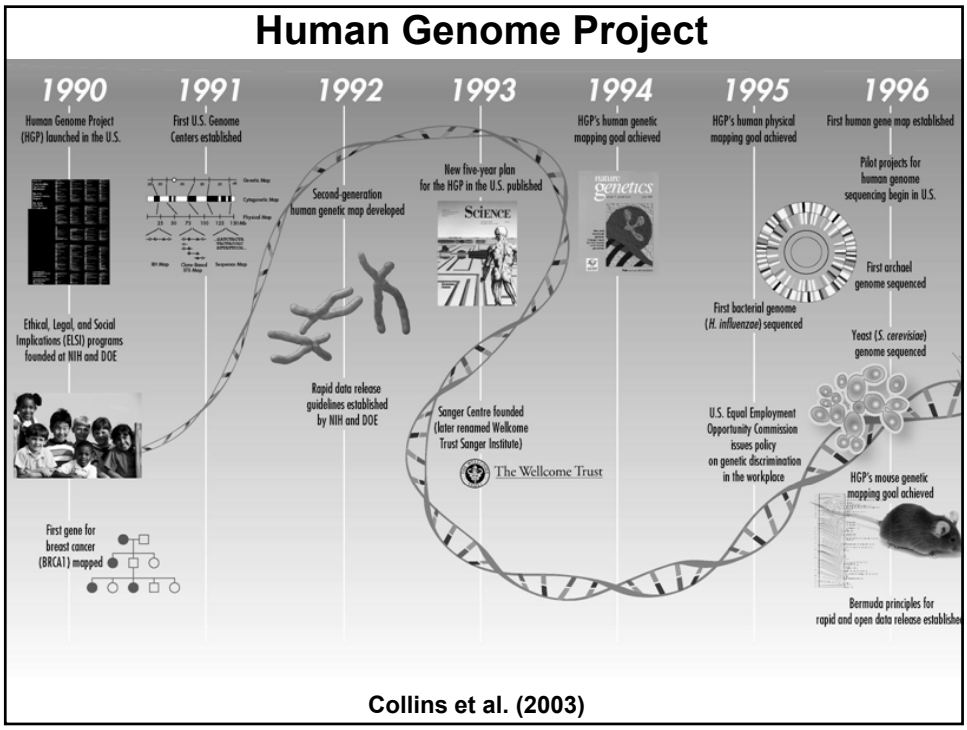
**Miescher** *1871*



**Avery** *1944*

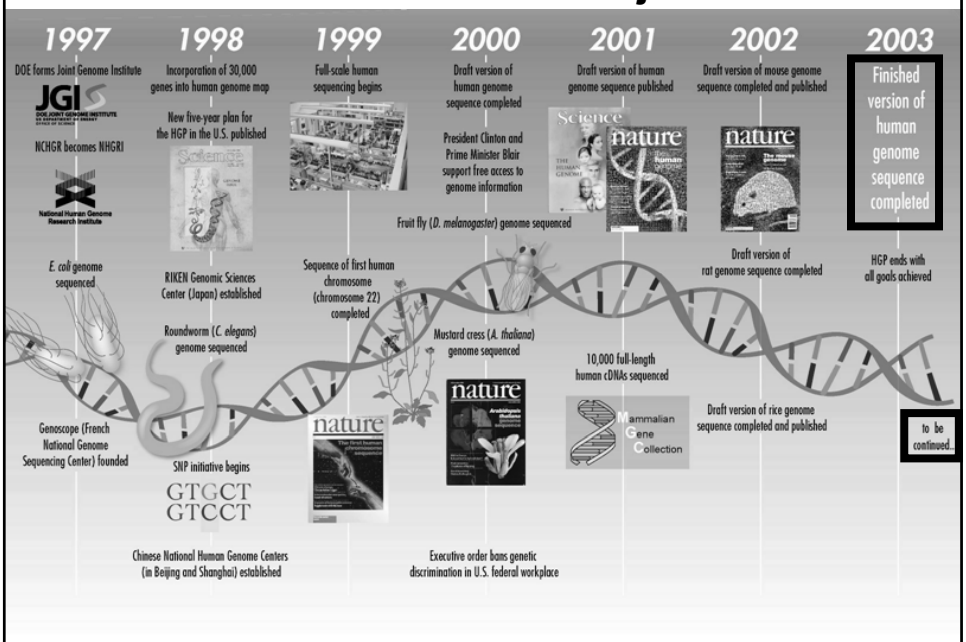

**Watson & Crick** *1953*






Collins et al. (2003)

## Human Genome Project




Collins et al. (2003)

## Outline

I. Fundamentals of Genome Mapping

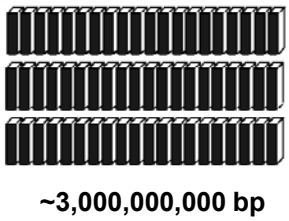
II. Fundamentals of Genome Sequencing

III. Mapping & Sequencing in the Human Genome Project

IV. Comparative Sequencing

V. New Frontiers in Genome Analysis

## Genome Sizes



Human Genome
Mouse Genome

~3,000,000,000 bp

Fruit Fly Genome

~160,000,000 bp

Nematode Genome

~100,000,000 bp

Yeast Genome

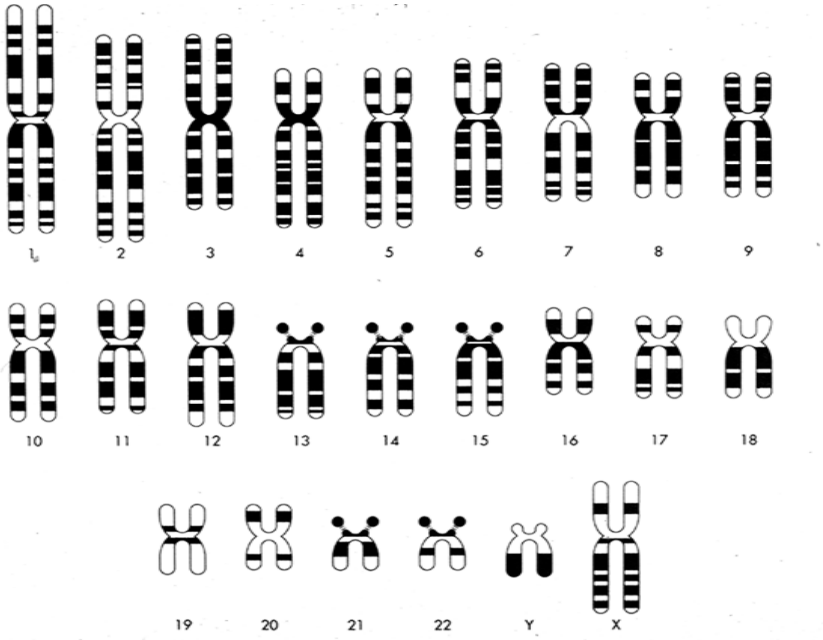
~15,000,000 bp

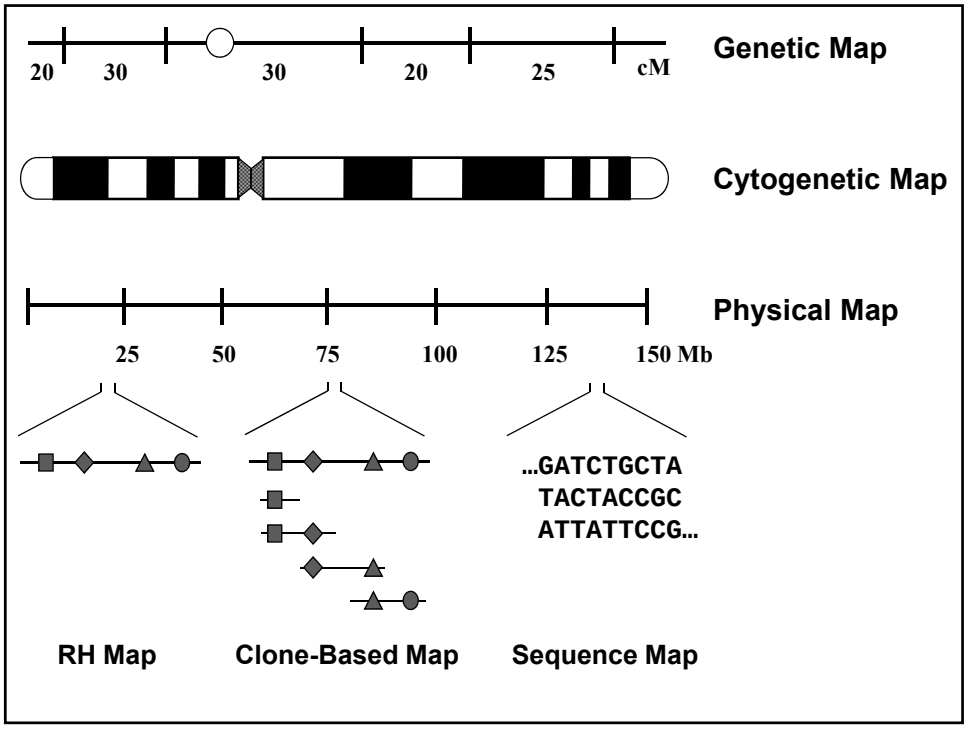
*E. coli* Genome

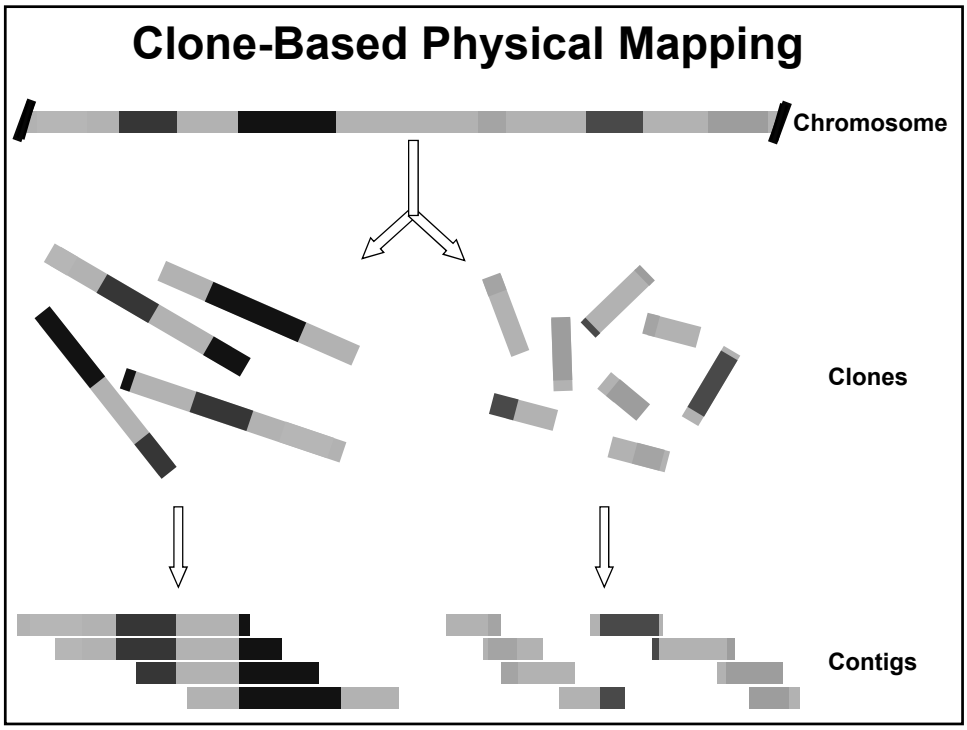


~5,000,000 bp

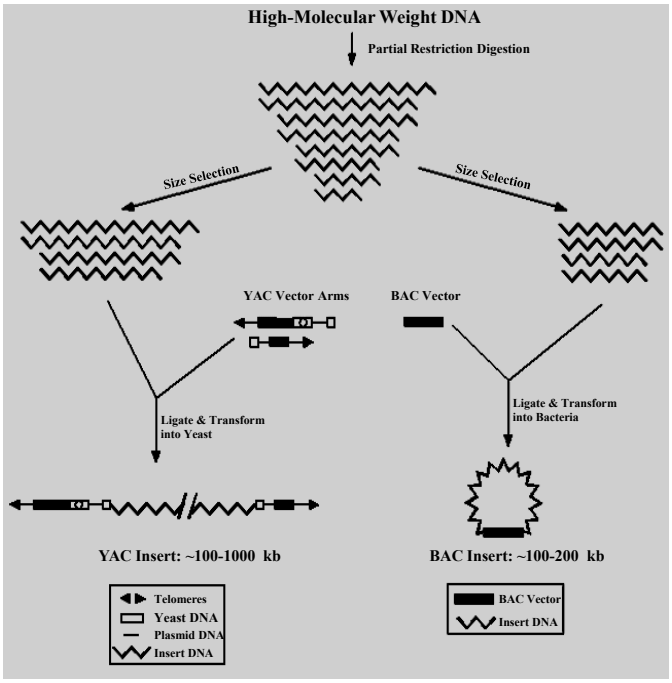
## The Human Cytogenetic Map



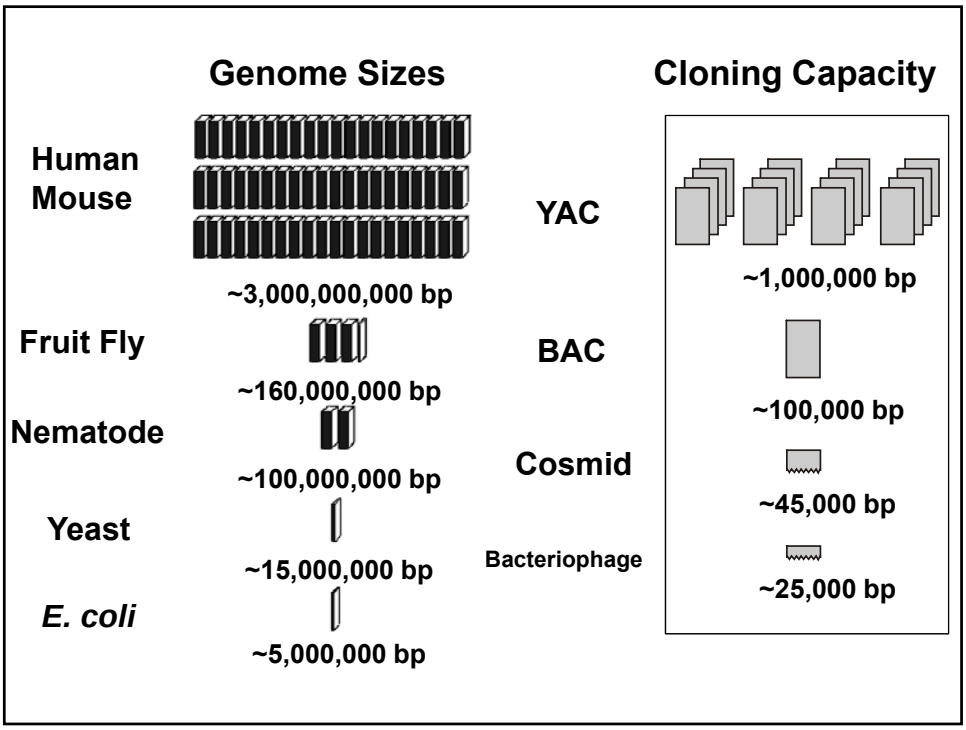

Genetic Map
20
30
30
20
25
cM
Cytogenetic Map
Physical Map
25
50
75
100
125
150 Mb
...GATCTGCTA
TACTACCGC
ATTATTCCG...
RH Map
Clone-Based Map
Sequence Map


Clone-Based Physical Mapping
Chromosome
Clones
Contigs

Construction of YACs and BACs



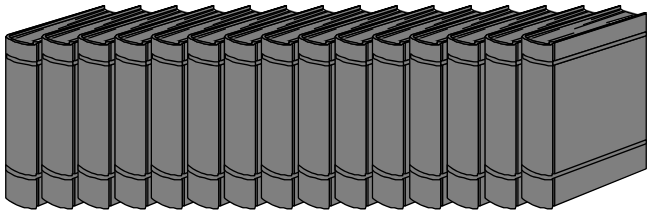

Green et al. (1998)
Birren et al. (1998)



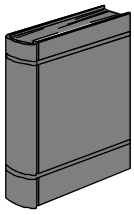
## Bacterial Artificial Chromosomes (BACs)

- 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

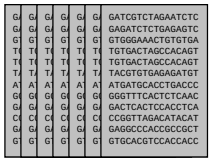
  Low Yields of DNA by Standard Methods
  Reasonably Stable
- See Birren et al. (1998)
- Availability of BAC Libraries from Many Vertebrate Species
  (e.g., www.chori.org/bacpac)



**Genome**
**(~3000 Mb)**



**Chromosome**
**(~130 Mb)**

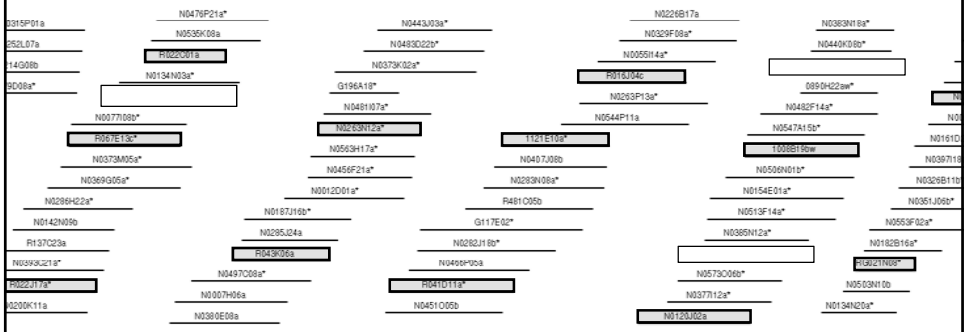



**YAC**
**(~0.5-1.0 Mb)**


**BAC**
**(~0.1-0.2 Mb)**

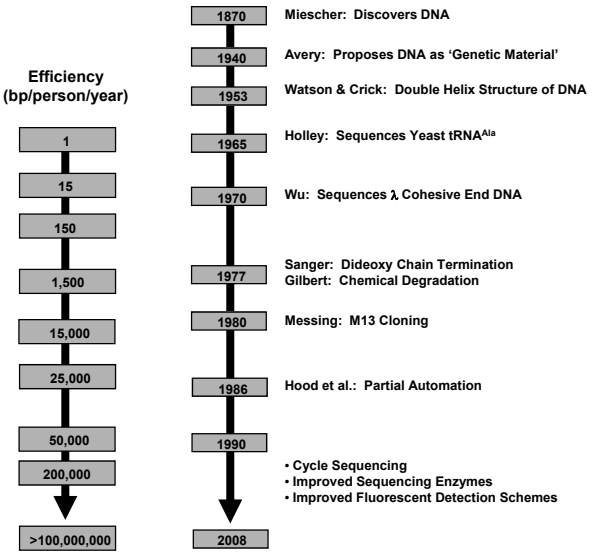
## Sequence-Ready BAC Contig Map

**Marra et al. (1997)**



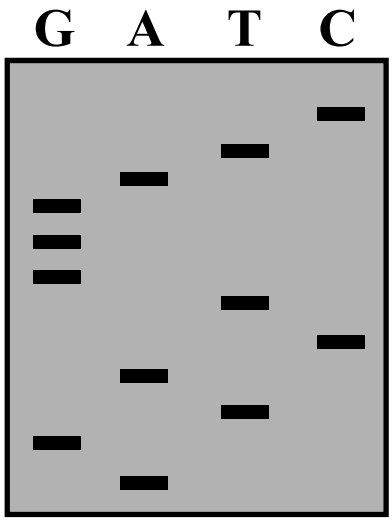

# DNA Sequencing

## History of DNA Sequencing




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

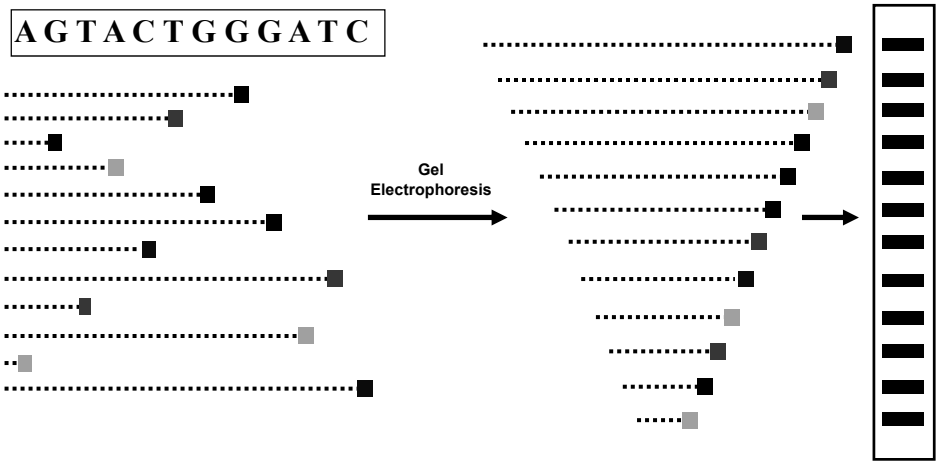
## DNA Tagged with Radioactivity



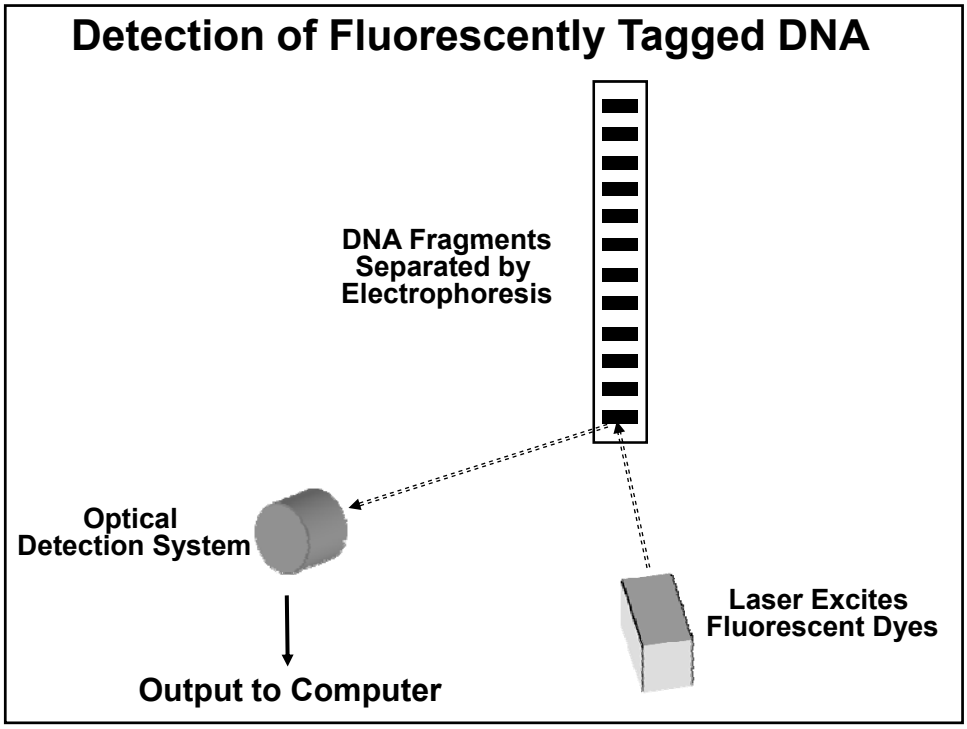

**G: G Reaction**
**A: A Reaction**
**T: T Reaction**
**C: C Reaction**

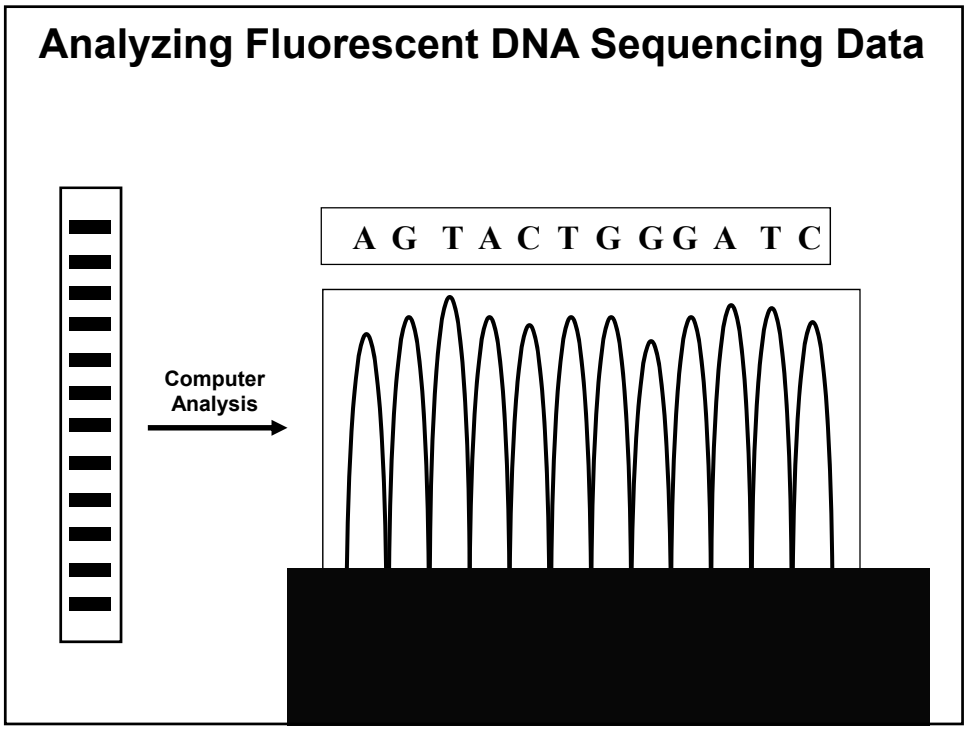
## Radioactive Sequencing

## Fluorescent DNA Sequencing

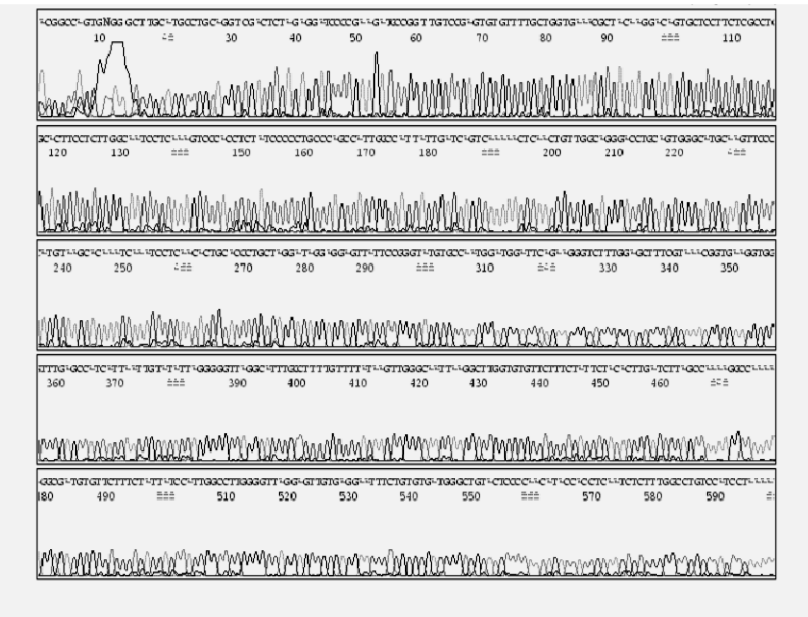



Wilson & Mardis (1997)

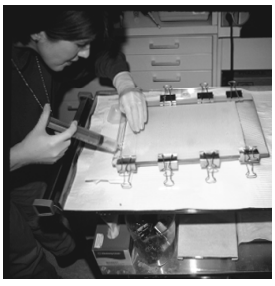

Detection of Fluorescently Tagged DNA
DNA Fragments Separated by Electrophoresis
Optical Detection System
Laser Excites Fluorescent Dyes
Output to Computer


Analyzing Fluorescent DNA Sequencing Data
A G T A C T G G G A T C
Computer Analysis

## 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**

Mammalian Gene Collection

**mgc.nci.nih.gov**

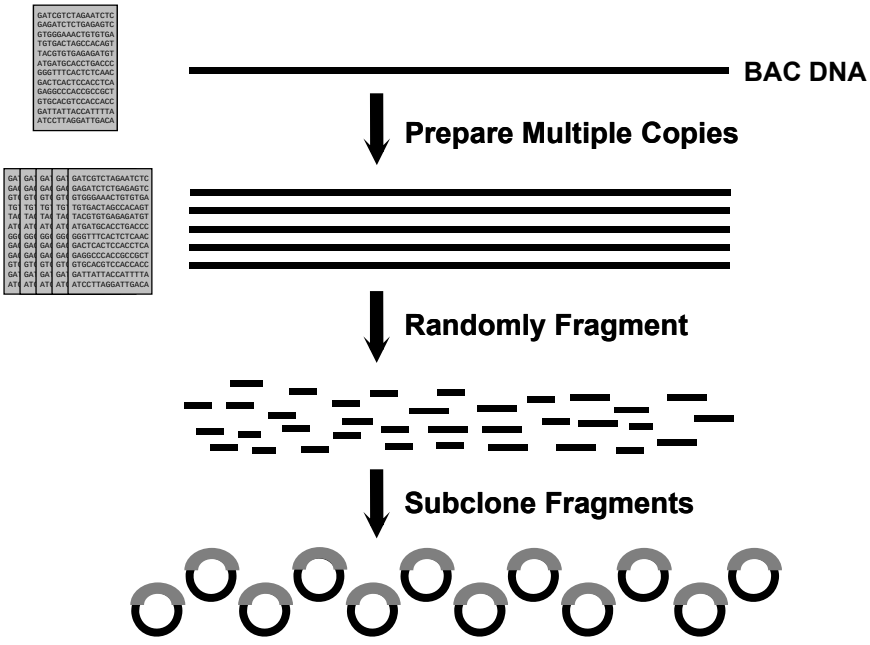
**Gerhard et al. (2004)**

# Large-Scale Genome Sequencing

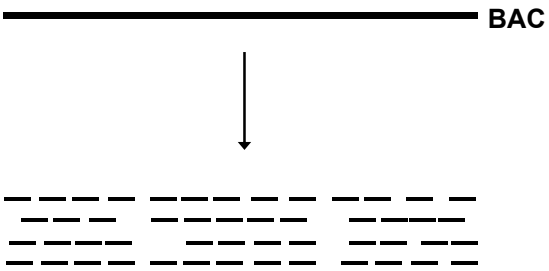
## Shotgun Sequencing

Wilson & Mardis (1997)
Green (2001)

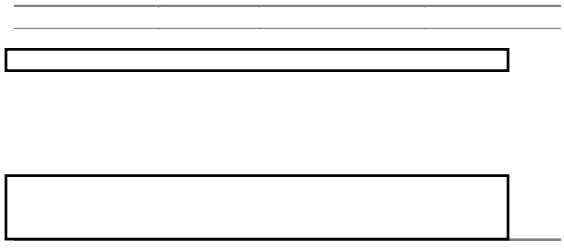
## Subclone Construction

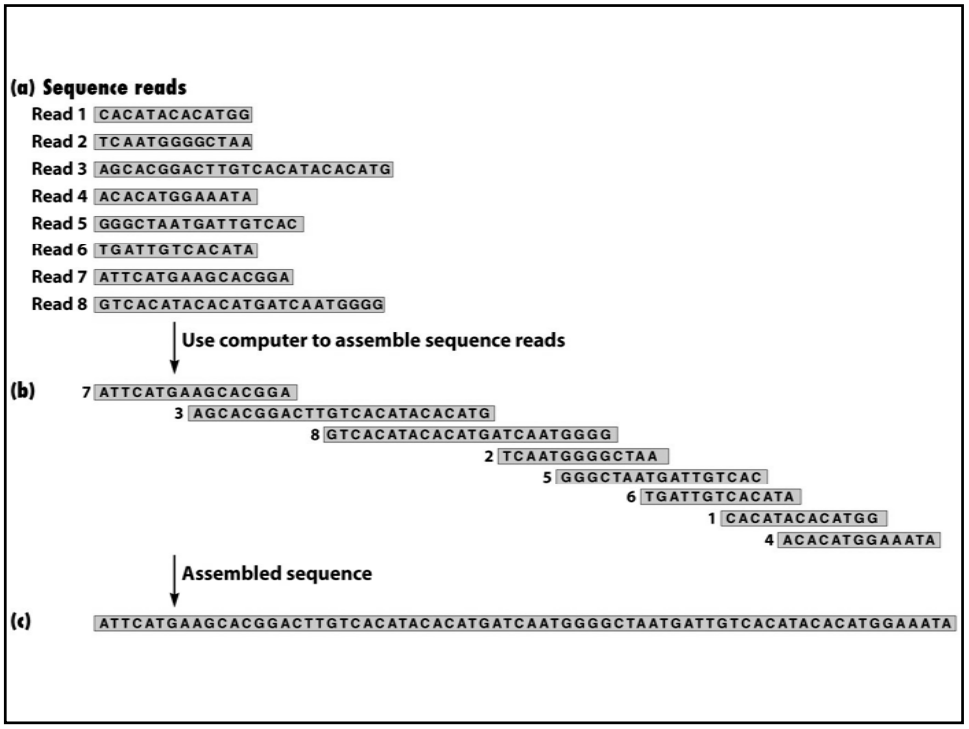


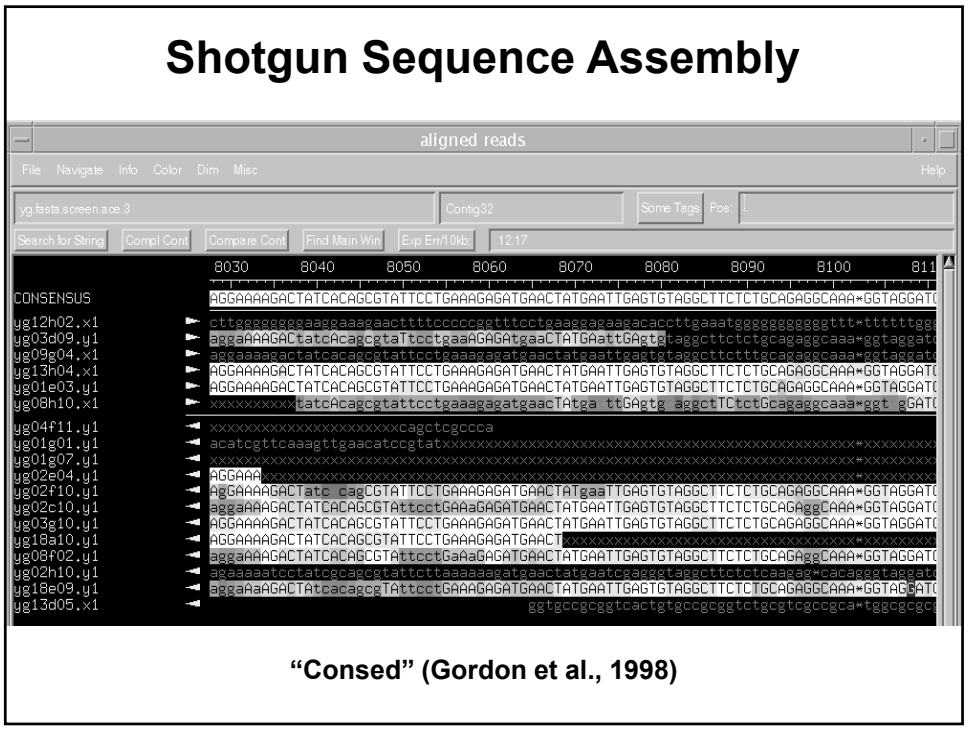
## Shotgun Sequencing Strategy



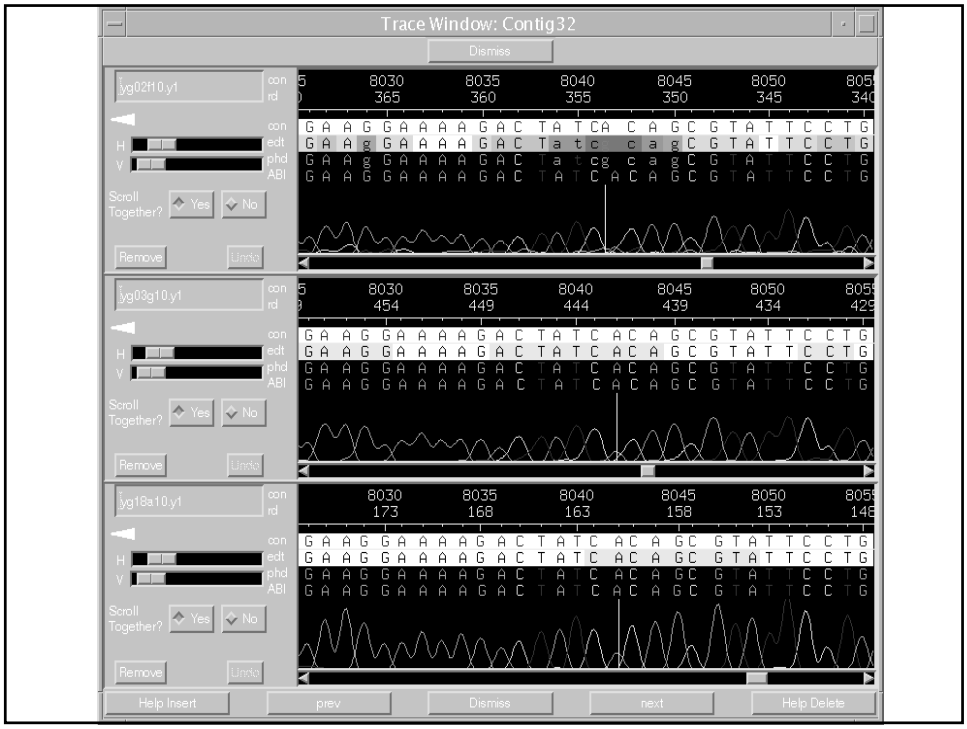

## Poisson Calculations

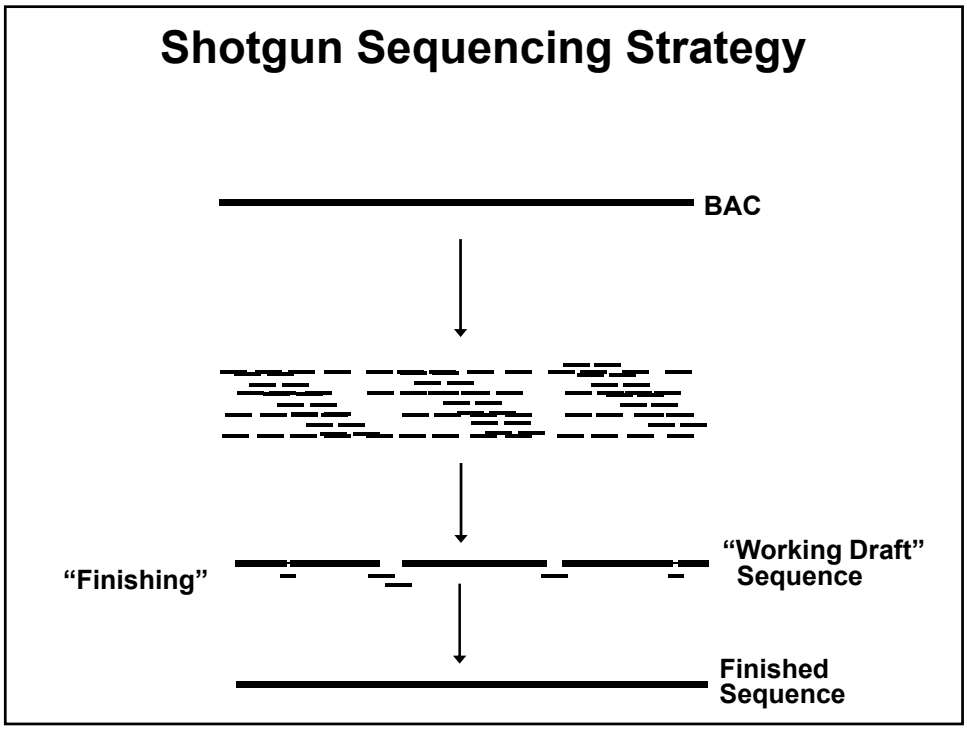




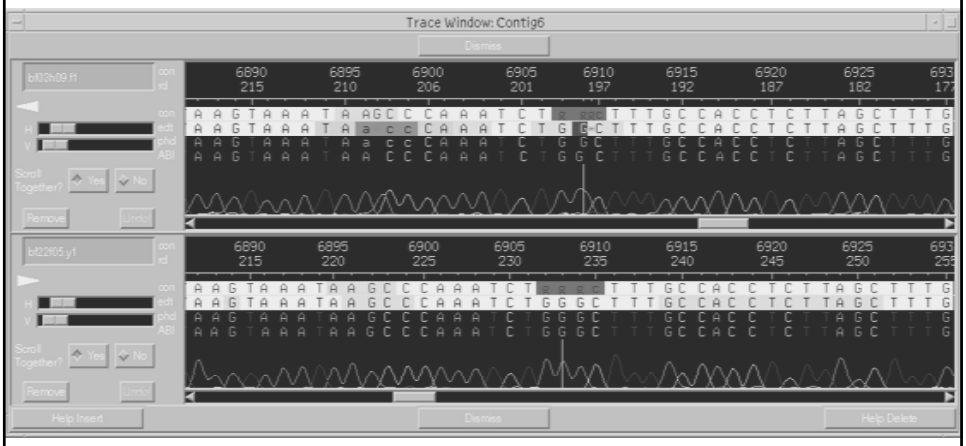




**"Consed" (Gordon et al., 1998)**


Trace Window: Contig32
Dismiss
Scroll Together?
Yes
No
Remove
Help Insert
prev
Dismiss
next
Help Delete


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

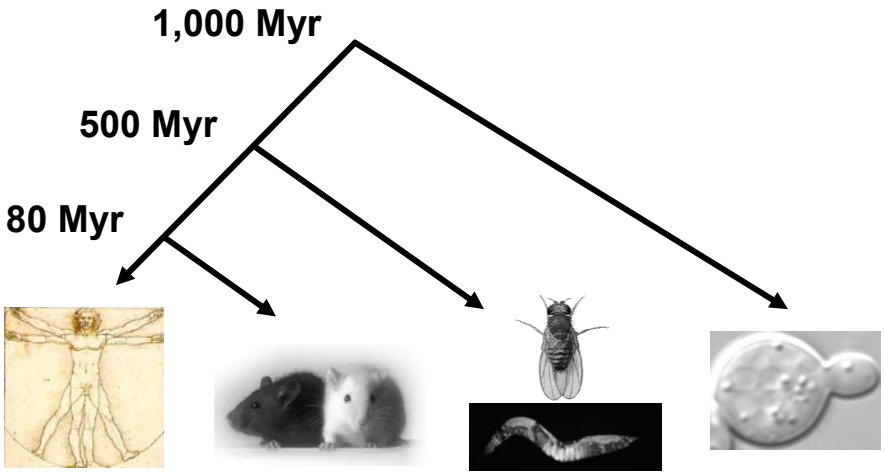
## Sequence Finishing: Resolving Ambiguities




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

## Historically Significant Genome Sequencing Projects

# Model Organisms

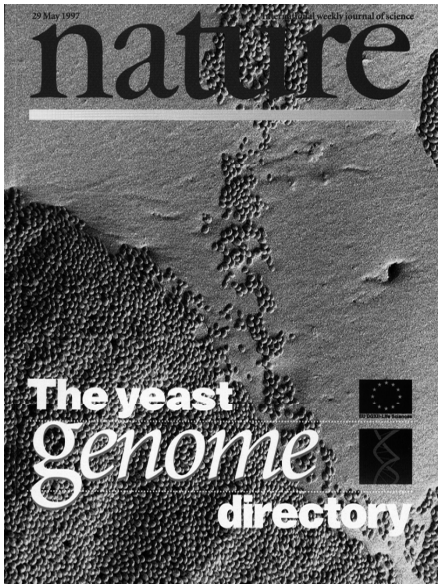



Human Biology | Mammalian Biology | Multicellular Biology | Unicellular Biology

# Microbial Genome Sequences

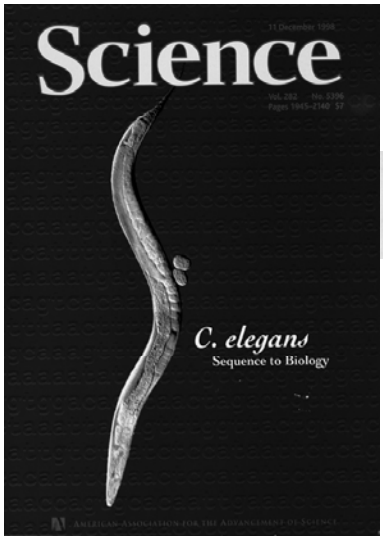

www.tigr.org

## First Eukaryotic Genome Sequence




Goffeau et al. (1997)

## First Animal Genome Sequence

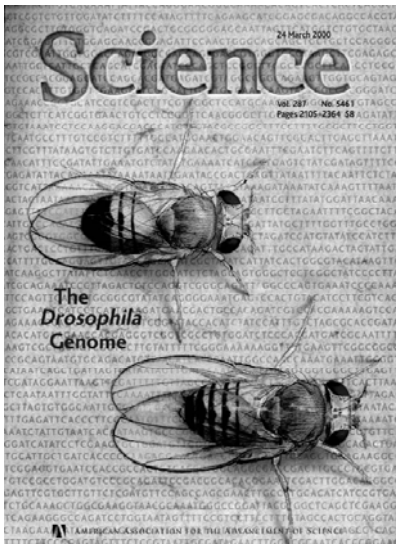



Genome Sequence of the Nematode *C. elegans*: A Platform for Investigating Biology

The *C. elegans* Sequencing Consortium*

*C. elegans* Sequencing Consortium (1998)

## Second Animal Genome Sequence




THE *DROSOPHILA* GENOME

REVIEW

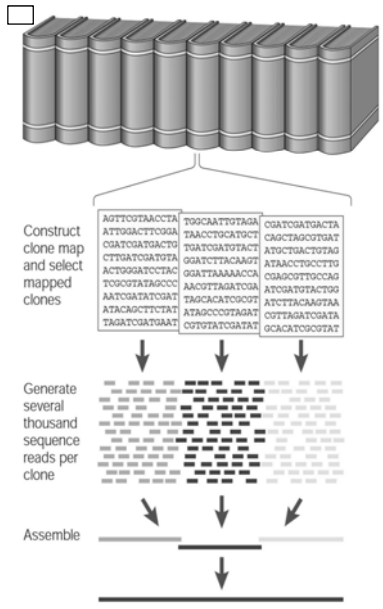
**The Genome Sequence of *Drosophila melanogaster***

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,[2] 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,[6] Catherine R. Nelson,[6] 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,[2] Deepali Bhandari,[1] Slava Bolshakov,[11] Dana Borkova,[12] Michael R. Botchan,[13] John Bouck,[3] Peter Brokstein,[6] 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,[3] Boris C. Dunkov,[22] Patrick Dunn,[1] Kenneth J. Durbin,[3] 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,[4] Ken Glasser,[1] Anna Glodek,[1] Fangcheng Gong,[1] J. Harley Gorrell,[4] 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,[6] 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,[6] Ali Moshrefi,[2] Stephen M. Mount,[27] Mee Moy,[1] Brian Murphy,[1] Lee Murphy,[28] Donna M. Muzny,[3] David L. Nelson,[3] 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,[6] 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] Aihui H. Wang,[1] Xin Wang,[1] Zhen-Yuan Wang,[1] David A. Wassarman,[33] George M. Weinstock,[3] Jean Weissenbach,[14] Sherita M. Williams,[1] Trevor Woodage,[1] Kim C. Worley,[3] 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] Xianquan H. Zheng,[1] Fei N. Zhong,[1] Wenyan Zhong,[1] Xiaojun Zhou,[4] Shiaoping Zhu,[1] Xiaohong Zhu,[1] Hamilton O. Smith,[1] Richard A. Gibbs,[3] Eugene W. Myers,[1] Gerald M. Rubin,[34] J. Craig Venter[1]

**Adams et al. (2000)**

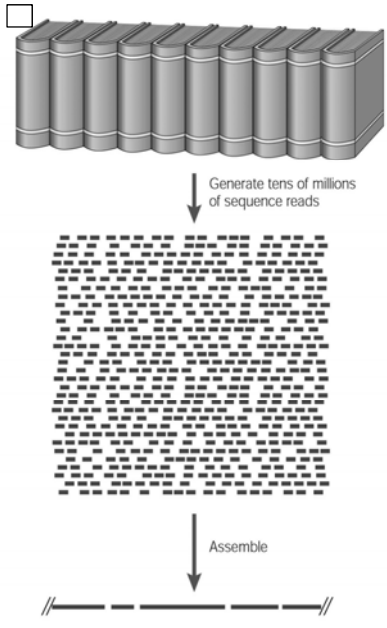
## Human Genome Sequencing Centers

## Clone-Based Shotgun Sequencing



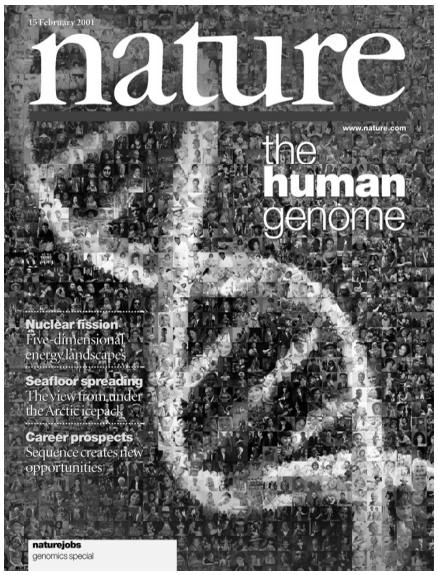

Green (2001)

## Whole-Genome Shotgun Sequencing

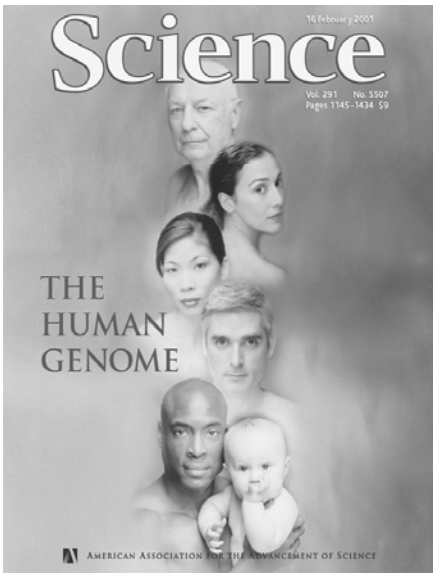



Green (2001)

## February, 2001 Draft Sequence



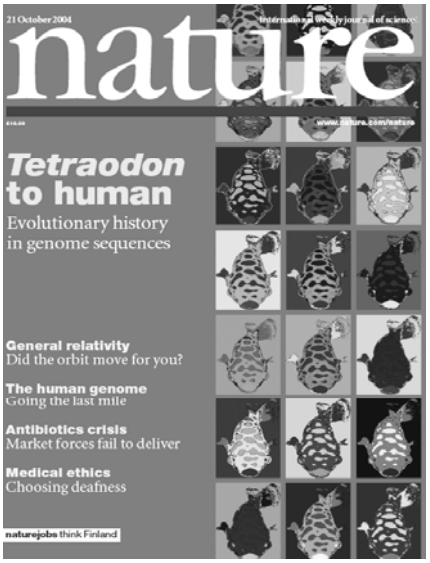

International Human Genome Sequencing Consortium (2001)




Venter et al. (2001)

## April, 2003 Completion

# October, 2004 Publication





articles

Finishing the euchromatic sequence of the human genome

International Human Genome Sequencing Consortium*

The sequence of the human genome encodes the genetic instructions for human physiology, as well as rich information about human evolution. In 2001, the International Human Genome Sequencing Consortium reported a draft sequence of the euchromatic portion of the human genome. Since then, the international collaboration has worked to convert this draft into a genome sequence with high accuracy and nearly complete coverage. Here, we report the result of this finishing process. The current genome sequence (Build 35) contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers ~99% of the euchromatic genome and is accurate to an error rate of ~1 event per 100,000 bases. Many of the remaining euchromatic gaps are associated with segmental duplications and will require focused work with new methods. The near-complete sequence, the first for a vertebrate, greatly improves the precision of biological analyses of the human genome including studies of gene number, birth and death. Notably, the human genome seems to encode only 20,000–25,000 protein-coding genes. The genome sequence reported here should serve as a firm foundation for biomedical research in the decades ahead.

**International Human Genome Sequencing Consortium (2004)**

# CNN's #1 Medical Story of Past 25 Years


## Top 25: Medical stories

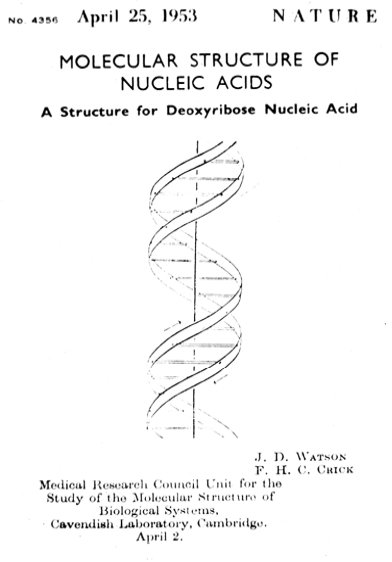
### Human genome mapping ranks No. 1 in health news

**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

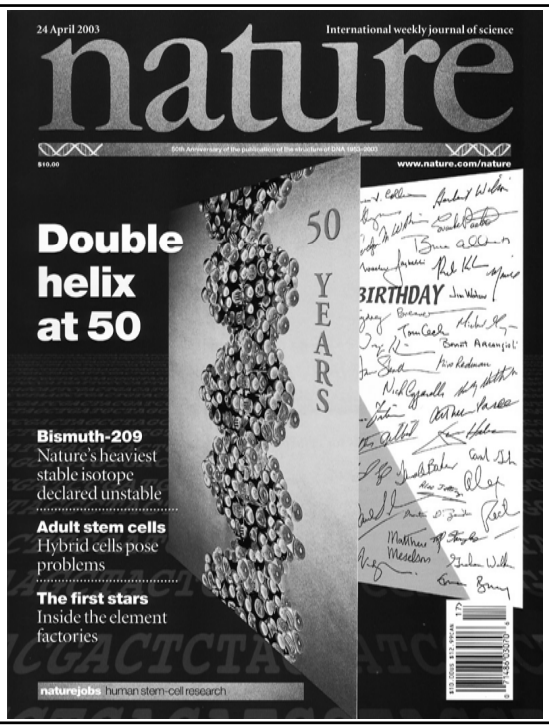
A Structure for Deoxyribose Nucleic Acid

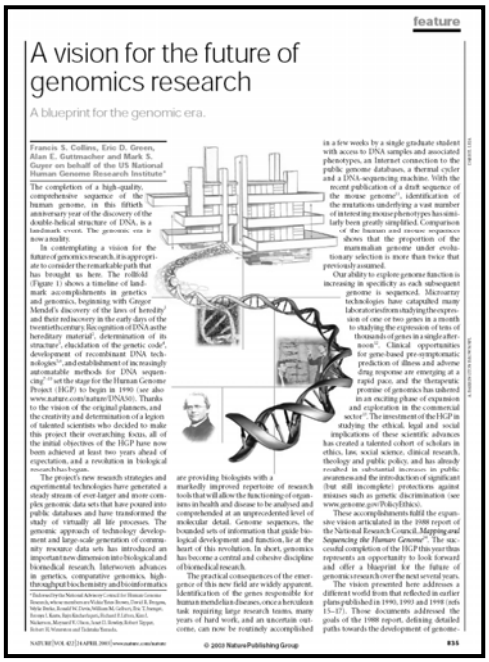
J. D. Watson
F. H. C. Crick

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?



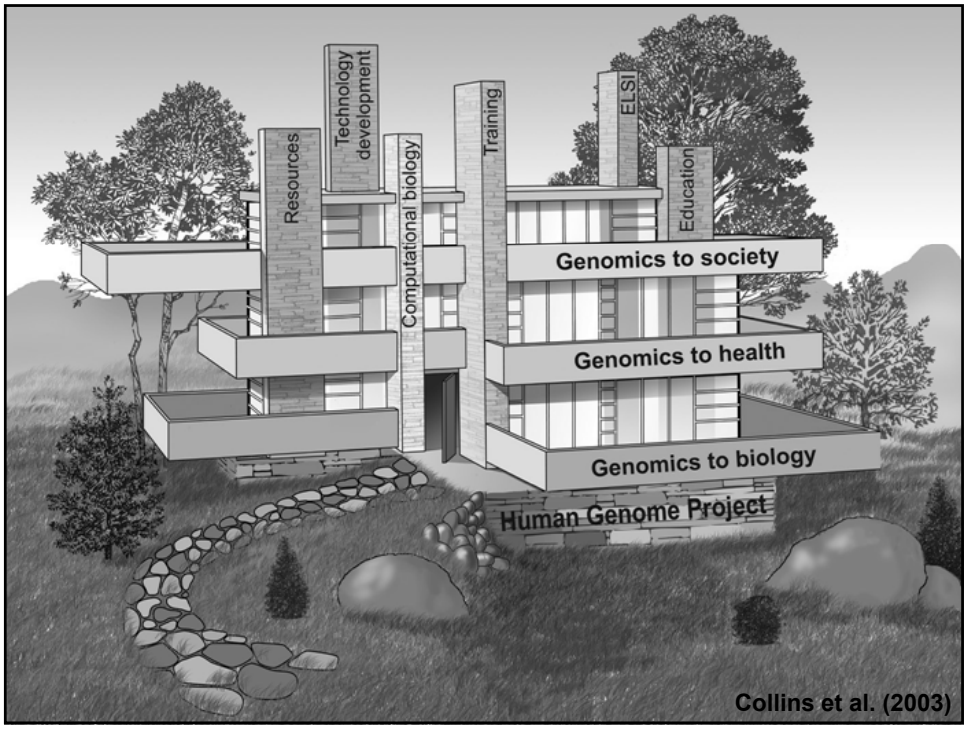


feature

A vision for the future of genomics research

A blueprint for the genomic era.

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

**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
AGAATCGGGAAAGGGAGGTGCGGGGCGGCGAGGGAGCGAAGGAGGAGAGGAGGAAGGAGCGGGAGGGGTGCTGGCGGGGGTGCGTAGTGGGTGGA
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TTTCTATTGTATGTTGTTAAATGCCTTAGAATTTAACTTTCTGAATAGGATCCCTTCAGTTTGAGAGTCATAAAAGAGTAAAATTATTATGGTAT

## The Human Genome… by the Numbers

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

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

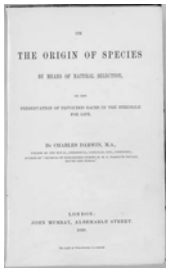
### ~1.5% Encodes for Protein (Genes)

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

### ~3.5% Functional But Non-Coding

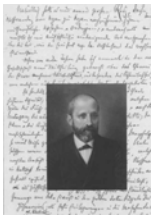
- Gene Regulatory Elements
- Chromosomal Functional Elements
- Undiscovered Functional Elements (NOT Yet in Textbooks!)
- Poor Inventory at Present

## Foundational Milestones in Genetics & Genomics

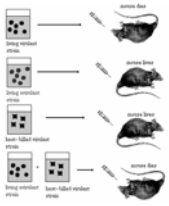



**Darwin** — *1859*

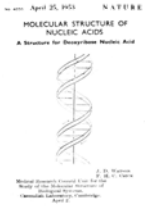
**Mendel** — *1865*



**Miescher** — *1871*

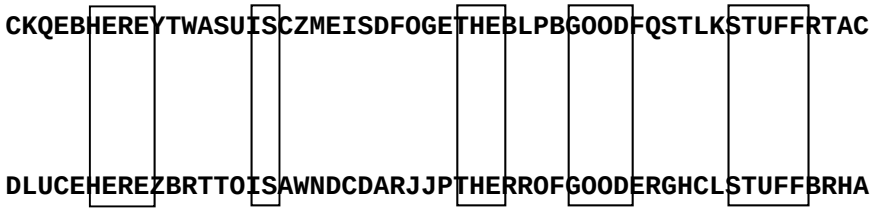


**Avery** — *1944*




**Watson & Crick** — *1953*

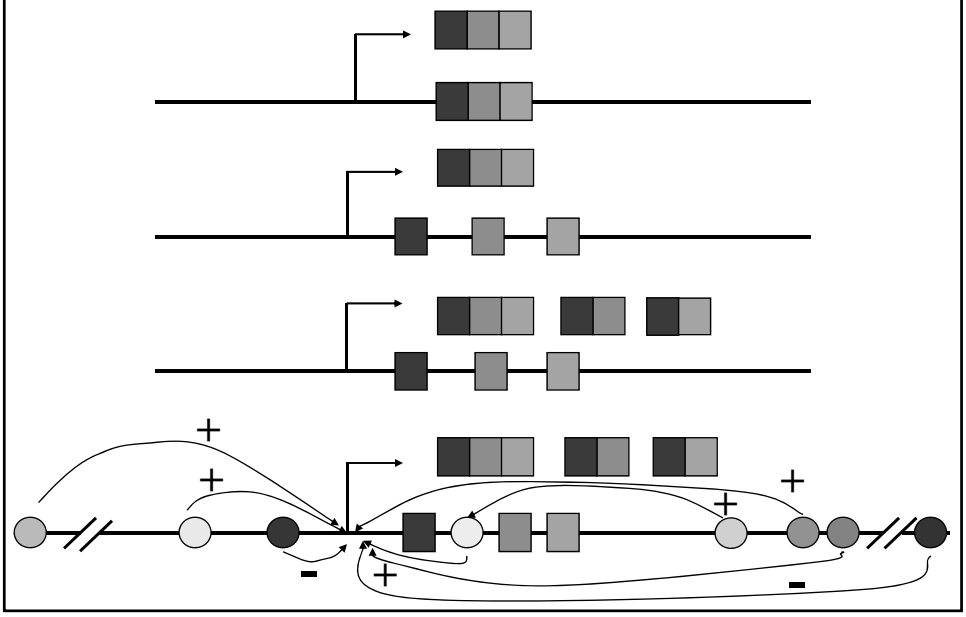
## Comparing Genomes is Like Cryptography




## 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




## Functional Elements: Coding vs. Non-Coding

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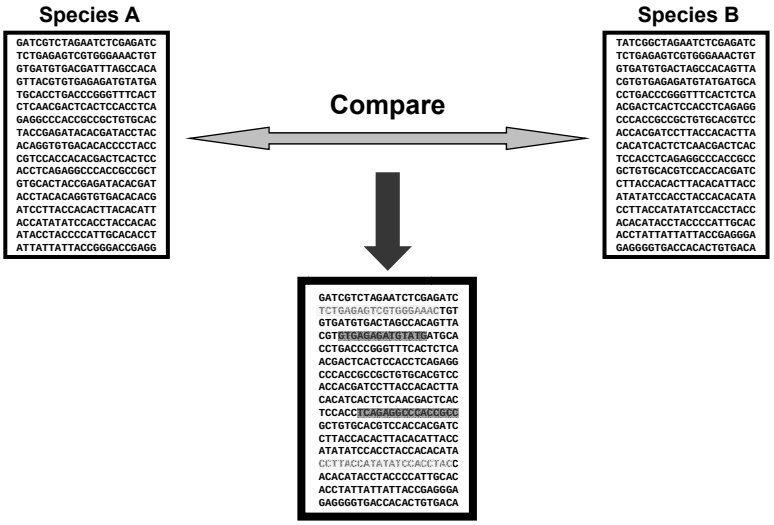
**Major role for comparative sequence analysis will be the identification of functionally important, non-coding sequences**

# Comparative Sequence Analysis

***Using the 'Experiments of Evolution' to Decode the Human Genome***




**Sequences in Common (i.e., 'Conserved' or 'Constrained')**

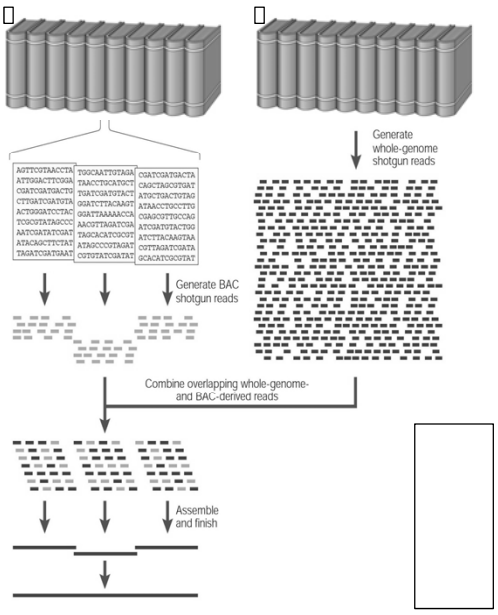
# Vertebrate Genome Sequences


**Mouse** **Rat** **Chicken** **Chimpanzee** **Dog** **Macaque**


**Monodelphis** **Orangutan** **Marmoset** **Horse** **Cow** **Platypus**

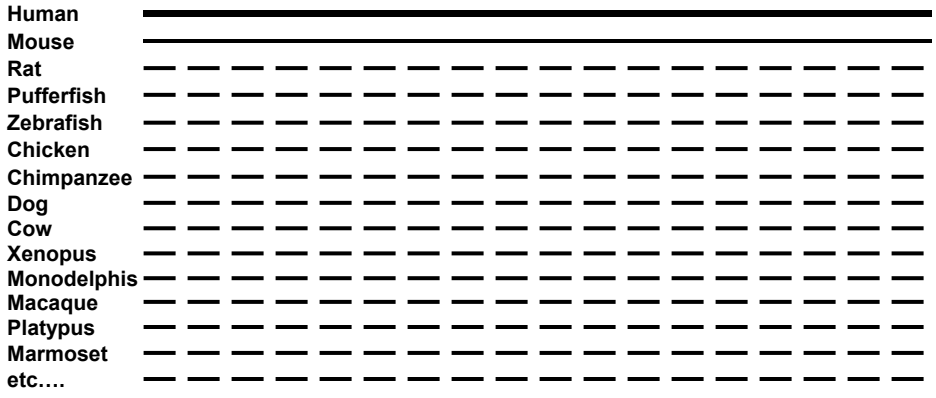
**Xenopus** **Zebrafish** **Pufferfish**

## Hybrid Shotgun Sequencing




Green (2001)

## Diverse Landscape of Genome Sequencing

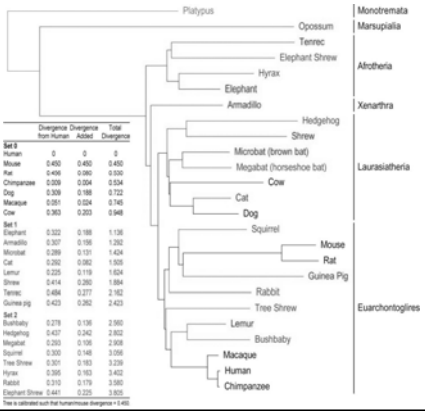


# Low-Redundancy, Whole-Genome Shotgun Sequencing

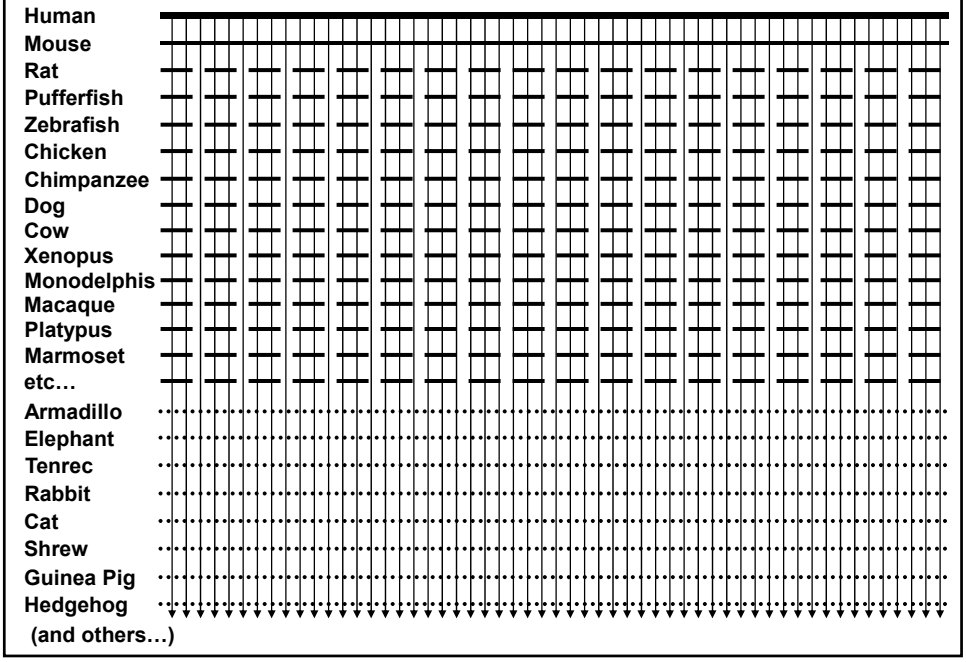
An initial strategy for the systematic identification of functional elements in the human genome by low-redundancy comparative sequencing

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†**

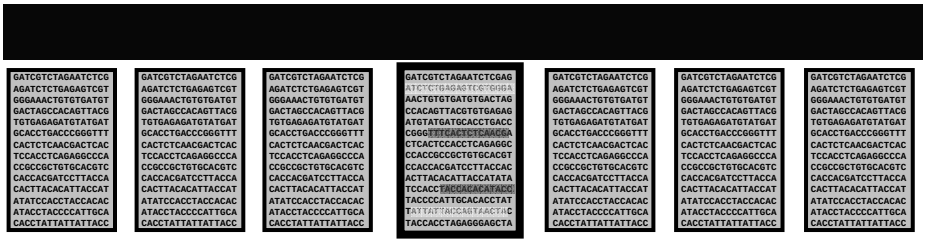
**Margulies et al. (2005)**




# Diverse Landscape of Genome Sequencing



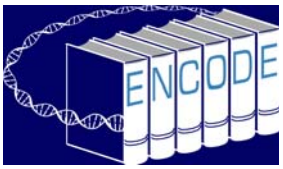
## Multi-Species Sequence Comparisons




**Multi-Species Conserved Sequences (MCSs)**

Margulies et al. (2003)
Thomas et al. (2003)

## 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

SPECIAL SECTION

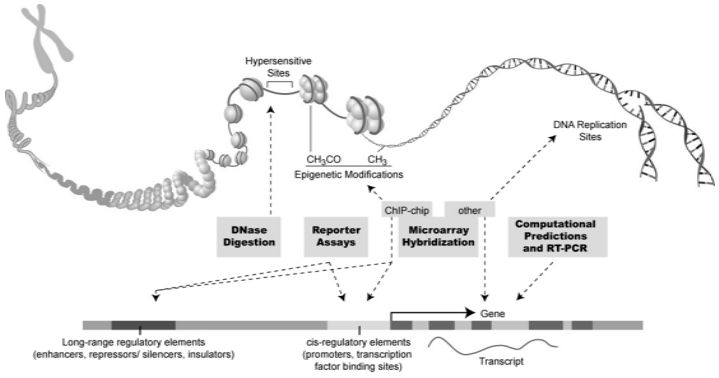
GENES IN ACTION

VIEWPOINT

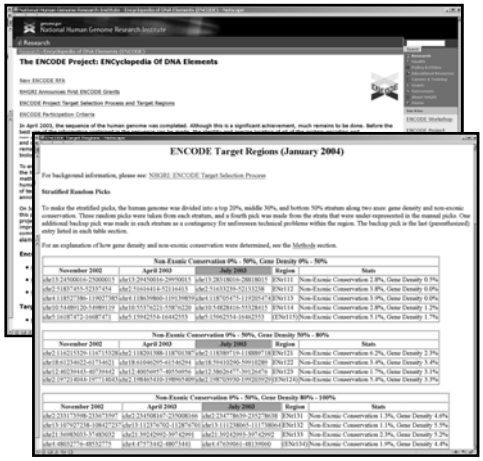
## The ENCODE (ENCyclopedia Of DNA Elements) Project

The ENCODE Project Consortium*†

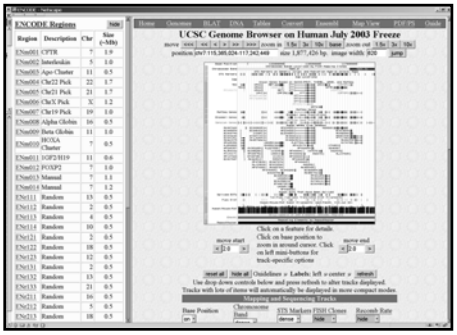
**ENCODE Project Consortium (2004)**



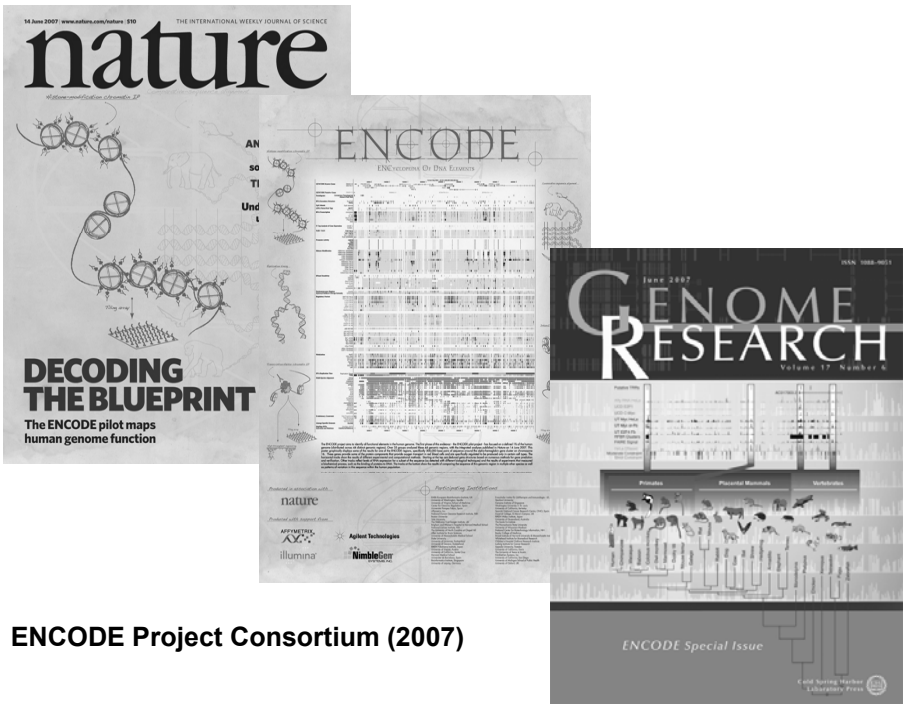

## ENCODE Project: Web Sites




**genome.gov/ENCODE**

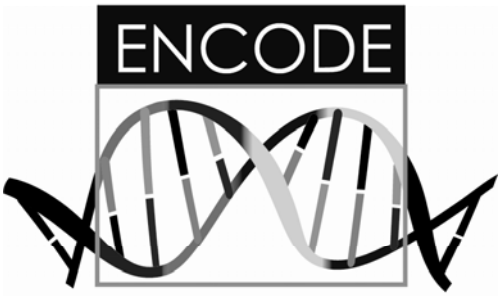


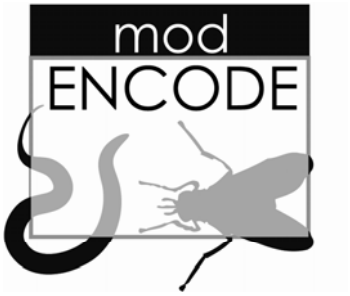

**genome.ucsc.edu/ENCODE**

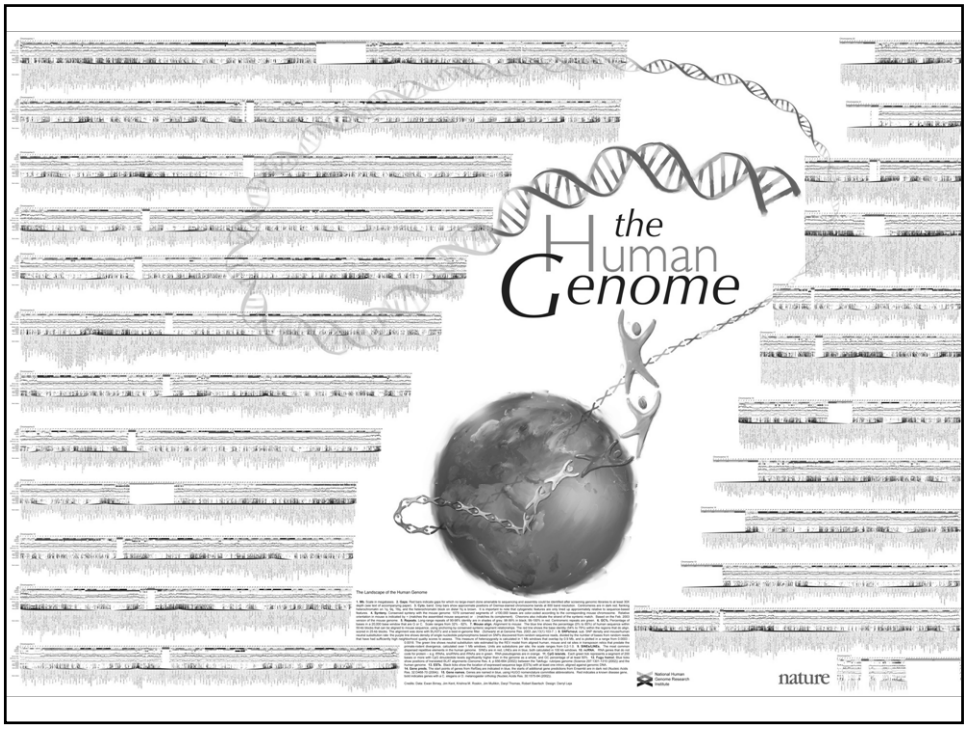



ENCODE Project Consortium (2007)

## Expanding ENCODE Portfolio

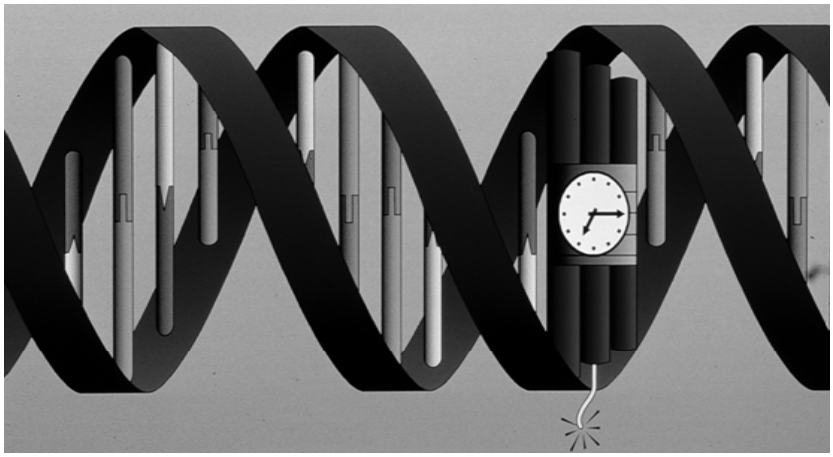


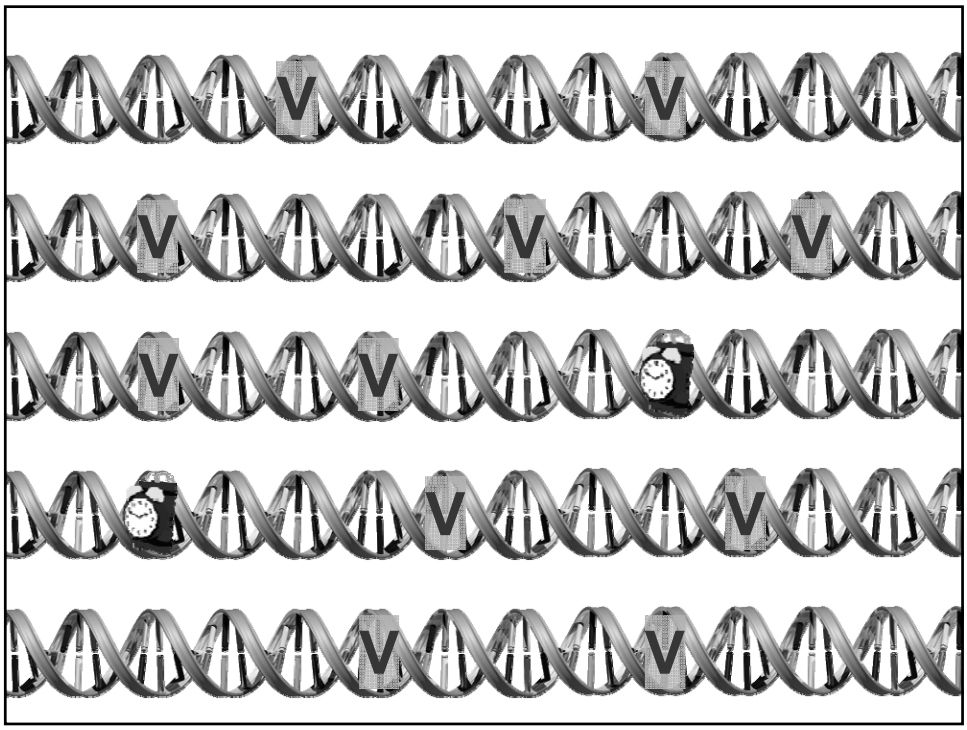

the
Human
Genome
nature


Inter-Species Sequence Comparisons
Intra-Species Sequence Comparisons

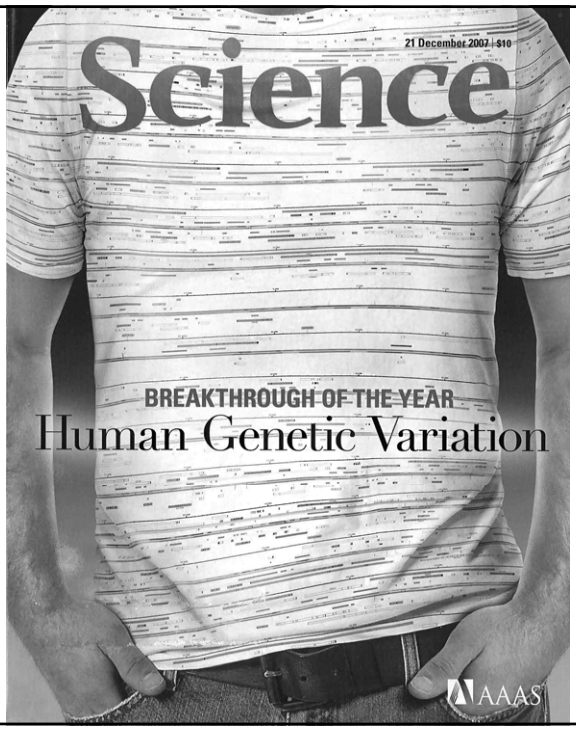
**All humans are ~99.9% identical at the DNA sequence level, and yet…**

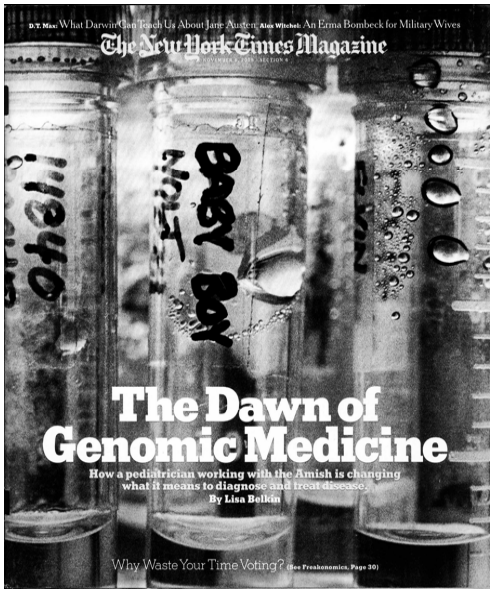


**all of us carry a significant number of 'glitches' in our genomes.**




**International HapMap Consortium (2005, 2007)**





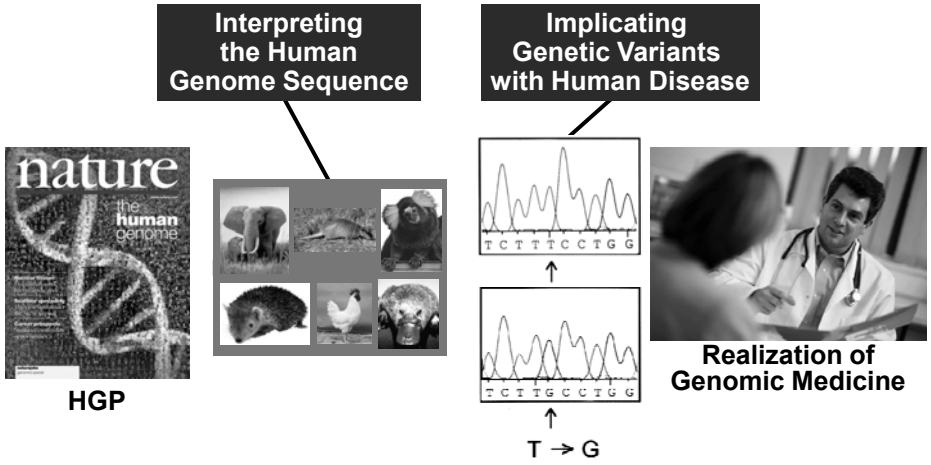


## The Pathway to Genomic Medicine


HGP

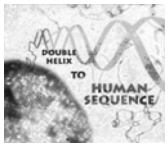

Realization of Genomic Medicine

## The Pathway to Genomic Medicine




## Human Genome Sequence

>$1,000,000,000




↓

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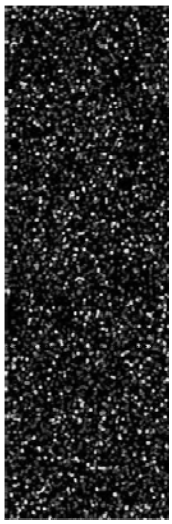
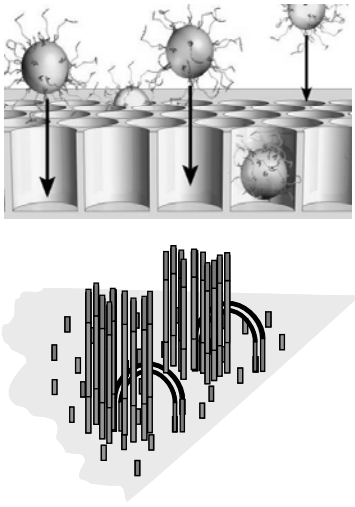
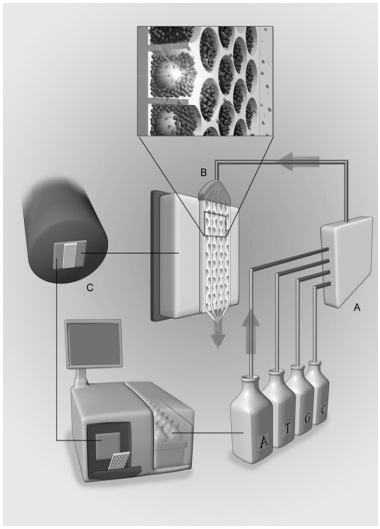
~$1,000

## *En Route to the $1000 Genome*





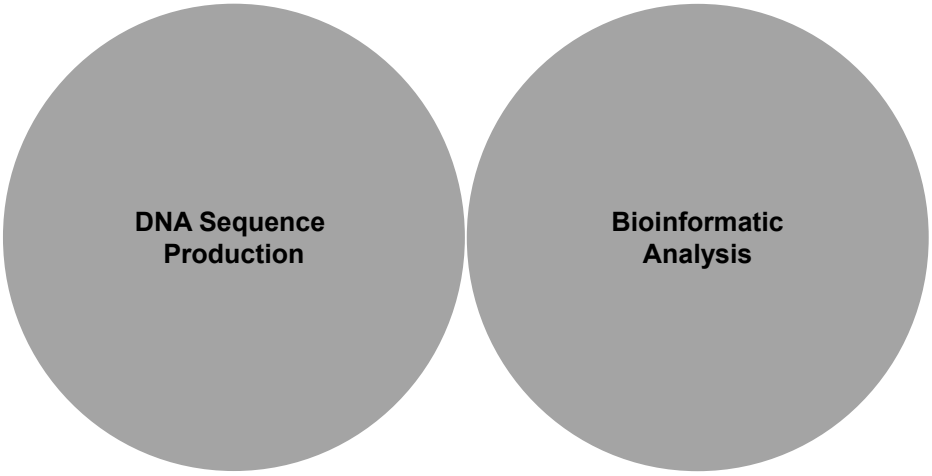




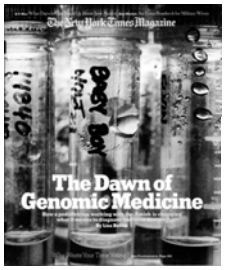
**Church (2006)**

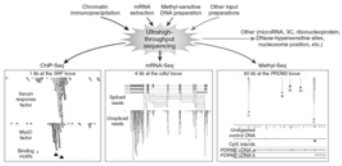
## Realities of New DNA Sequencing Technologies…

## Changing Infrastructure Requirements



## Expanding Universe of Sequence-Based Explorations

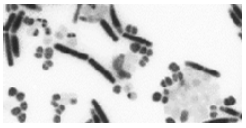


Wold and Myers (2008)


Enard and Paabo (2004)


Collins and Barker (2007)



Turnbaugh et al. (2007)


Green et al. (2006)

## *The Human Genome Sequence to Genomic Medicine…*

***…from base pairs to bedside.***

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