BIG DATA
BIOINFORMATICS

or why medical doctors need computers

Wojciech Makałowski
Institute of Bioinformatics
University of Münster, Germany

It's sink or swim as a tidal wave of data approaches

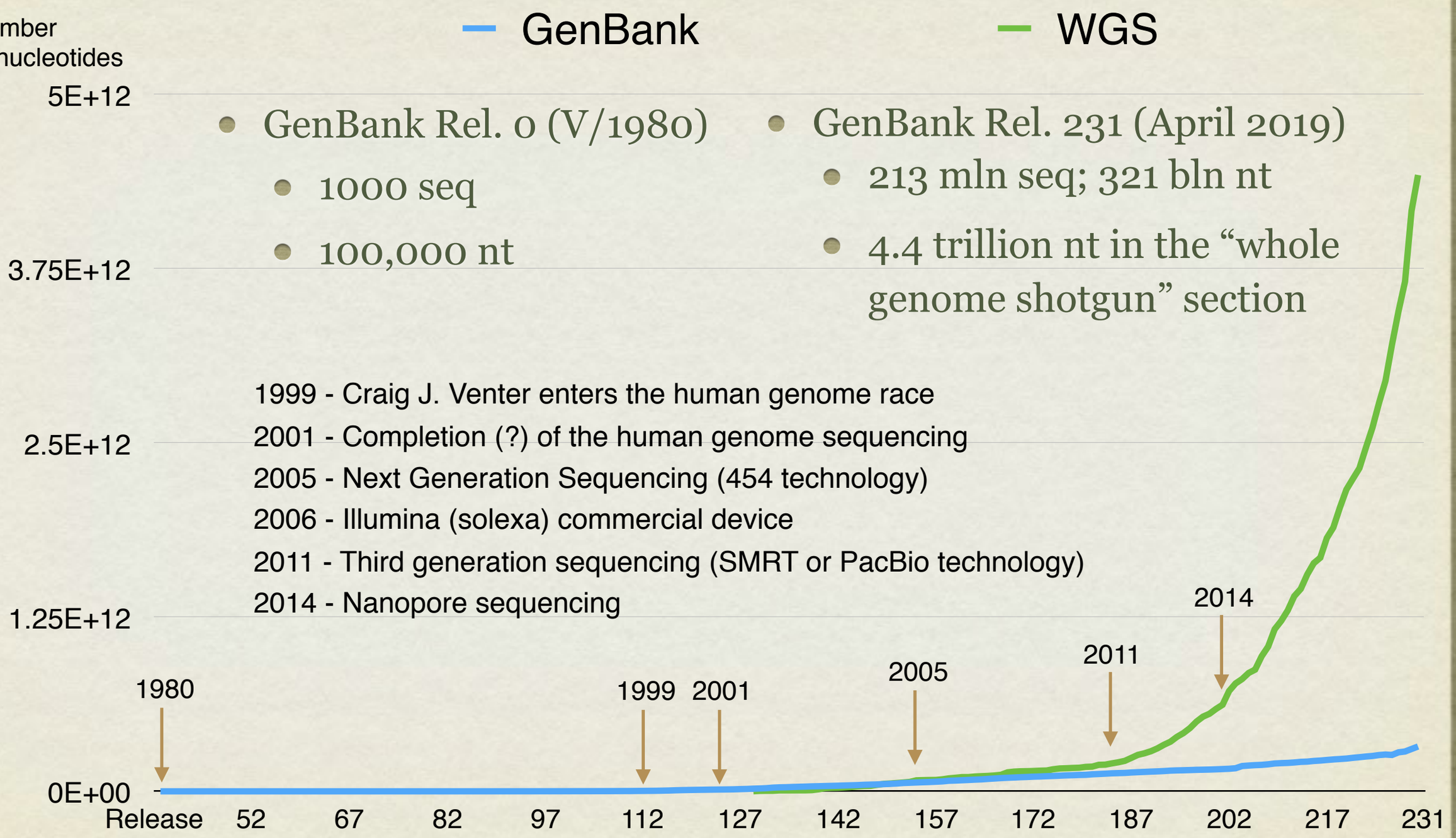
Nature 399:517 10 June 1999

Unfortunately, it's not a tidal wave,
it's a tsunami!

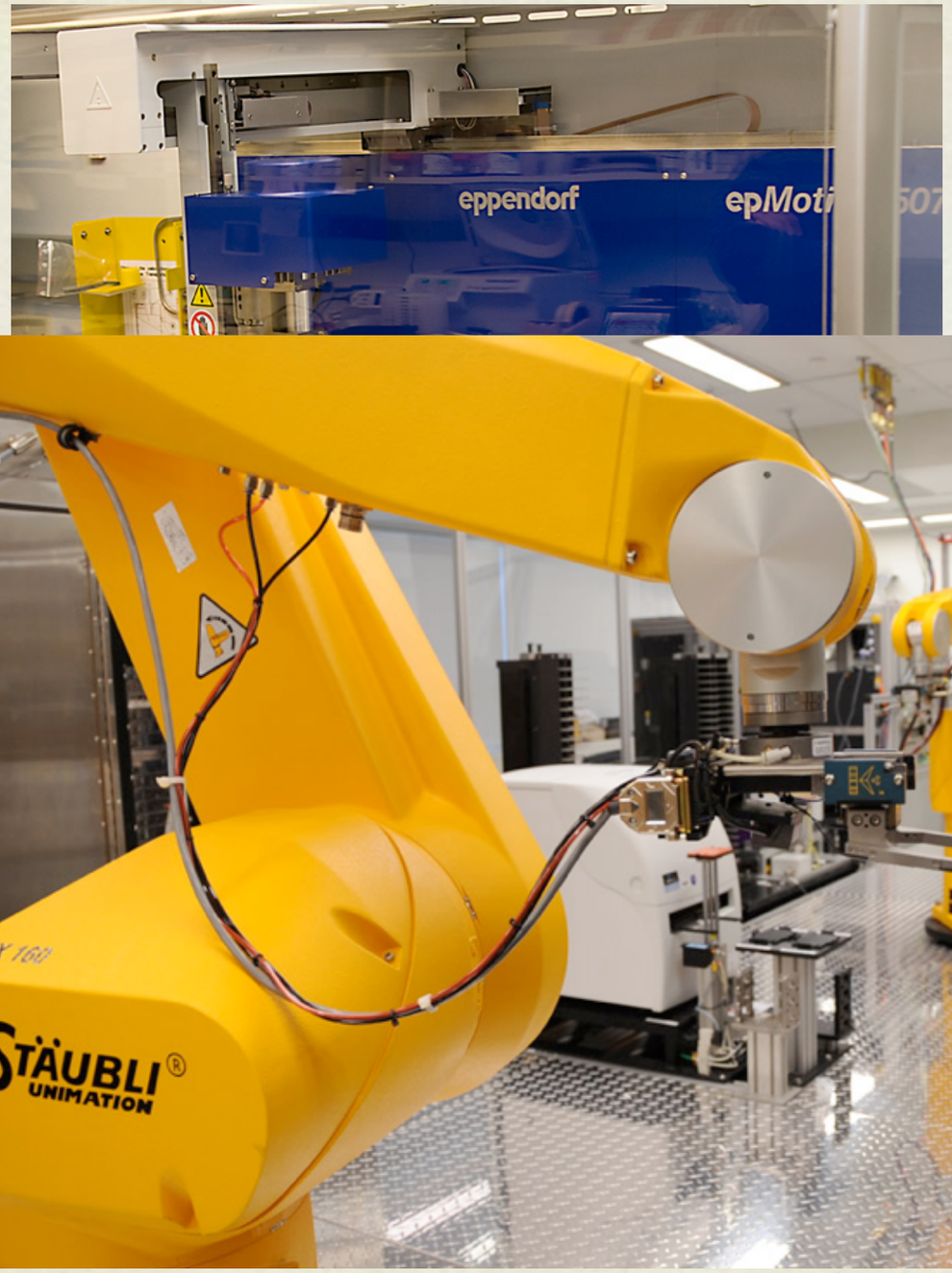
GROWTH OF BIOMEDICAL INFORMATION - GENBANK

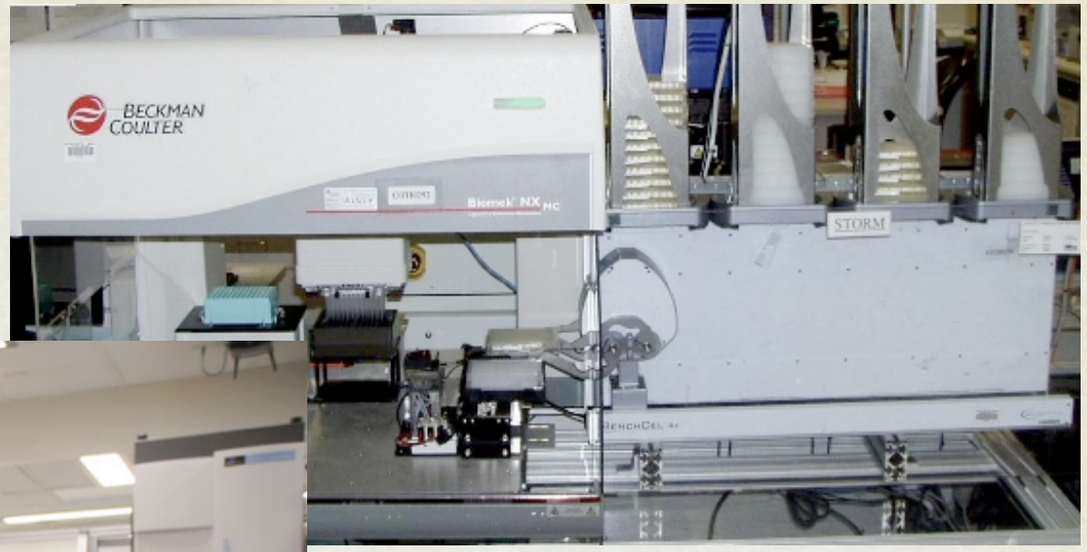
- GenBank Rel. 0 (V/1980)
  - 1000 seq
  - 100,000 nt

- GenBank Rel. 231 (April 2019)
  - 213 mln seq; 321 bln nt
  - 4.4 trillion nt in the “whole genome shotgun” section

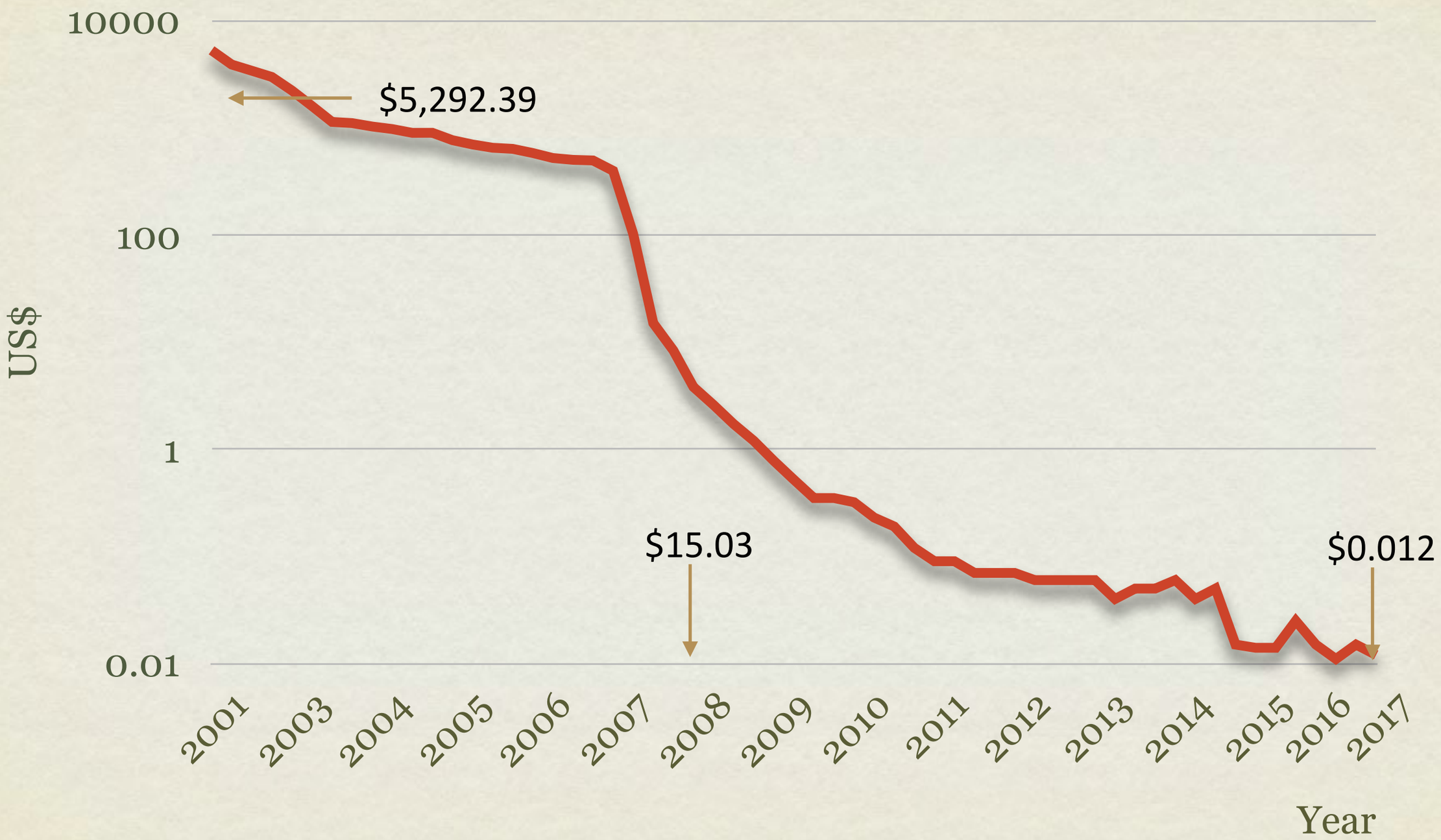


TECHNOLOGY MEETS BIOLOGY

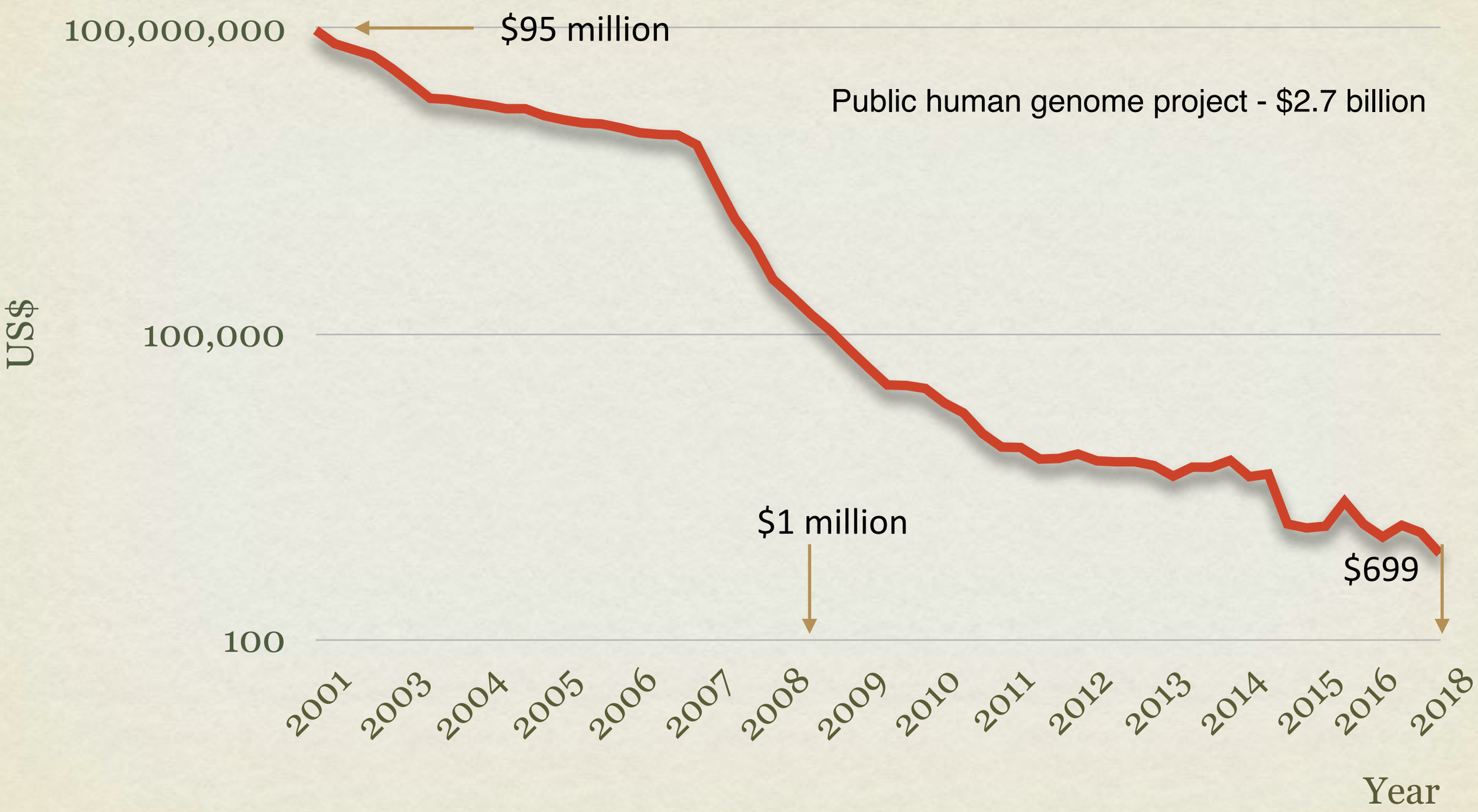




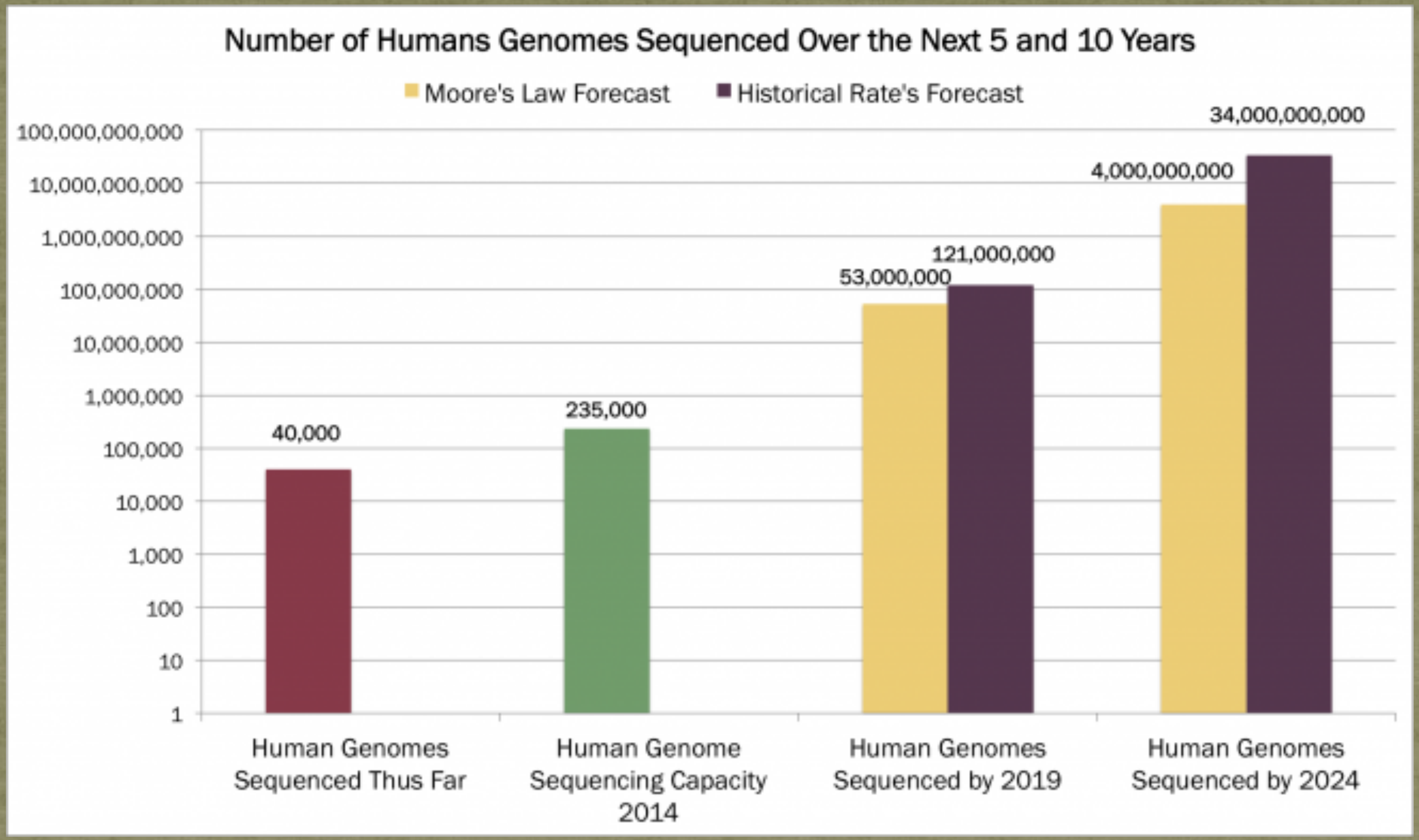
SEQUENCING COST PER MB



SEQUENCING COST PER GENOME



IMPROVING TECHNOLOGY



http://ark-invest.com/genomic-revolution/declining-costs-of-genome-sequencing

GETTING SEQUENCES

TGCATCGATCGTAGCTAGCTAGCGCATGCTAGCTAGCTAGCTAGCTACGATGCATCG
TGCATCGATCGATGCATGCTAGCTAGCTAGCTAGCATGCTAGCTAGCTAGCTATTGG
CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
CGCGCGCATTATGCCGCGGCATGCTGCGCACACACAGTACTATAGCATTAGTAAAAA
GGCCGCGTATATTTTACACGATAGTGCGGCGCGGCGCGTAGCTAGTGCTAGCTAGTC
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT
AGCTAGTGTAGCTAGCTAGCATGCTGCTAGCATGCAGCATGCATCGGGCGCGATGCT
GCTAGCGCTGCTAGCTAGCTAGCTAGCTAGGCGCTAATTATTTATTTTGGGGGGTTA
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AGCTCTCATCGCGCGGGGGGATGCTTAGCGTGGTGTGTGTGTGTGGTGTGTGTGGTC
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GGCCGCGTATATTTTACACGATAGTGCGGCGCGGCGCGTAGCTAGTGCTAGCTAGTC
AGCTCTCATCGCGCGGGGGGATGCTTAGCGTGGTGTGTGTGTGTGGTGTGTGTGGTC
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CTATAATTAGTGCATCGGCGCATCGATGGCTAGTCGATCGATCGATTTTATATATCT
CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT

READING ≠ UNDERSTANDING

Carmina qui quondam studio
florente peregi, flebilis heu maestos
cogor inire modos.

Ecce mihi lacerae dictant scribenda
Camenae et ueris elegi fletibus ora
rigant.

Boethius, *Consolatio Philosophiae*

READING ≠ UNDERSTANDING

We shall best understand the probable course of natural selection by taking the case of a country undergoing some physical change. If the country were open were open on its borders, new forms would certainly immigrate, and this also would bla, bla bla become extinct inhabitants.

Charles Darwin - *The Origin of Species*

READING ≠ UNDERSTANDING

We shall best understand the probable course of [redacted] by taking the case of a country undergoing some physical change. If the country were open were open on its borders, new forms would certainly immigrate, and this also would bla, bla bla become extinct inhabitants.

Charles Darwin - *The Origin of Species*

CHALLENGE: HOW FROM THIS...

TGCATCGATCGTAGCTAGCTAGCGCATGCTAGCTAGCTAGCTAGCTACGATGCATCG
TGCATCGATCGATGCATGCTAGCTAGCTAGCTAGCATGCTAGCTAGCTAGCTATTGG
CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
CGCGCGCATTATGCCGCGGCATGCTGCGCACACACAGTACTATAGCATTAGTAAAAA
GGCCGCGTATATTTTACACGATAGTGCGGCGCGGCGCGTAGCTAGTGCTAGCTAGTC
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT
AGCTAGTGTAGCTAGCTAGCATGCTGCTAGCATGCAGCATGCATCGGGCGCGATGCT
GCTAGCGCTGCTAGCTAGCTAGCTAGCTAGGCGCTAATTATTTATTTTGGGGGGTTA
AAAAAAAAAATTTCGCTGCTTATACCCCCCCCCACATGATGATCGTTAGTAGCTACT
AGCTCTCATCGCGCGGGGGGATGCTTAGCGTGGTGTGTGTGTGTGGTGTGTGTGGTC
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CGCTAGCTAGCATGCATGCATGCATCGATGCATCGATTATAAGCGCGATGACGTCAG
TCCGGTTACACAGGTAGCTAGCTAGCTGCTAGCTAGCTGCTGCATGCATGCATTAGT

Infer this

HOW TO SOLVE THE PROBLEM - A HUMAN OR A COMPUTER?

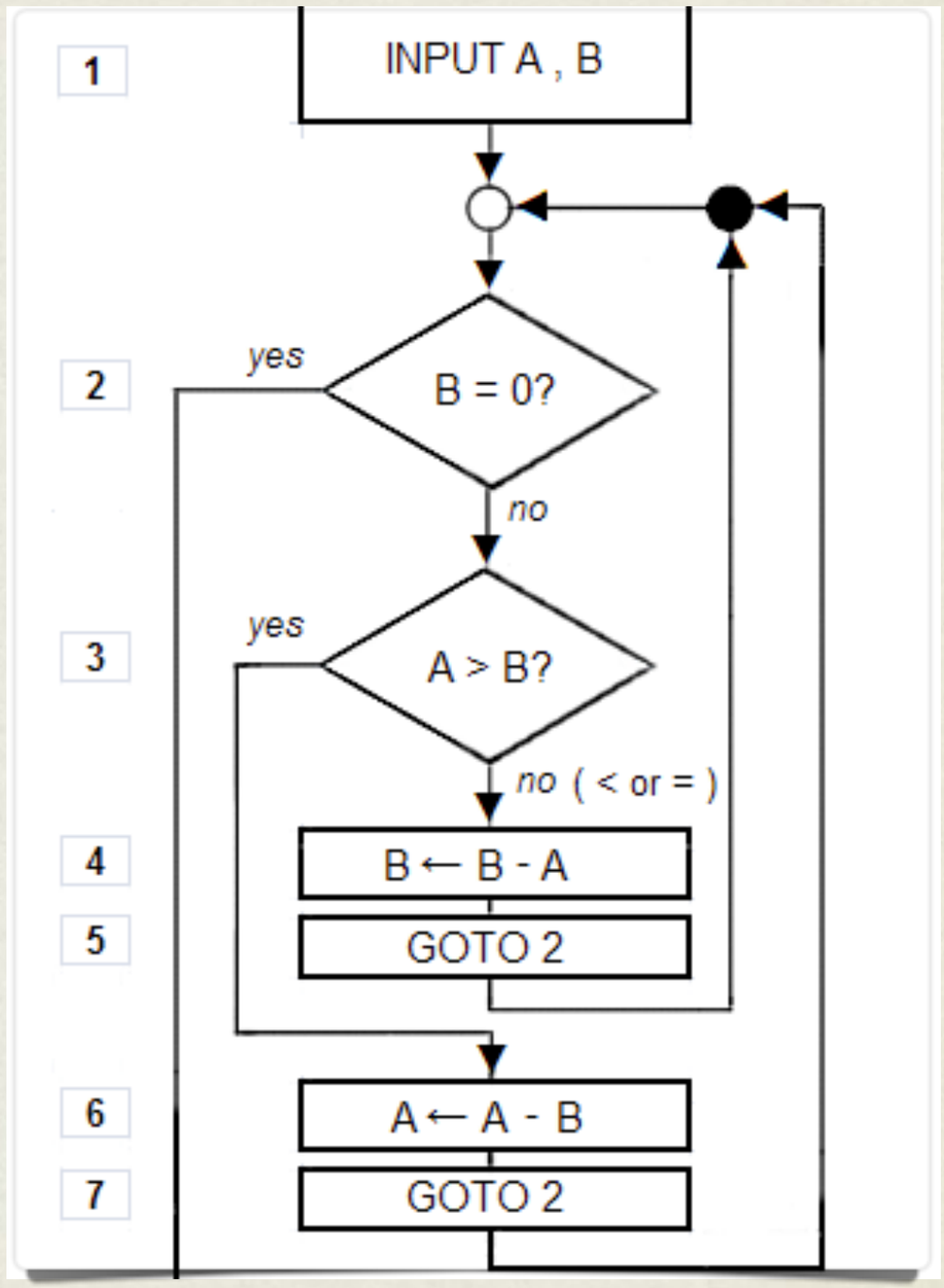
- very smart
- slow
- error prone
- doesn’t like repetitive tasks

- not so smart (stupid)
- extremely fast
- very accurate
- doesn’t understand human languages;

needs instruction provided in a special way

ALGORITHM

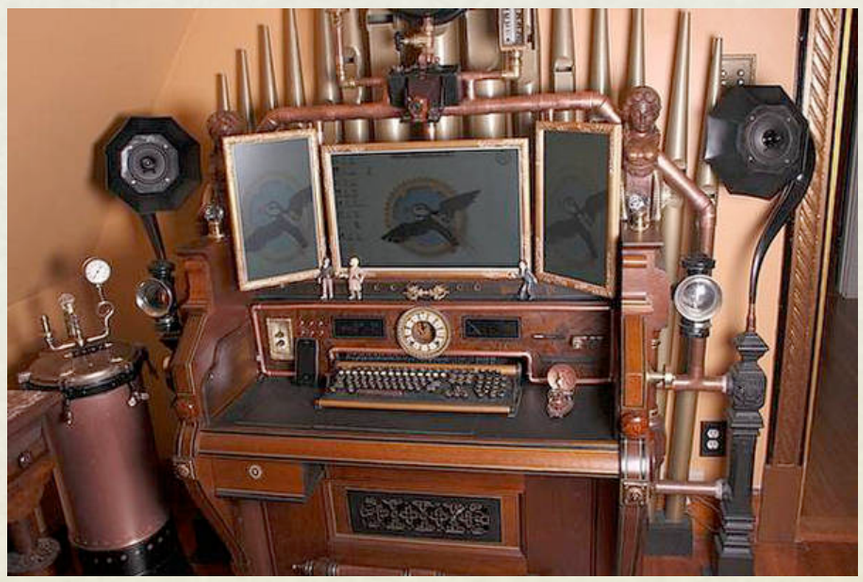
A step-by-step problem-solving procedure, especially an established, recursive computational procedure for solving a problem in a finite number of steps.



EXAMPLE TASK: PUT SHOES ON!

A human just understands an order and often executes it automatically even without thinking

A computer needs detailed instruction (an algorithm)



PUT SHOES ON!
INSTRUCTION FOR A COMPUTER

1. Find two the same shoes
2. Check if you have left and right shoe
3. Check if they are of the same size
4. Check if this is the right size
5. Put the left shoe on
6. Put the right shoe on
7. Tie the laces

THE ORIGIN OF THE FIELD

Paulien Hogeweg coined the term *bioinformatica* to define “the study of informatic processes in biotic systems”. Hesper B, Hogeweg P (1970) Bioinformatica: een werkconcept. Kameleon 1(6): 28–29. (In Dutch.) Leiden: Leidse Biologen Club.

… but its origin can be tracked back many decades earlier.

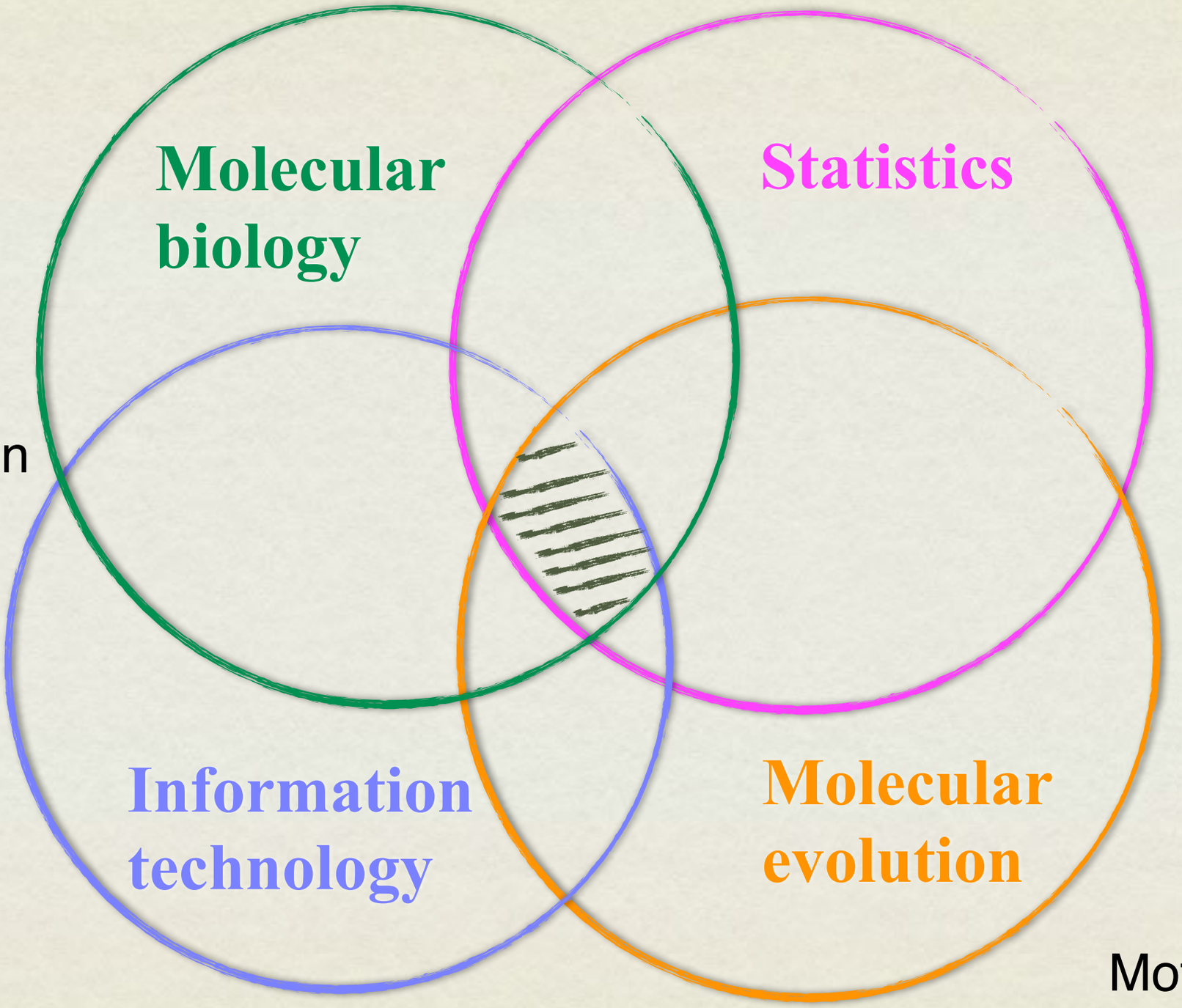
BIOINFORMATICS EMERGED AS AN INTERSECTION BETWEEN DIFFERENT DISCIPLINES

James Watson

Thomas Bayes

Alan Turing

Motoo Kimura



BIOINFORMATICS - DEFINITION

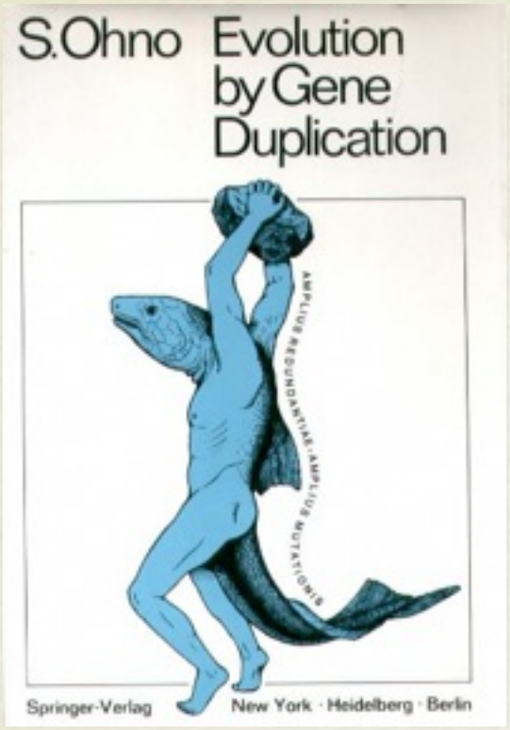
- Research, development, or application of computational tools and approaches for expanding the use of biological data, including those to acquire, store, organize, archive, analyze, or visualize such data.

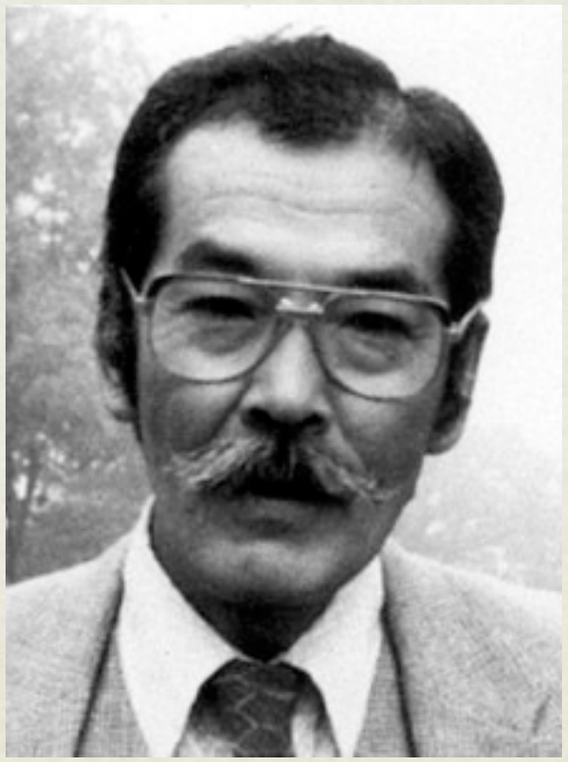
- Its goal is to enable biological discovery based on existing information or in other words transform biological data into information and eventually into knowledge.

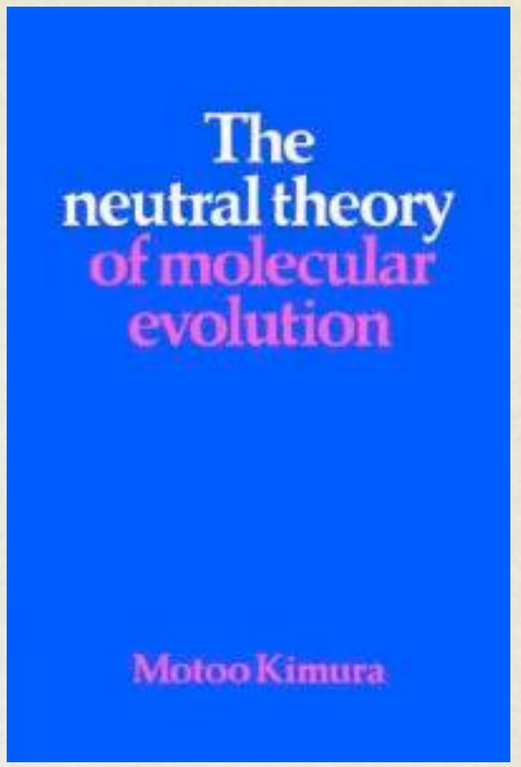
ROLE OF BIOINFORMATICS IN MODERN LIFE SCIENCES

- molecular biology
- molecular evolution
- genomics
- system biology
- protein engineering
- drug design
- human genetics
- personalized medicine

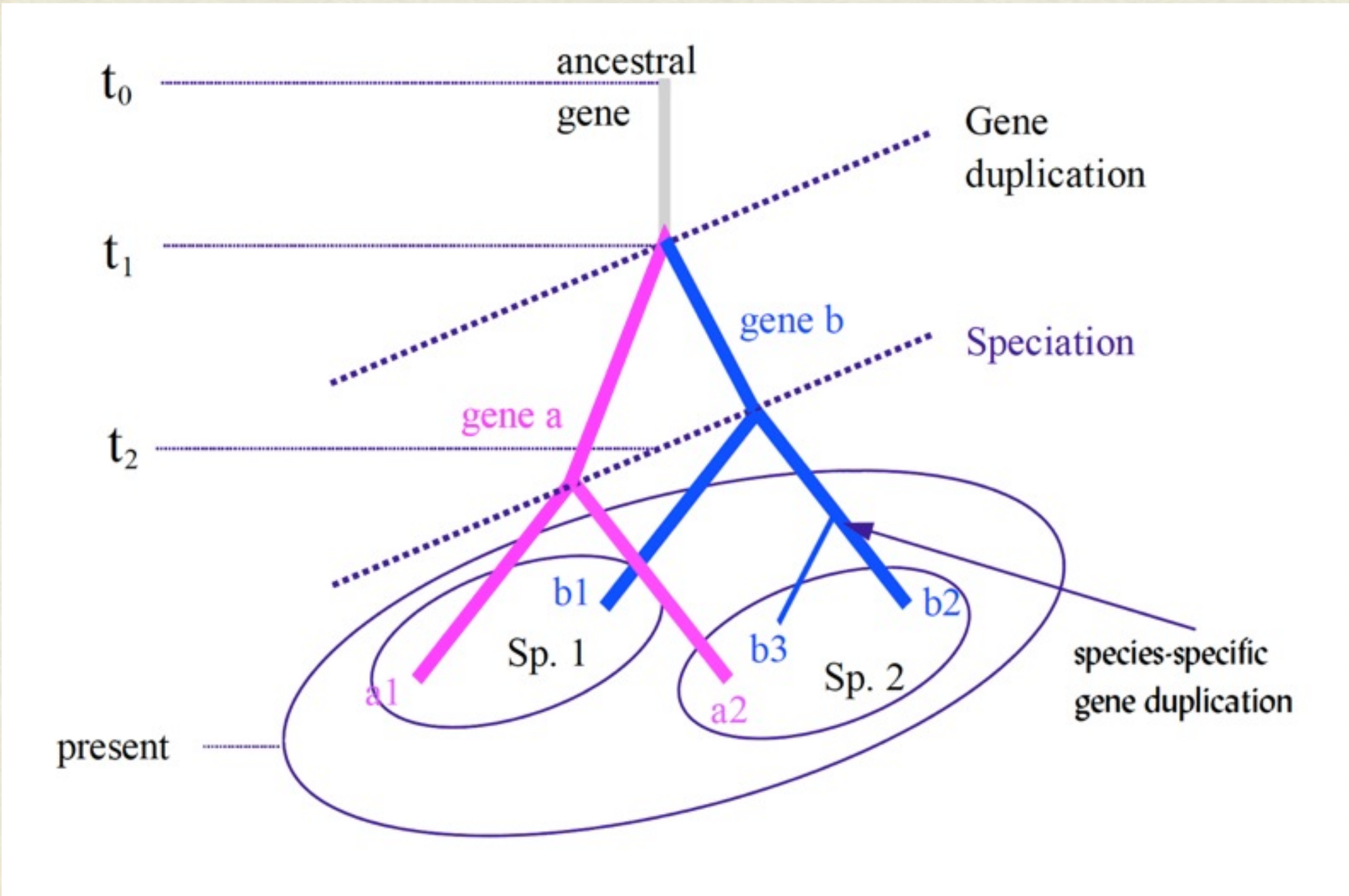
EVOLUTIONARY BASIS OF BIOINFORMATICS



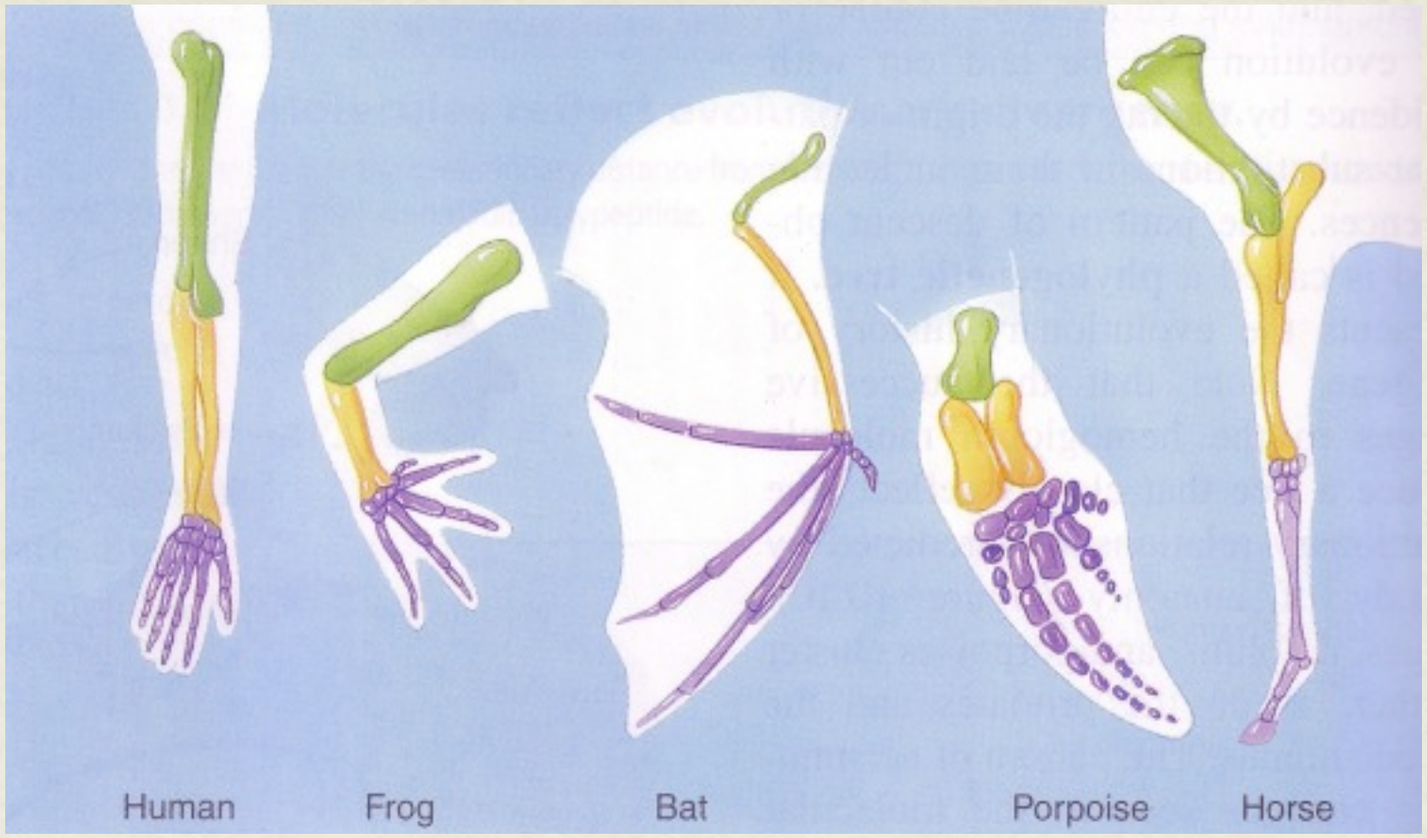




EVOLUTIONARY BASIS OF BIOINFORMATICS



HOMOLOGS



Two anatomical structures or behavioral traits within different organisms which originated from a structure or trait of their common ancestral organism. The structures or traits in their current forms may not necessarily perform the same functions in each organism, nor perform the functions it did in the common ancestor. An example: the wing of a bat, the fin of a whale and the arm of a man are homologous structures.

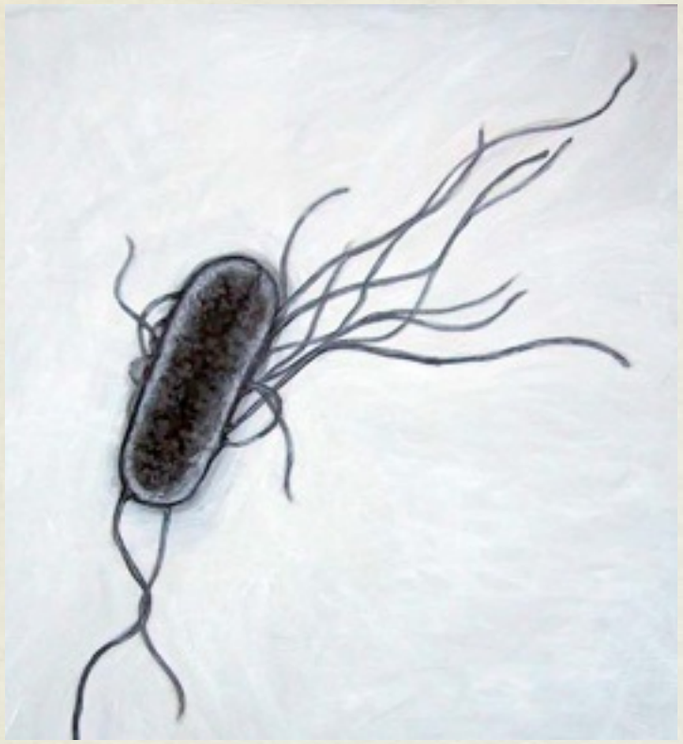
http://www.everythingbio.com/glos/definition.php?ID=3385

HOMOLOGS AT THE MOLECULAR LEVEL

```
cow       ATG---ACTAACATTCGAAAGTCCCACCCACTAATAAAAATTGTAAAC
sheep     ATG---ATCAACATCCGAAAAACCCACCCACTAATAAAAATTGTAAAC
goat      ATG---ACCAACATCCGAAAGACCCACCCATTAATAAAAATTGTAAAC
horse     ATG---ACAAACATCCGGAAATCTCACCCACTAATTAAAATCATCAAT
donkey    ATG---ACAAACATCCGAAAATCCCACCCGCTAATTAAAATCATCAAT
ostrich   ATGGCCCCCAACATTCGAAAATCGCACCCCCTGCTCAAAATTATCAAC
emu       ATGGCCCCTAACATCCGAAAATCCCACCCTCTACTCAAAATCATCAAC
turkey    ATGGCACCCAATATCCGAAAATCACACCCCCTATTAAAAACAATCAAC
```

Two sequences that share common ancestry. Significant sequence similarity usually suggests homology, however sequence similarity may occur also by chance and some homologous sequences may diverge beyond detectable similarity.

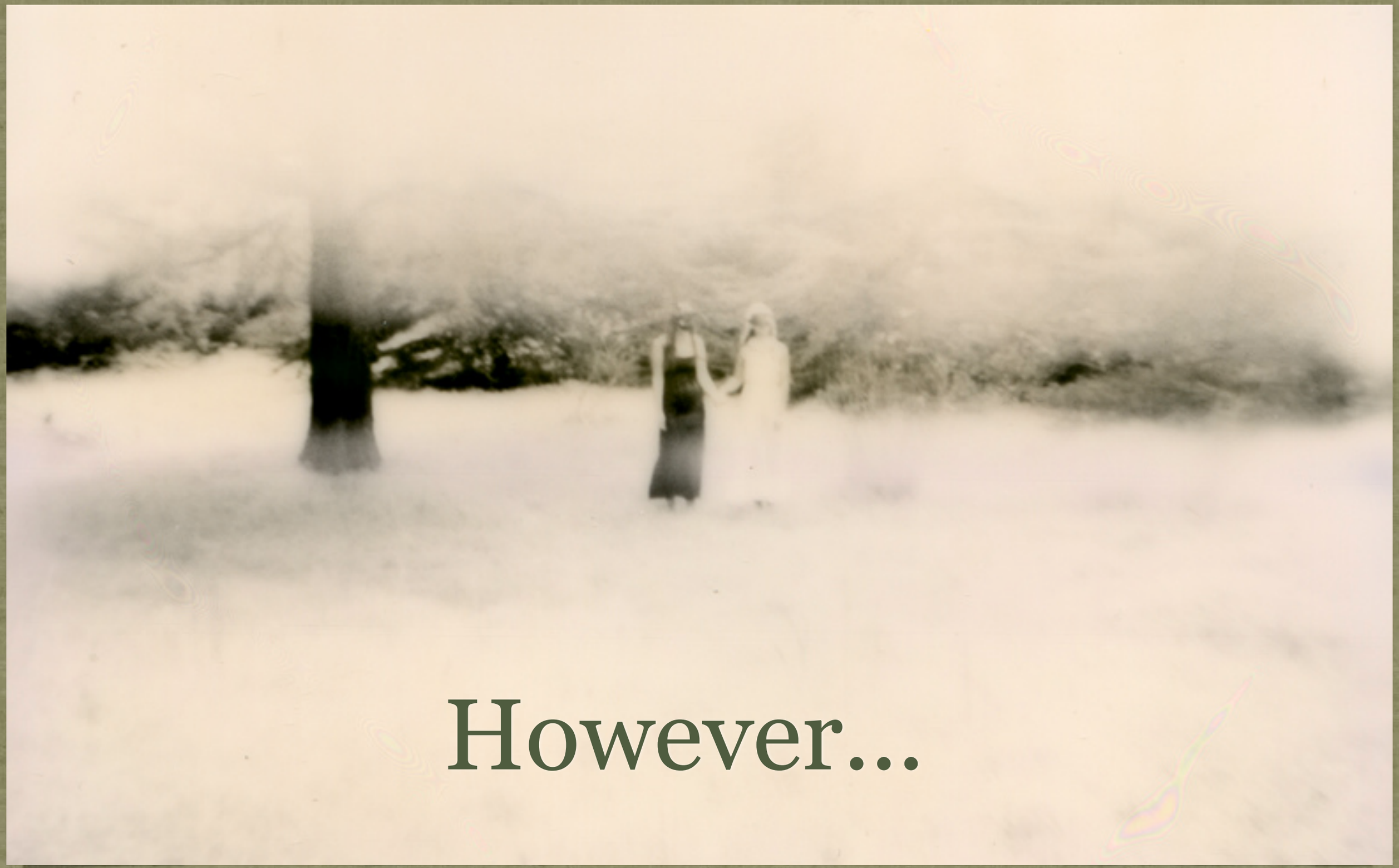
COMPARATIVE GENOMICS



What is true for *E. coli* is also true for elephant.

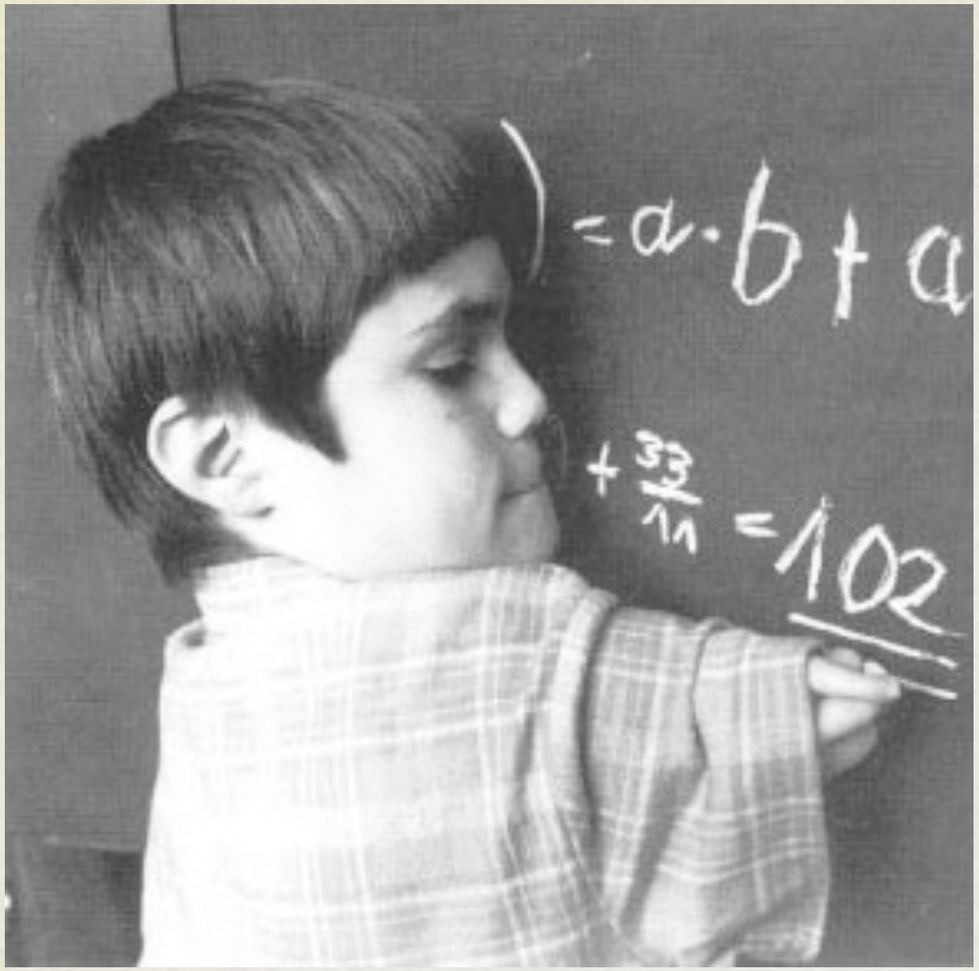
J. Monod, c. 1961

COMPARATIVE GENOMICS



However...

COMPARATIVE GENOMICS

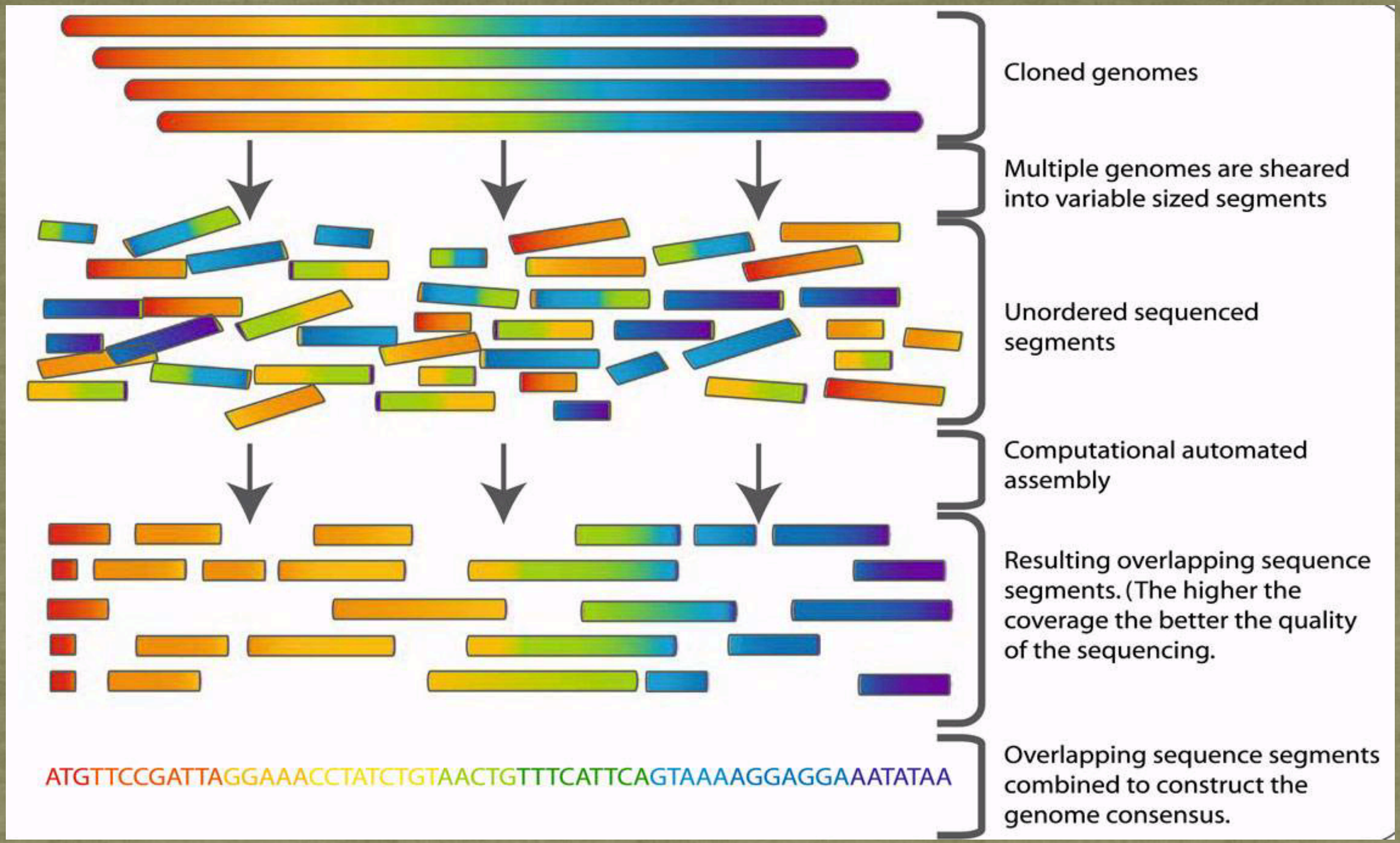


15 000 victims of thalidomide

What is true for mouse is not necessarily true for human…

Nucleotide Sequence Assembly

NUCLEOTIDE SEQUENCE ASSEMBLY



From Commins et al. 2009

Similarity Search

Basic Local Alignment Search Tool

BLAST finds regions of similarity between biological sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance. Learn more

NEWS

BLAST+ 2.9.0 is here!
The latest version has enhanced support for the new database format.
Tue, 02 Apr 2019 17:00:00 EST

More BLAST news...

Web BLAST

Nucleotide BLAST
nucleotide ▶ nucleotide

blastx
translated nucleotide ▶ protein

tblastn
protein ▶ translated nucleotide

Protein BLAST
protein ▶ protein

BLAST Genomes

Enter organism common name, scientific name, or tax id

Search

Human Mouse Rat Microbes

FUN WITH BLAST

Job title: Wojciech Makalowski

RID	BXXS14F8014 (Expires on 04-24 19:29 pm)		
Query ID	lcl|Query_303143	**Database Name**	nr
Description	Wojciech Makalowski	**Description**	All non-redundant GenBank CDS translations+PDB+SwissProt+PIR+PRF excluding environmental samples from WGS projects
Molecule type	amino acid	**Program**	BLASTP 2.9.0+ ▷Citation
Query Length	18		

Other reports: ▷Search Summary [Taxonomy reports] [Distance tree of results] [Multiple alignment] [MSA viewer]

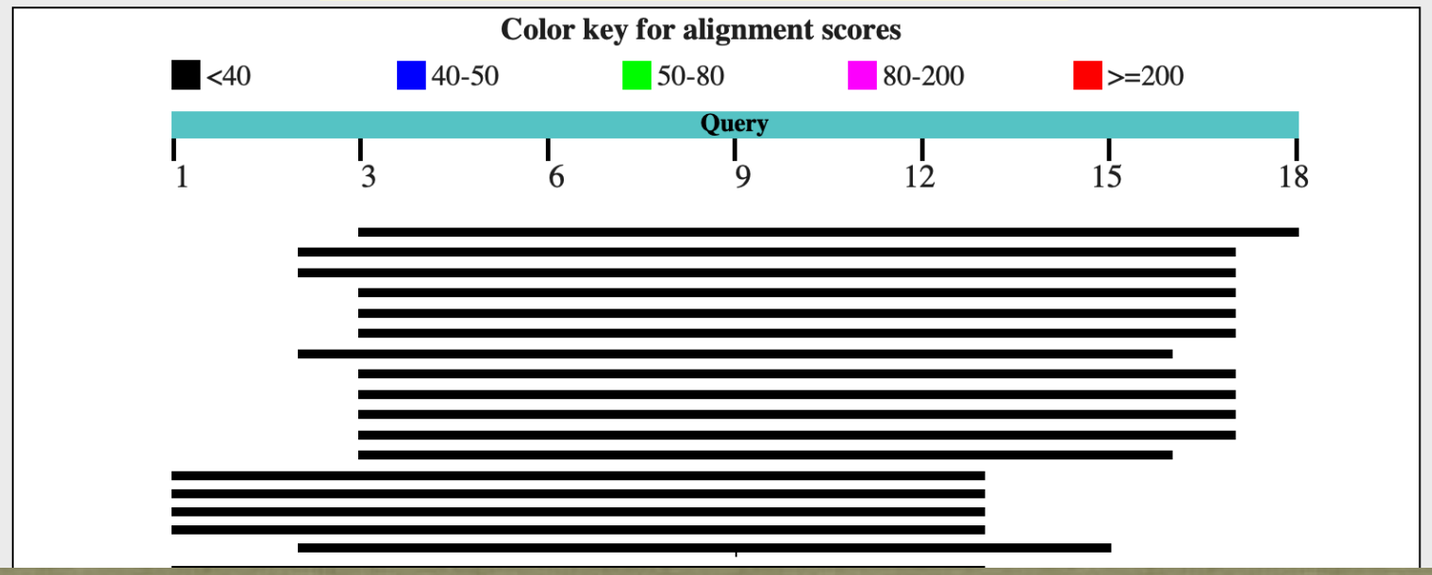
Graphic Summary

Show Conserved Domains

No putative conserved domains have been detected

Distribution of the top 104 Blast Hits on 100 subject sequences

Mouse over to see the title, click to show alignments



FUN WITH BLAST

Download GenPept Graphics

HNH endonuclease [Klebsiella michiganensis]

Sequence ID: WP_122117762.1 **Length:** 122 **Number of Matches:** 1

See 1 more title(s)

Range 1: 81 to 91 GenPept Graphics Next Match Previous Match

Score	Expect	Identities	Positives	Gaps
33.3 bits(71)	7.5	8/11(73%)	8/11(72%)	0/11(0%)

```
Query  1   WOJCIECHMAK  11
           W  CIECH AK
Sbjct  81  WTLCIECHSAK  91
```

Download GenPept Graphics

hypothetical protein [Desulforhopalus singaporensis]

Sequence ID: WP_092225757.1 **Length:** 351 **Number of Matches:** 1

See 1 more title(s)

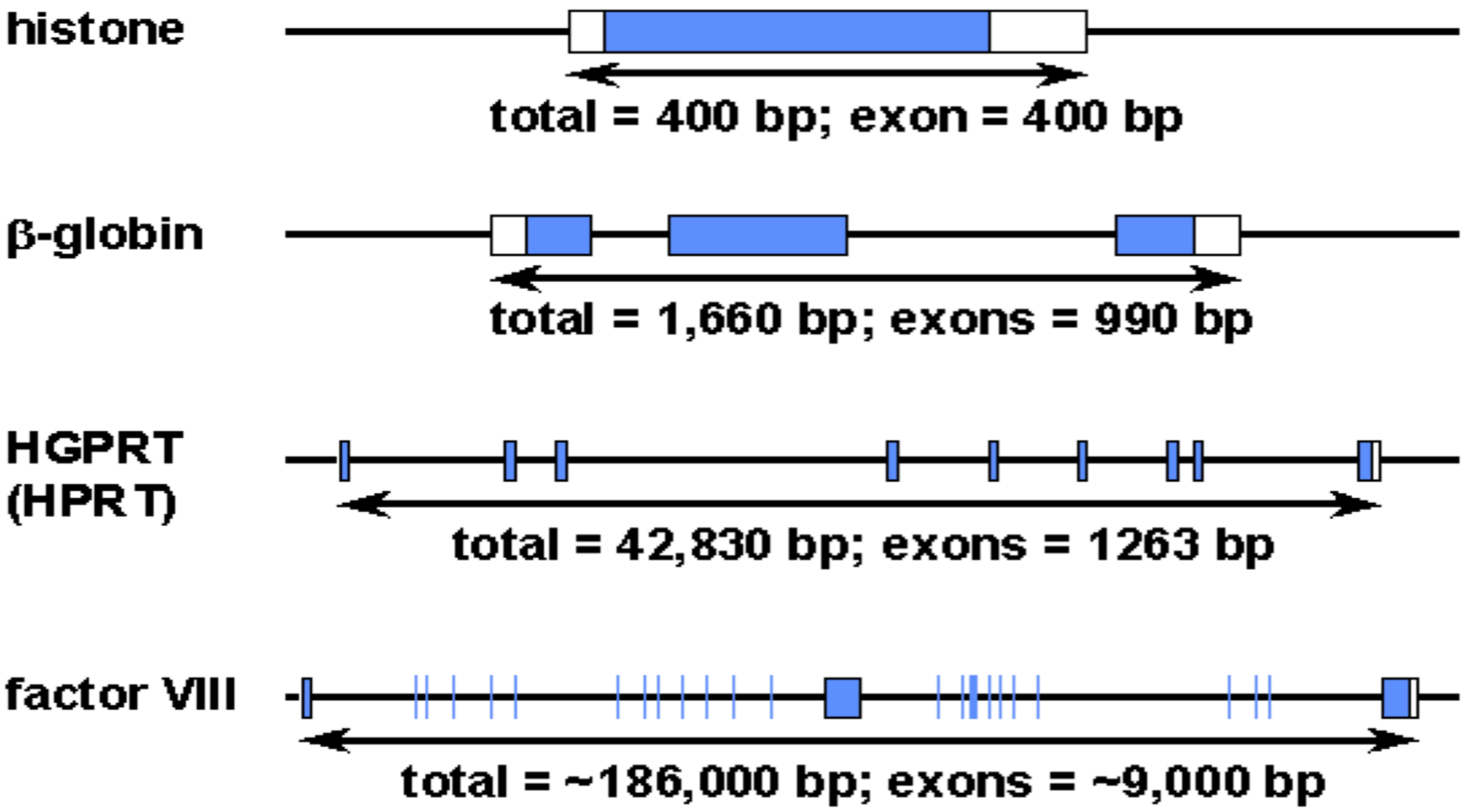
Range 1: 267 to 277 GenPept Graphics Next Match Previous Match

Score	Expect	Identities	Positives	Gaps
32.0 bits(68)	21	10/14(71%)	10/14(71%)	3/14(21%)

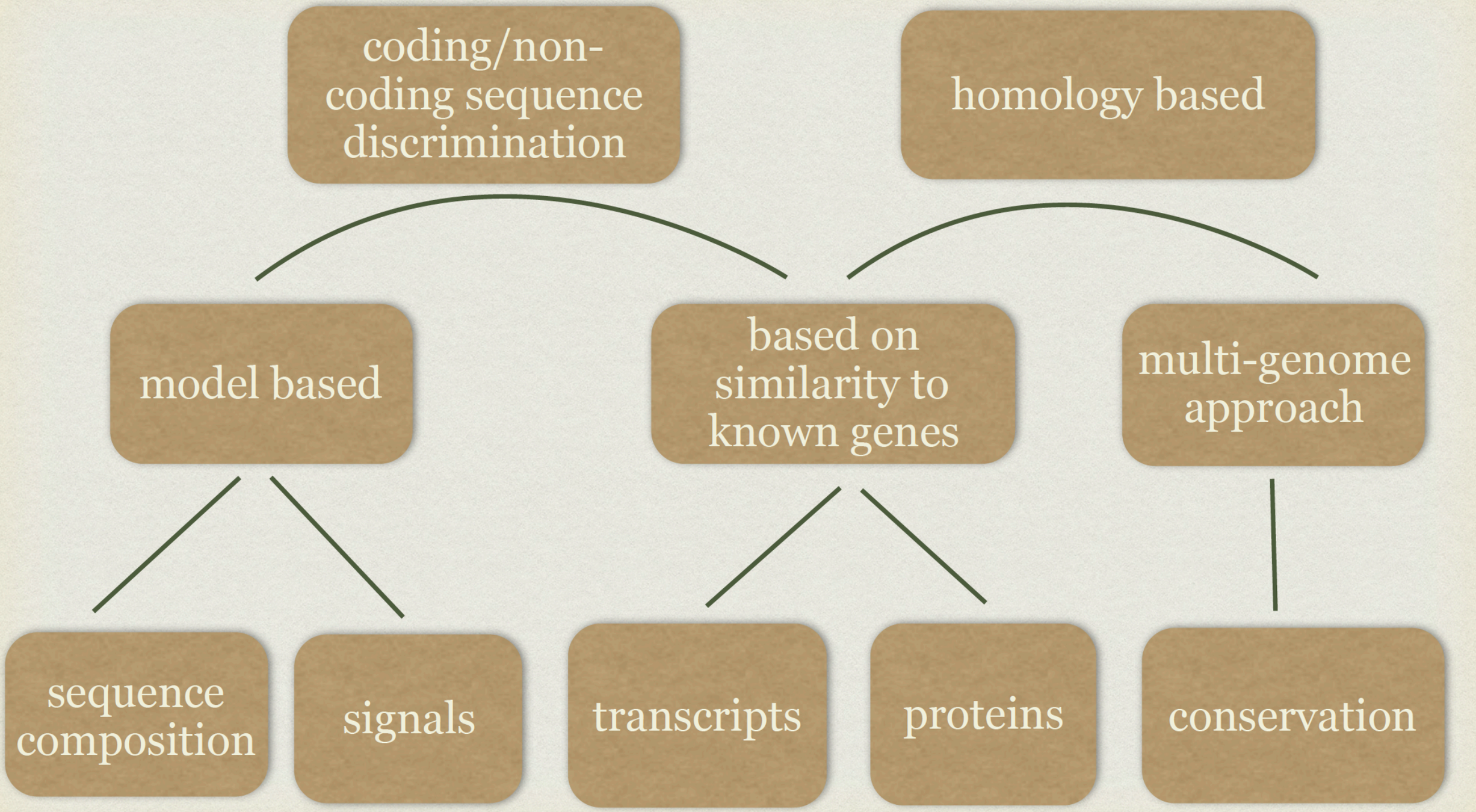
```
Query  4    CIECHMAKALOWSK  17
            CIECHM KA   SK
Sbjct  267  CIECHMPKA---SK  277
```

Gene Prediction

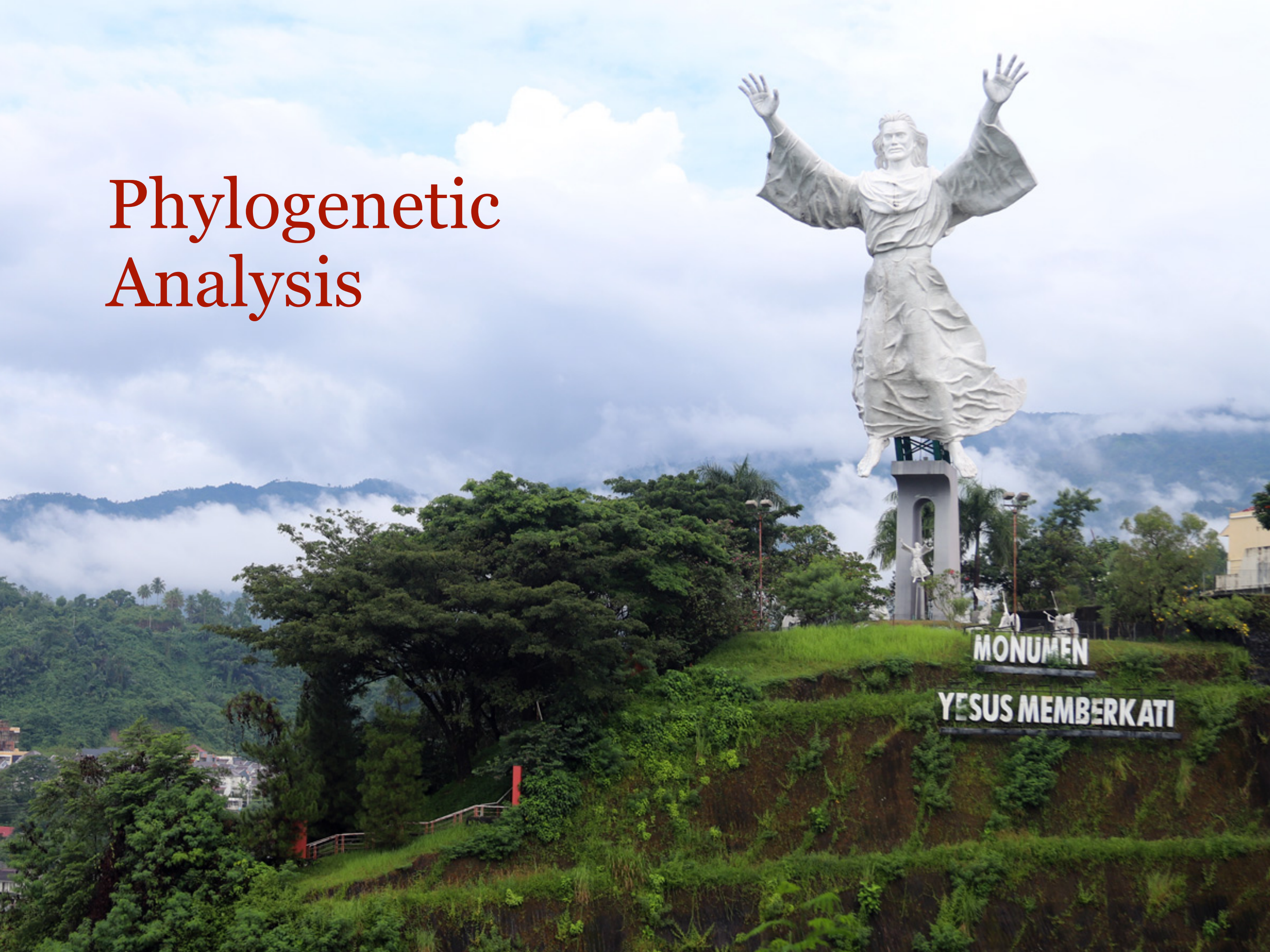
(exon-intron-exon)$_n$ structure of various genes



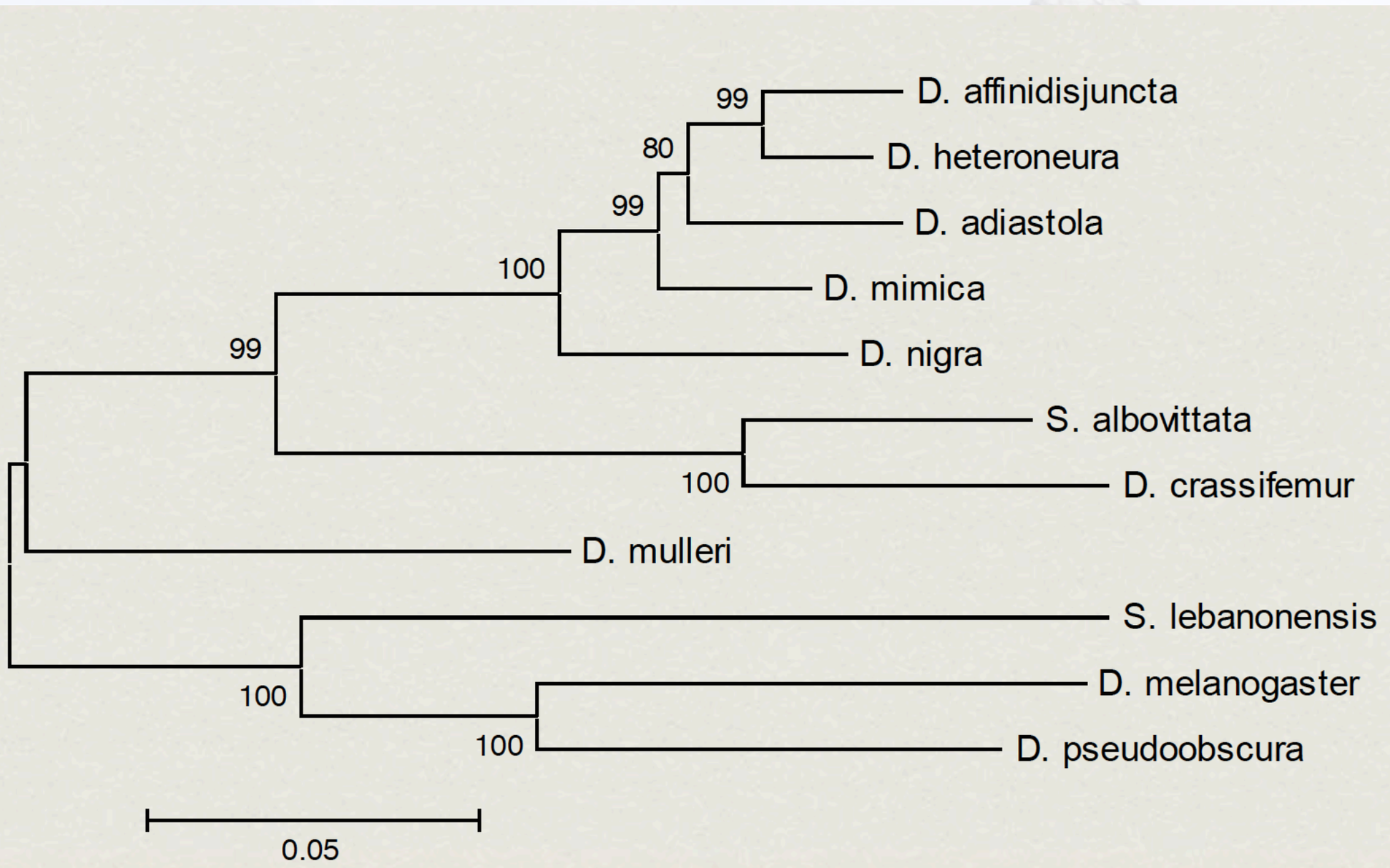
GENE FINDING METHODS



Phylogenetic Analysis



Phylogenetic Analysis

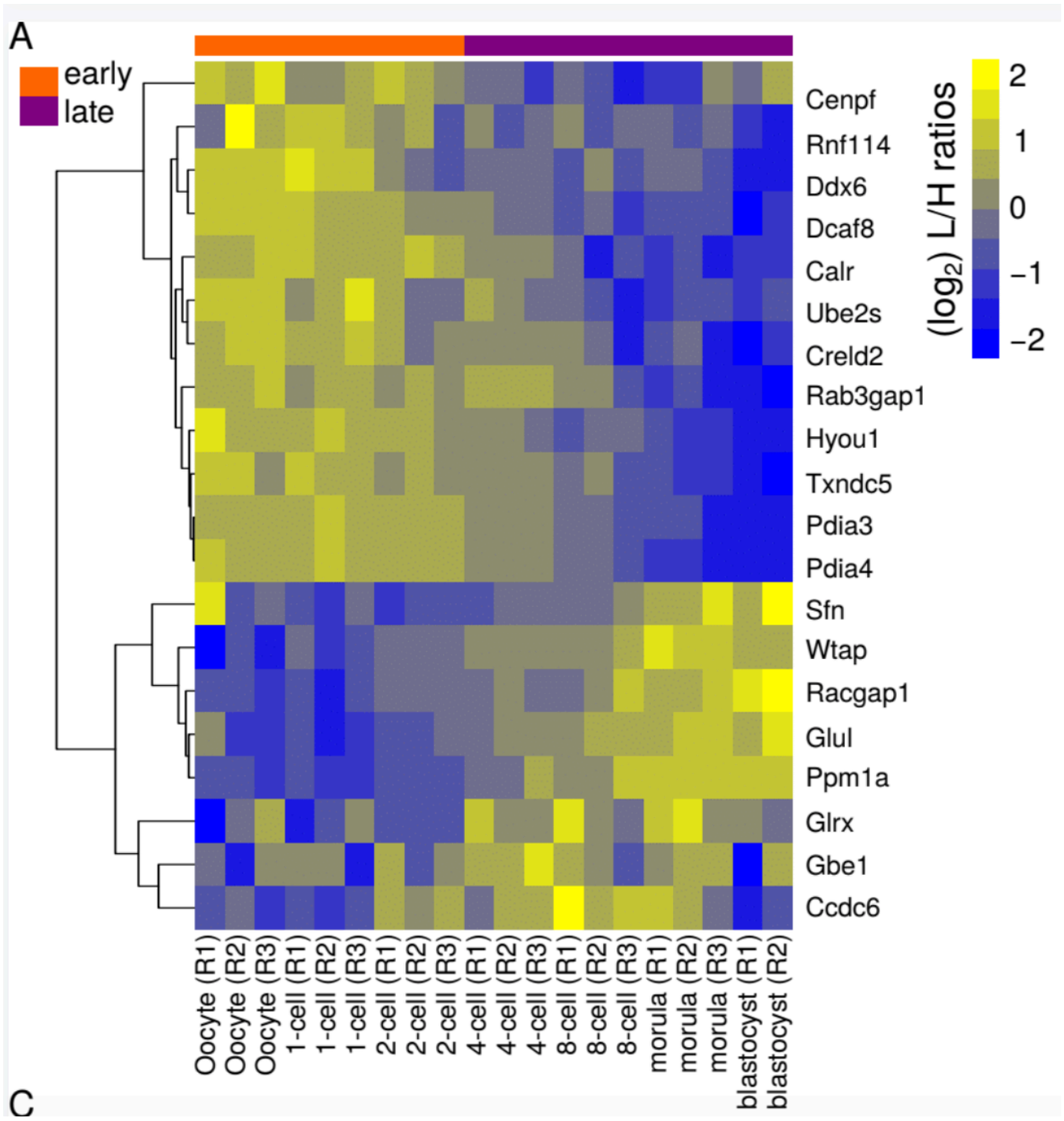


Systems Biology

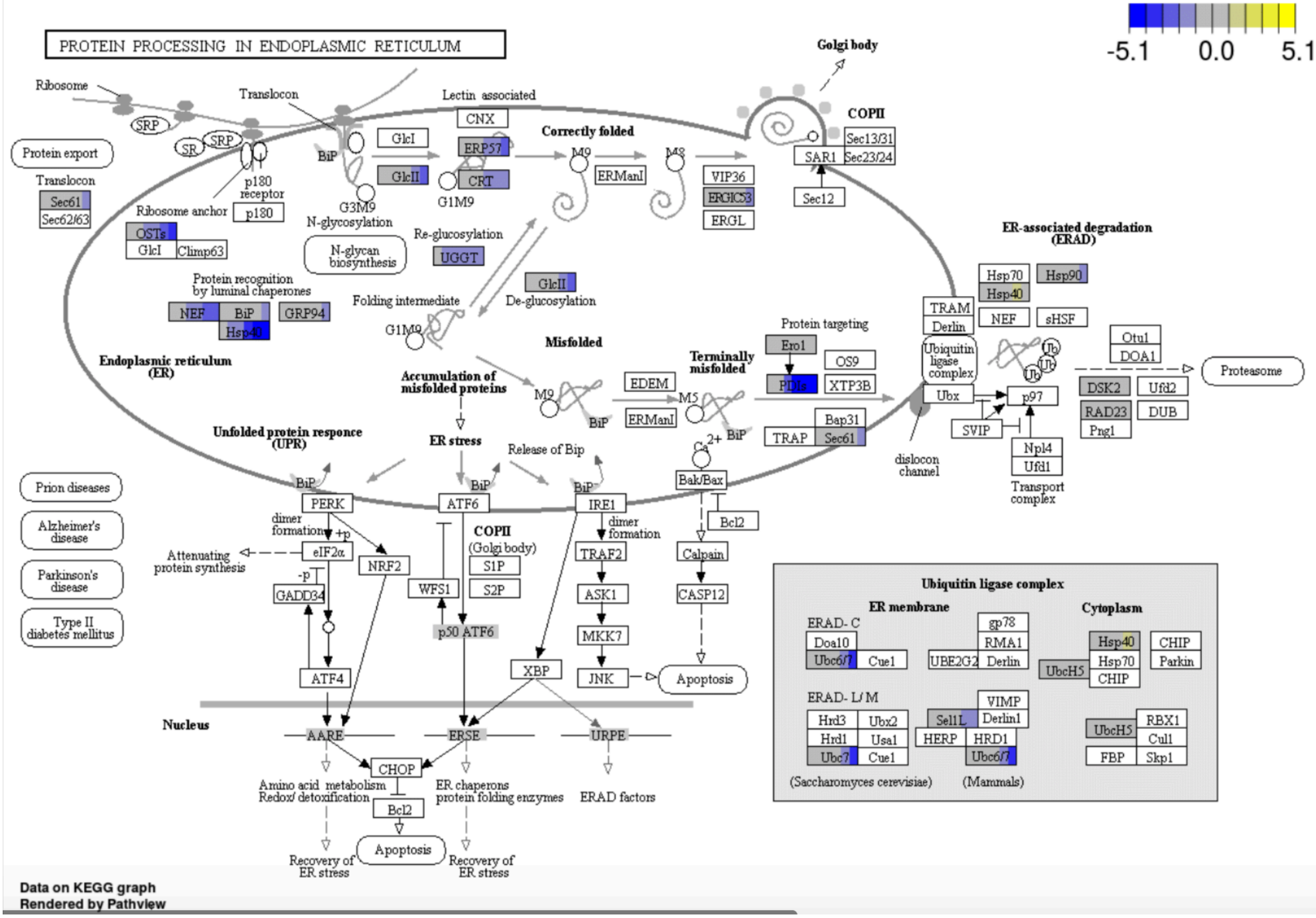
Systems biology is the computational and mathematical modeling of complex biological systems. It is a biology-based interdisciplinary field of study that focuses on complex interactions within biological systems, using a holistic approach (holism instead of the more traditional reductionism) to biological research.

From Wikipedia, the free encyclopedia

Differential gene expression during mouse early embryogenesis



Israel et al. *Genome Research,* under revision



Israel et al. *Genome Research,* under revision

Translational Bioinformatics

Translational Bioinformatics

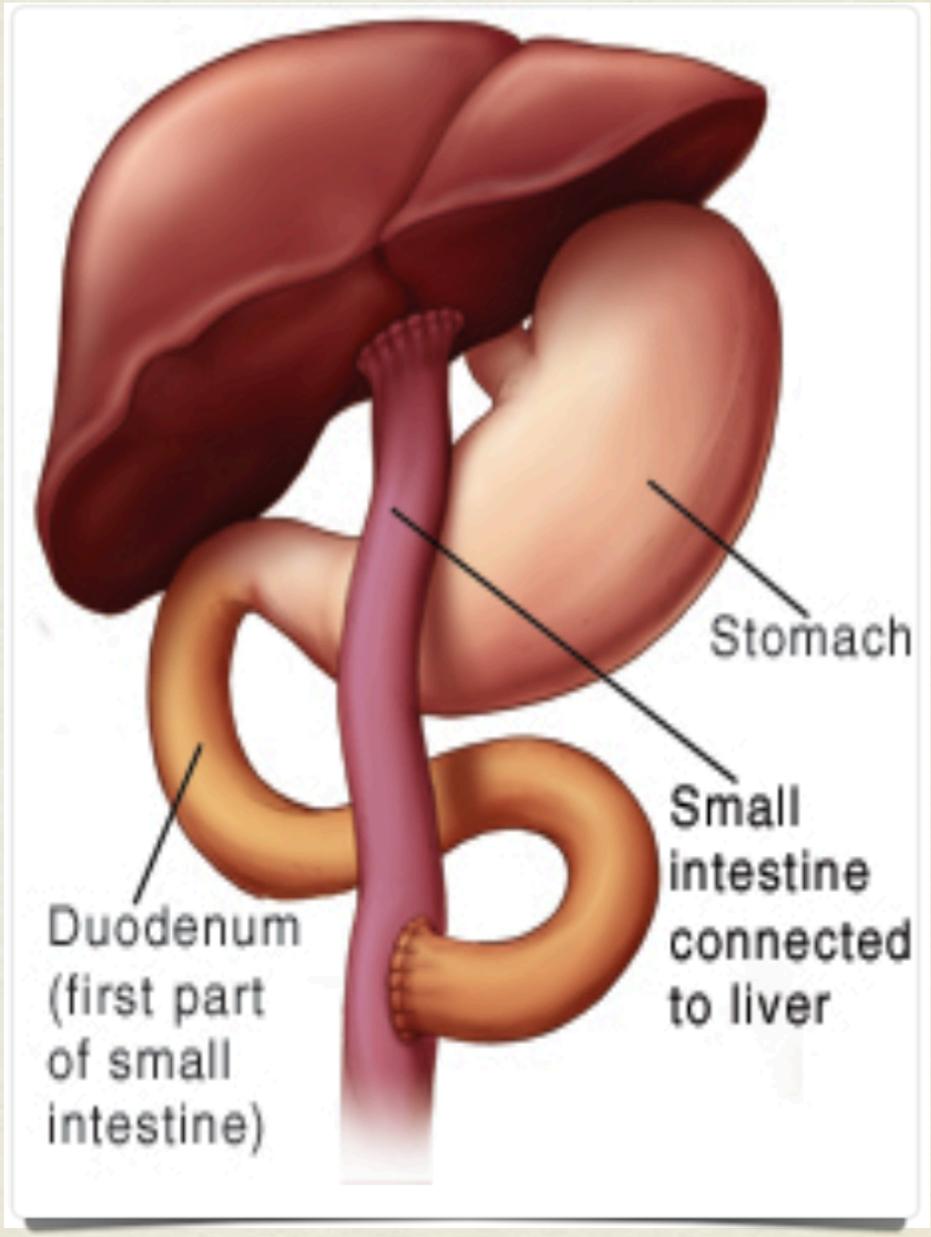
Russ Altman defines translational bioinformatics as ‘the translation of basic capabilities and discoveries provided by informatics methods into clinically useful tools.’

One of the major challenges of medical genomics and translational bioinformatics in particular is the translation of genomic data into clinically applicable knowledge.

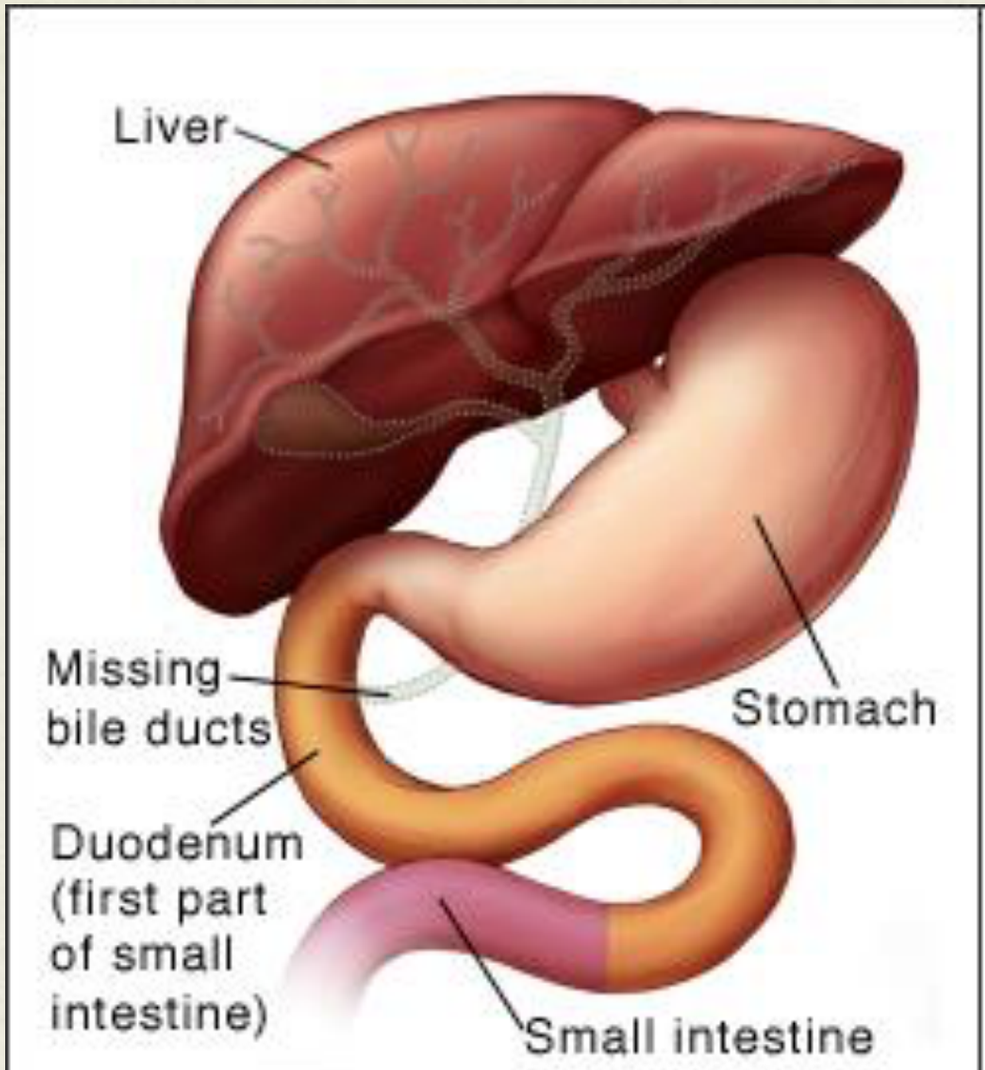
CLINICAL SUCCESS STORY

RADY CHILDREN'S HOSPITAL BABY 6026

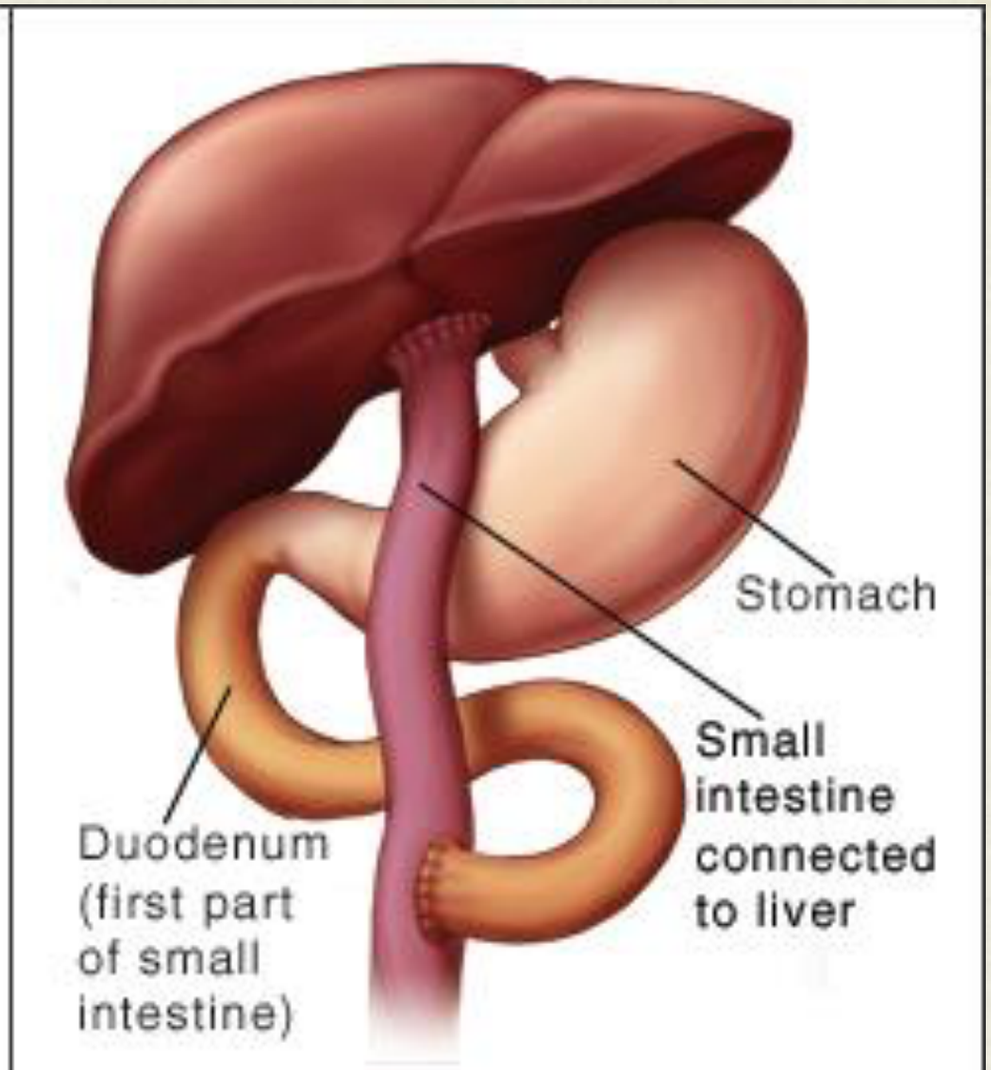
- Two month old child admitted to PICU with severe jaundice & poor weight gain for one month
- Echo: Congenital heart disease, underdeveloped pulmonary arteries
- Clinical diagnosis: biliary atresia
  - one incidence in ten thousand
- Empiric treatment: Kasai procedure



KASAI PROCEDURE

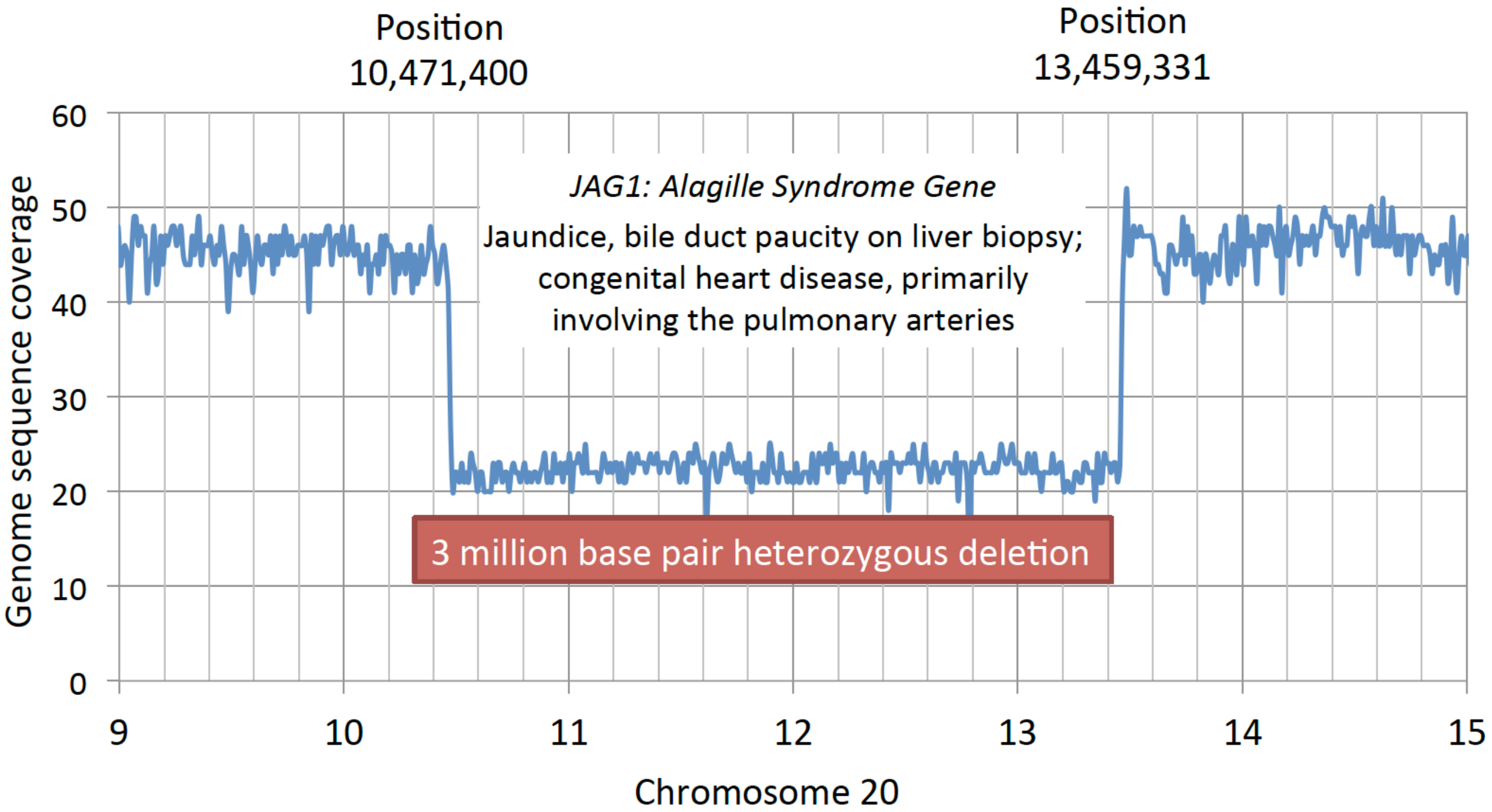


The dotted lines show areas that can be affected by biliary atresia.



During the Kasai procedure, the intestine is attached to the liver. This allows bile to drain.

43 HOURS LATER: PROVISIONAL DIAGNOSIS



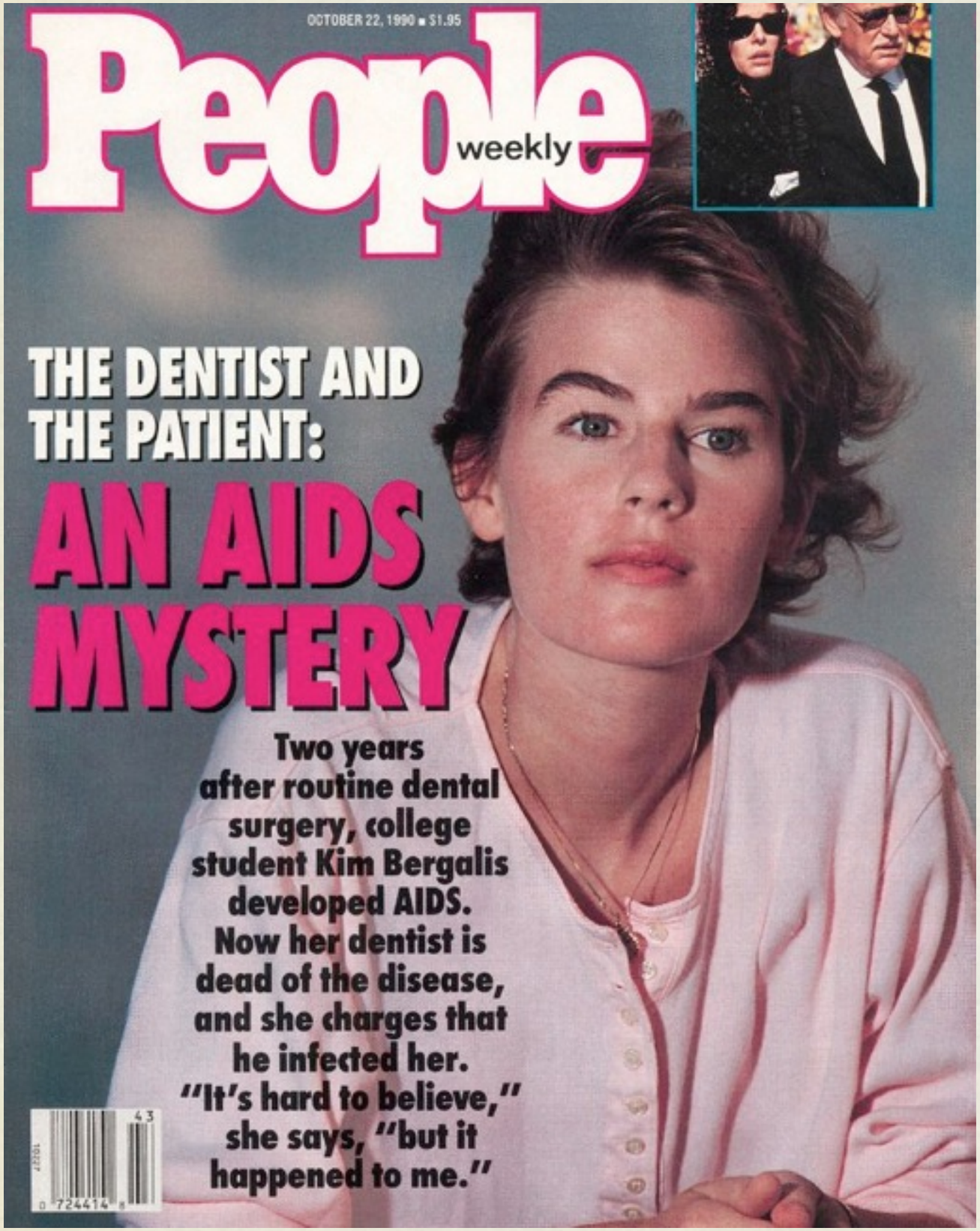
CLINICAL IMPACT & OUTCOME

- Kasai procedure scheduled for 11:00 am
- Genetic diagnosis communicated to clinical team just before surgery – procedure cancelled
- Infants with Alagille syndrome are occasionally misdiagnosed as biliary atresia and subsequently undergo Kasai operation during infancy
- Among 15 children with Alagille syndrome, mortality was 60% after Kasai procedure, and only 10% among those without Kasai procedure. Liver transplantation was performed in 100% of the Kasai group, and 20% of the non-Kasai group.

Dr. Narayanan Veeraraghavan, personal communication

Data Volume Problem

Type of cancer	Number of whole genome	Number of whole exome	Data volume (Tb)	Time to download
Colon Adenocarcinoma (COAD)	302	443	33.04	24 days
Lung	134	582	40.95	30 days
Breast	248	1050	69.82	50 days
Prostate Adenocarcinoma (PRAD)	272	1049	26.53	10 days



Did the Florida Dentist infect his patients with HIV?

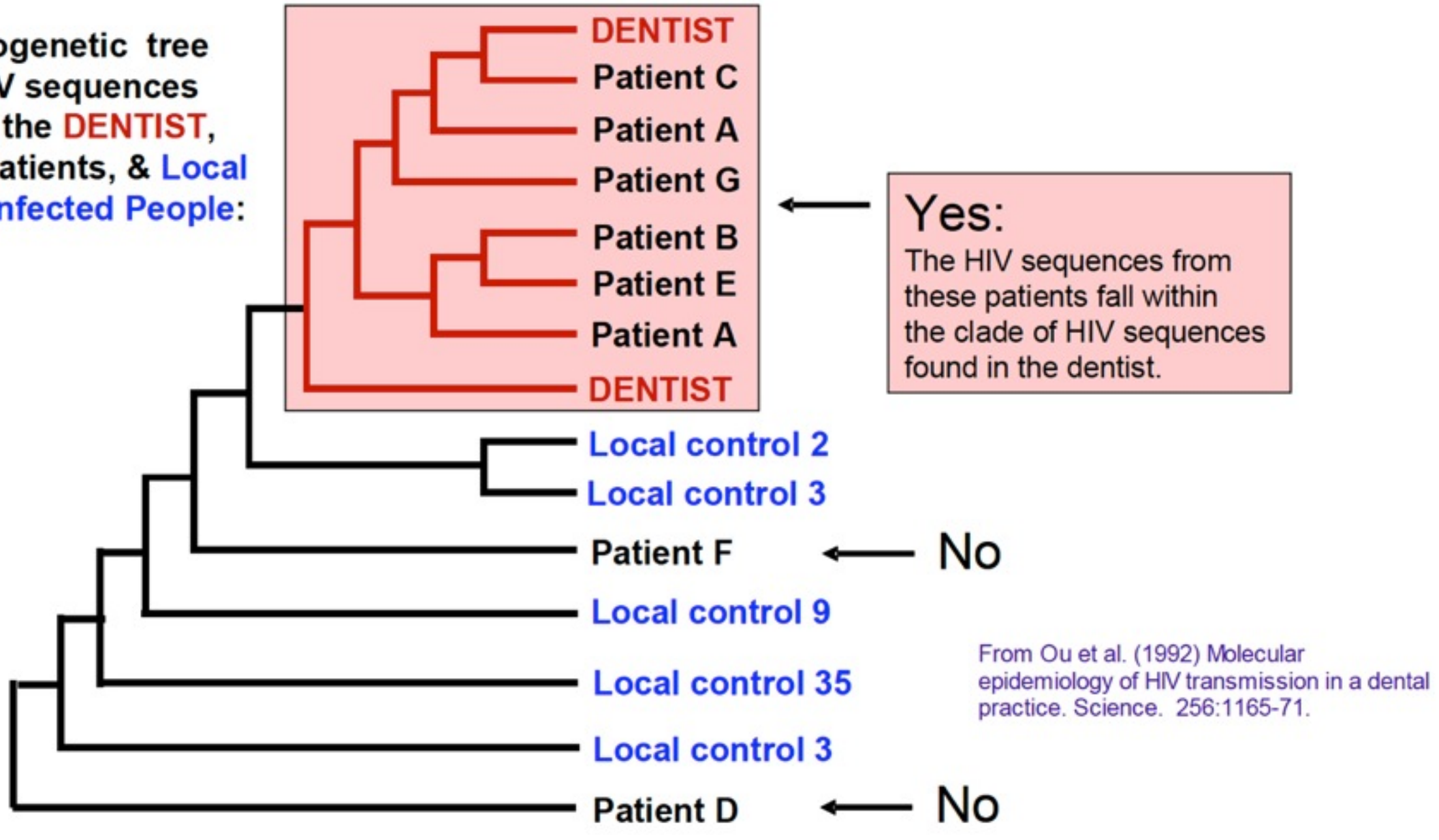
Kimberly Bergalis

(1968-1991)

David J. Acer

(1940-1990)

DID THE FLORIDA DENTIST INFECT HIS PATIENTS WITH HIV?



THE MYSTERY OF THE CHILEAN BLOB

THE MYSTERY OF THE CHILEAN BLOB

>Chilean_Blob
TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGG
GTTGAGGAGGACTAAACCAGACTCAACTCCGAAAAATTA
TAGCTTACTCATCAATCGCCCACATAGGATGAATAACCA
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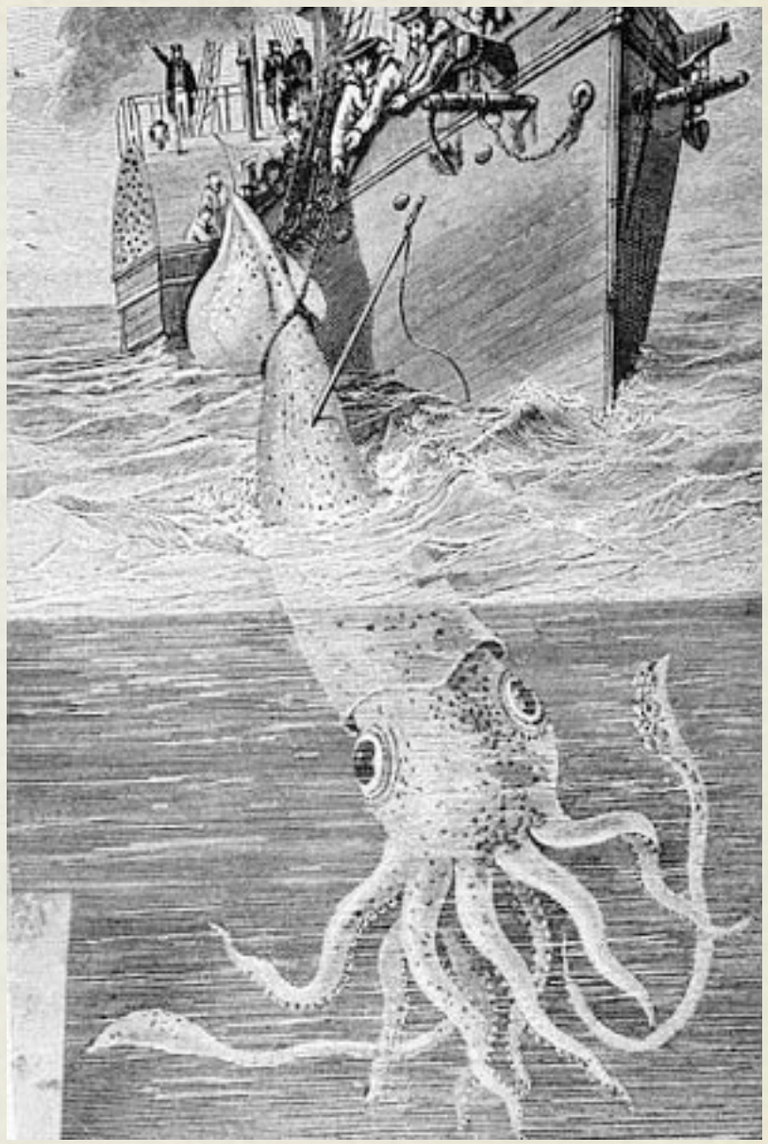

THE MYSTERY OF THE CHILEAN BLOB

Lineage Report

Cetacea [whales & dolphins]				
. Odontoceti [whales & dolphins]				
. . Physeteridae [whales & dolphins]				
. . . Physeter catodon	1085	3 hits	[whales & dolphins]	Physeter catodon NADH dehydrogenase subunit 2 (nad2) gene,
. . . Kogia breviceps	638	1 hit	[whales & dolphins]	Kogia breviceps complete mitochondrial genome
. . Orcaella brevirostris	593	1 hit	[whales & dolphins]	Orcaella brevirostris isolate 97 mitochondrion, complete ge
. . Grampus griseus	593	1 hit	[whales & dolphins]	Grampus griseus mitochondrion, complete genome
. . Feresa attenuata	592	2 hits	[whales & dolphins]	Feresa attenuata isolate 36 mitochondrion, complete genome
. . Tursiops truncatus (bottle-nosed dolphin)	592	1 hit	[whales & dolphins]	Tursiops truncatus mitochondrion, complete genome
. . Globicephala melas	586	3 hits	[whales & dolphins]	Globicephala melas isolate GlomelG42 mitochondrion, partial
. . Peponocephala electra	580	2 hits	[whales & dolphins]	Peponocephala electra isolate M6 mitochondrion, complete ge
. . Globicephala macrorhynchus	580	4 hits	[whales & dolphins]	Globicephala macrorhynchus isolate Glomac65 mitochondrion,
. . Pseudorca crassidens	577	3 hits	[whales & dolphins]	Pseudorca crassidens mitochondrion, complete genome
. . Orcinus orca (Orca)	569	54 hits	[whales & dolphins]	Orcinus orca isolate ENPTGA2 mitochondrion, complete genome
. . Sotalia fluviatilis	569	2 hits	[whales & dolphins]	Sotalia fluviatilis haplotype 10 NADH dehydrogenase subunit
. . Platanista minor	569	1 hit	[whales & dolphins]	Platanista minor complete mitochondrial genome
. . Steno bredanensis	566	2 hits	[whales & dolphins]	Steno bredanensis isolate StebreS9 mitochondrion, partial g
. Megaptera novaeangliae	636	5 hits	[whales & dolphins]	Megaptera novaeangliae voucher GOM9049 NADH dehydrogenase s
. Balaenoptera bonaerensis	630	1 hit	[whales & dolphins]	Balaenoptera bonaerensis mitochondrial DNA, complete genome
. Eubalaena japonica	619	1 hit	[whales & dolphins]	Eubalaena japonica mitochondrial DNA, complete genome
. Balaenoptera brydei	614	2 hits	[whales & dolphins]	Balaenoptera brydei mitochondrial DNA, complete genome, iso
. Balaena mysticetus (Greenland right whale)	614	2 hits	[whales & dolphins]	Balaena mysticetus mitochondrial DNA, complete genome
. Balaenoptera musculus				
. Balaenoptera edeni				
. Balaenoptera omurai				
. Eschrichtius robustus (California gray whale)				
. Balaenoptera borealis				
. Caperea marginata				
. Balaenoptera physalus (finback whale)				

THE MYSTERY OF THE CHILEAN BLOB

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>emb|AJ277029.2|  Physeter macrocephalus mitochondrial genome
Length=16428

 Score = 1074 bits (581),  Expect = 0.0
 Identities = 585/587 (99%), Gaps = 0/587 (0%)
 Strand=Plus/Plus

Query  1     TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGGGTTGAGGAGGACTAAACCAGA  60
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4400  TAATACTAACTATATCCCTACTCTCCATTCTCATCGGGGGTTGAGGAGGACTAAACCAGA  4459

Query  61    CTCAACTCCGAAAAATTATAGCTTACTCATCAATCGCCCACATAGGATGAATAACCACAA  120
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Sbjct  4460  CTCAACTCCGAAAAATTATAGCTTACTCATCAATCGCCCACATAGGATGAATAACCACAA  4519

Query  121   TCCTACCCTACAATACAACCATAACCCTACTAAACCTACTAATCTATGTCACAATAACCT  180
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Sbjct  4520  TCCTACCCTACAATACAACCATAACCCTACTAAACCTACTAATCTATGTCACAATAACCT  4579

Query  181   TCACCATATTCATACTATTTATCCAAAACTCAACCACAACCACACTATCTCTGTCCCAGA  240
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Query  241   CATGAAACAAAACACCCATTACCACAACCCTTACCATACTTACCCTACTTTCCATAGGGG  300
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Sbjct  4640  CATGAAACAAAACACCCATTACCACAACCCTTACCATACTTACCCTACTTTCCATAGGGG  4699

Query  301   GCCTCCCACCACTCTCGGGCTTTATCCCCAAATGAATAATTATTCAAGAACTAACAAAAA  360
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Query  361   ACGAAACCCTCATCATACCAACCTTCATAGCCACCACAGCATTACTCAACCTCTACTTCT  420
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Query  421   ATATACGCCTCACCTACTCAACAGCACTAACCCTATTCCCCTCCACAAATAACATAAAAA  480
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Query  481   TAAAATGACAATTCTACCCCACAAAACGAATAACCCTCCTGCCAACAGCAATTGTAATAT  540
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Query  541   CAACAATACTCCTACCCCTTACACCAATACTCTCCACCCTATTATAG  587
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Sbjct  4940  CAACAATACTCCTACCCCTTACACCAATACTCTCCACCCTATTATAG  4986
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BIOINFORMATICS IN MEDICINE CHALLENGES

- Computational skills for in-depth analyses
- Data interpretation
- Research translation
- Data volume!!!

http://bioinformatics.uni-muenster.de