CS681: Advanced Topics in Computational Biology

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CS681

- Class hours:
  - Wed 9:40 - 10:30; Fri 10:40 - 12:30
- Class room: EA502
- Office hour: Wed 14:00-15:00 or app't by email
- Grading:
  - 1 project or literature survey: 50%
    - Teams up to 3 people (1-3)
  - Class participation: 10%
  - Paper presentation (2 papers) & summary report: 40%

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- Textbook: None
- Recommended Material
  - Genome Scale Algorithm Design, Veli Makinen, et al., Cambridge University Press, 2015
  - An Introduction to Bioinformatics Algorithms (Computational Molecular Biology), Neil Jones and Pavel Pevzner, MIT Press, 2004
  - Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids, Richard Durbin, Sean R. Eddy, Anders Krogh, Graeme Mitchison, Cambridge University Press
  - Bioinformatics: The Machine Learning Approach, Second Edition, Pierre Baldi, Soren Brunak, MIT Press
  - Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology, Dan Gusfield, Cambridge University Press
  - Scientific journals and conference proceedings (RECOMB and ISMB)

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- This course is about **algorithms** in the field of bioinformatics / computational biology; mostly genomics:
  - What are the problems?
  - What algorithms are developed for what problem?
  - What is missing / needs advances in the field.
  - Possible research directions for graduate students.

CS681: Assumptions

- You are assumed to know/understand
  - Advanced algorithms
    - Dynamic programming, greedy algorithms, graph theory
    - CS473 is desired
    - CS573 is better
  - Programming: C, C++, Java
- You don't *have to* be a "biology expert" but MBG 101 or 110 would be beneficial

INTRODUCTION, CONCEPTS AND TERMS

Bioinformatics & Computational Biology

- Bioinformatics: Development of methods based on computer science for problems in biology &medicine
  - Sequence analysis (combinatorial and statistical/probabilistic methods)
  - Graph theory
  - Data mining

  CS 481 and CS 681
  - Database
  - Statistics
  - Image processing
  - Visualization
  - …..
- Computational biology: Application of computational methods to address questions in biology & medicine

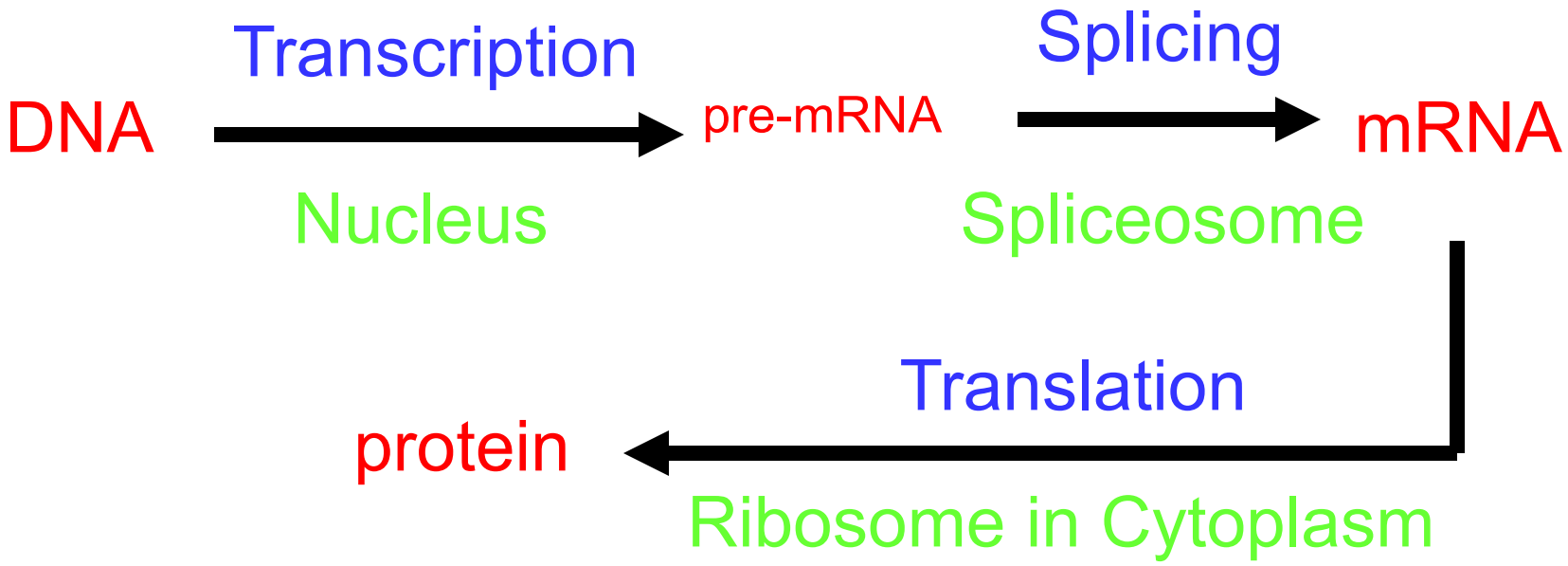
Concepts

- Gene: discrete units of hereditary information located on the chromosomes and consisting of DNA.
- Genetics: study of inherited phenotypes
- Genotype: The genetic makeup of an organism
- Phenotype: the physical expressed traits of an organism
- Genome: entire hereditary information of an organism
- Genomics: analysis of the whole genome (that is, the DNA content for most organisims; RNA content for retroviruses)
- Transcriptome: set of all RNA molecules
- Proteome: set of all protein molecules

All life depends on 3 critical molecules

- DNAs
  - Hold information on how cell works
- RNAs
  - Act to transfer short pieces of information to different parts of cell
  - Provide templates to synthesize into protein
- Proteins
  - Form enzymes that send signals to other cells and regulate gene activity
  - Form body's major components (e.g. hair, skin, etc.)
- For a computer scientist, these are all strings derived from three alphabets.

Central dogma of biology



- Base Pairing Rule: A and T or U is held together by 2 hydrogen bonds and G and C is held together by 3 hydrogen bonds.
- Note: Some RNA stays as RNA (ie tRNA,rRNA, miRNA, snoRNA, etc.).

Alphabets

DNA:

$\sum$ = {A, C, G, T}

A pairs with T; G pairs with C

RNA:

$\sum$ = {A, C, G, U}

A pairs with U; G pairs with C

Protein:

$\sum$ = {A,C,D,E,F,G,H,I,K,L,M,N,P,Q,R,S,T,V,W,Y} *and*

B = N | D

Z = Q | E

X = *any*

DNA is organized into Chromosomes

- Chromosomes:
  - Found in the nucleus of the cell which is made from a long strand of DNA, "packaged" by proteins called *histones*. Different organisms have a different number of chromosomes in their cells.
  - Human genome has 23 pairs of chromosomes
    - 22 pairs of *autosomal* chromosomes (chr1 to chr22)
    - 1 pair of *sex* chromosomes (chrX+chrX or chrX+chrY)
- Ploidy: number of sets of chromosomes
  - Haploid (n): one of each chromosome
    - Sperm & egg cells; hydatidiform mole
  - Diploid (2n): two of each chromosome
    - All other cells in mammals (human, chimp, cat, dog, etc.)
  - Triploid (3n), Tetraploid (4n), etc.
    - Tetraploidy is common in plants

Genomes

- Definition (again): the entire collection of hereditary material
  - Most organisms: DNA content
  - Retroviruses (like HIV, influenza): RNA content
- Eukaryotes can have 2-3 genomes:
  - Nuclear (default)
  - Mitochondrial
  - Plastid
- Libraries & instruction sets for the cells
- Identical in most cells, except the immune system cells
- Germline DNA: material that may be transmitted to the child (germ cell)
  - Germ cell: cells that give rise to gametes (sperm/egg)
- Somatic DNA: material in cells other than germ cells & gametes
  - Changes in somatic cells do not transmit to offspring

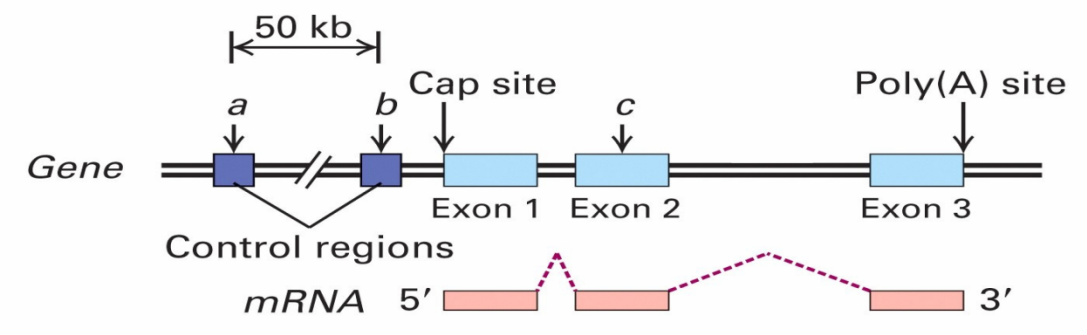
How big are genomes?

Organism	Genome Size (Bases)	Estimated Genes
Human (*Homo sapiens*)	3 billion	20,000
Laboratory mouse (*M. musculus*)	2.6 billion	20,000
Mustard weed (*A. thaliana*)	100 million	18,000
Roundworm (*C. elegans*)	97 million	16,000
Fruit fly (*D. melanogaster*)	137 million	12,000
Yeast (*S. cerevisiae*)	12.1 million	5,000
Bacterium (*E. coli*)	4.6 million	3,200
Human immunodeficiency virus (HIV)	9700	9

Genome "table of contents"

- Genes (~35%; but only 1% are coding exons)
  - Protein coding
  - Non-coding (ncRNA only)
- Pseudogenes: genes that lost their expression ability:
  - Evolutionary loss
  - Processed pseudogenes
- Repeats (~50%)
  - Transposable elements: sequence that can copy/paste themselves. Typically of virus origin.
  - Satellites (short tandem repeats [STR]; variable number of tandem repeats [VNTR])
  - Segmental duplications (5%)
    - Include genes and other repeat elements within

Genes



- Subsequences of DNA that are transcribed into RNA
  - Some encode for proteins, some do not
- Regulatory regions: up to 50 kb upstream of +1 site
- Exons: protein coding and untranslated regions (UTR)
  1 to 178 exons per gene (mean 8.8)
  8 bp to 17 kb per exon (mean 145 bp)
- Introns: sequence between exons; spliced out before translation
  average 1 kb – 50 kb per intron
- Gene size: Largest – 2.4 Mb (Dystrophin). Mean – 27 kb.

Genes can be switched on/off

- In an adult multicellular organism, there is a wide variety of cell types seen in the adult. eg, muscle, nerve and blood cells.
- The different cell types contain the *same* DNA.
- This differentiation arises because different cell types express different genes.
- Type of gene regulation mechanisms:
  - Promoters, enhancers, methylation, RNAi, etc.

Repeats

- Transposons (mobile elements): generally of viral origin, integrated into genomes millions of years ago
- Can copy/paste; most are fixed, some are still active
  - Retrotransposon: intermediate step that involves transcription (RNA)
  - DNA transposon: no intermediate step

Retrotransposons

- LTR: long terminal repeat
- Non-LTR:
  - LINEs: Long Interspersed Nucleotide Elements
    - L1 (~6 kbp full length, ~900 bp trimmed version): Approximately 17% of human genome
      - They encode genes to copy themselves
  - SINEs: Short Interspersed Nucleotide Elements
    - *Alu* repeats (~300 bp full length): Approximately 1 million copies = ~10% of the genome
      - They use cell's machinery to replicate
      - Many subfamilies; AluY being the most active, AluJ most ancient

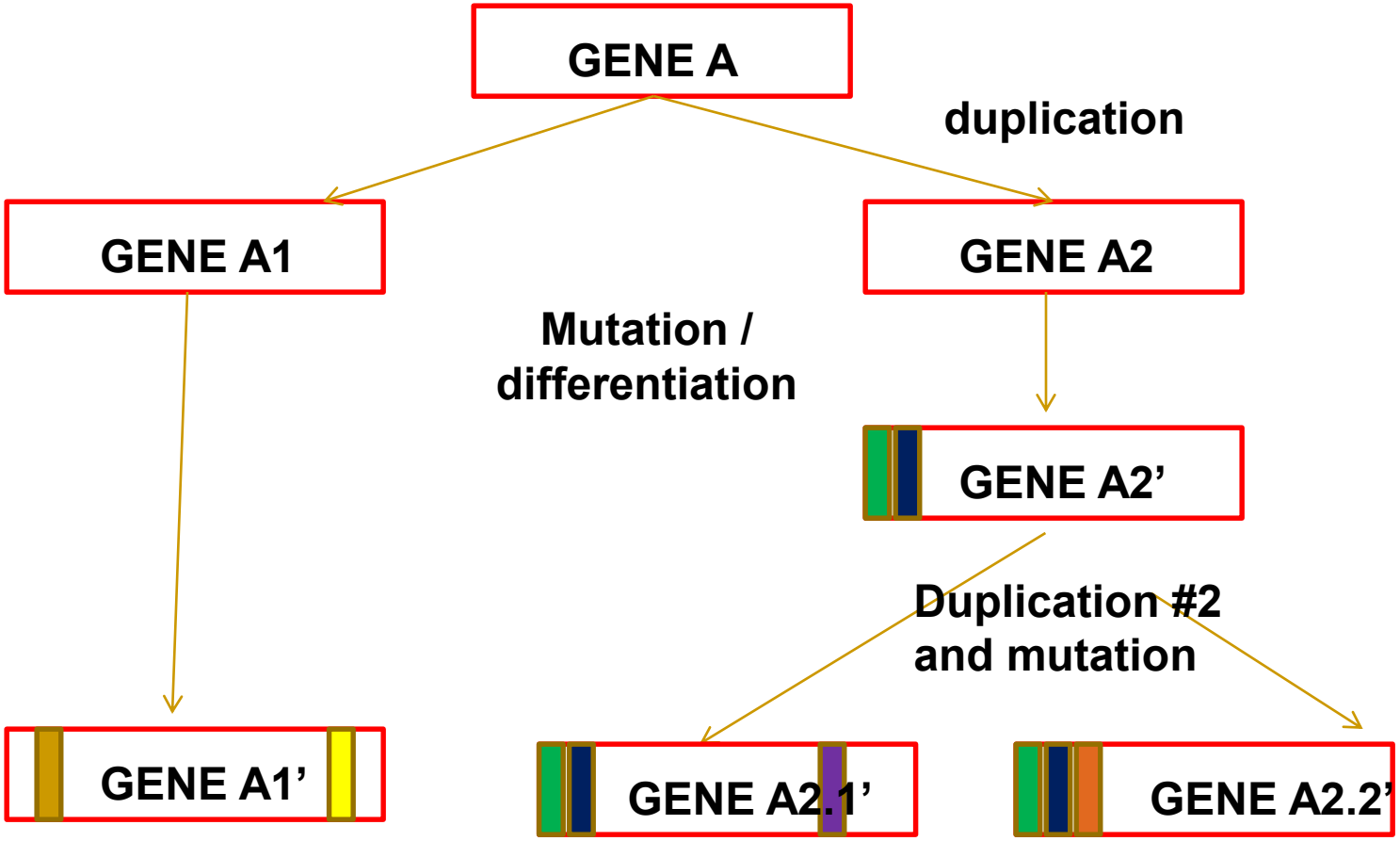
Satellites

- Microsatellites (STR=short tandem repeats) 1-10 bp
  - Used in population genetics, paternity tests and forensics
- Minisatellites (VNTR=variable number of tandem repeats): 10-60 bp
- Other satellites
  - Alpha satellites: centromeric/pericentromeric, 171bp in humans
  - Beta satellites: centromeric (some), 68 bp in humans
  - Satellite I (25-68 bp), II (5bp), III (5 bp)

Segmental duplications

- Low-copy repeats, >1 kbp & > 90% sequence identity between copies
- Covers ~5% of the human genome
  - Both tandem and interspersed in humans, about half inter chromosomal duplications
  - Tandem in mice, no inter chromosomal duplications
- Gene rich
- Provides elasticity to the genome:
  - More prone to rearrangements (and causal)
  - Gene innovation through duplication: Ohno, 1970

Gene innovation through duplication



Sequenced Genomes

- Many many bacteria & single cell organisms (E. coli, etc.)
- Plants: rice, wheat, potato, tomato, grape, corn, etc.
- Insects: ant, mosquito, etc.
- Nematodes: C. elegans, etc.
- Many fish
- Mammals: human, chimp, bonobo, gorilla, orangutan, macaque, baboon, marmoset, horse, cat, dog, pig, panda, elephant, mouse, rat, opossum, armadillo, etc.

Non-human genomes

- BGI (China) has 1000 Plants and Animals Project
- Genome 10K (www.genome10k.org): Open-source like collaboration network that aims to sequence the genomes of 10.000 vertebrate species
  - Computational challenges / competition:
    - Alignathon
    - Assemblathon
- i5K: 5.000 insect species

Human genome project

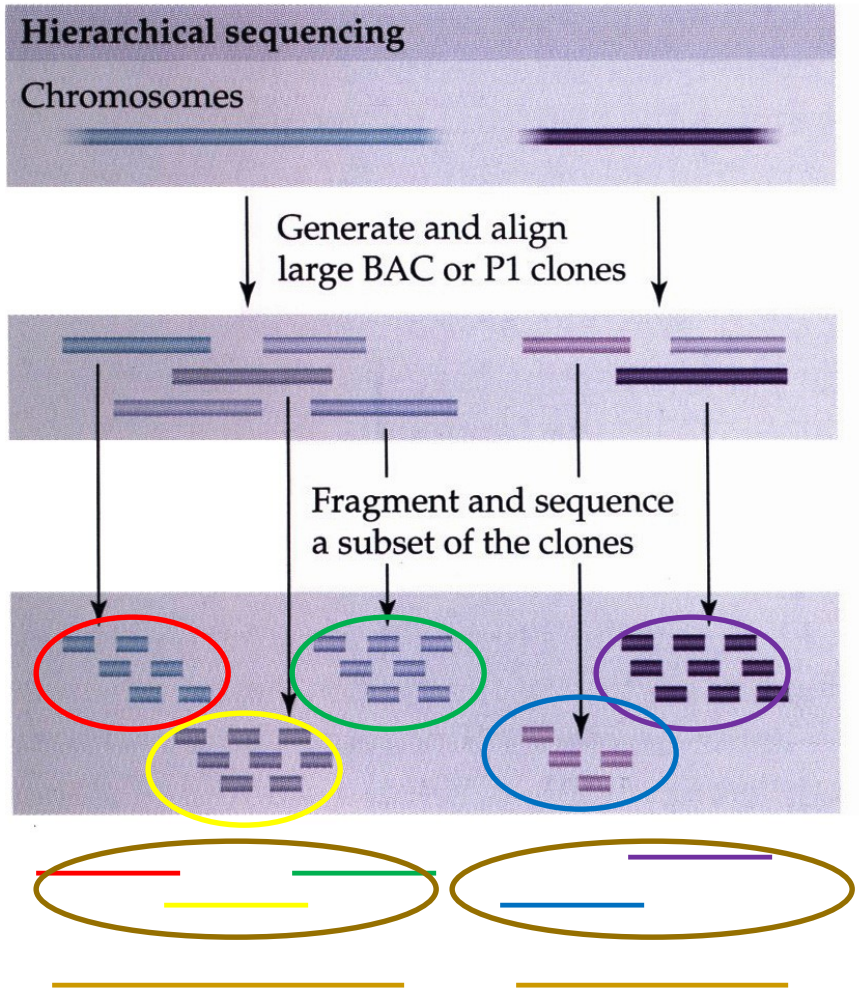
- 1986: Announced (USA+UK)
- 1990: Started
- 1999: Chromosome 22 sequenced
- 2001: First draft
- 2004: Finished

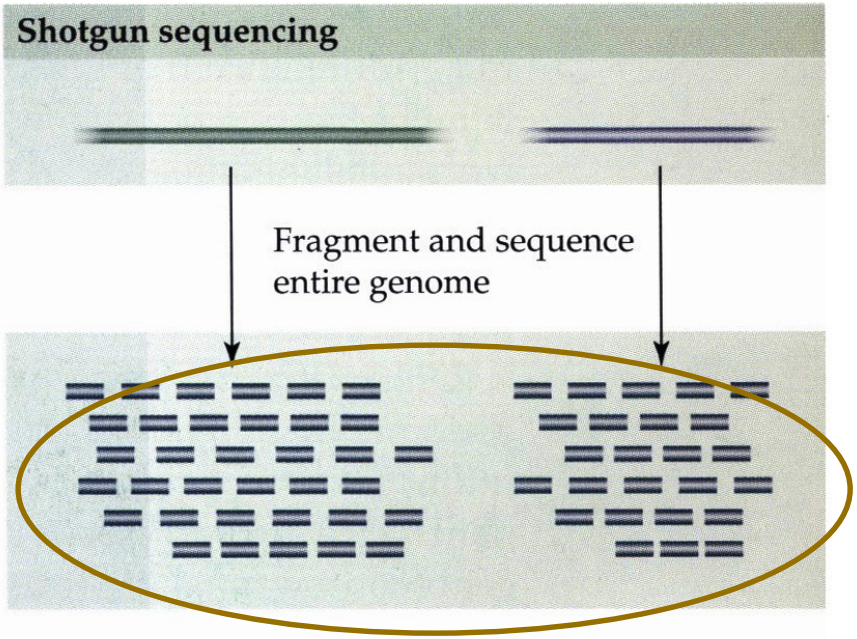
4 human samples, 14 years, 3-10 billion dollars

Sequencing basics

- No technology can read a chromosome from start to finish; all sequencers have limits for the read lengths
- Two major approaches
  - Hierarchical sequencing (used by the human genome project)
    - High quality, very low error rate, little fragmentation
    - Slow and expensive!
  - Whole genome shotgun (WGS) sequencing
    - Lower quality, more errors, assembly is more fragmented
    - Fast and cheap(er)

Hierarchical vs. shotgun sequencing

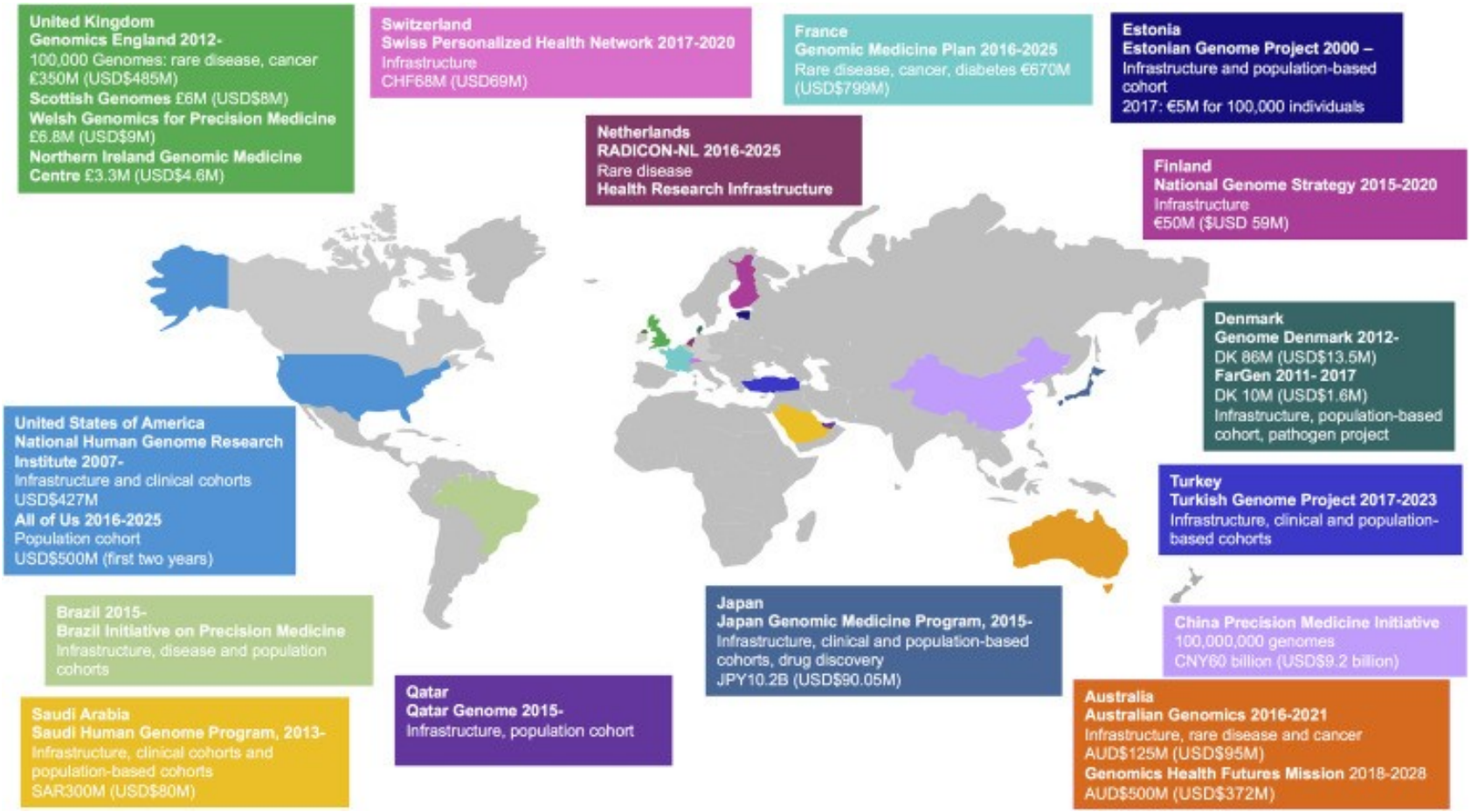




Assemble all

Assemble step by step

Genomics and healthcare



Stark et al., AJHG 2019