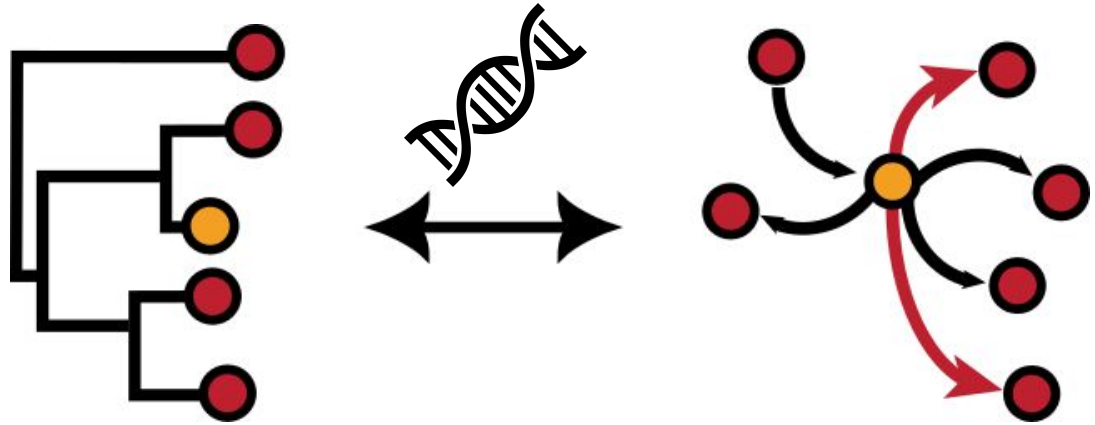
EPAH6052: Pathogen Genomic Epidemiology

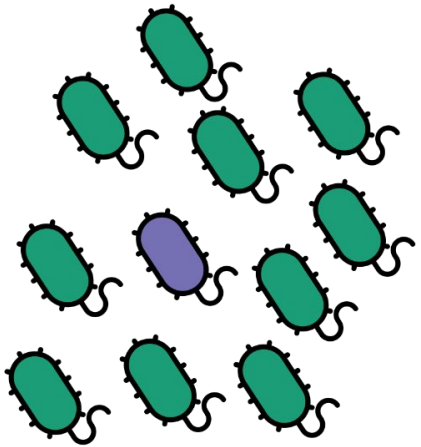


Finlay Maguire
Dalhousie University
Shared Hospital Laboratory
Public Health Alliance for Genomic Epidemiology

Outcomes

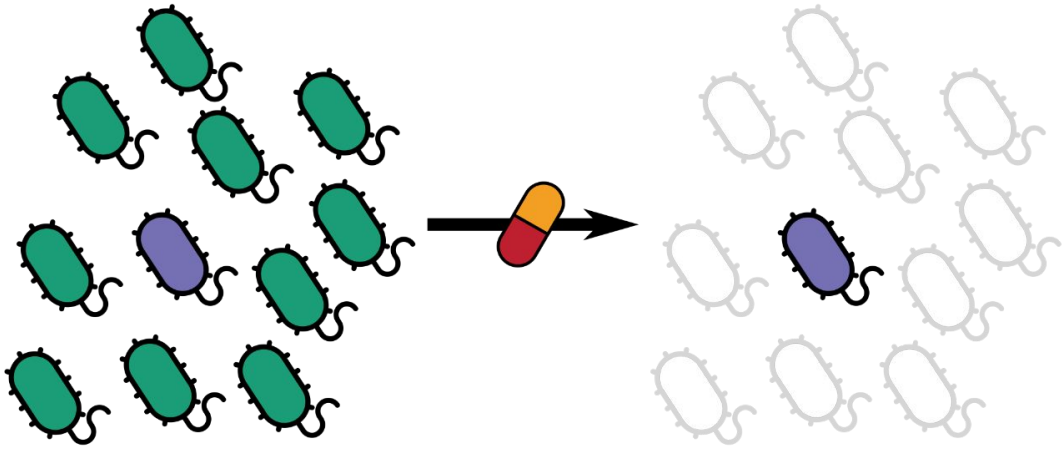
- Explain how evolution and infectious disease epidemiology are connected
- Identify what additional information genomic data can provide
- Give example of how genomics can be used for diagnostics
- Explain how you can infer an evolutionary tree (phylogeny)
- Provide examples of processes which determine the shape of a phylogeny
- Articulate the role of Bayesian models in genomic epidemiology
- List at least 3 ways in which a phylogeny can be used in epidemiology

Agents of infectious diseases undergo evolution



Mostly
Suceptible

Agents of infectious diseases undergo evolution



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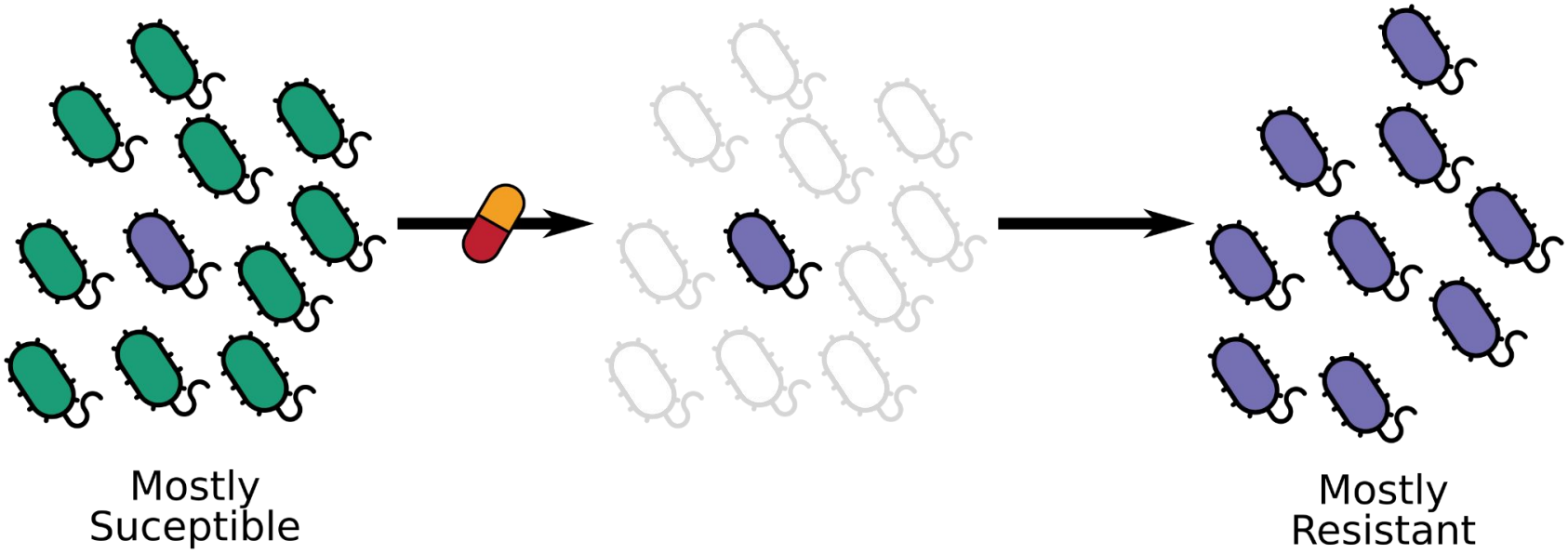
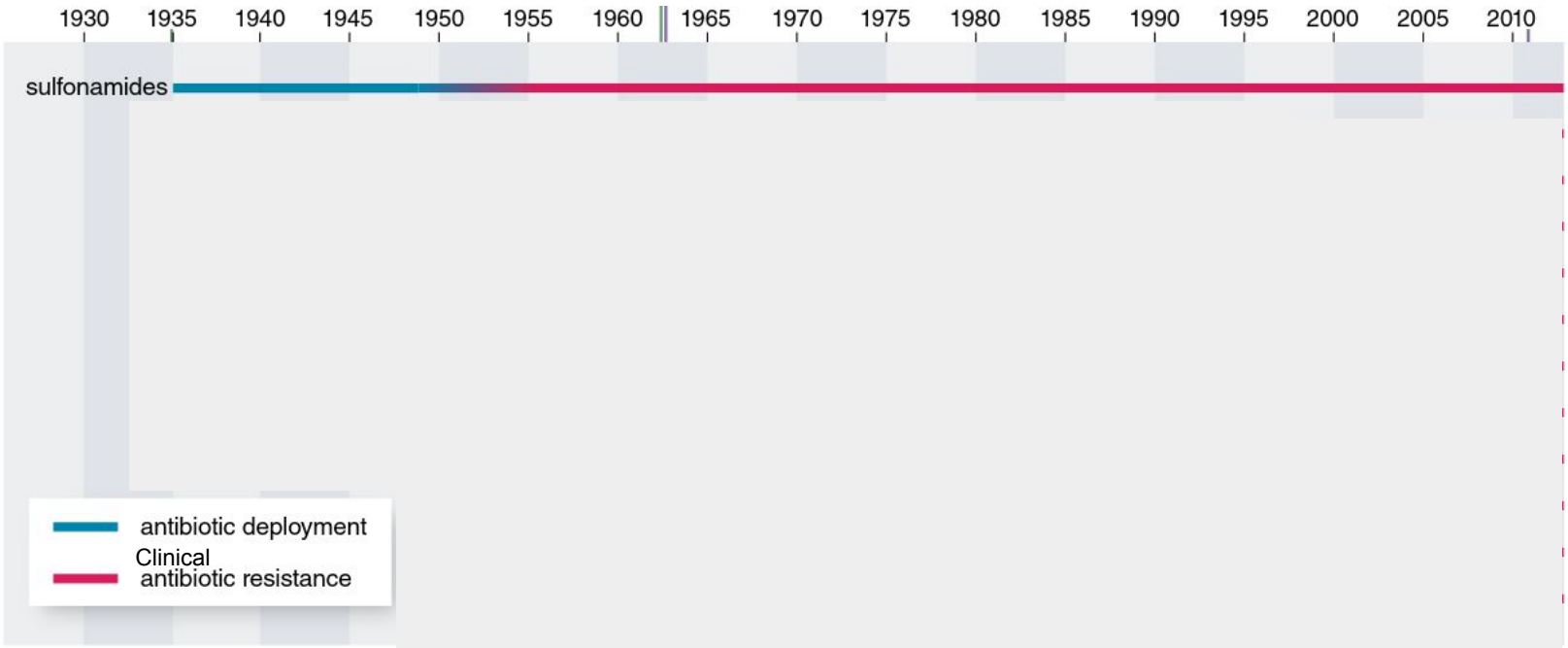


Pathogen evolution impacts treatment



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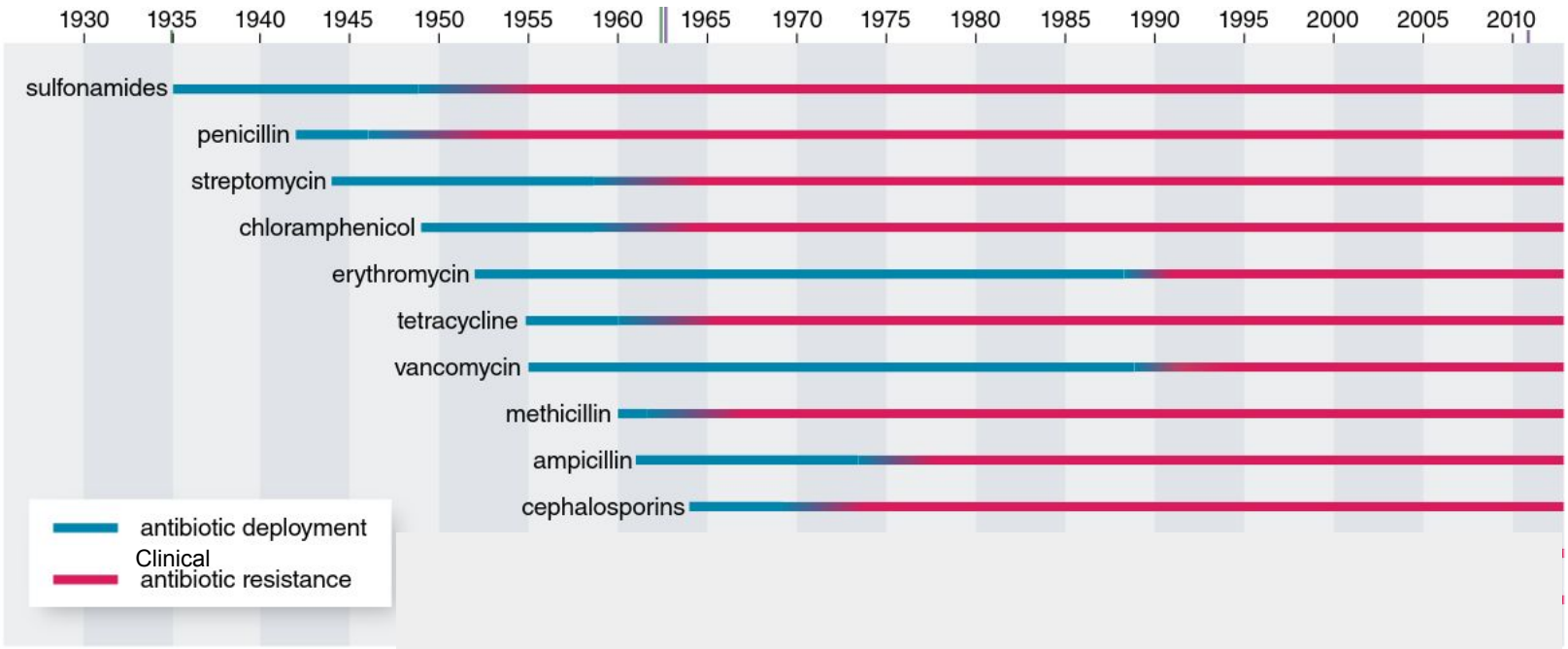
Pathogen evolution impacts treatment



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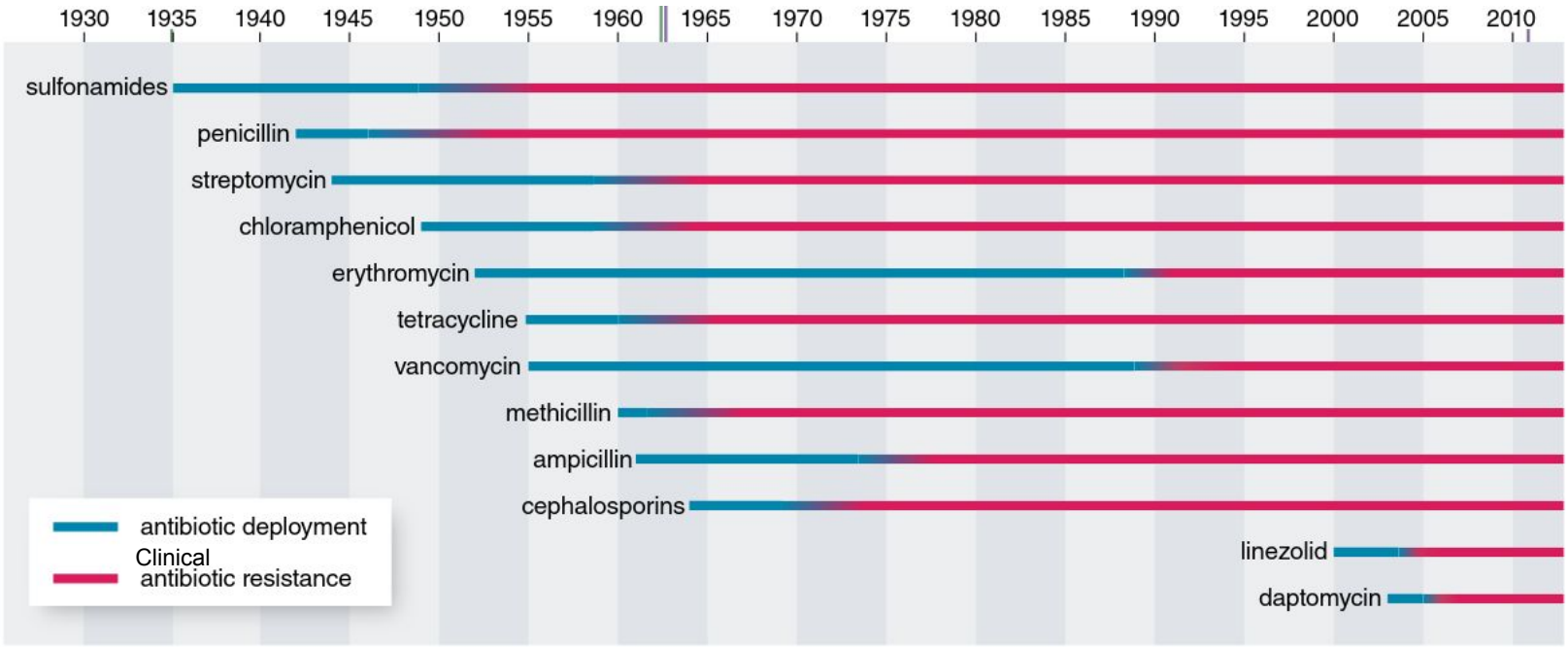

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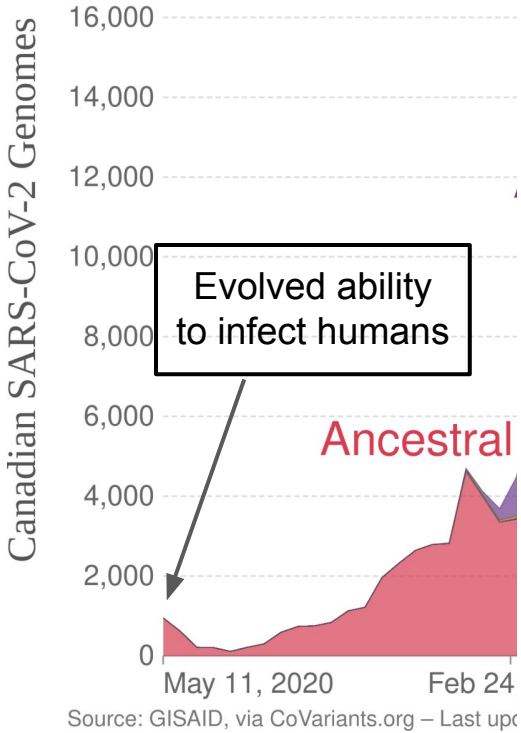
Evolution drives cases: SARS-CoV-2 waves



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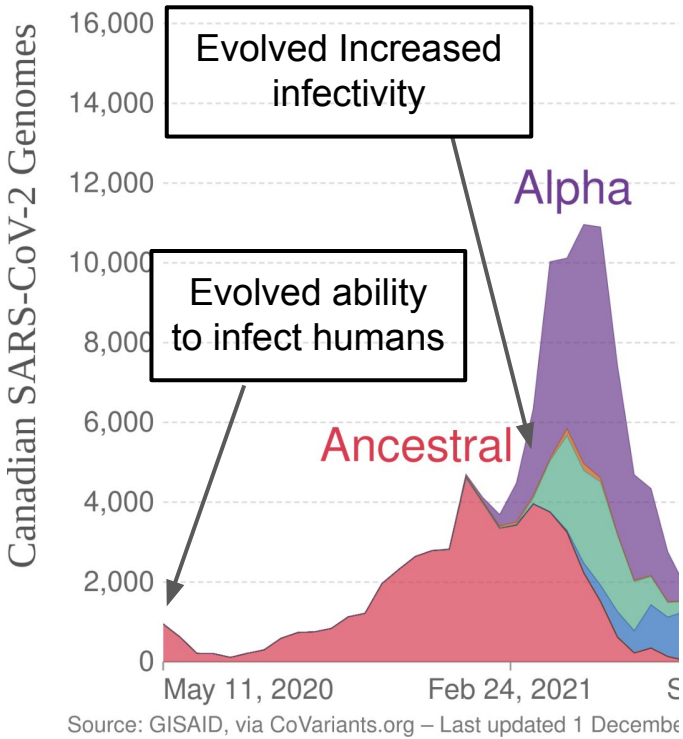

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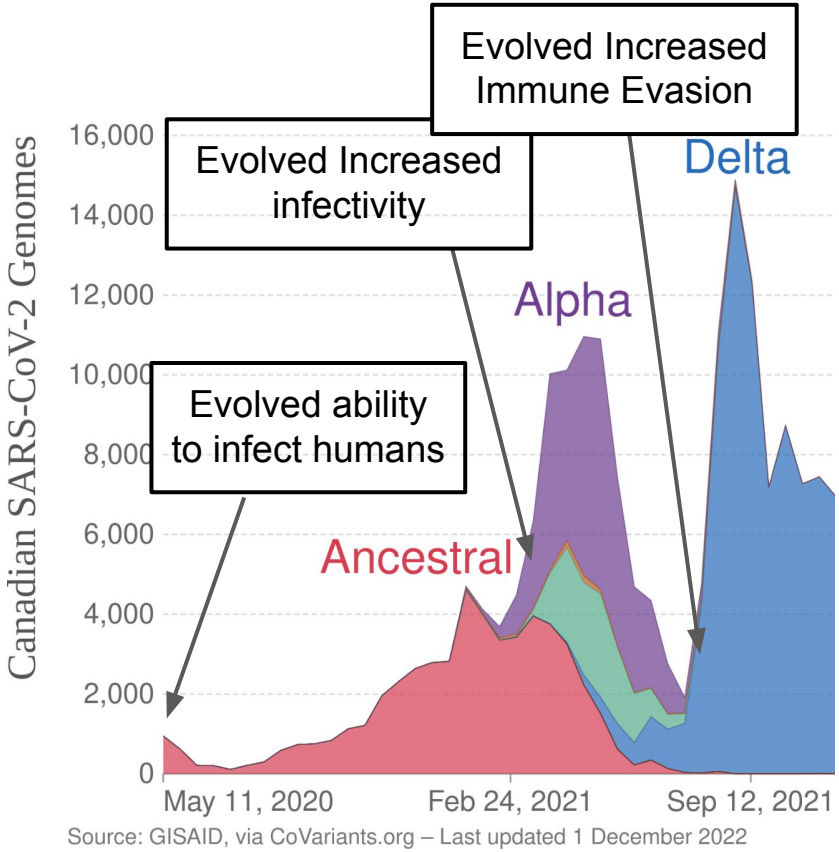

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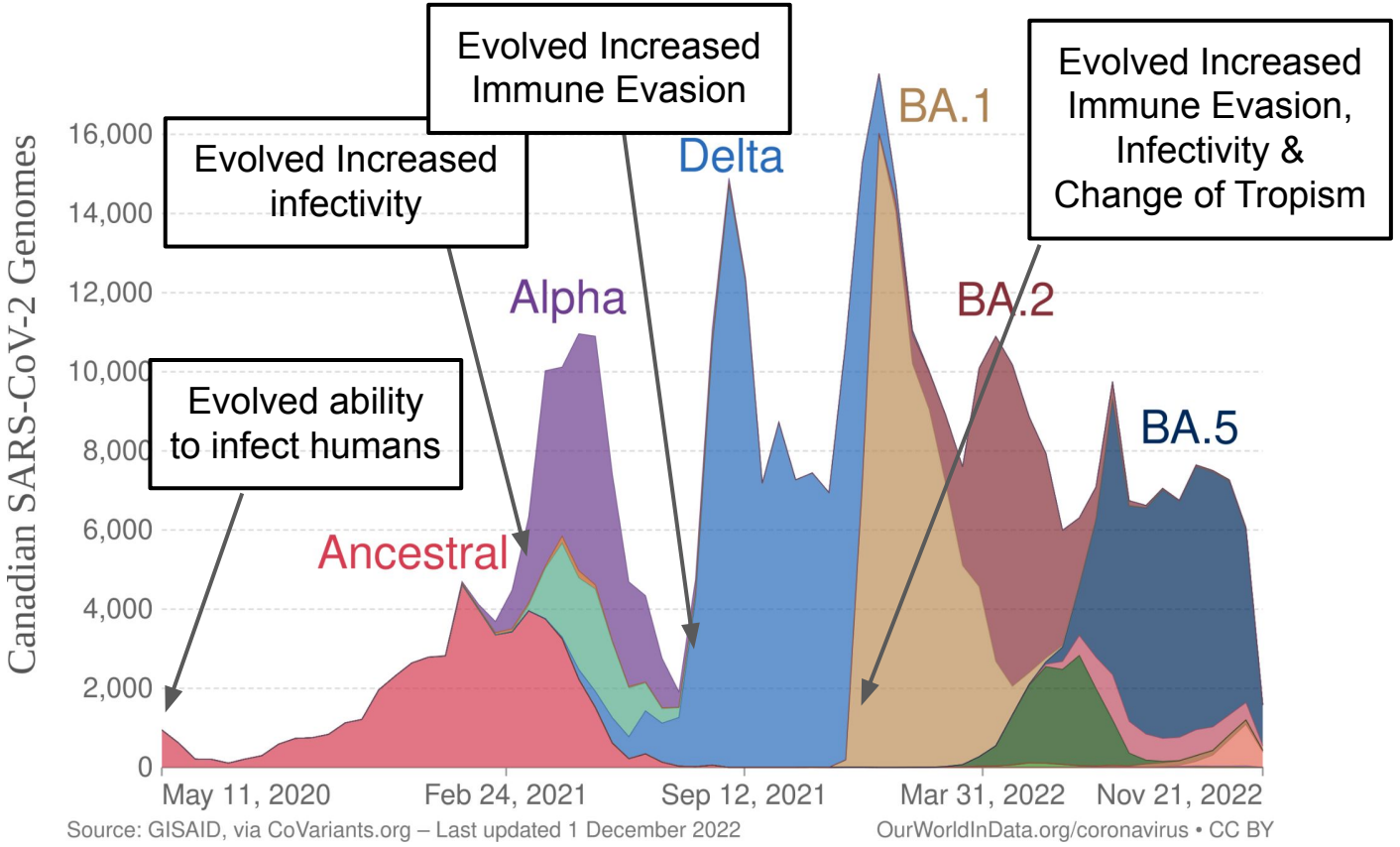
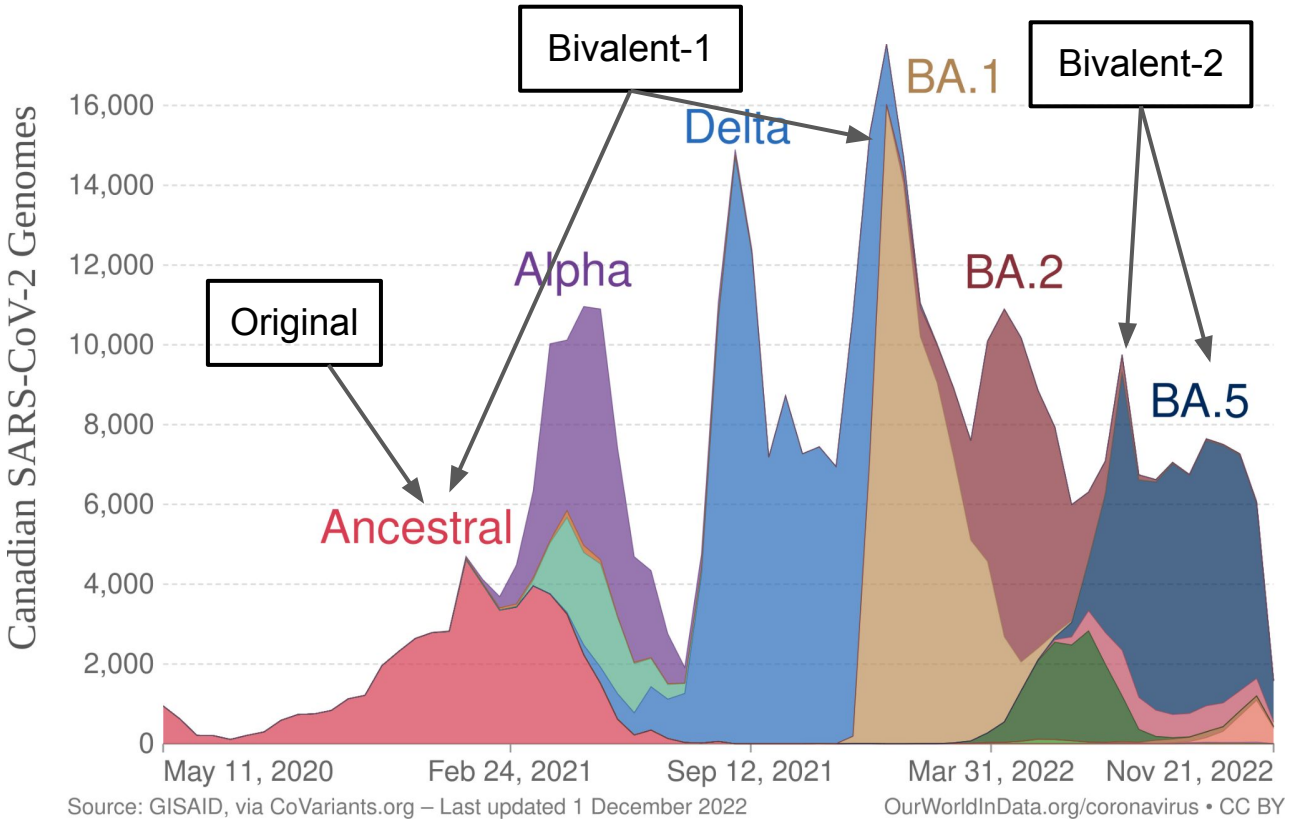
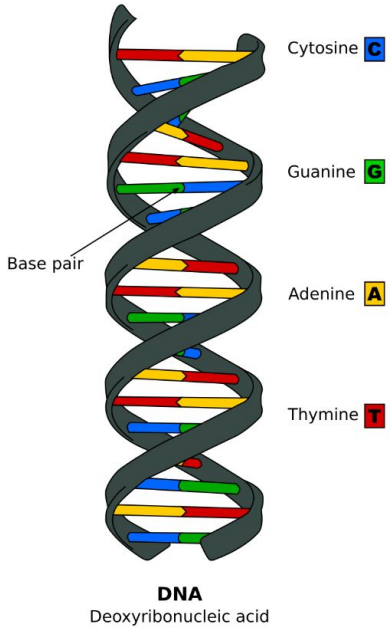


Evolution drives vaccine design/effectiveness



How can we monitor evolution?

Genomes are the substrate of evolution



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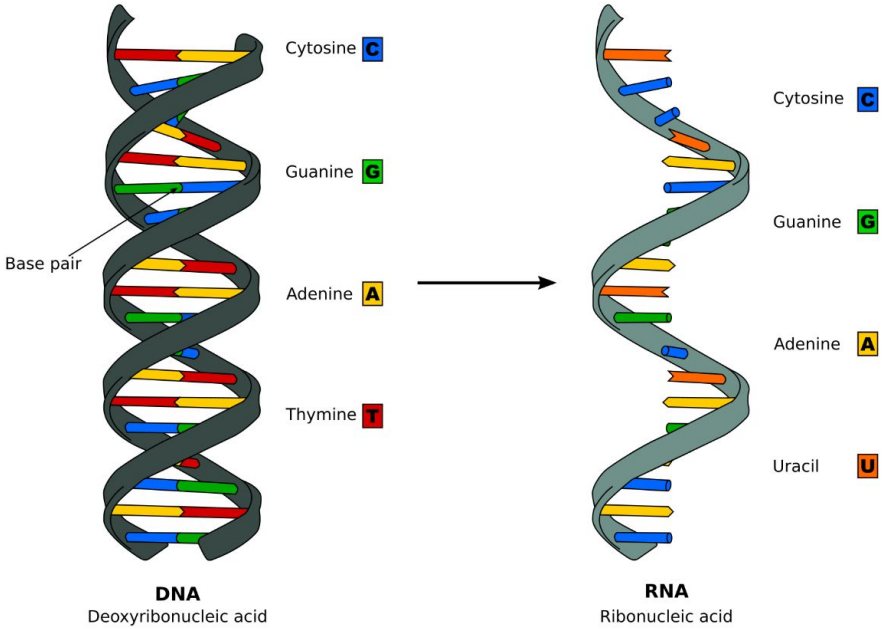

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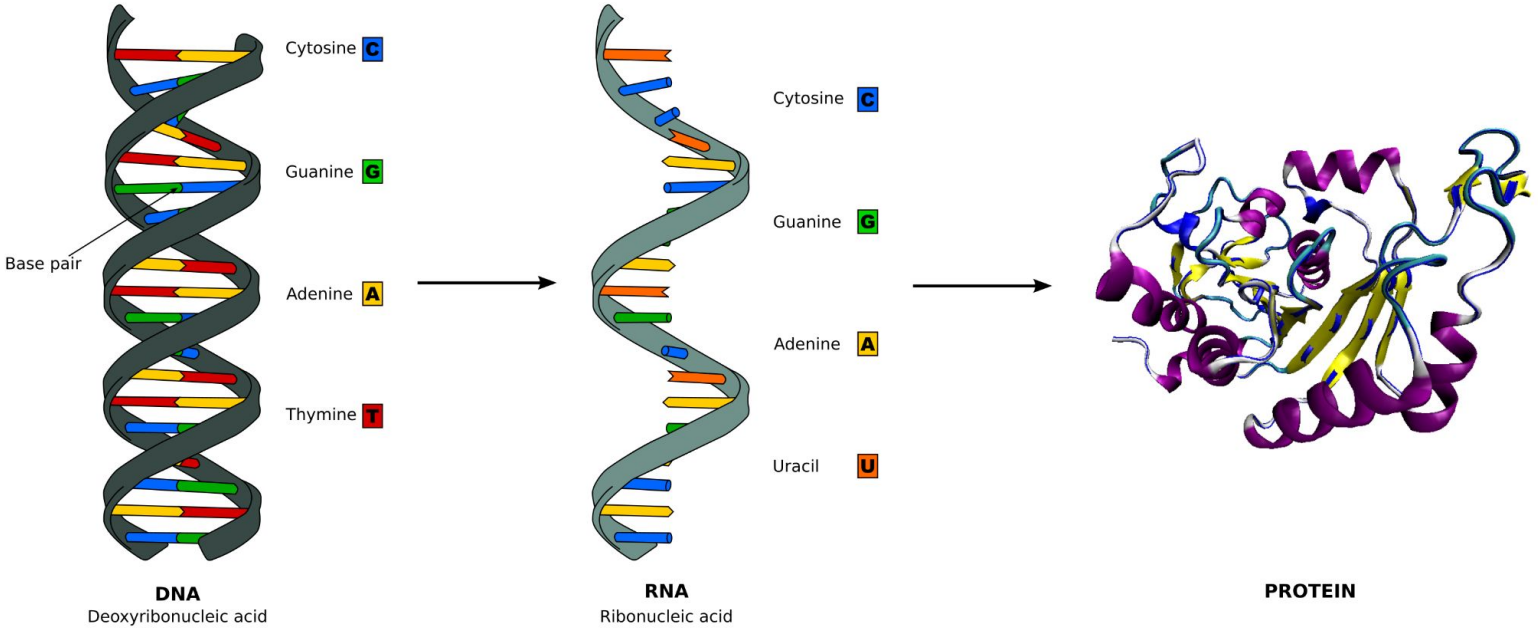
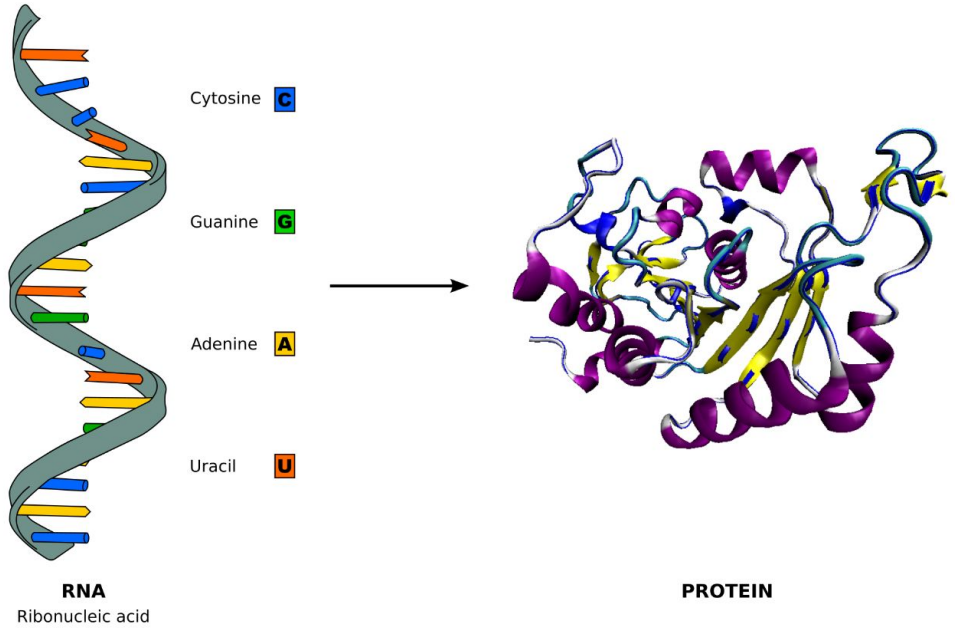


- DNA encodes RNA which encodes proteins

Genomes are the substrate of evolution



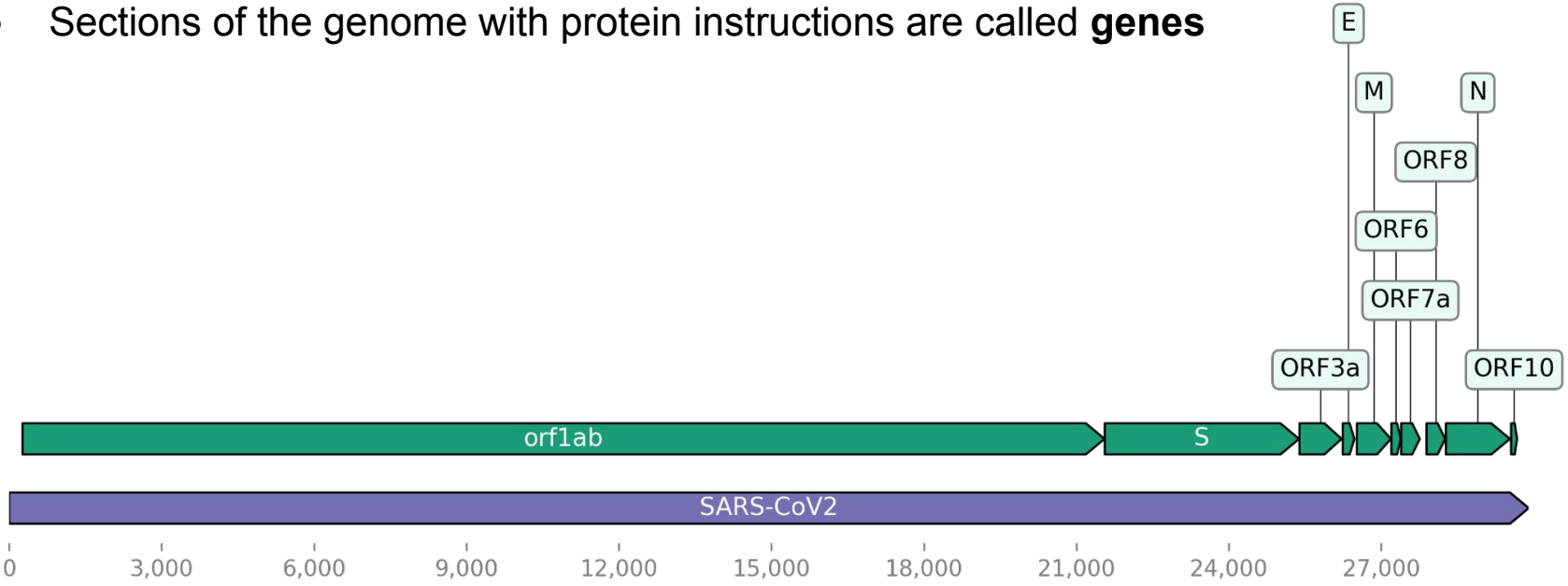
- DNA encodes RNA which encodes proteins
- Viruses like SARS-CoV-2 skip DNA

Genomes are the substrate of evolution

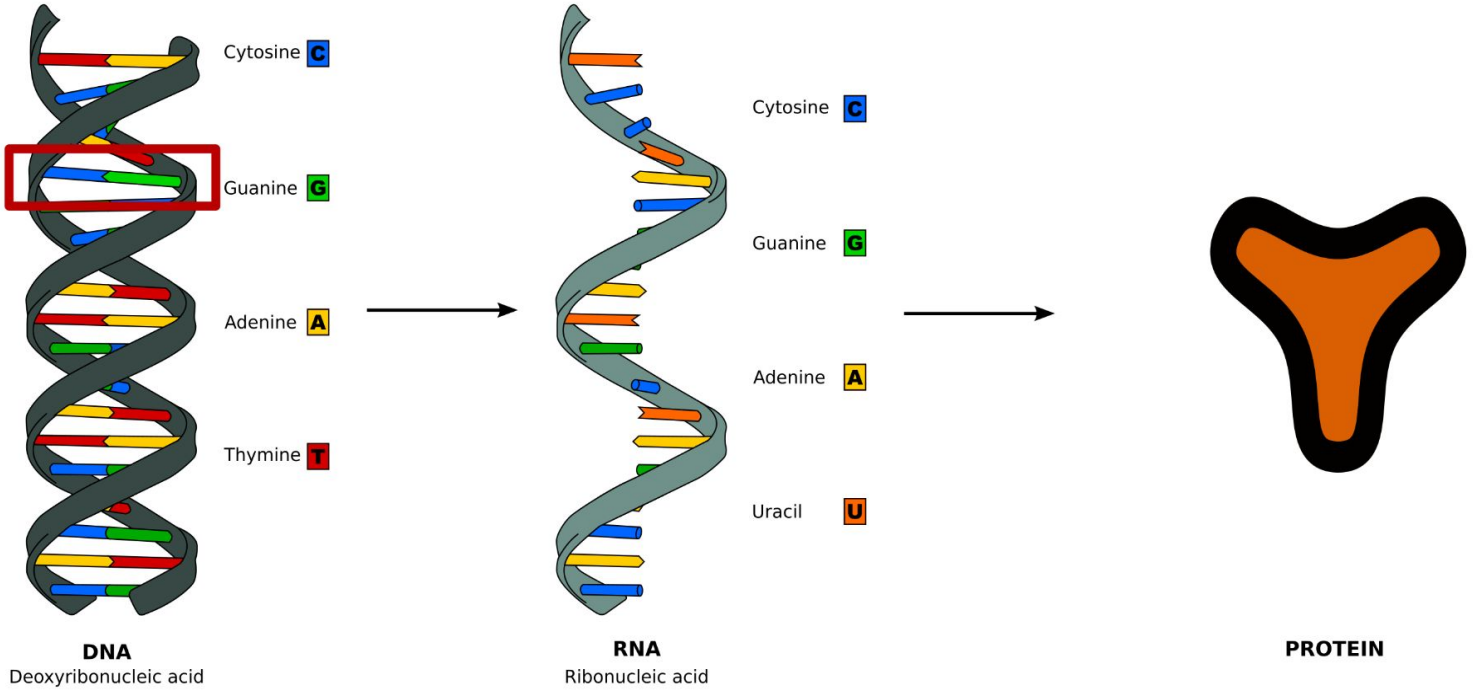
- Genomes are the complete collection of genetic instructions

Genomes are the substrate of evolution

- Genomes are the complete collection of genetic instructions
- Sections of the genome with protein instructions are called **genes**

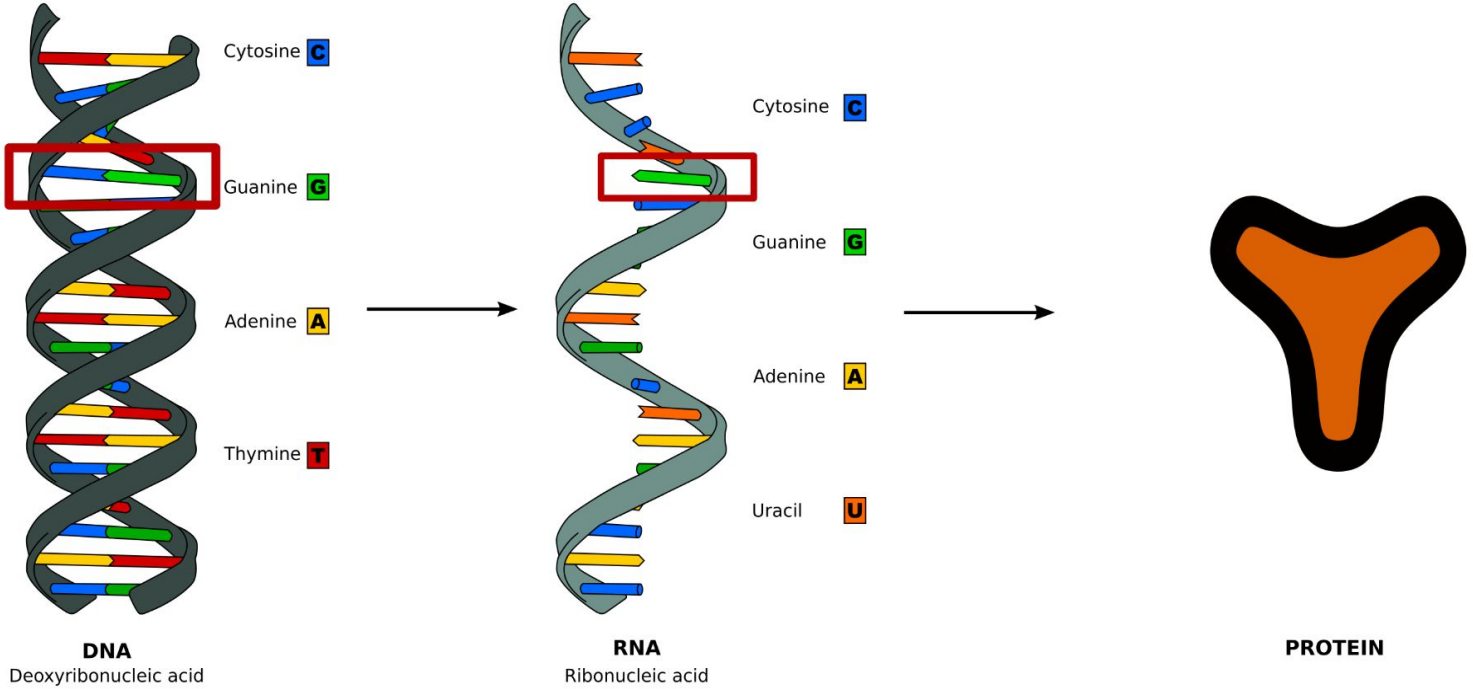


Mutations provide the variation upon which evolution acts



- Genome copying is error-prone

Mutations provide the variation upon which evolution acts



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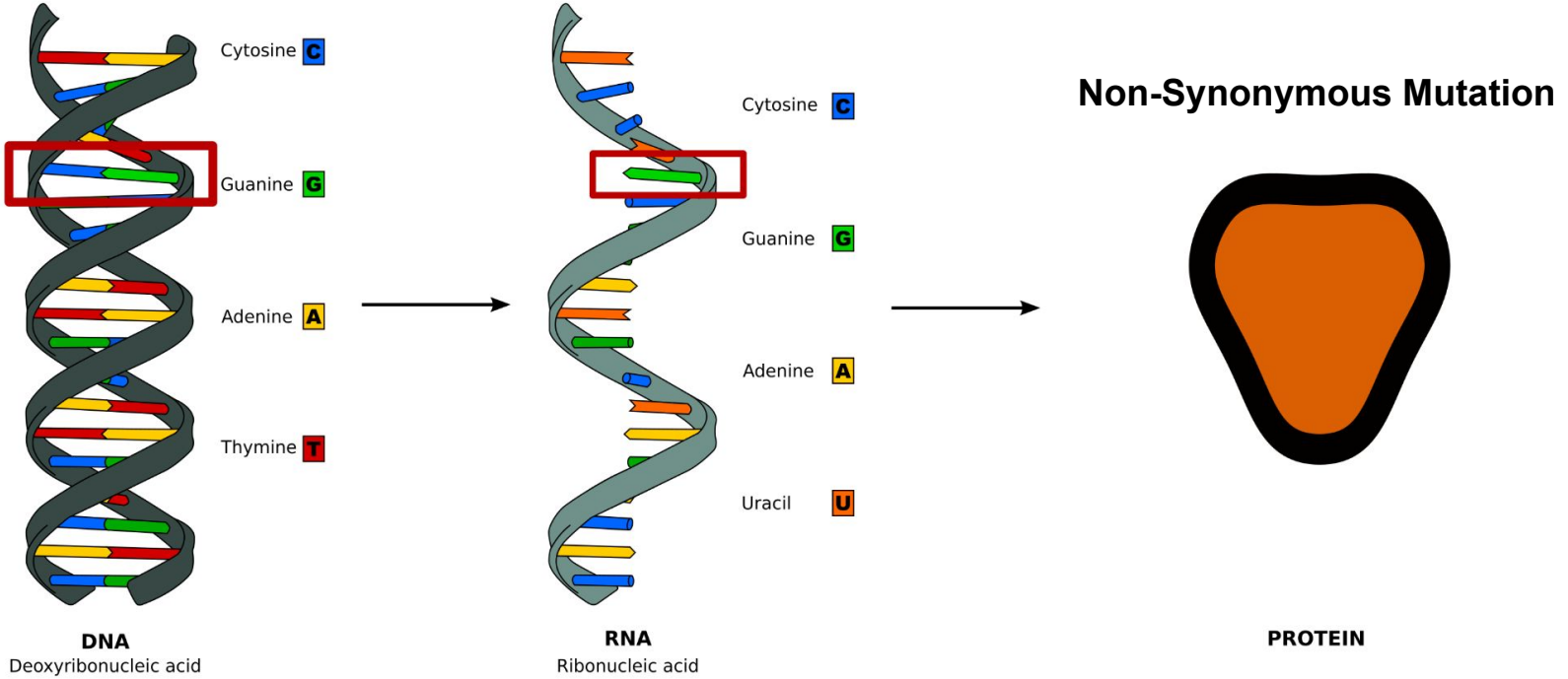

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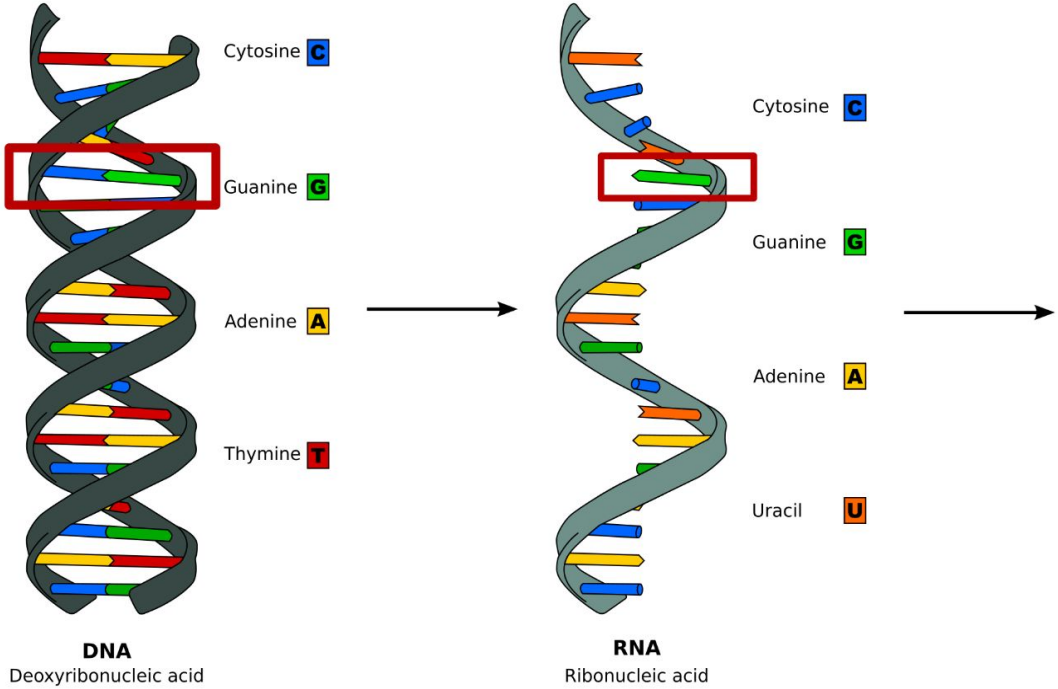
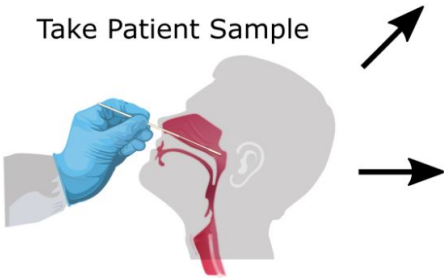


- Genome copying is error-prone
- Errors are called mutations
- Mutations can change protein sequence - *but don't always*

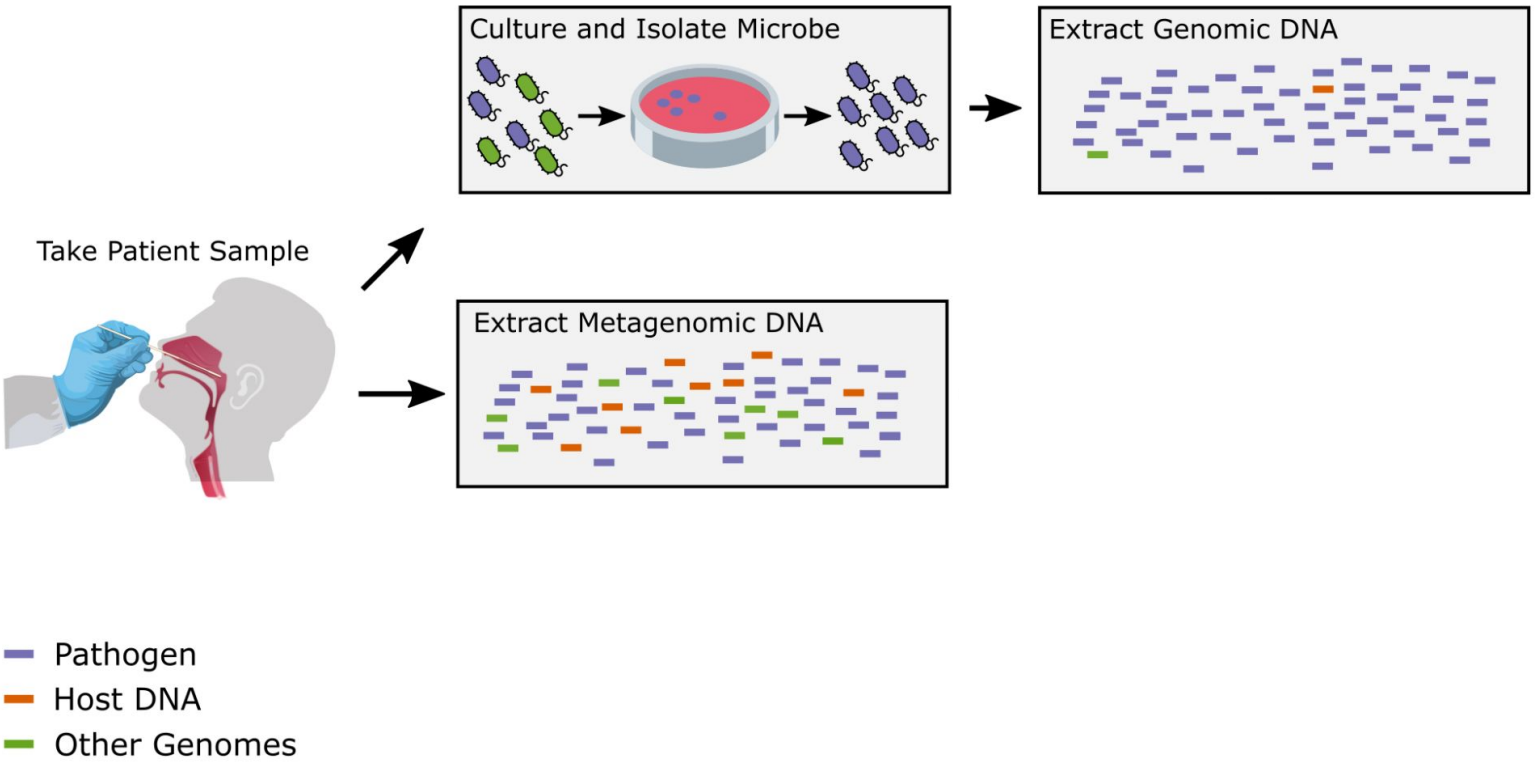
So, how do we get genomes?

Sequencing Pathogen Genomes



- Pathogen
- Host DNA
- Other Genomes

Sequencing Pathogen Genomes



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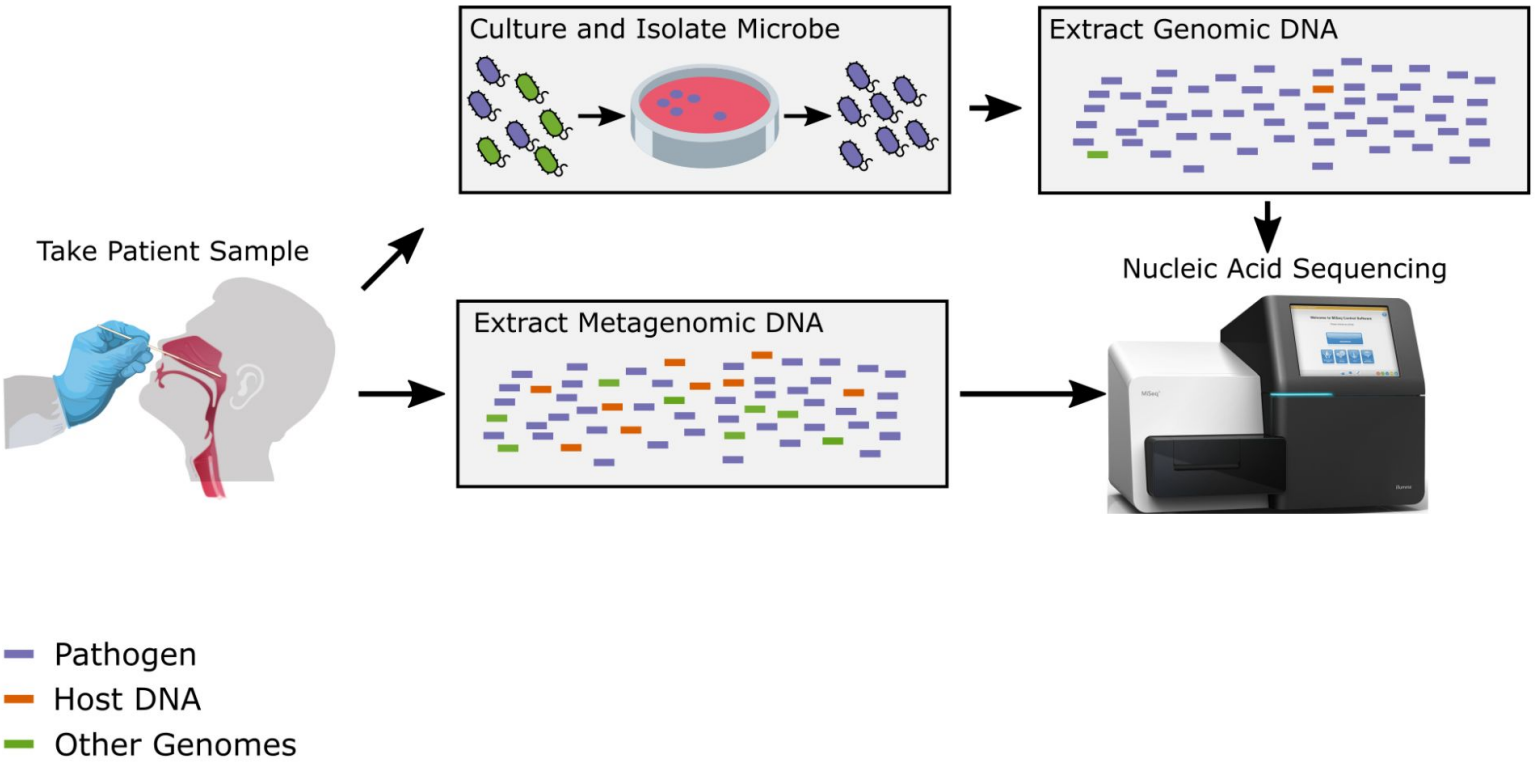

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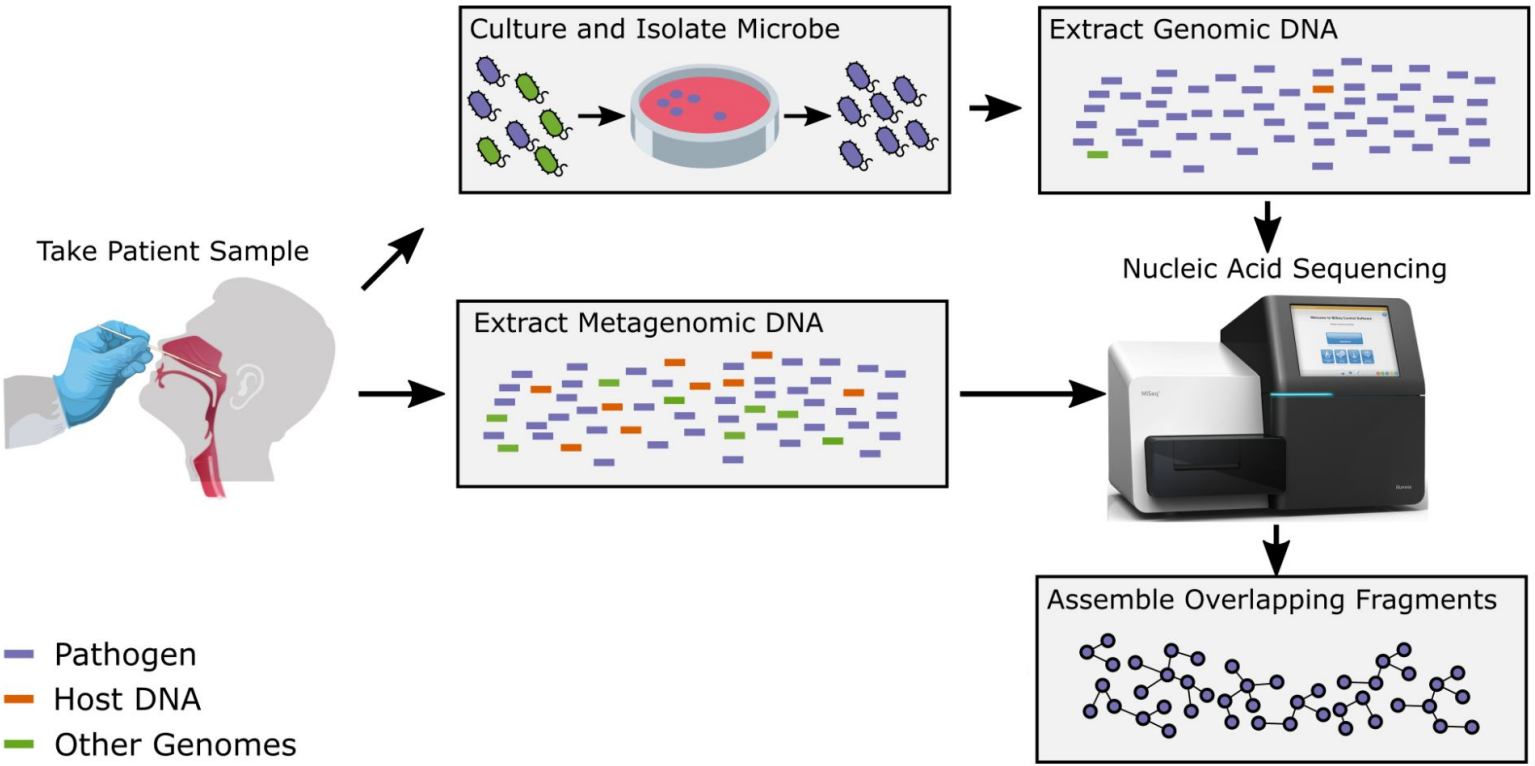

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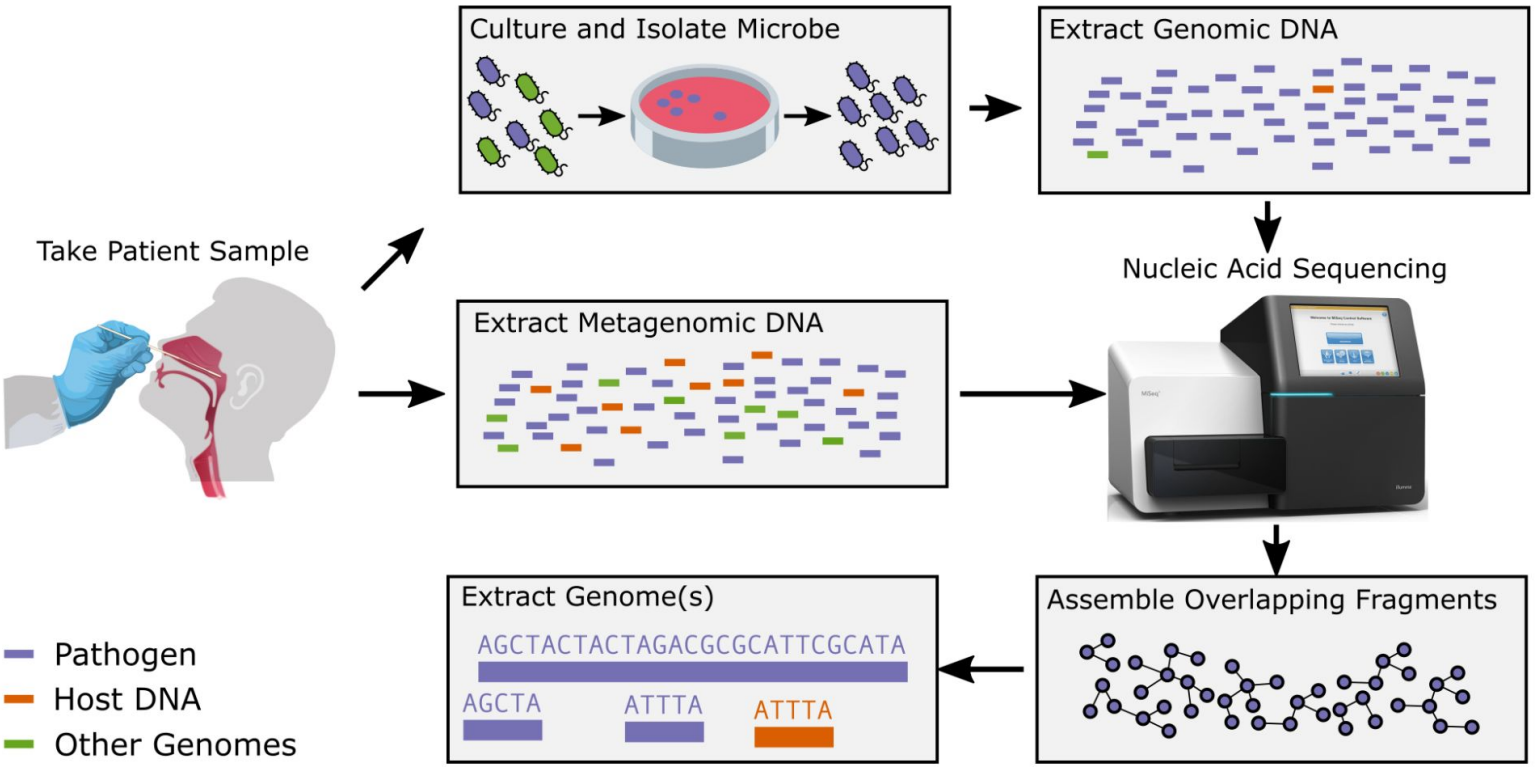
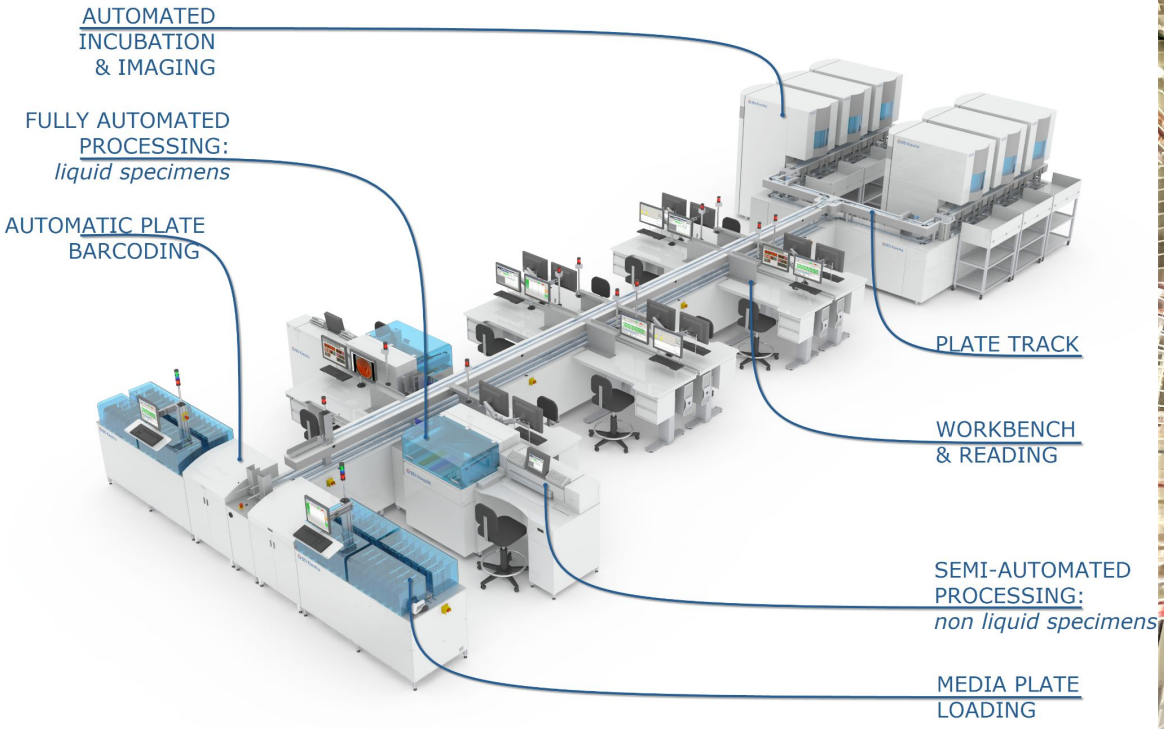


How do we do this at scale?

Automation of labour intensive steps



https://www.bd.com/scripts/europe/labautomation/productsdrilldown.asp?CatID=455&SubID=1836&siteID=20309&d=&s=europe%2Flabautomation&sTitle=Lab+Automation&metaTitle=Total+Lab+Automation&dc=europe&dcTitle=Europe

Dr. Vermeiren

Automation of labour intensive steps

MEDIA PLATE LOADING

https://www.bd.com/scripts/europe/labautomation/productsdrilldown.asp?CatID=455&SubID=1836&siteID=20309&d=&s=europe%2Flabautomation&sTitle=Lab+Automation&metaTitle=Total+Lab+Automation&dc=europe&dcTitle=Europe

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Sequencing technology has rapidly changed and improved

First generation

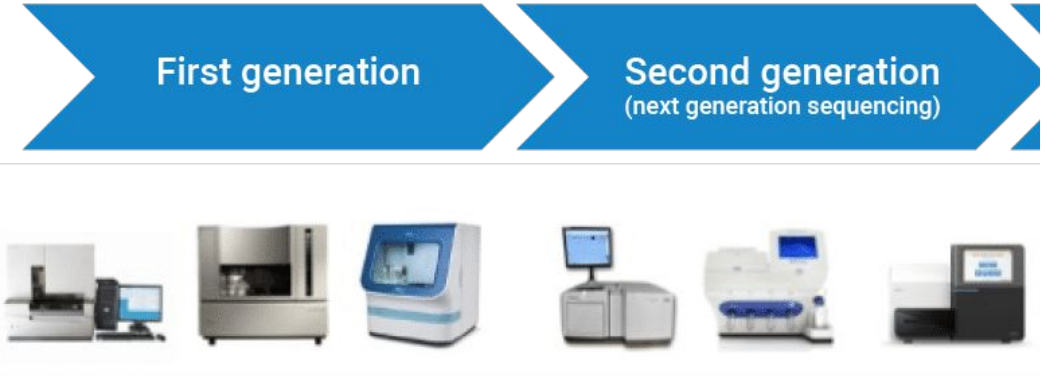
Sanger sequencing
Maxam and Gilbert
Sanger chain termination

Infer nucleotide identity using dNTPs, then visualize with electrophoresis

500–1,000 bp fragments

https://www.pacb.com/blog/the-evolution-of-dna-sequencing-tools/

Sequencing technology has rapidly changed and improved



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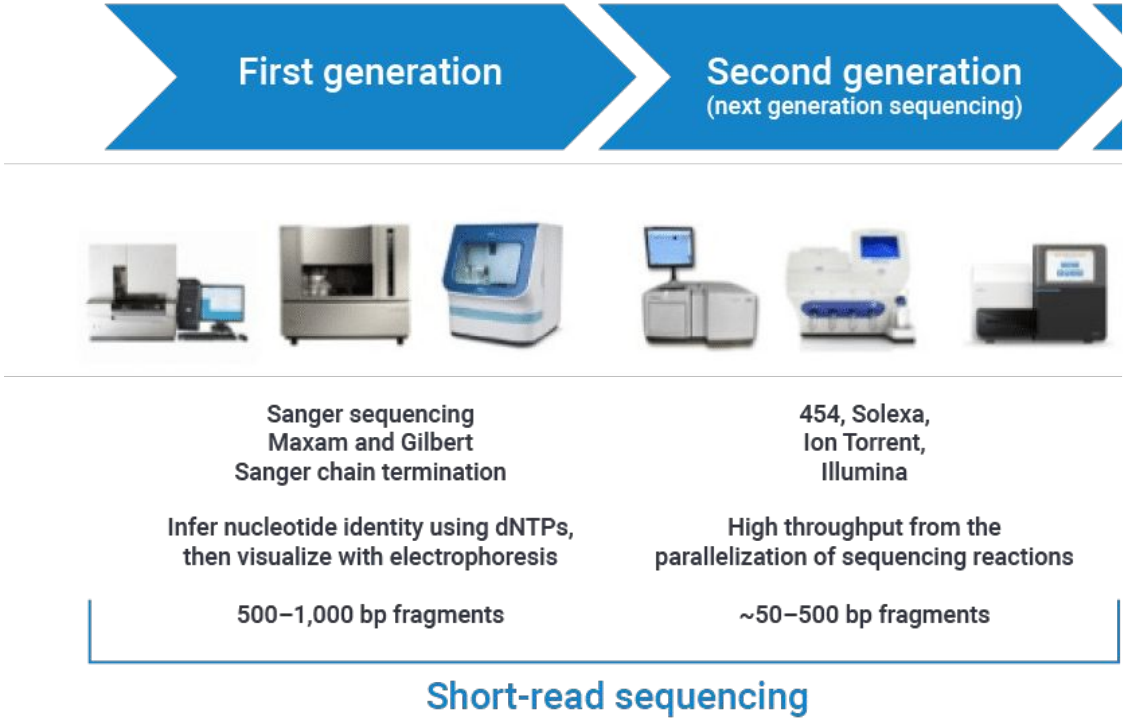

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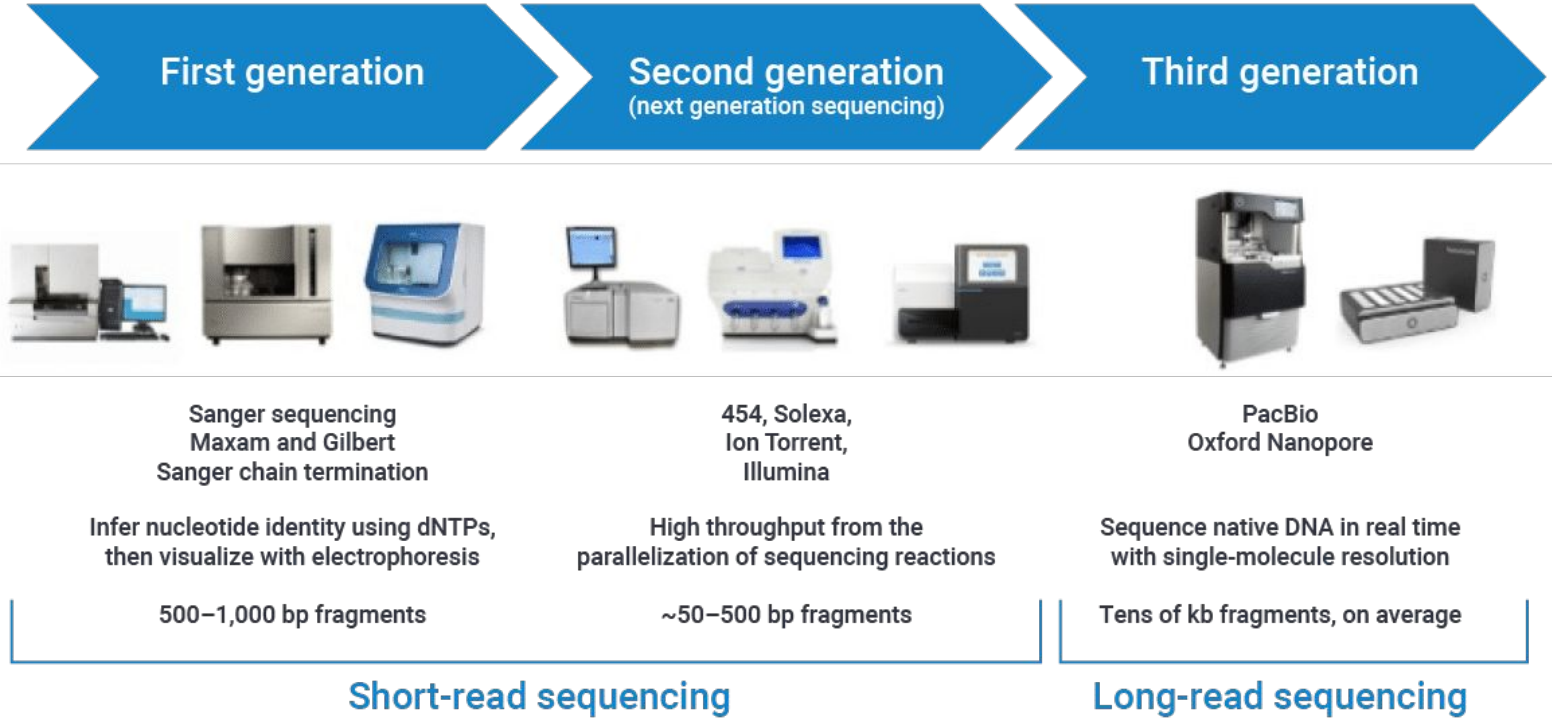

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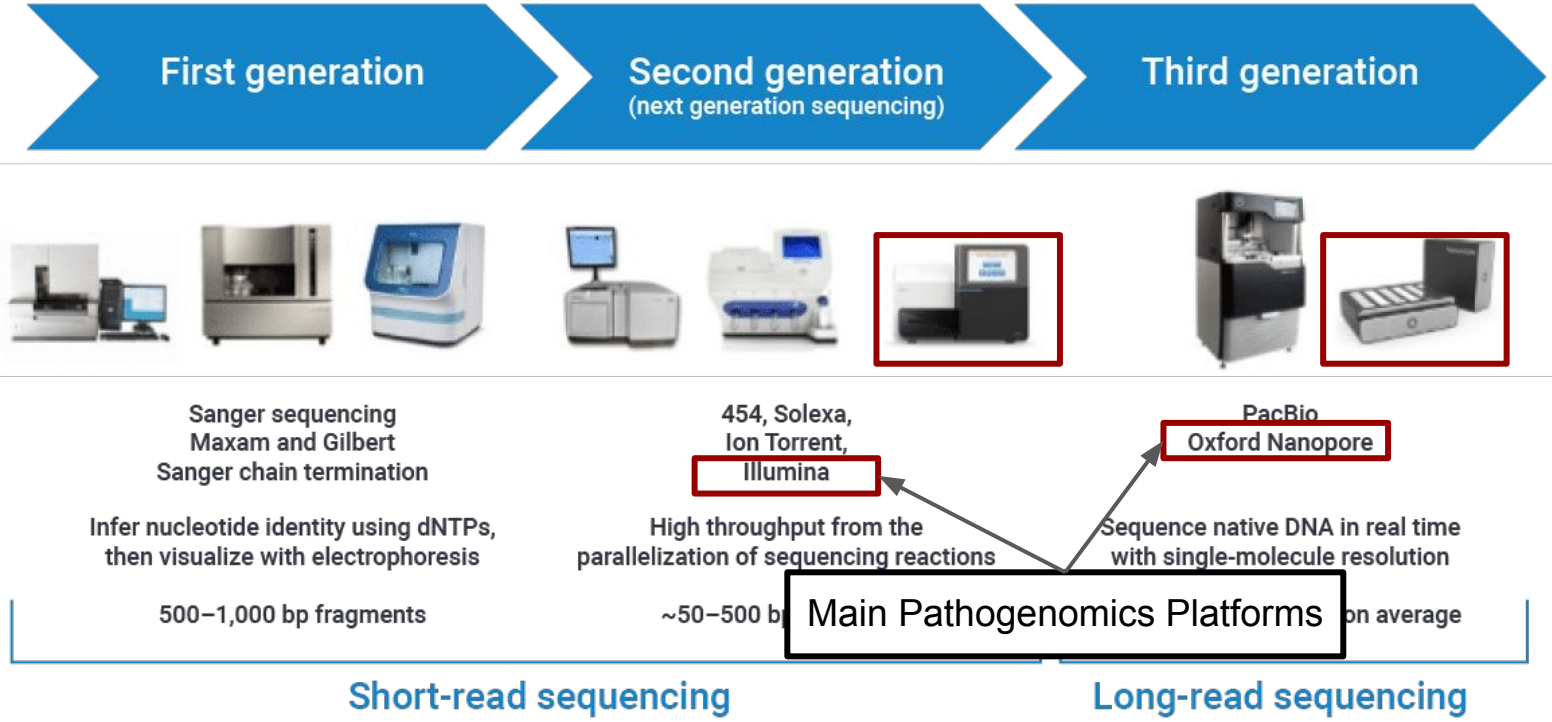

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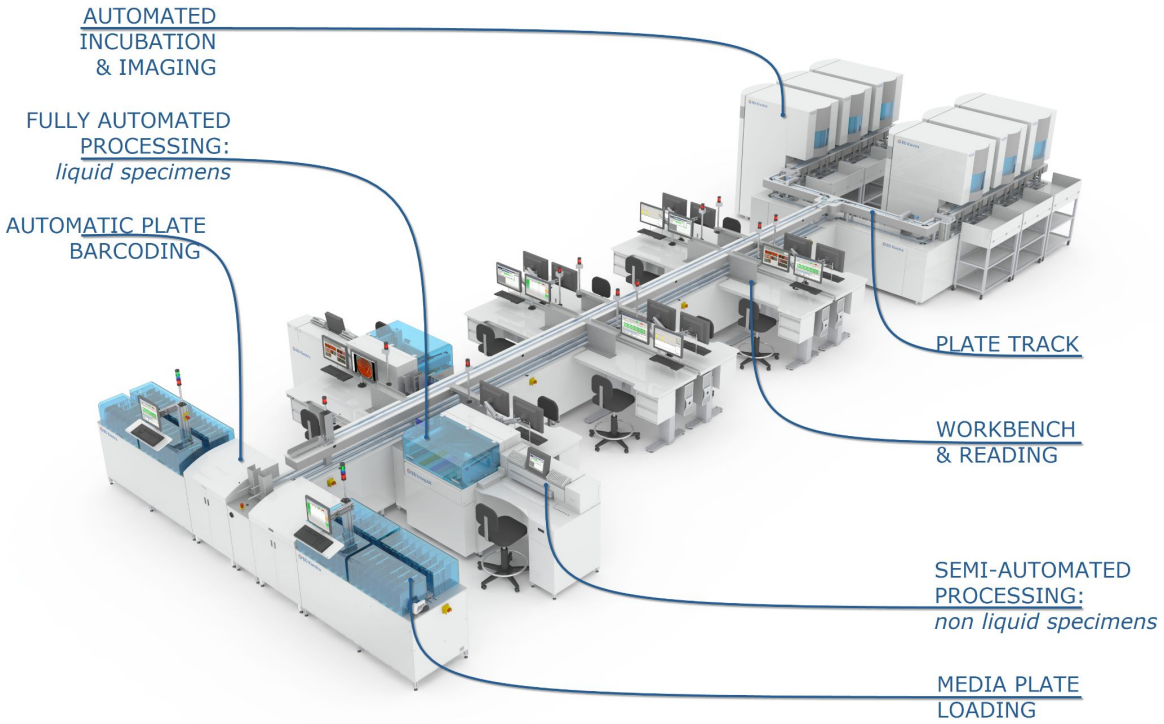
Mobile sequencing lab in a suitcase



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Mobile sequencing lab in a suitcase

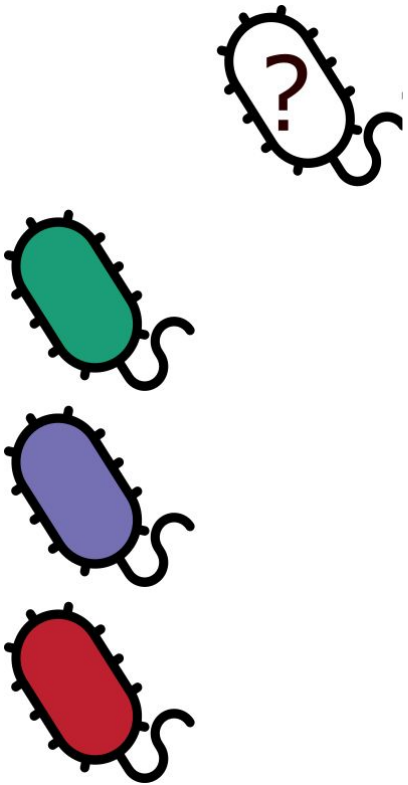
https://crain-platform-genomeweb-prod.s3.amazonaws.com/s3fs-public/styles/1200x630/public/lab_in_a_suitcase.jpeg

See lecture reading: Loman & Gardy 2017

Got a genome, now what?

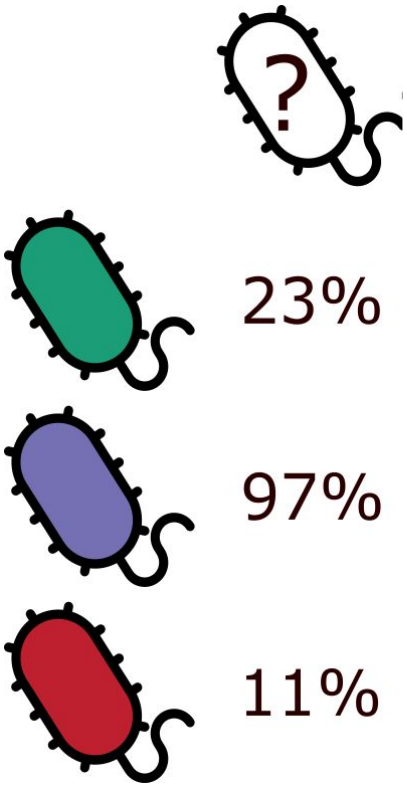
Genomic Diagnostics: What is the pathogen?

Genomic Diagnostics: What is the pathogen?



- Compare to genomes in database from known organisms

Genomic Diagnostics: What is the pathogen?



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- Average Nucleotide Identity (ANI) is an example of a similarity metric

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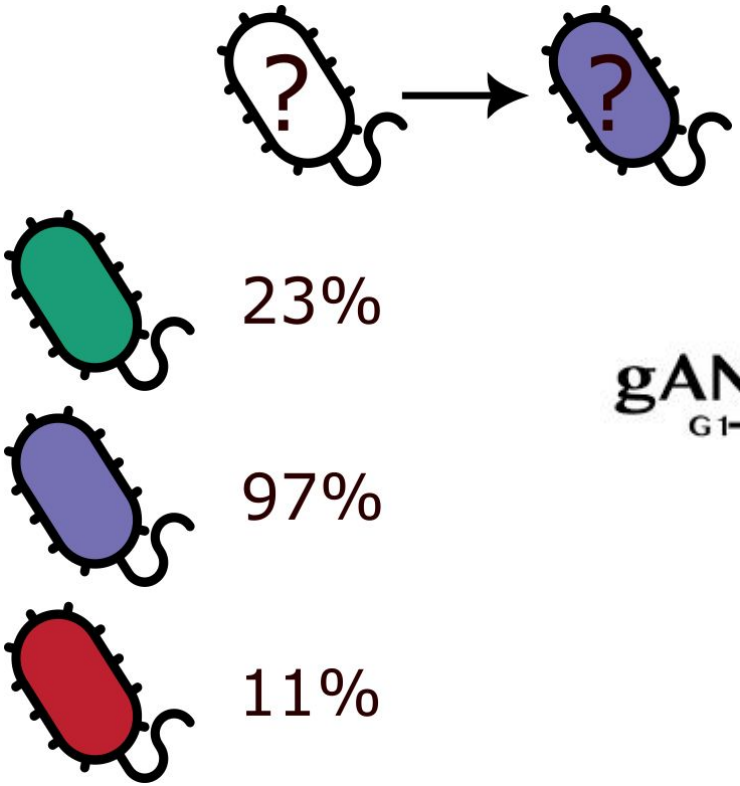
Genomic Diagnostics: What is the pathogen?



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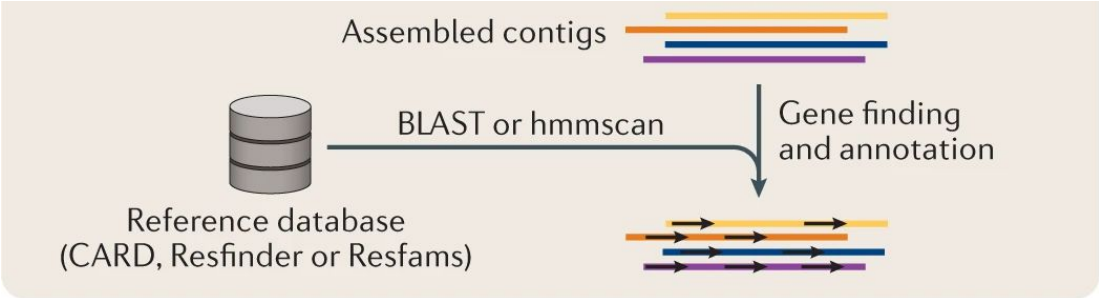
- Identify pathogen as closest reference genome taxa
- Use identity to drive treatment (if x then treat by y)

- Typing for outbreak investigation linkage

Genomic Diagnostics: What drugs will work?



10.1038/s41576-019-0108-4

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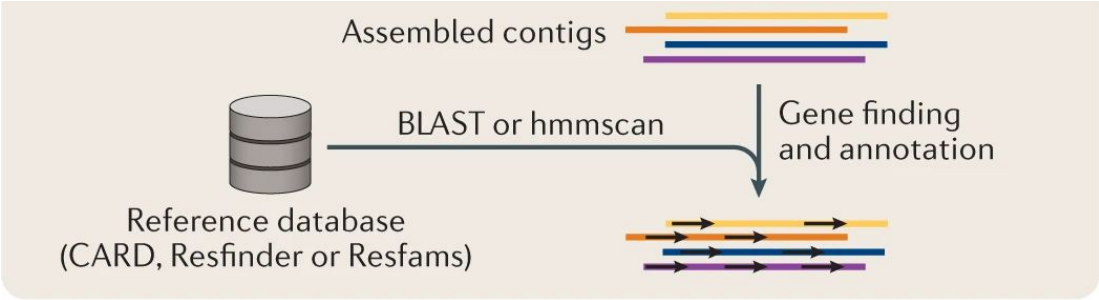


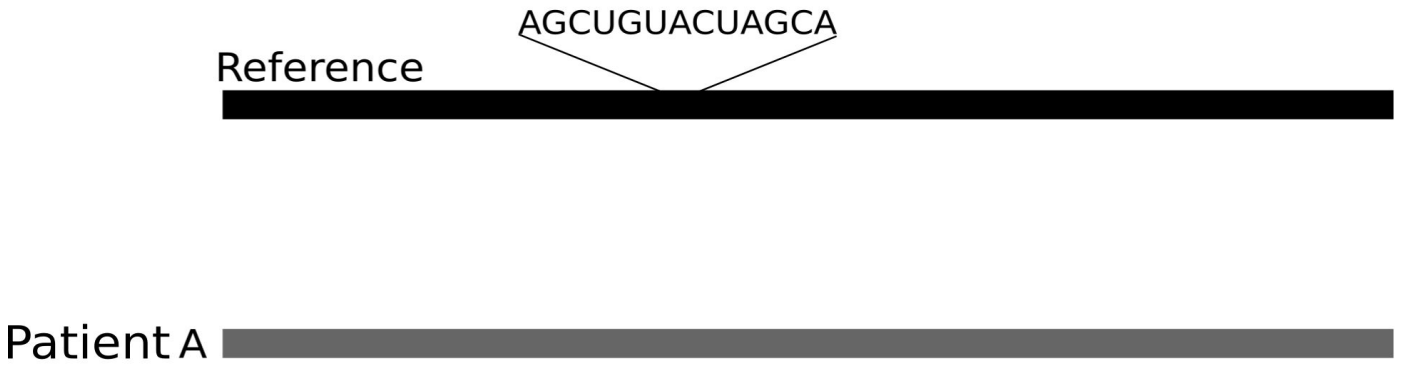
10.1038/s41576-019-0108-4

- Detect NDM-1 carbapenemase gene
- Pathogen protein that destroys many antibiotics (beta-lactams)
- => Treat with alternative class of antibiotics (e.g., colistin)

- Hours vs weeks for some pathogens (TB)

OK, but what else can we do with genomes?

Detection mutations relative to reference



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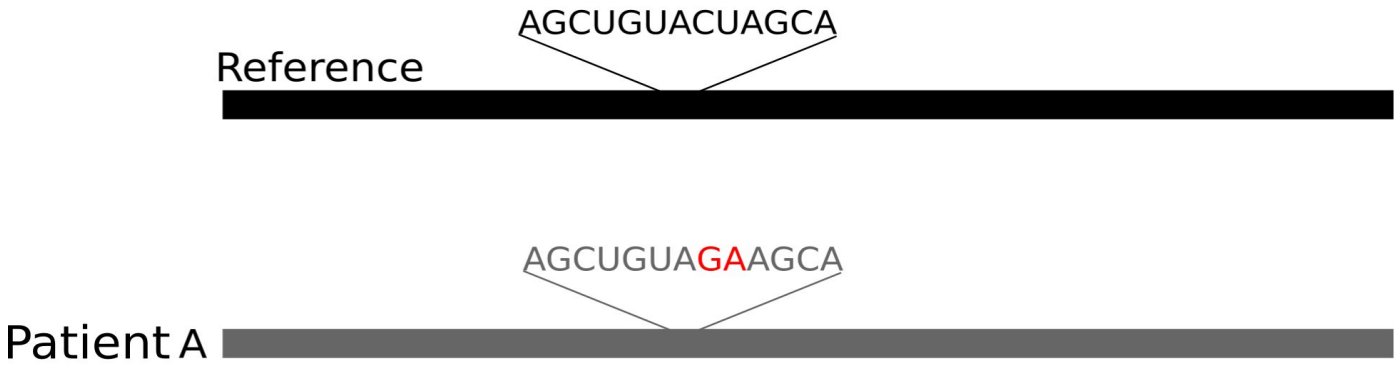

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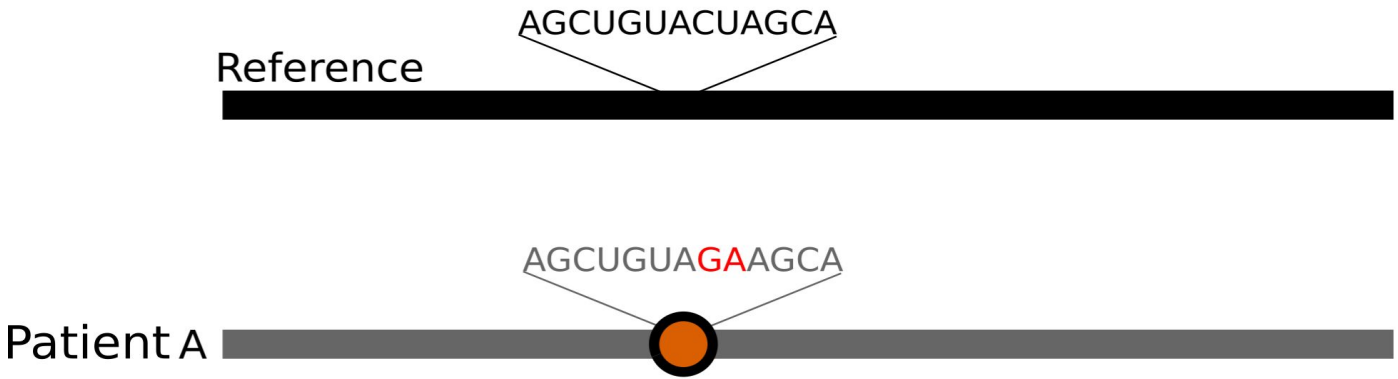
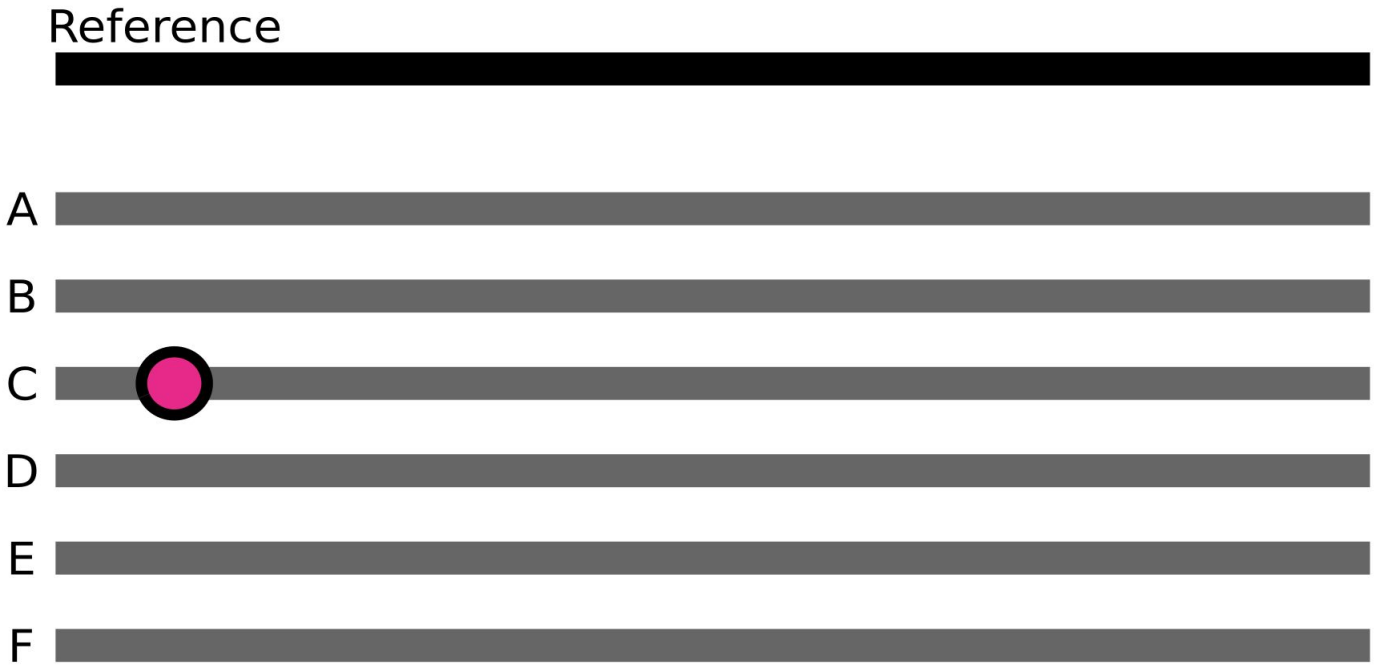


Compare mutations across patients



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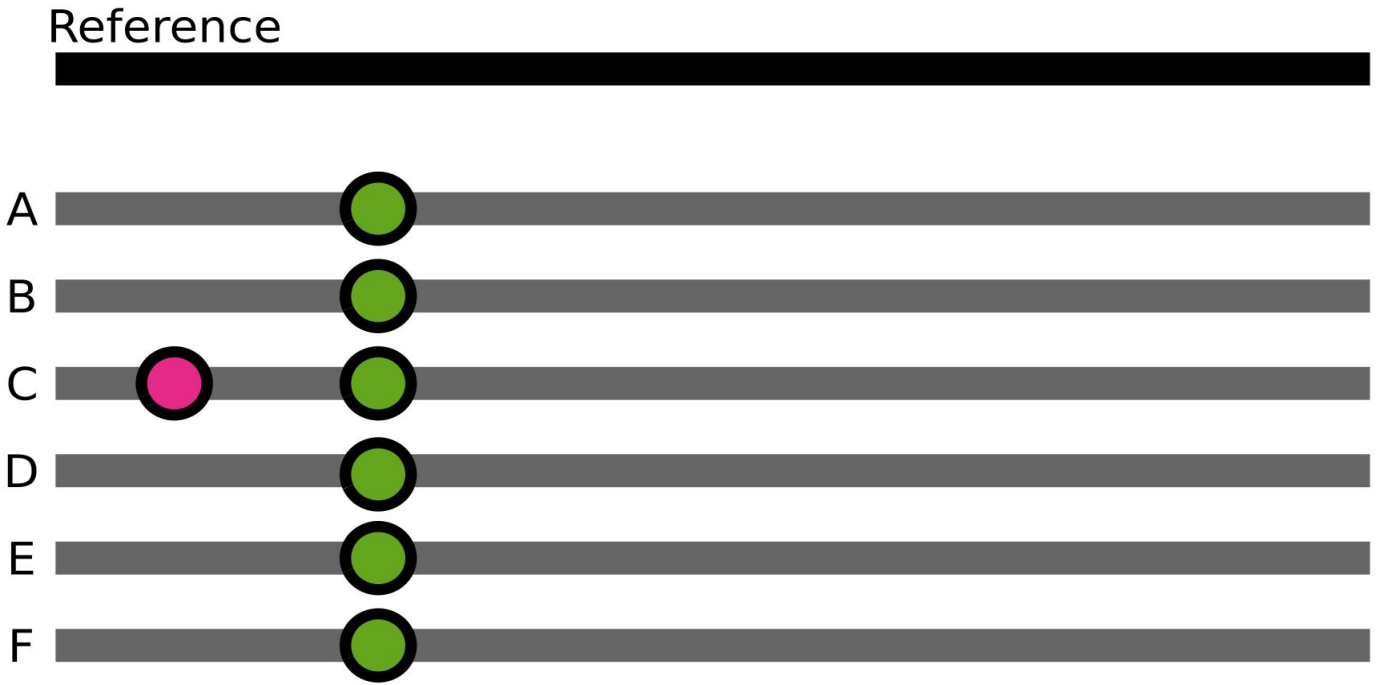

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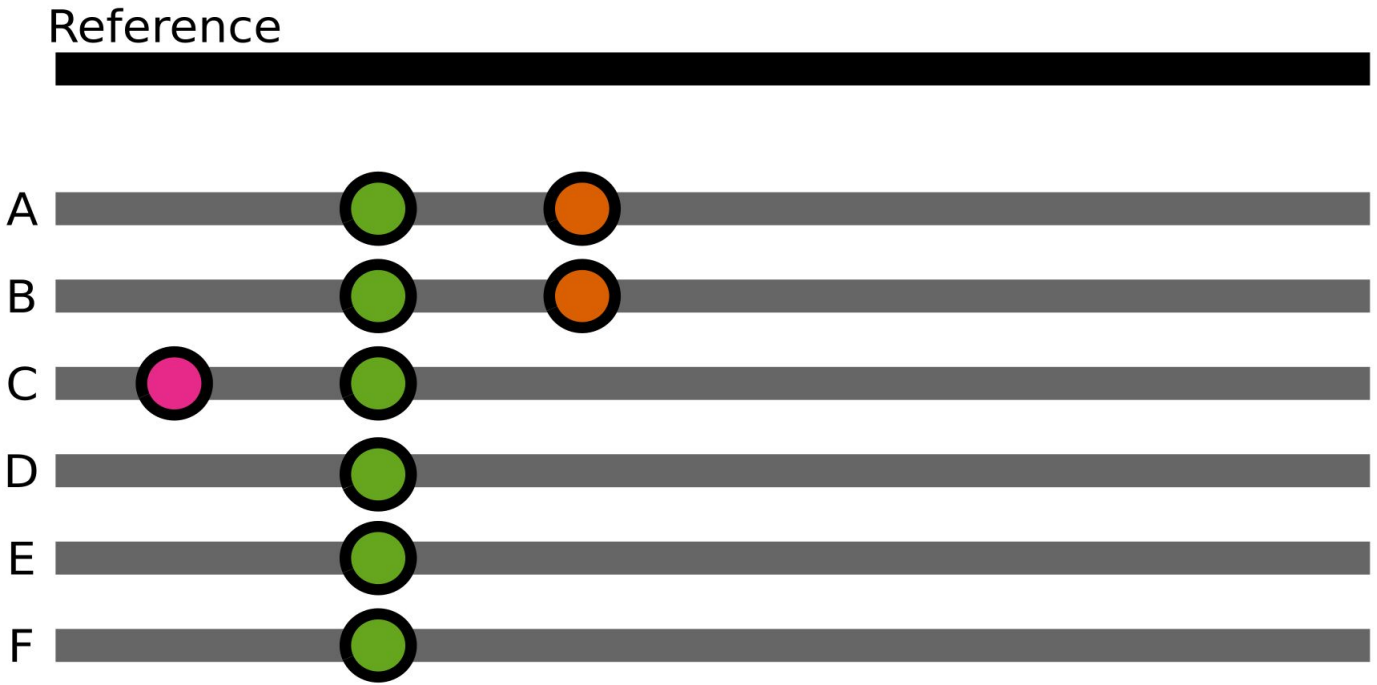
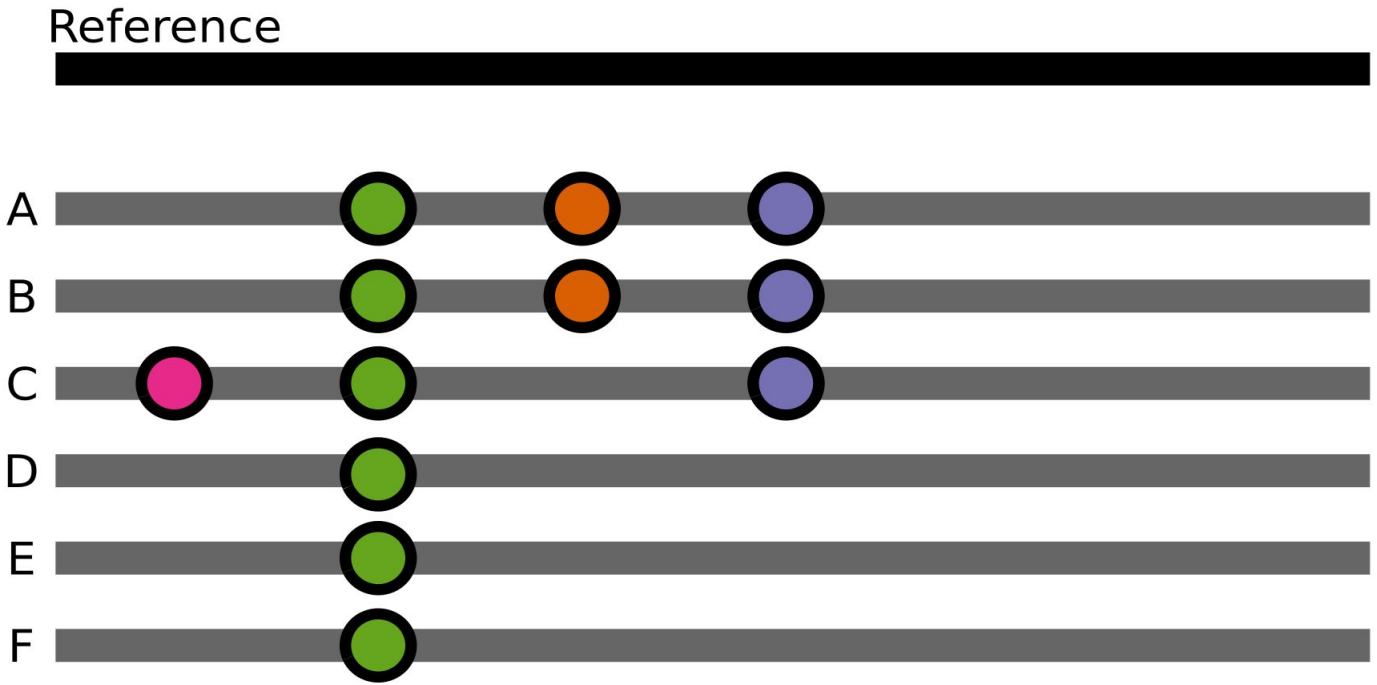
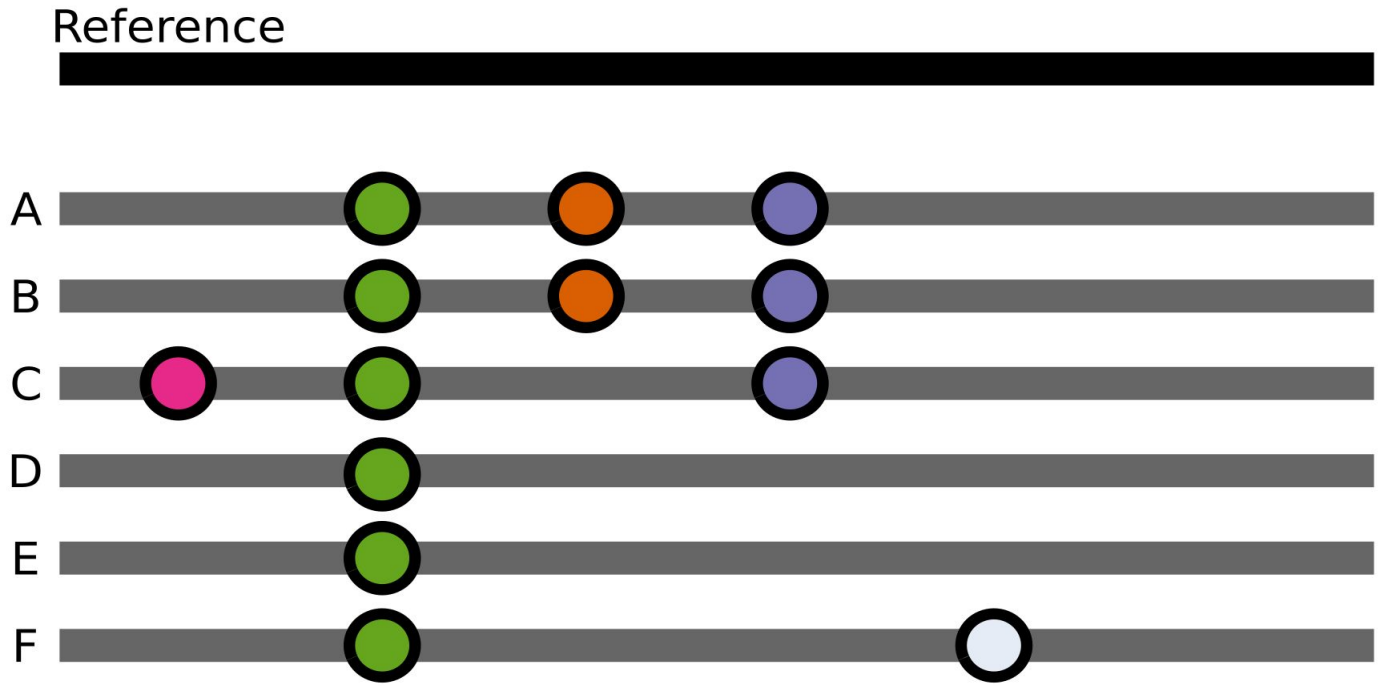


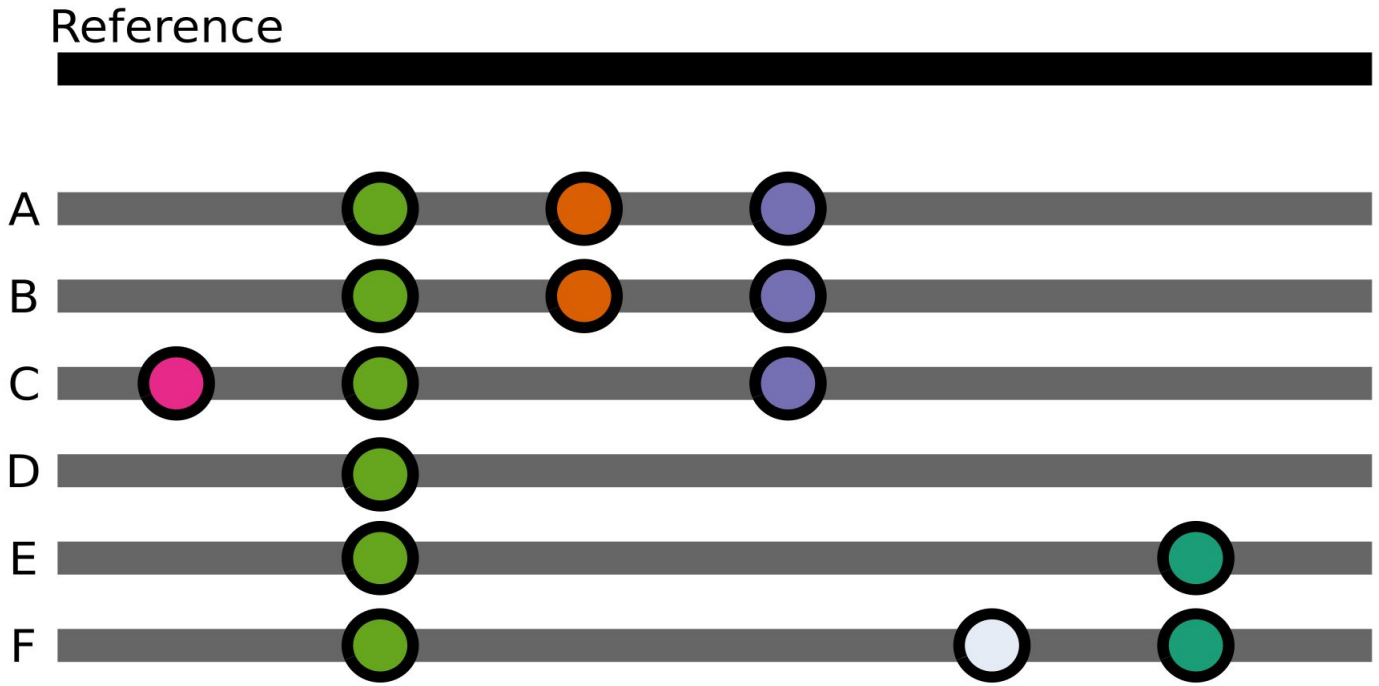
Compare mutations across patients



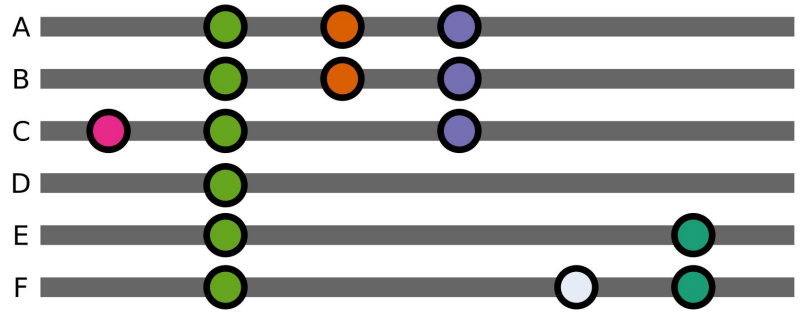
Compare mutations across patients



Compare mutations across patients



Using pattern of mutations to infer relationships



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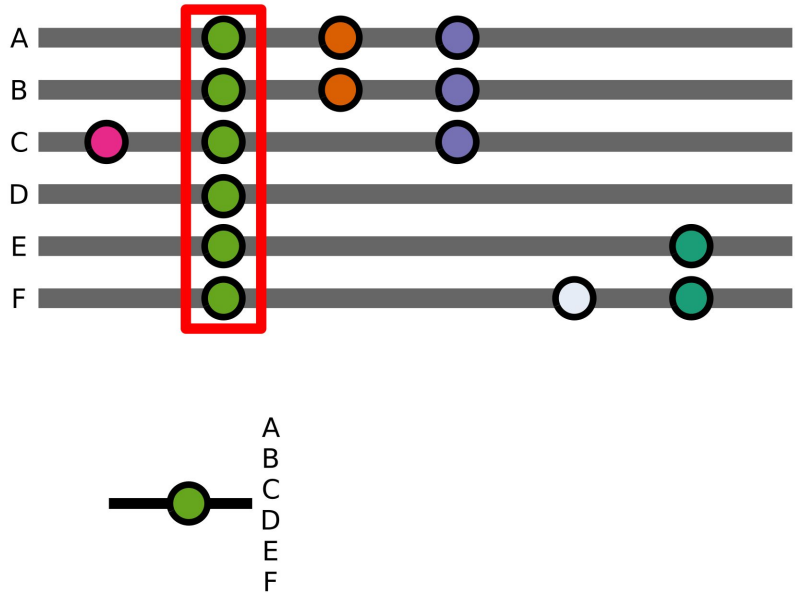
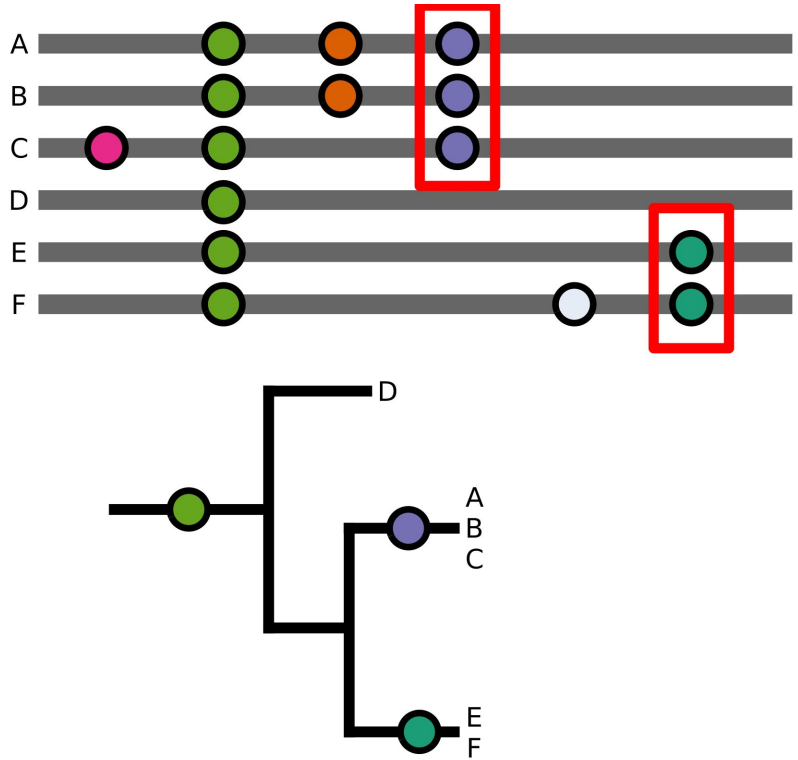
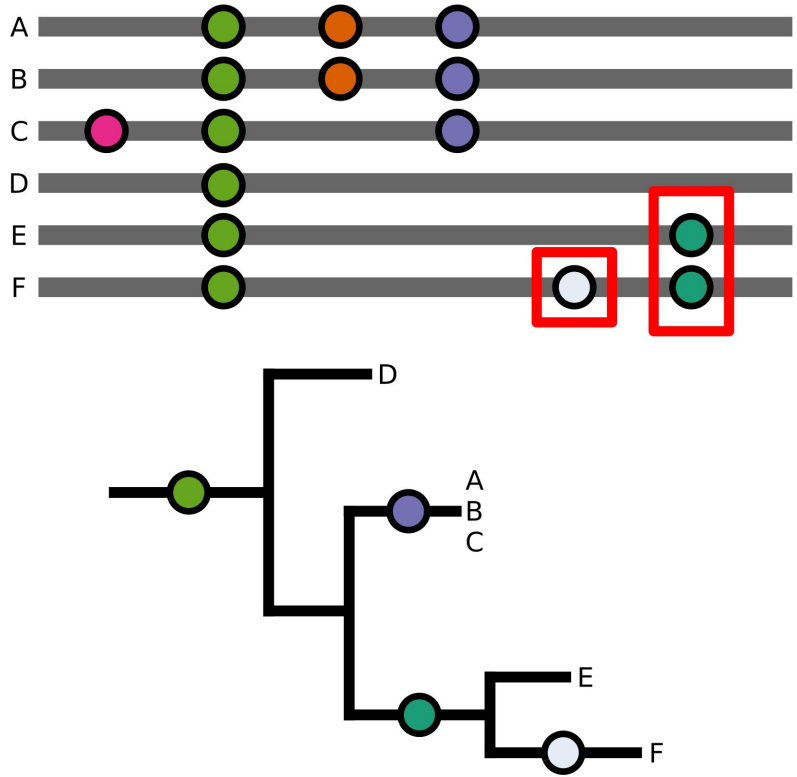


Using pattern of mutations to infer relationships



Using pattern of mutations to infer relationships



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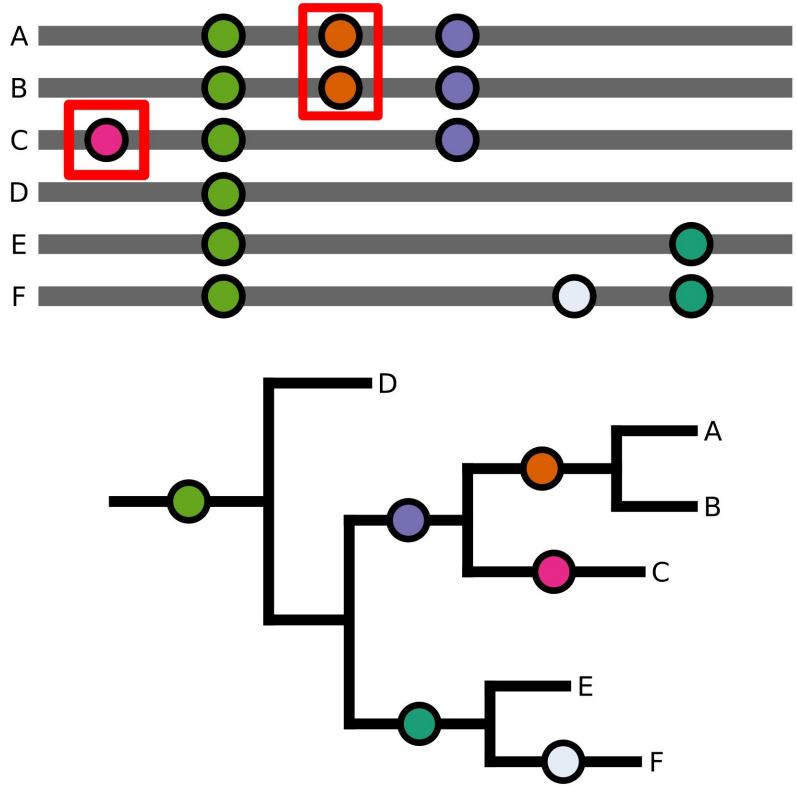

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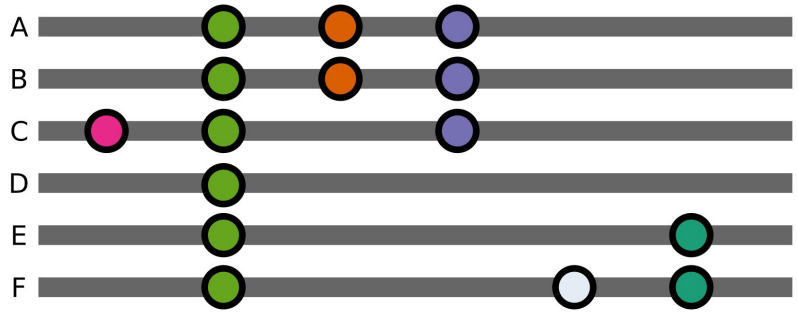
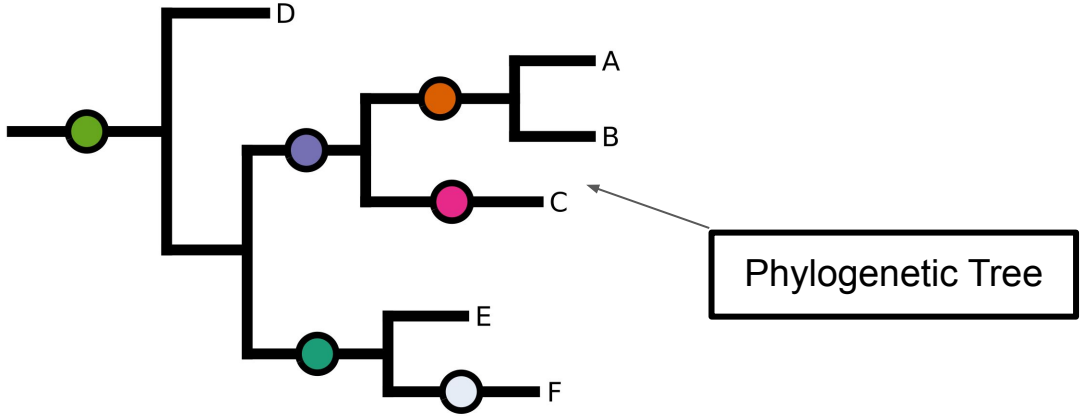
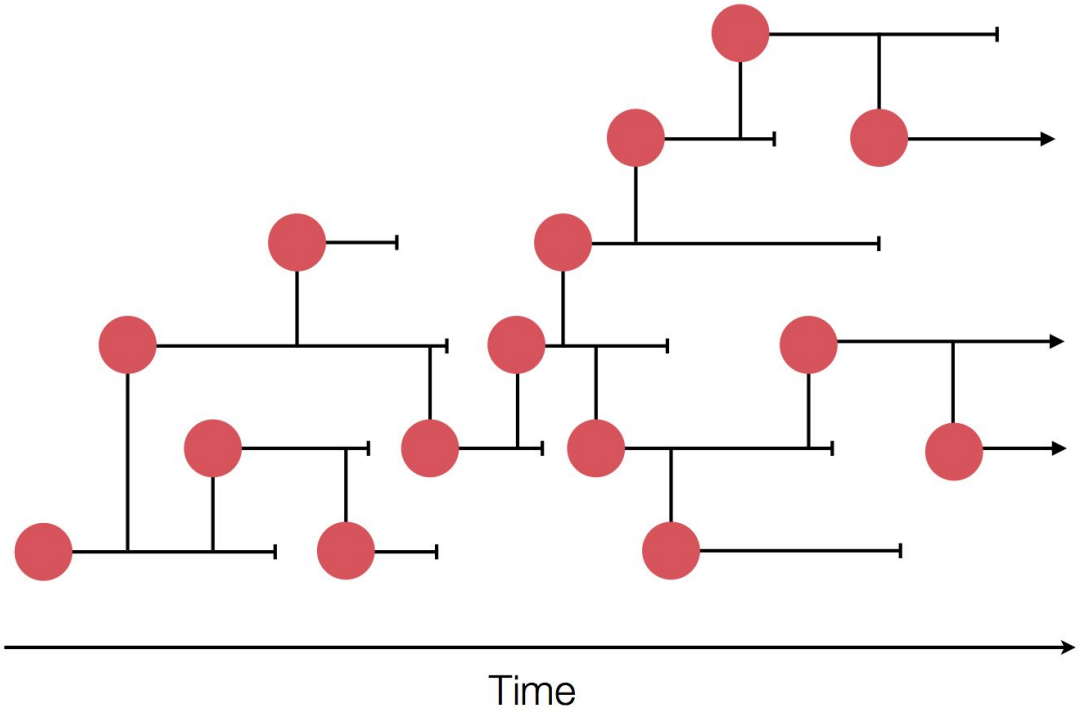




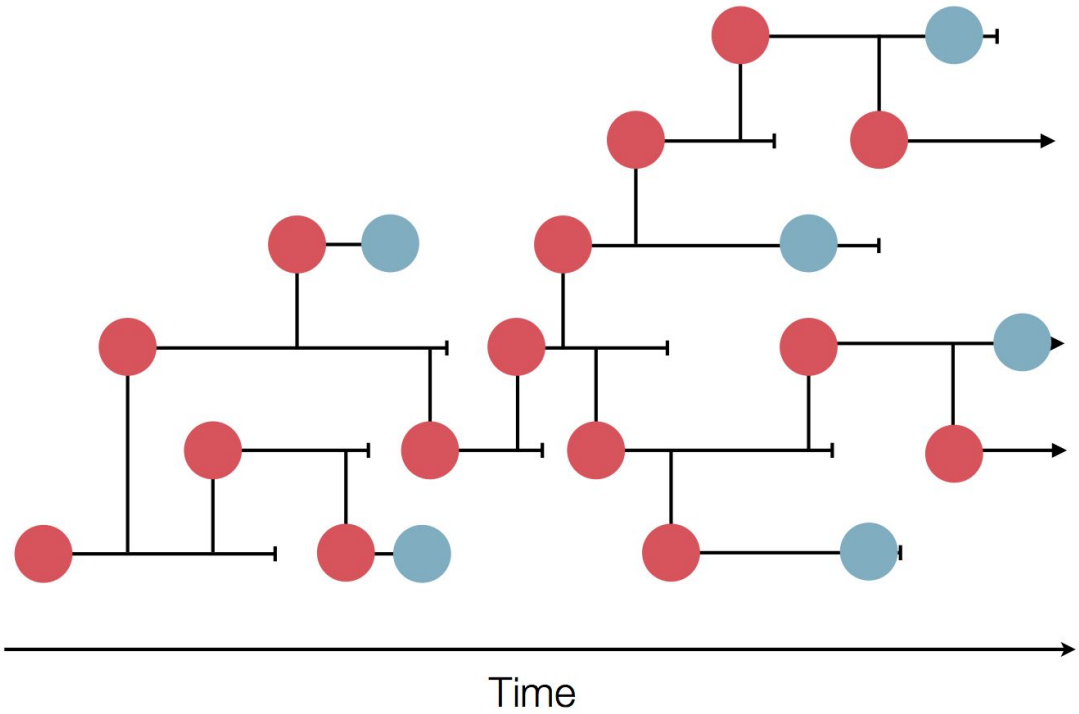
What does this tree actually represent?

Sampling & partially reconstructing underlying epidemic process



https://github.com/trvrb/phylodynamics-lecture

Sampling & partially reconstructing underlying epidemic process



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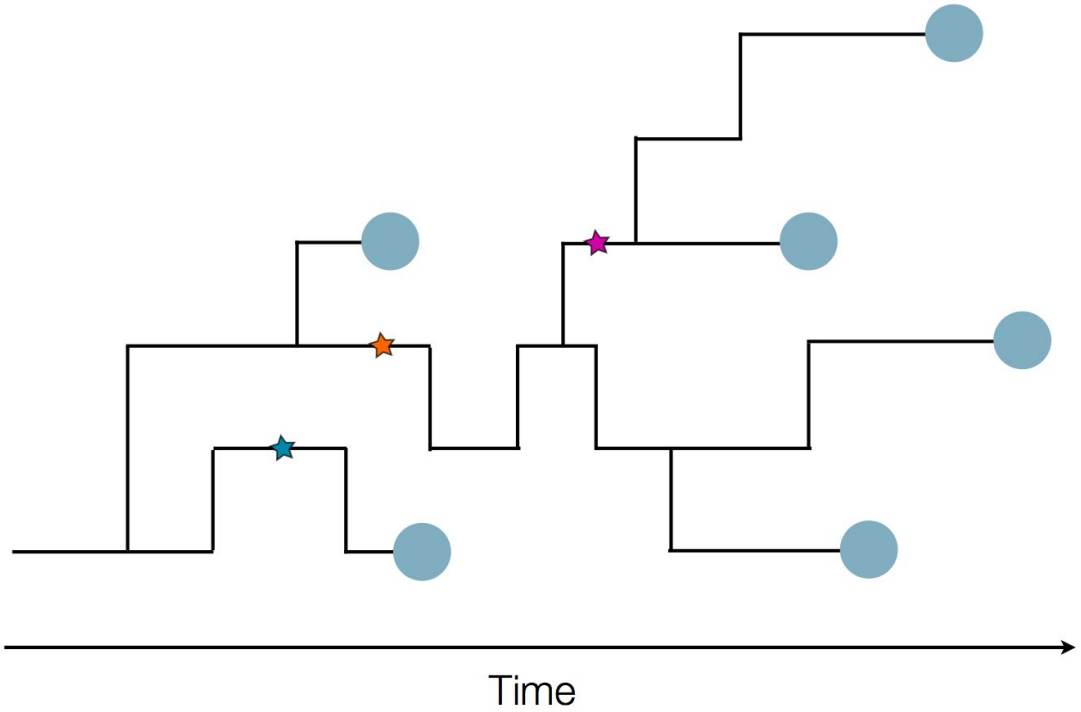
Sampling & partially reconstructing underlying epidemic process



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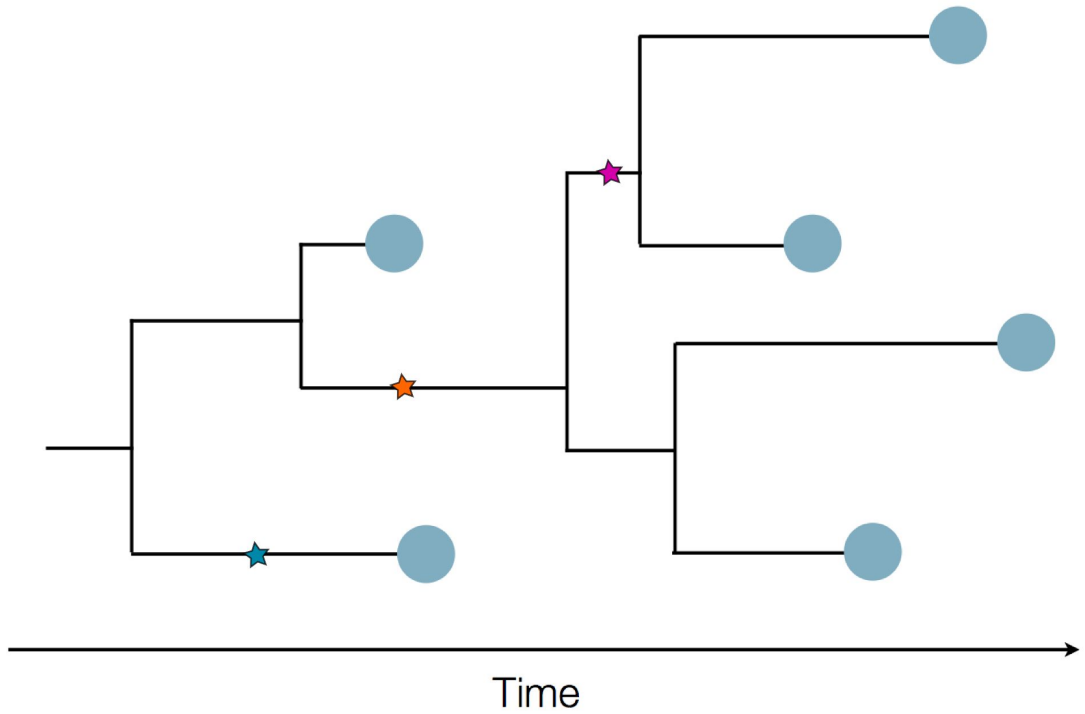
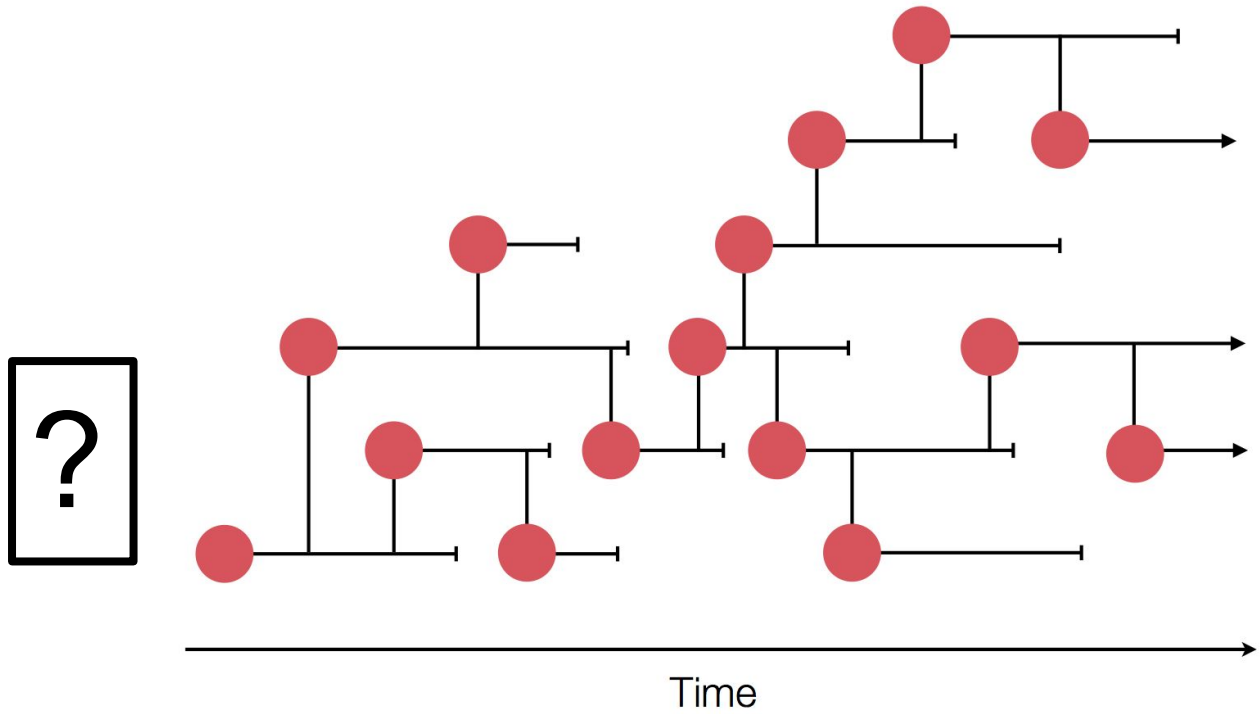
Sampling & partially reconstructing underlying epidemic process



https://github.com/trvrb/phylodynamics-lecture

What determines underlying process?

Many forces shaping underlying process



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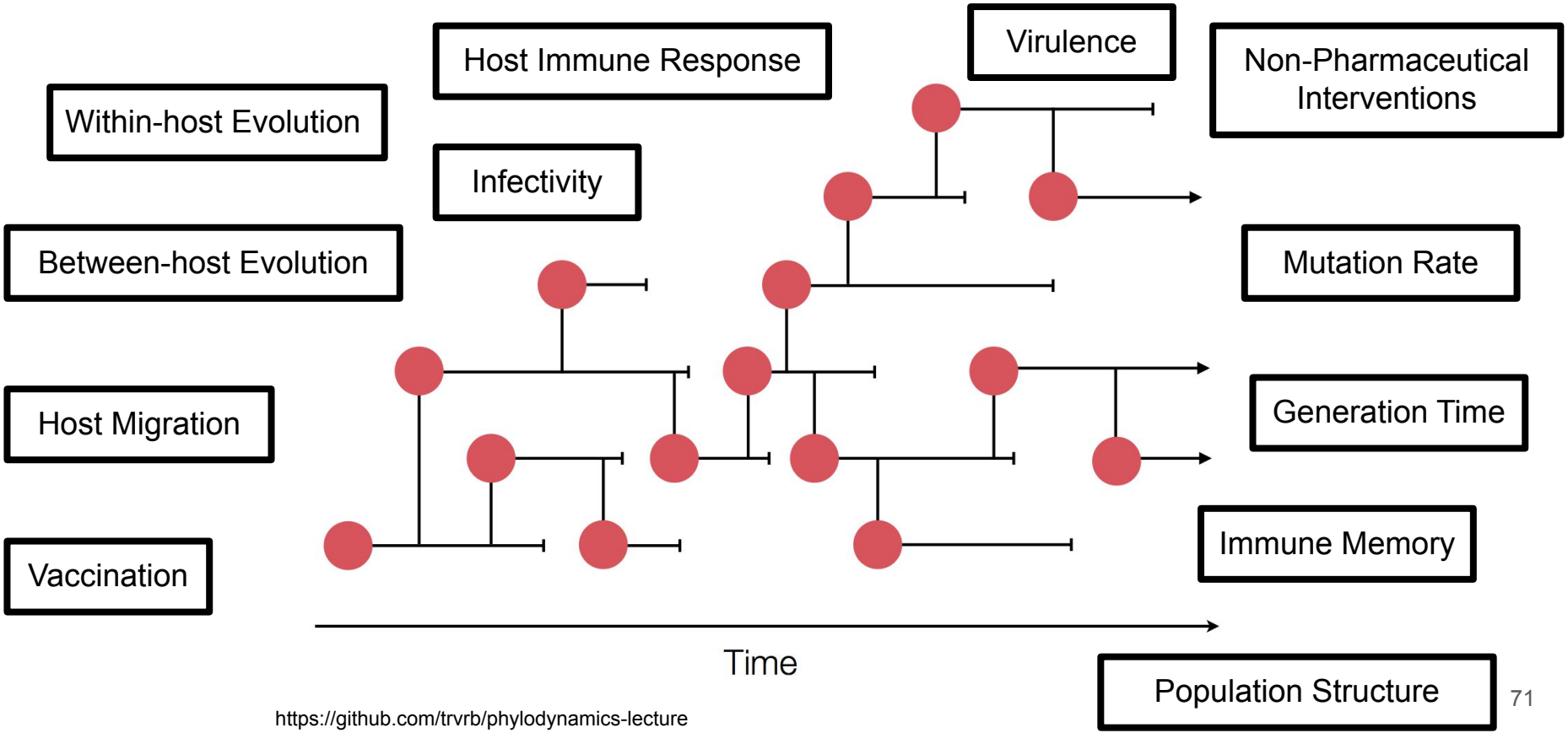
Many forces shaping underlying process



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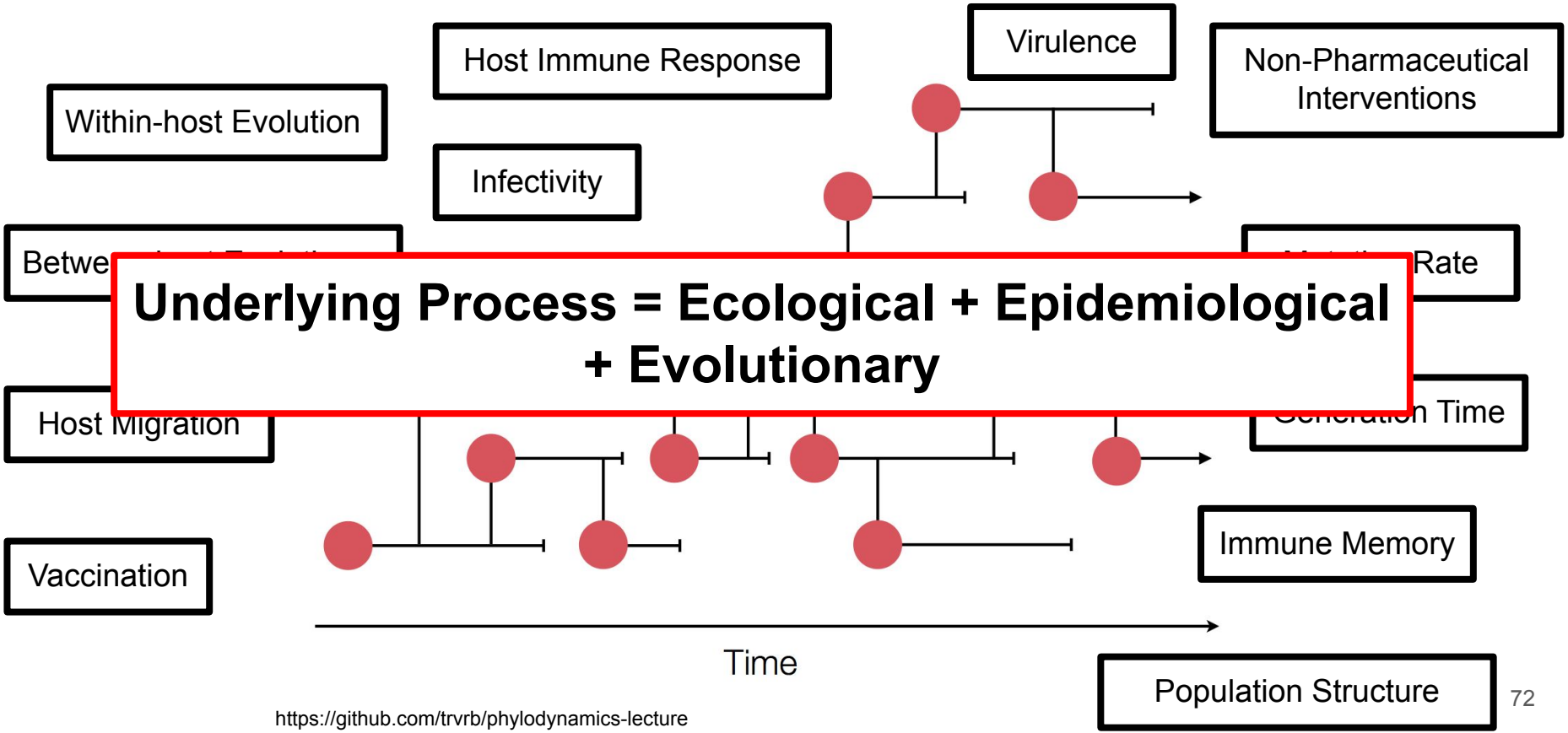
Many forces shaping underlying process



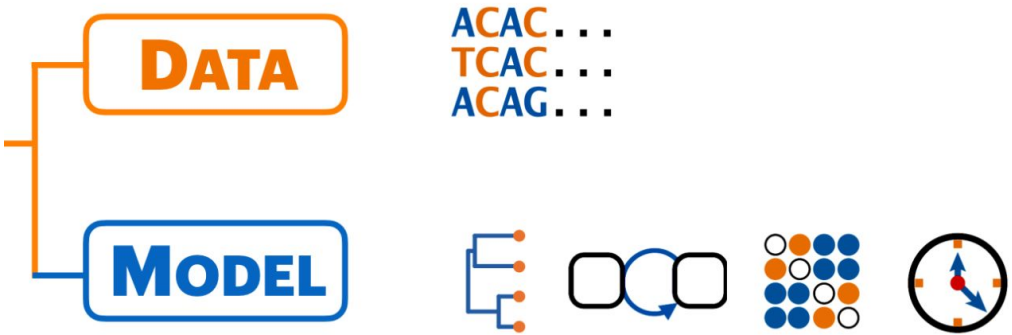
https://github.com/trvrb/phylodynamics-lecture

How can we can model this process?

Bayesian inference is a key tool in genomic epidemiology

https://github.com/Taming-the-BEAST/Taming-the-BEAST-2021-Online-Lectures/raw/master/Day4_Structured_Phylodynamics_-_Denise_Kuehnert.pdf

Bayesian inference is a key tool in genomic epidemiology



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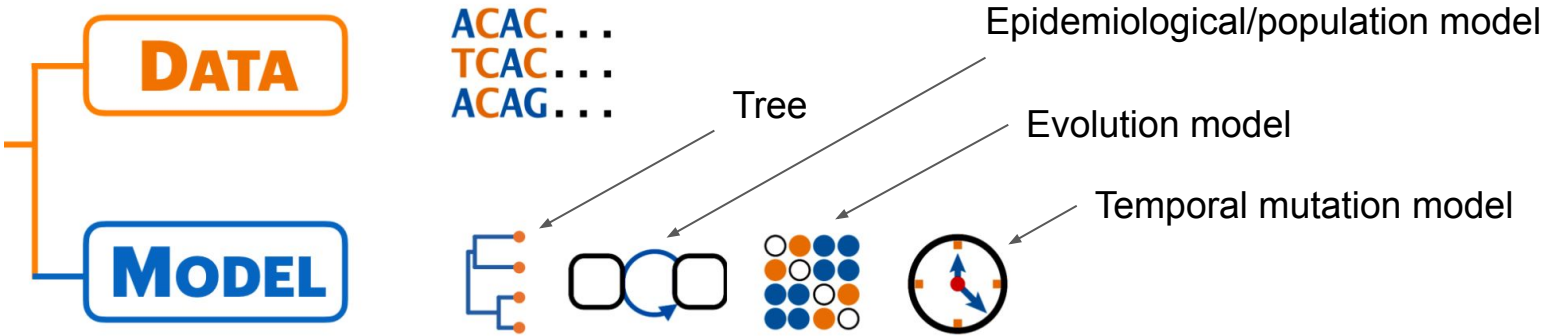

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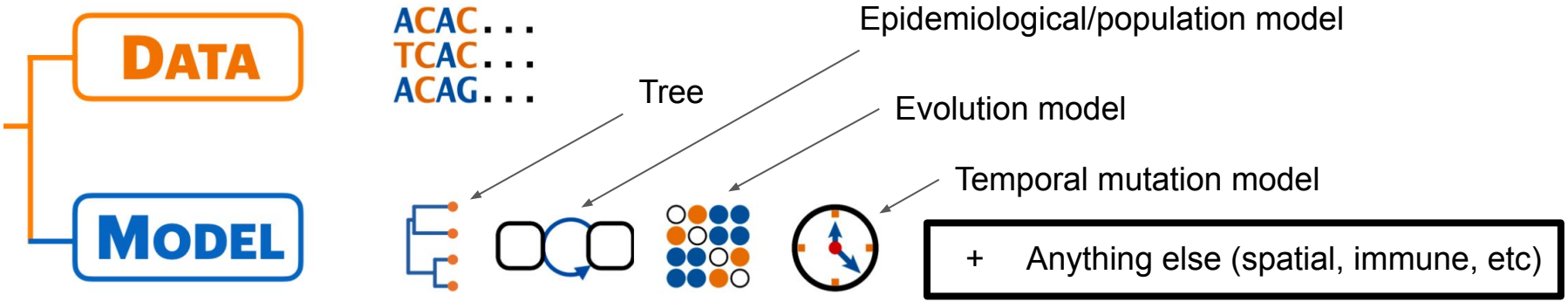

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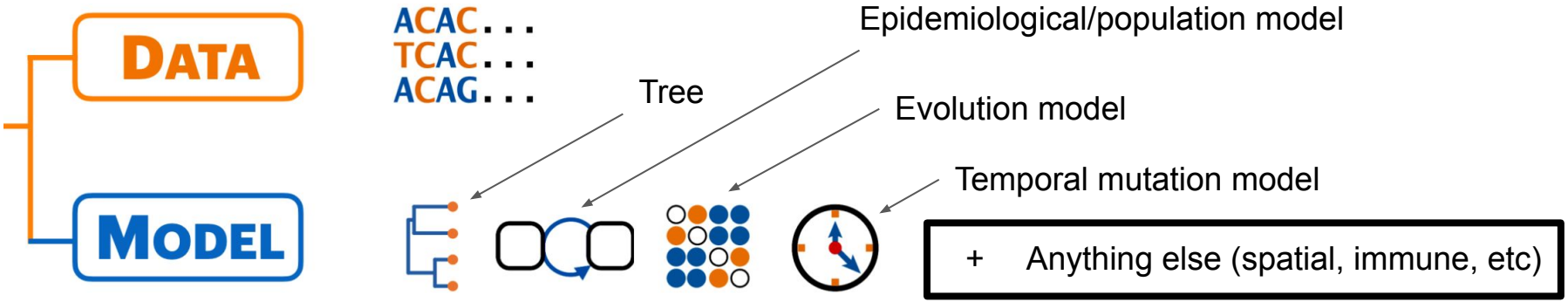
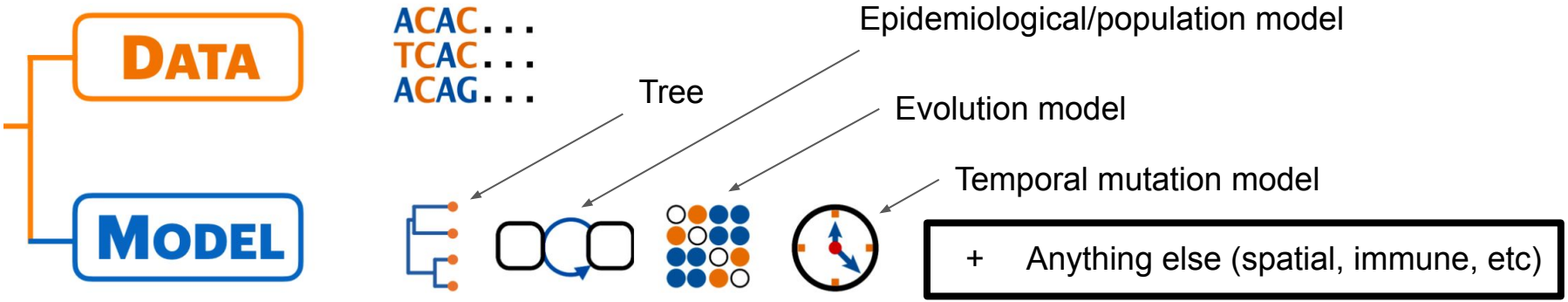


Bayesian inference is a key tool in genomic epidemiology



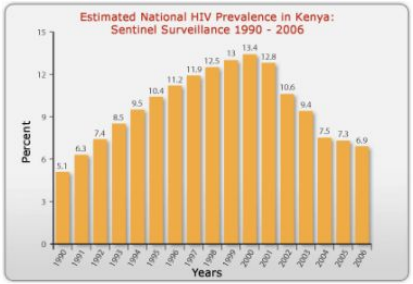
$$P(\text{tree}, \text{model} \mid \text{ACAC...}, \text{TCAC...}, \text{ACAG...}) = \frac{P(\text{ACAC...}, \text{TCAC...}, \text{ACAG...} \mid \text{tree}, \text{model})\, P(\text{tree}, \text{model})}{P(\text{ACAC...}, \text{TCAC...}, \text{ACAG...})}$$

https://github.com/Taming-the-BEAST/Taming-the-BEAST-2021-Online-Lectures/raw/master/Day4_Structured_Phylodynamics_-_Denise_Kuehnert.pdf

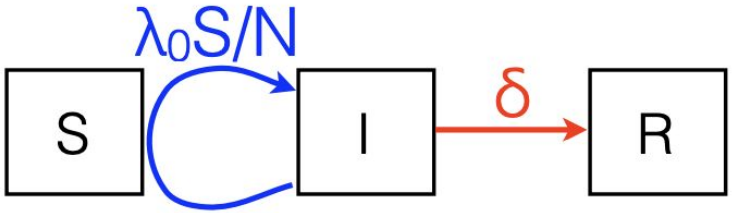
Why not just use case information?

Genomics can be used to infer unobserved events

of infected individuals through time



Population dynamics described by SIR models:



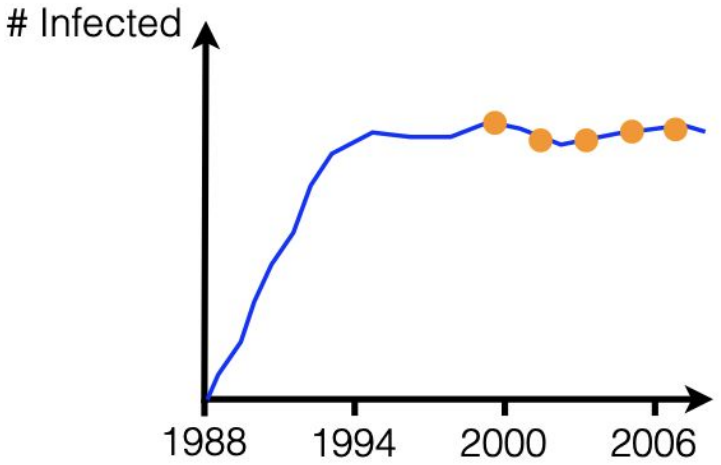
$$\frac{dS}{dt} = -\lambda_0 IS/N$$
$$\frac{dI}{dt} = \lambda_0 IS/N - \delta I$$
$$\frac{dR}{dt} = \delta I$$

https://github.com/Taming-the-BEAST/Taming-the-BEAST-2021-Online-Lectures/raw/master/Day2_Phylodynamics_-_Tanja_Stadler.pdf

Genomics can be used to infer unobserved events

If sampling in early epidemic was missed:

- **Time of epidemic outbreak?**
- **Basic reproductive number R_0?**



https://github.com/Taming-the-BEAST/Taming-the-BEAST-2021-Online-Lectures/raw/master/Day2_Phylodynamics_-_Tanja_Stadler.pdf

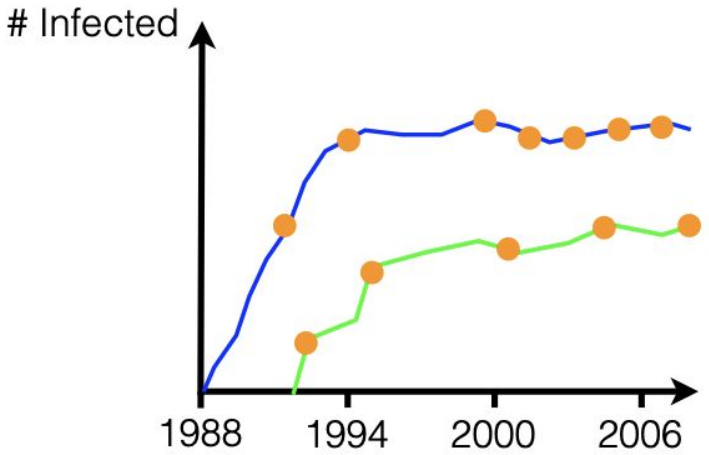
Genomics can be used to infer unobserved events

If sampling in early epidemic was missed:

- **Time of epidemic outbreak?**
- **Basic reproductive number R_0?**

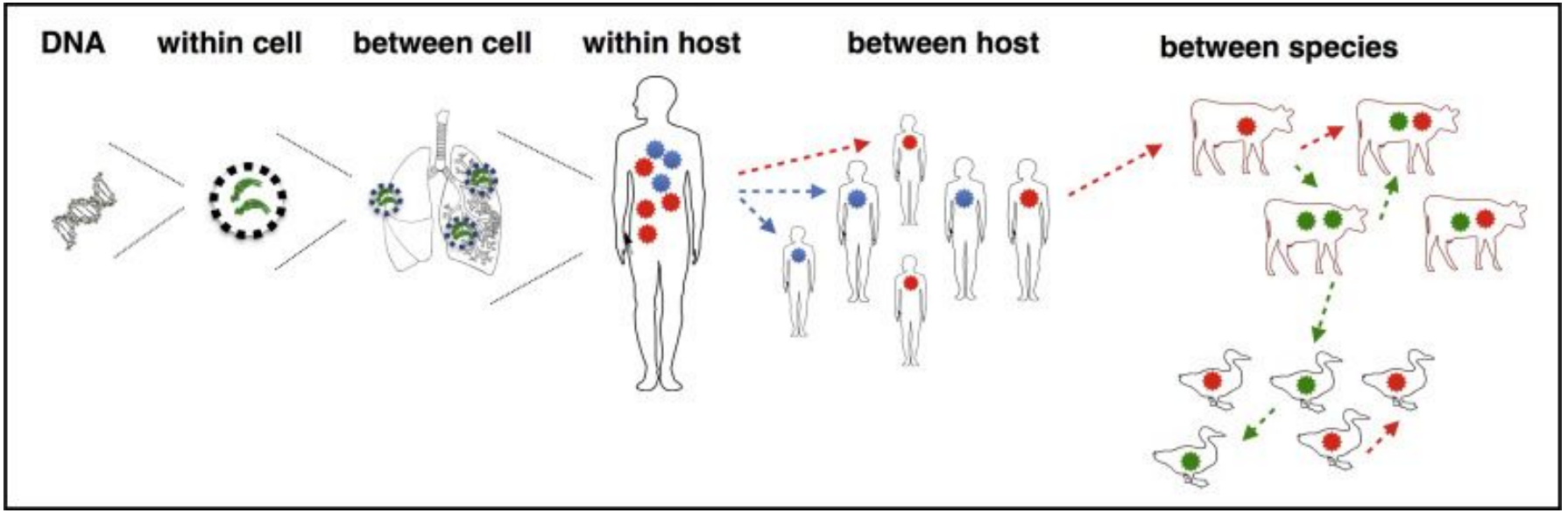
Data does not tell who infected whom:

- **Population structure?**



https://github.com/Taming-the-BEAST/Taming-the-BEAST-2021-Online-Lectures/raw/master/Day2_Phylodynamics_-_Tanja_Stadler.pdf

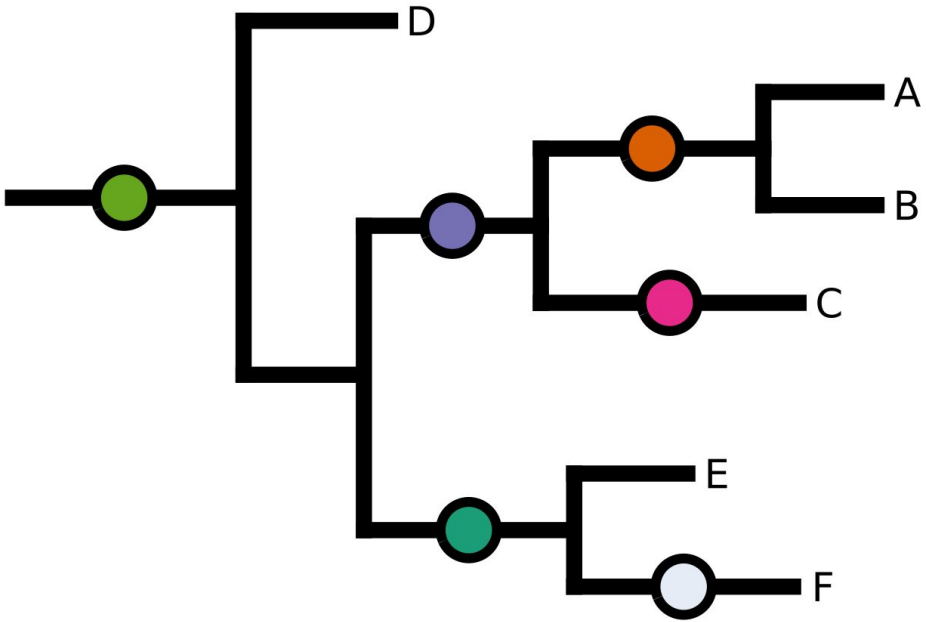
Cases don’t tell you (much) about pathogen evolution



https://www.sciencedirect.com/science/article/pii/S1755436514000723

So, we can use genomes for modelling but how do we actually use all this in infectious disease epidemiology?

Define lineages (groups) of pathogens



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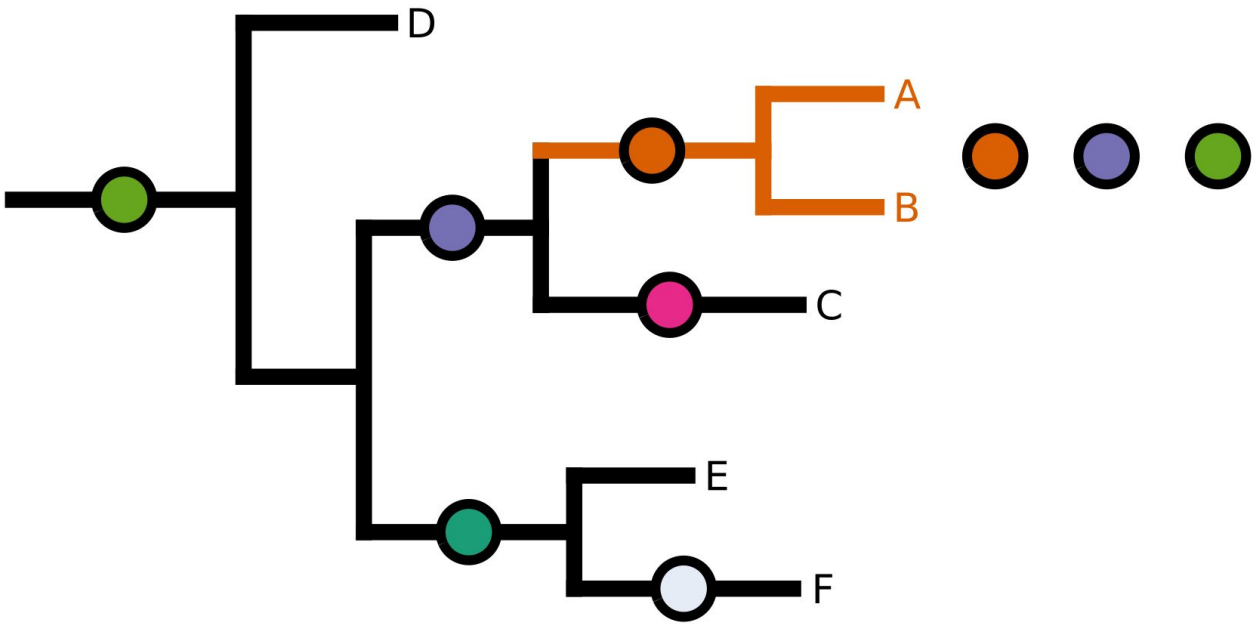

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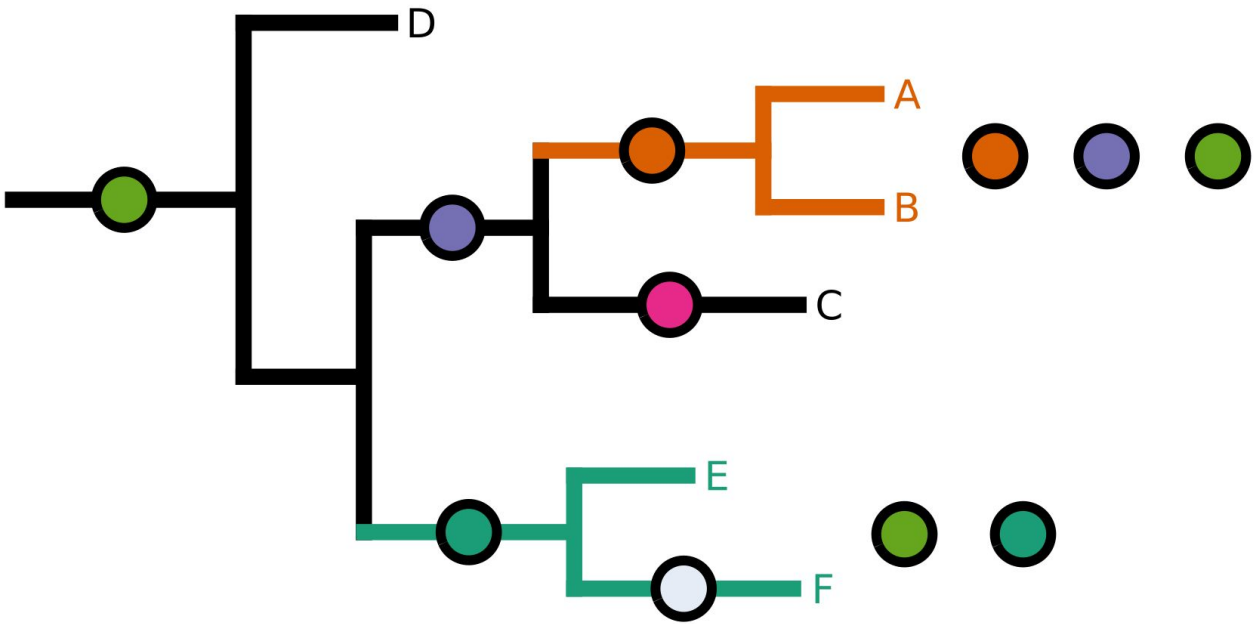
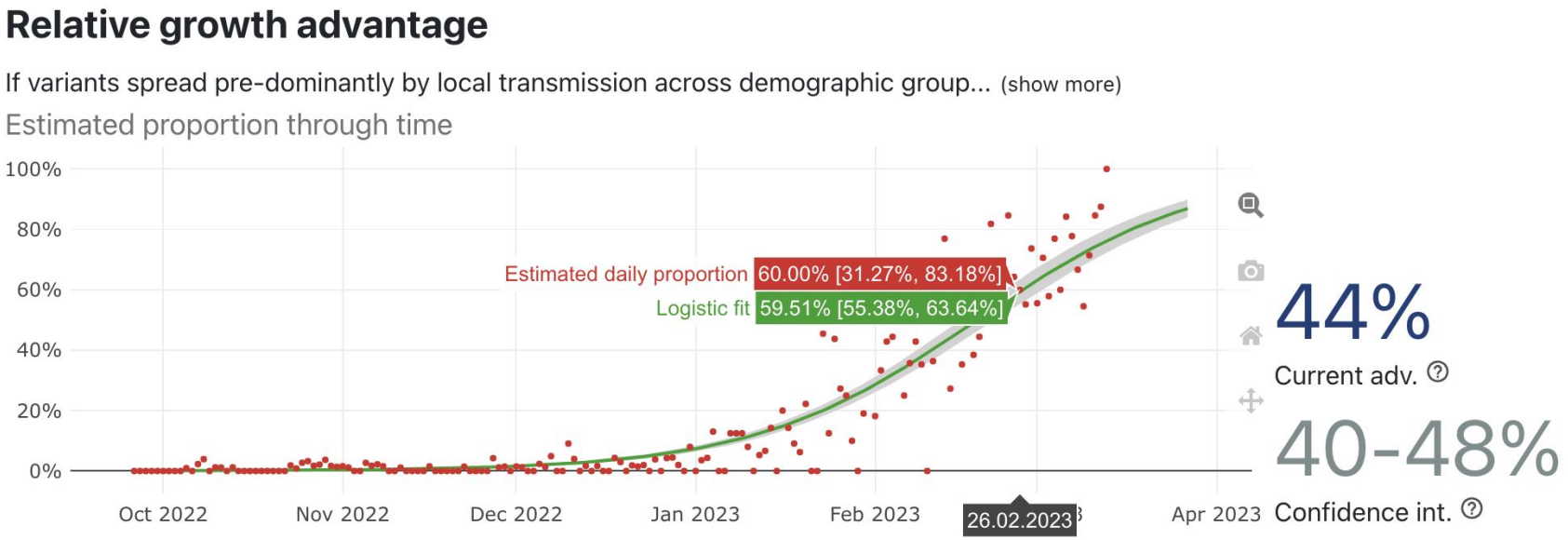
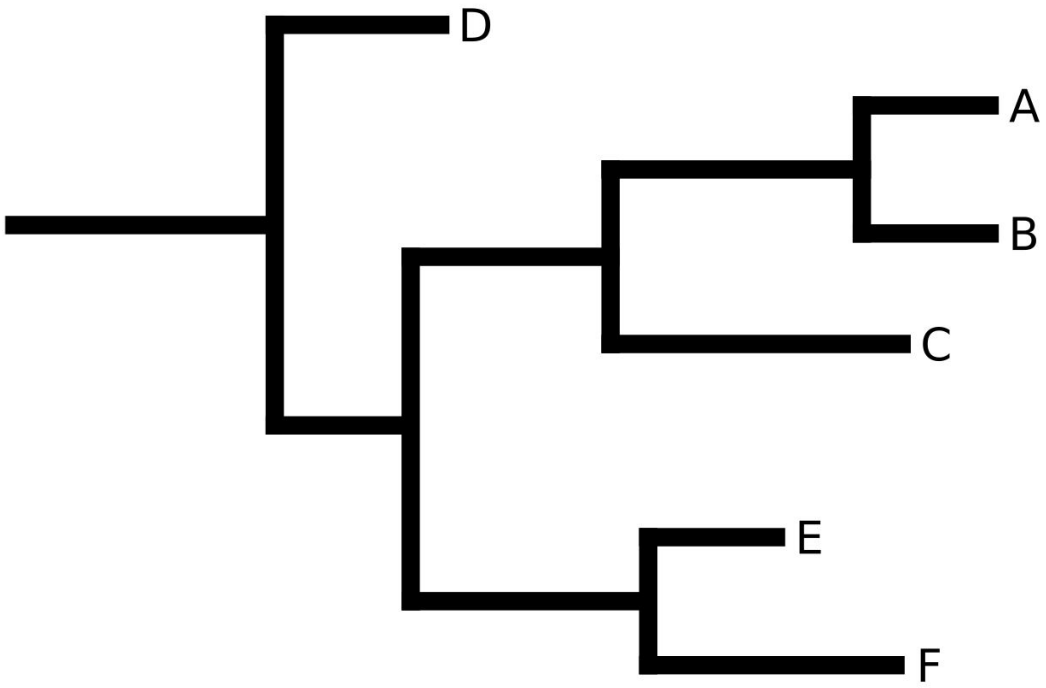


Early warning modelling lineage relative growth advantage



https://cov-spectrum.org/explore/Switzerland/Surveillance/Past6M/variants?nextcladePangoLineage=xbb*&

Identify clinically relevant mutations



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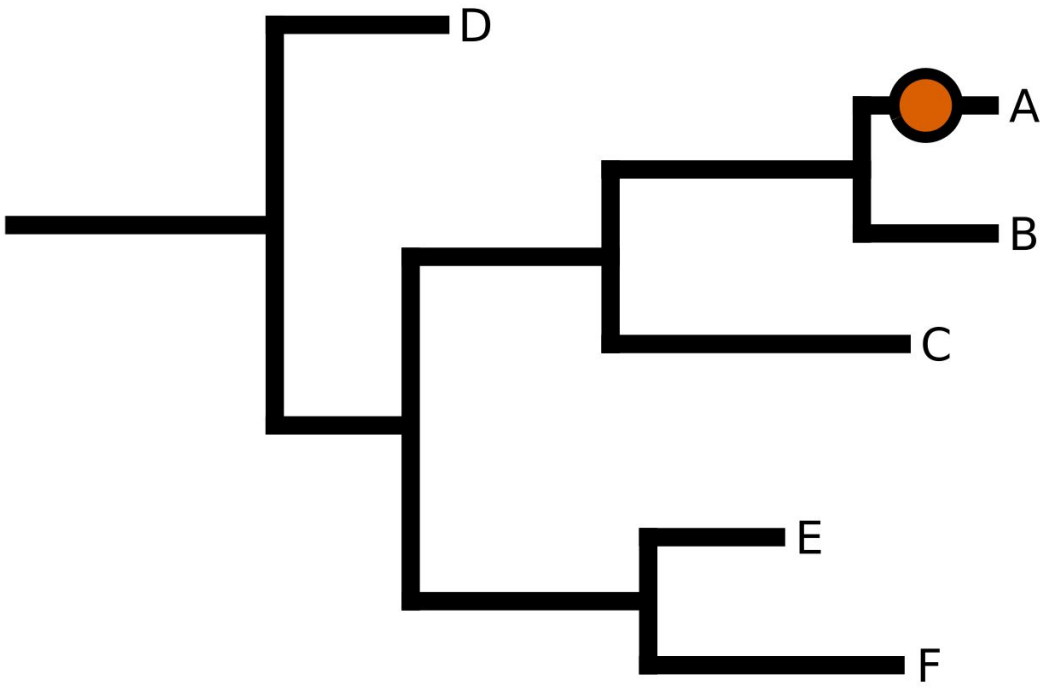

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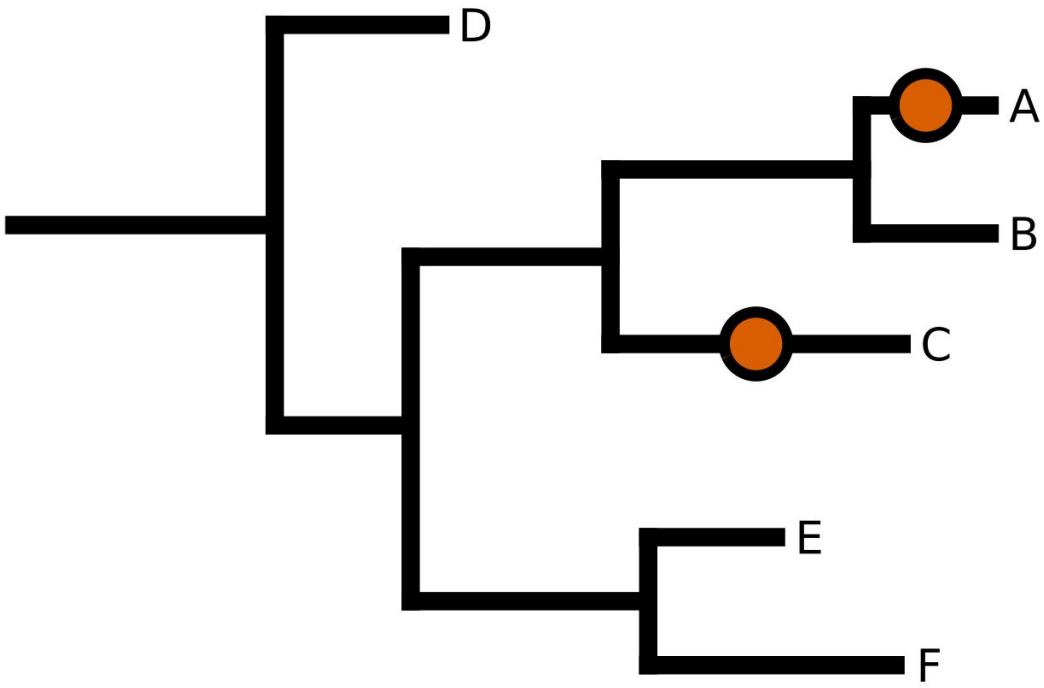

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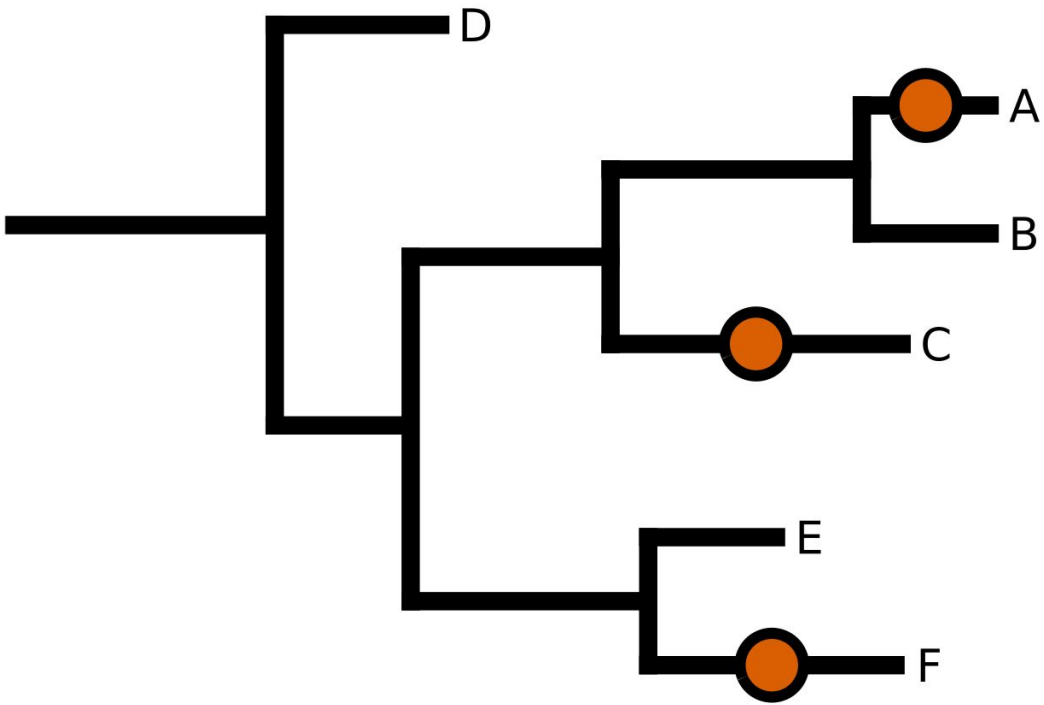

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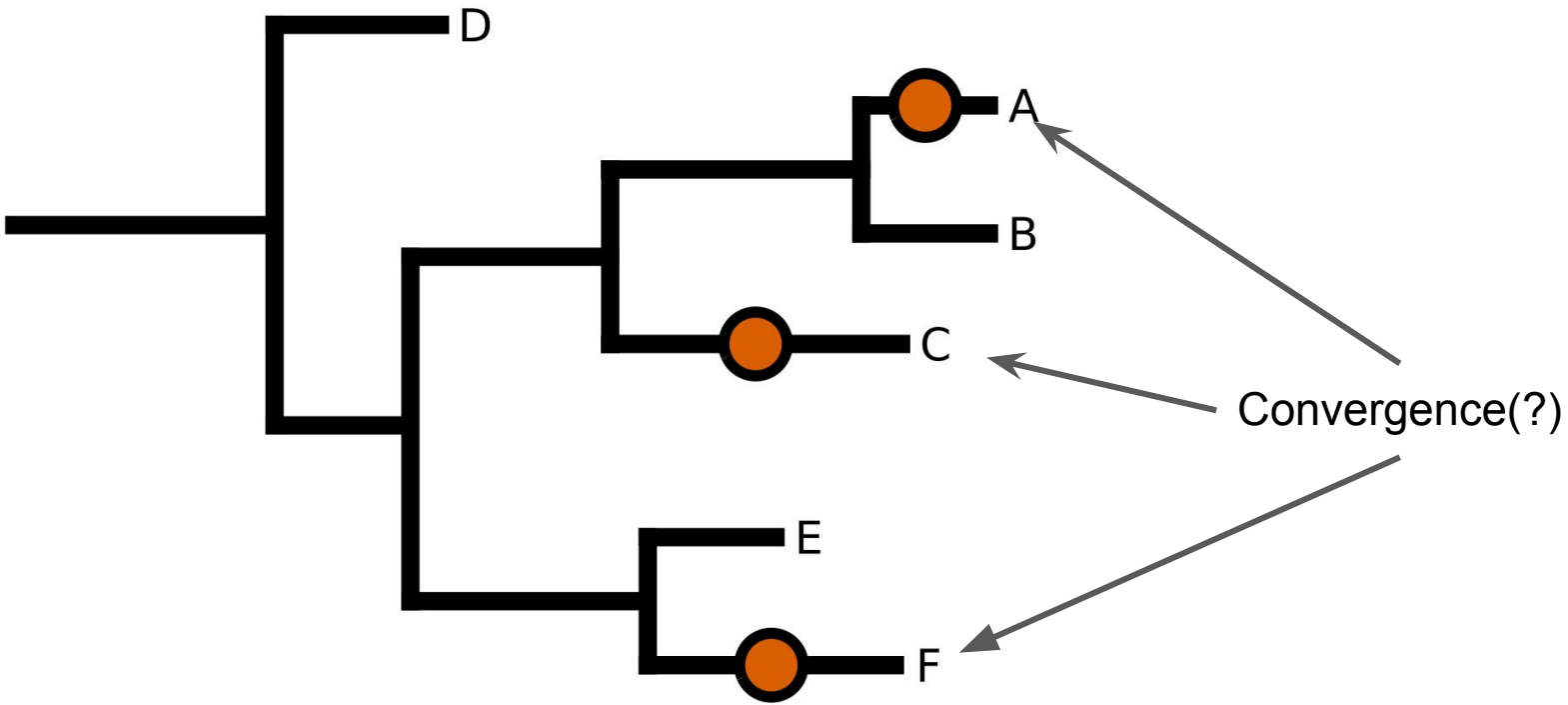

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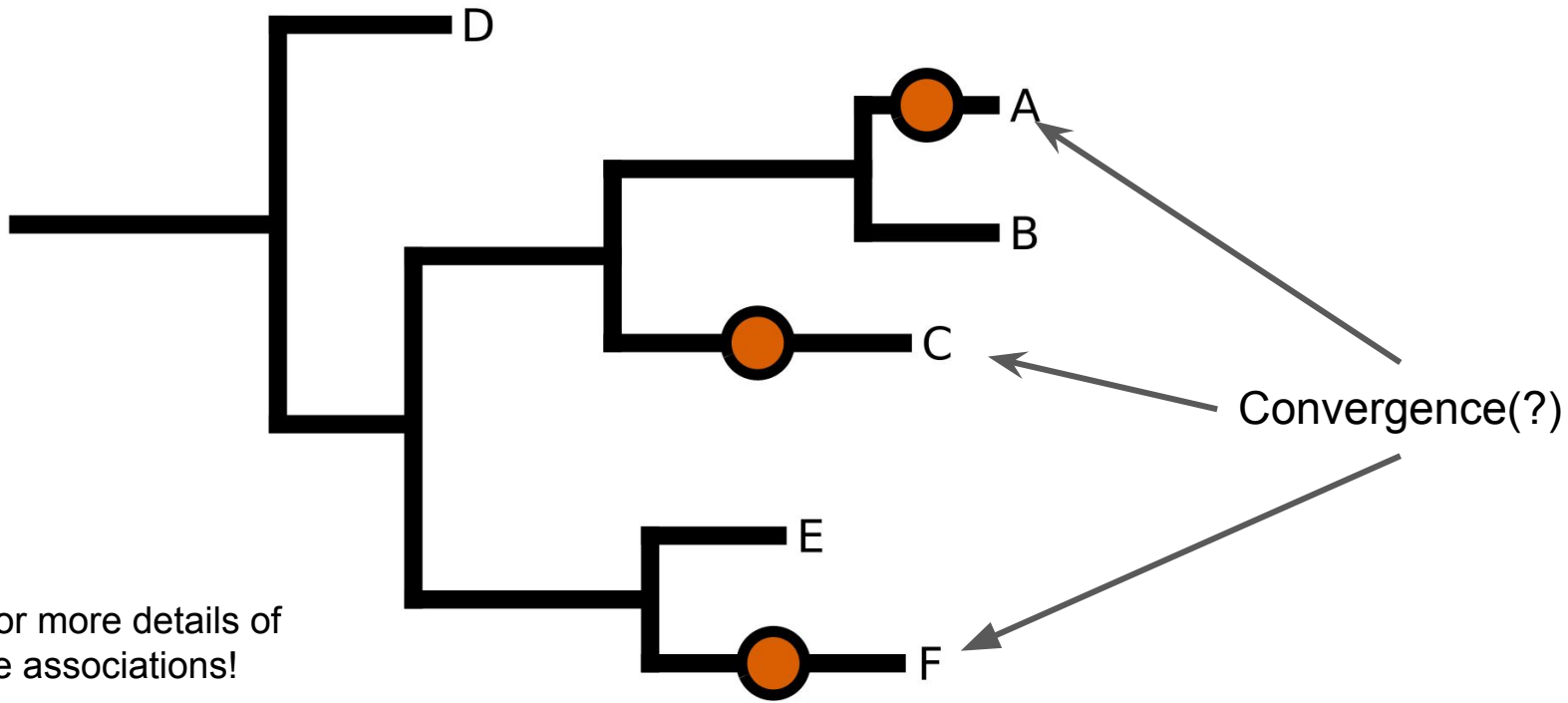
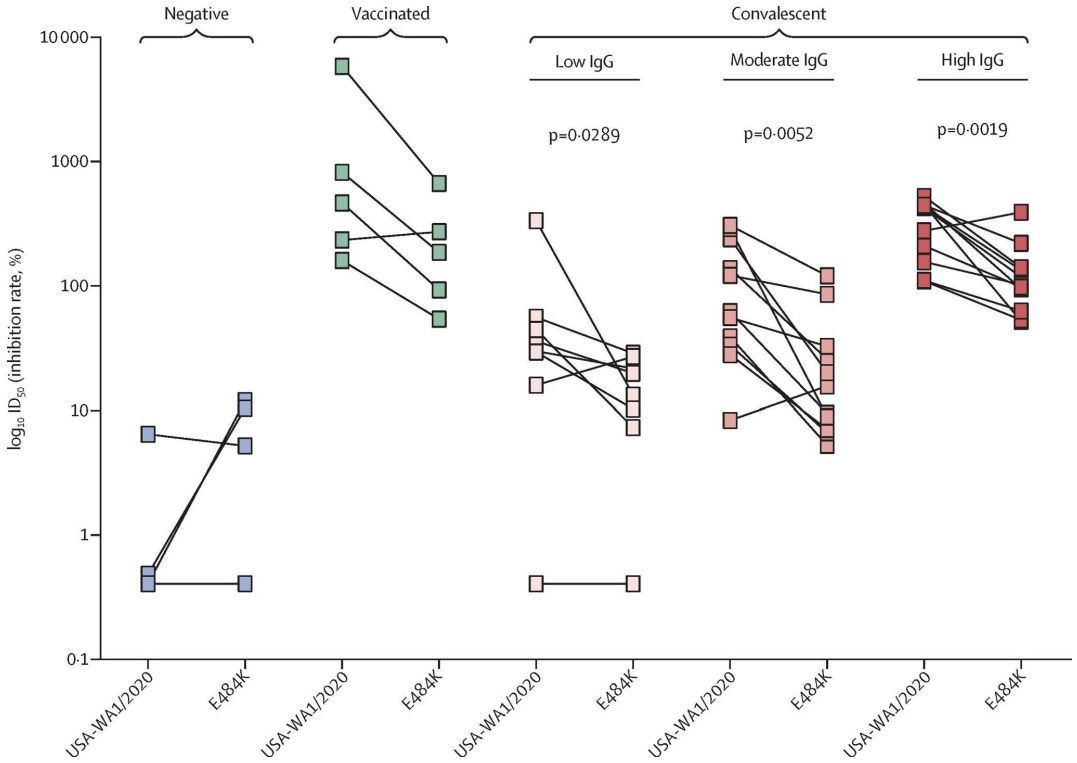


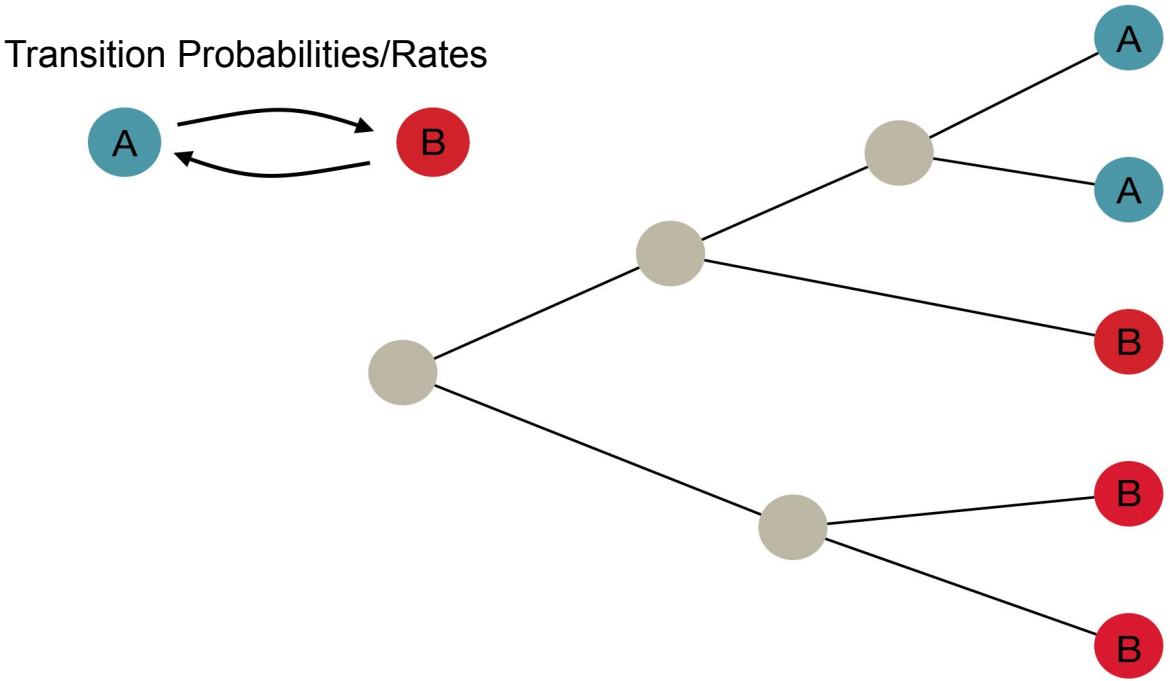
See part 2 for more details of testing these associations!

Prioritise characterisation of mutations: S:E484K



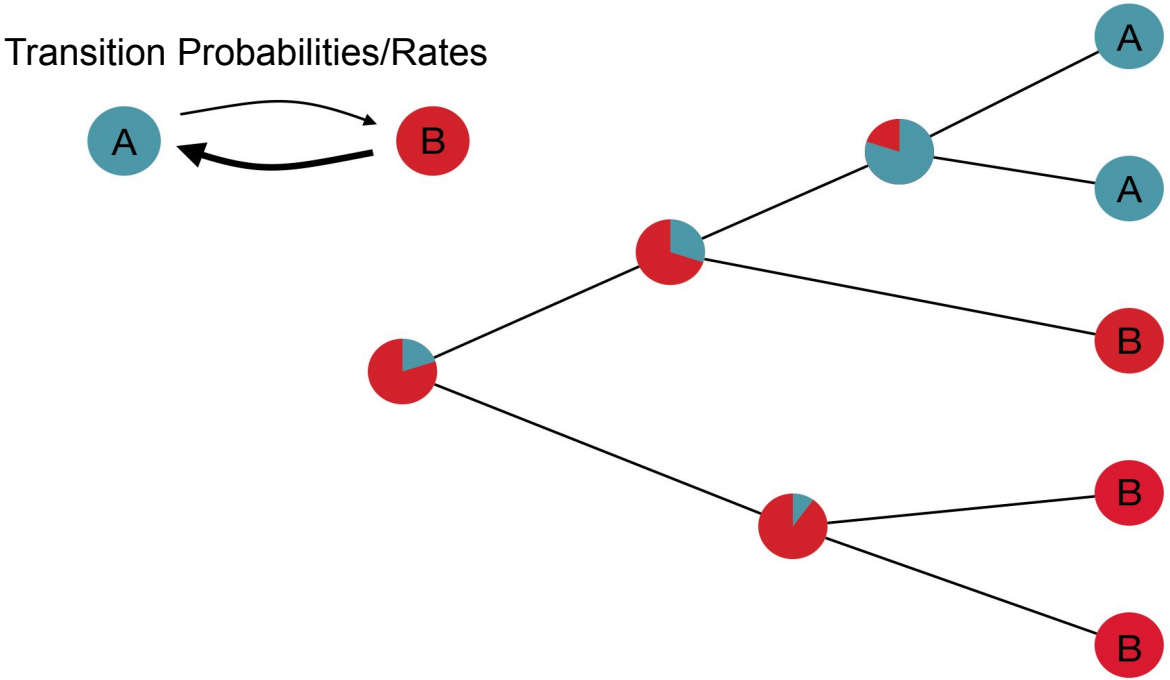
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00068-9

Inferring internal ancestral states from observed tips



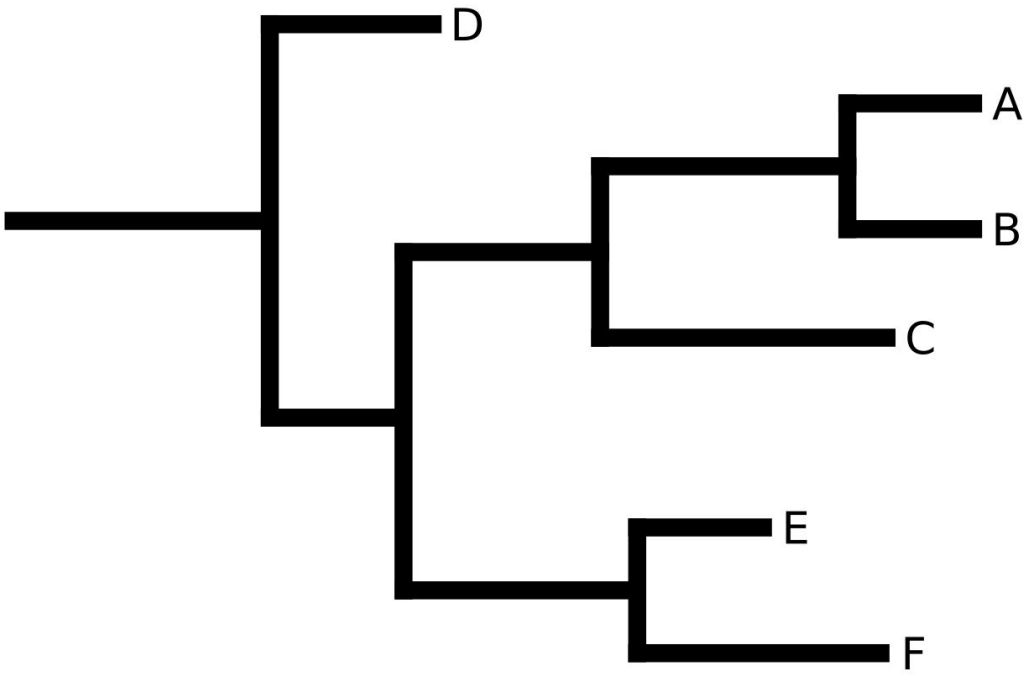
https://github.com/trvrb/gs541-phylodynamics

Inferring internal ancestral states from observed tips



https://github.com/trvrb/gs541-phylodynamics

Trace sources of outbreaks



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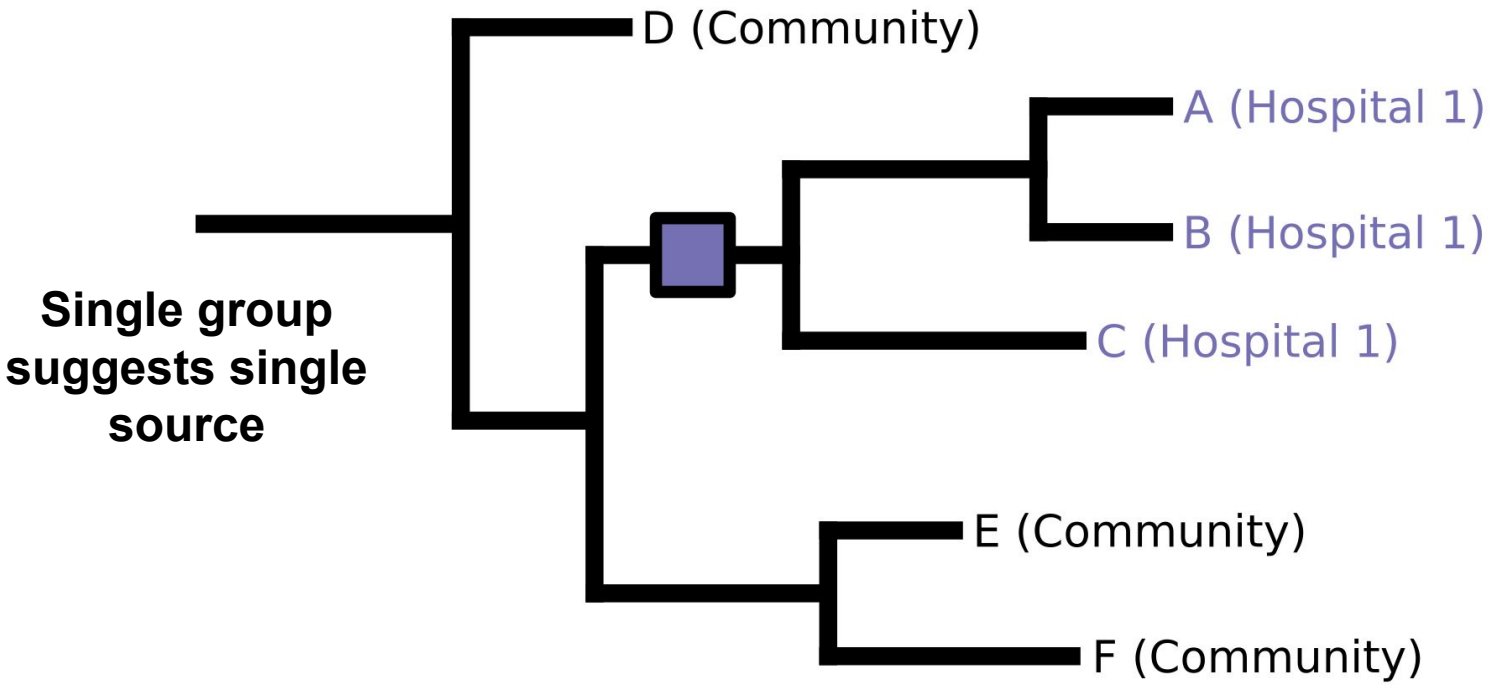
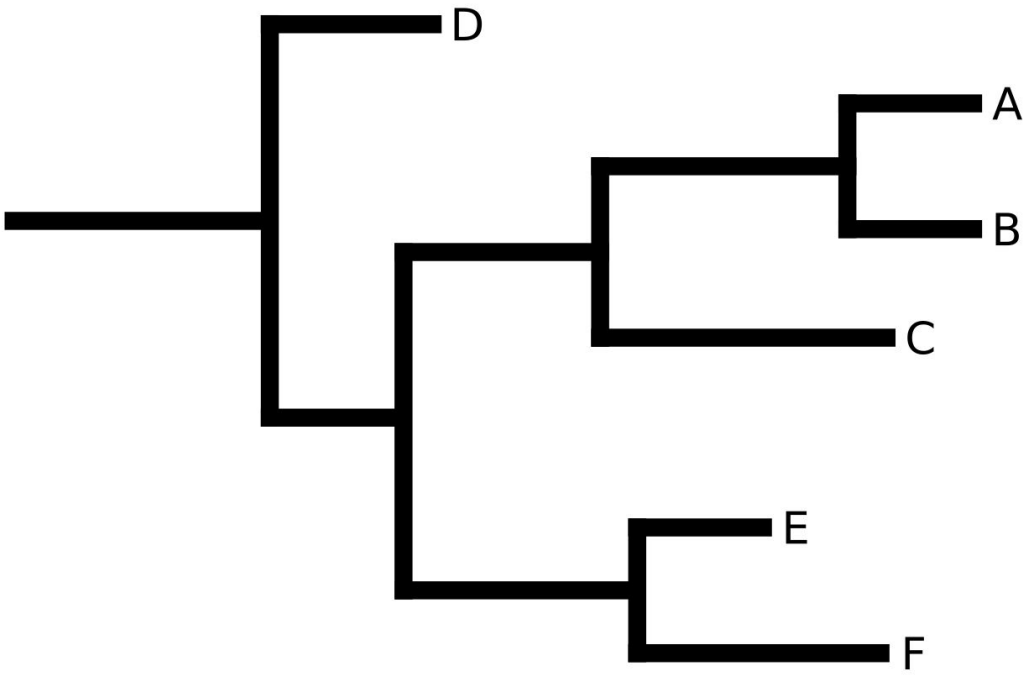


Trace sources of outbreaks



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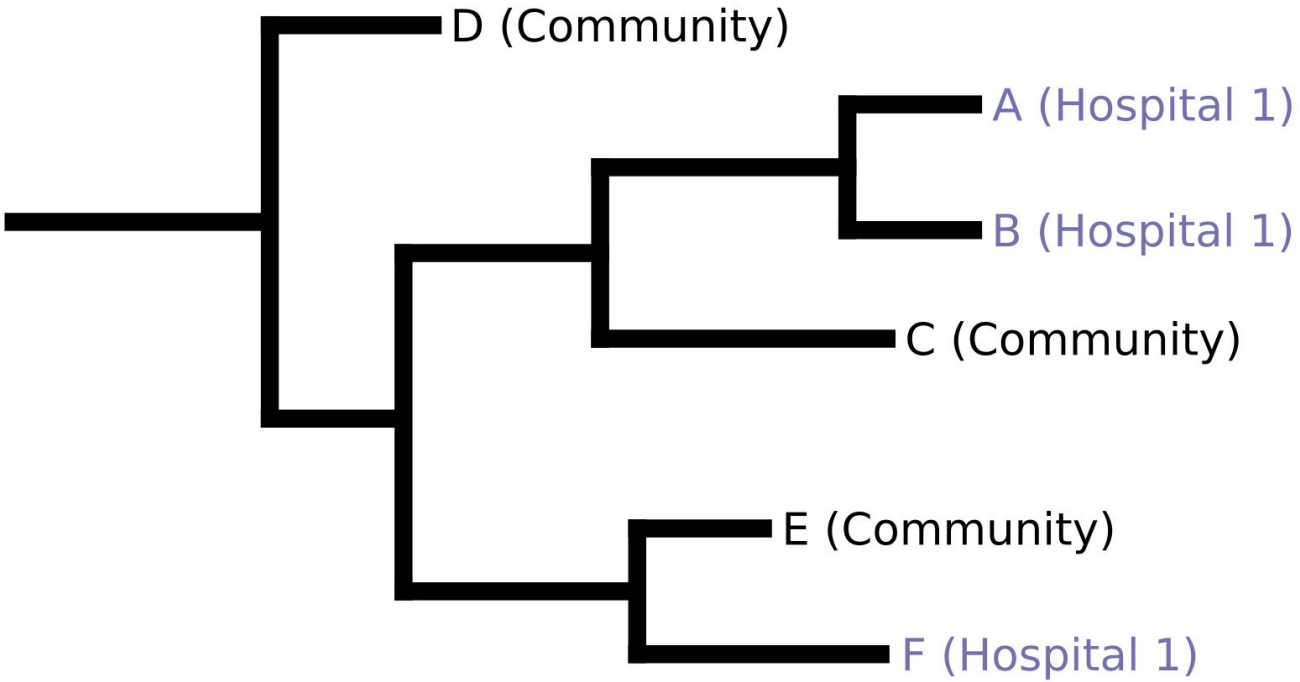
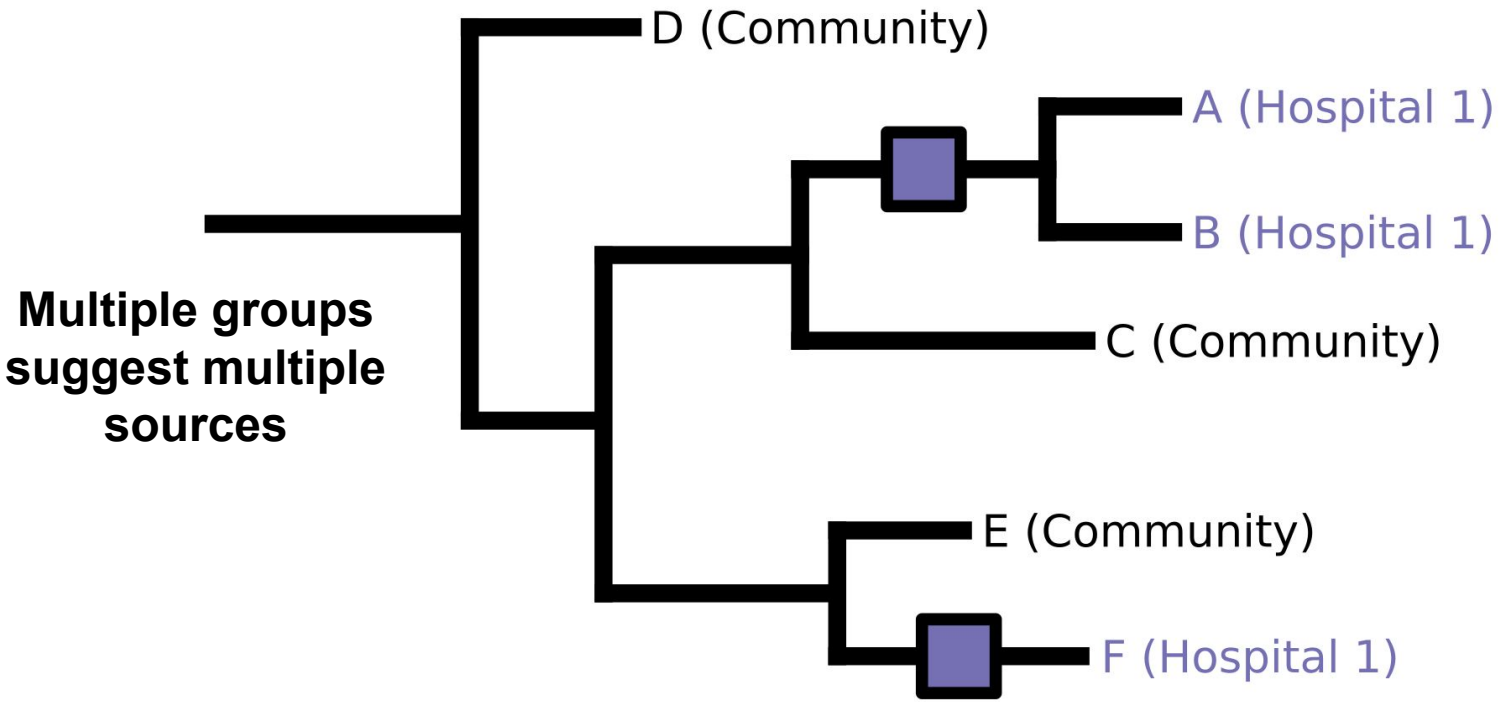
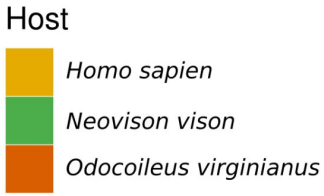


Trace sources of outbreaks



Multiple groups suggest multiple sources

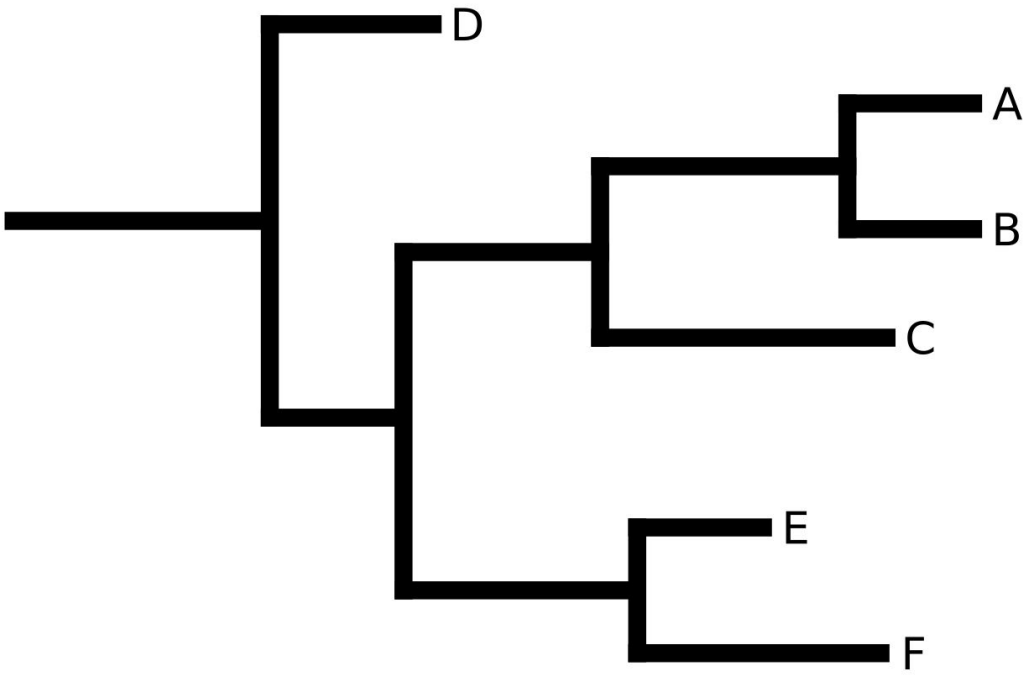
Finding Deer-to-Human transmission



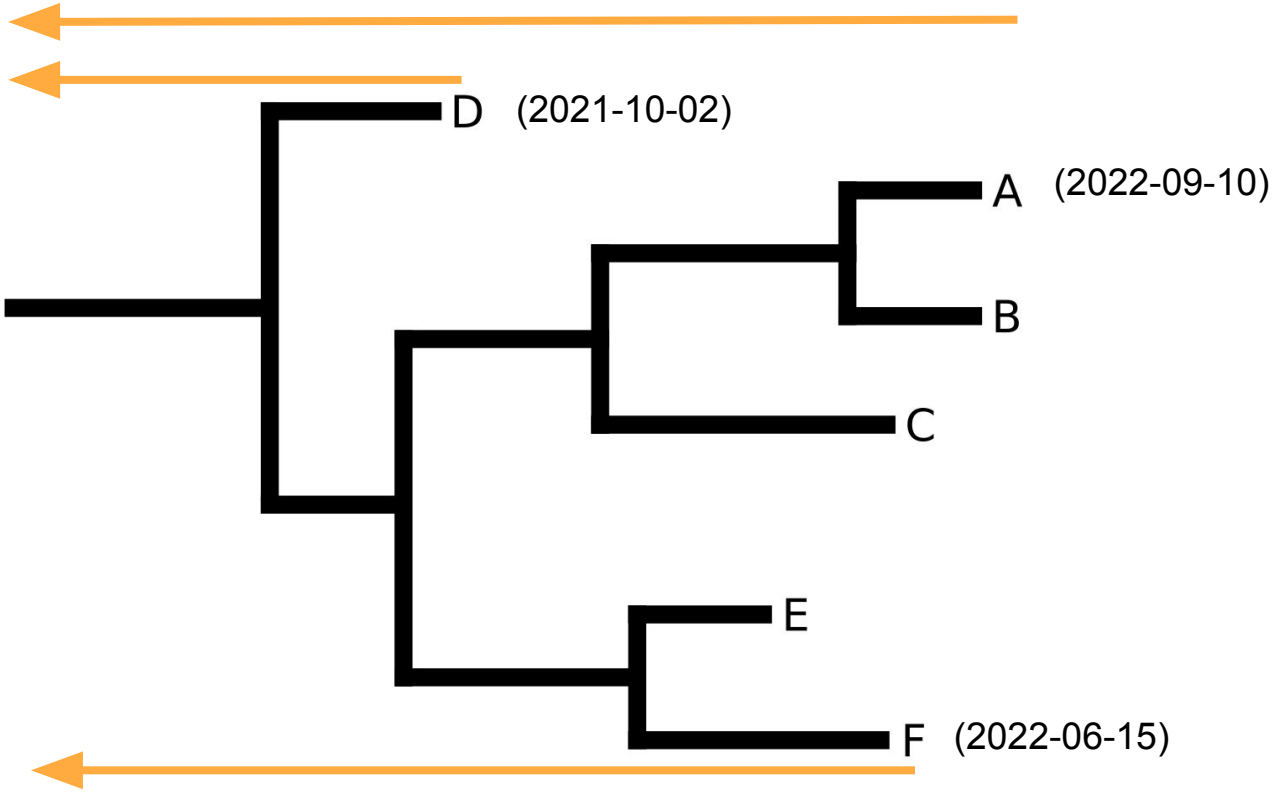
Supporting Circumstantial Evidence:

- Spatially congruent
- Temporally congruent
- Plausible Epidemiological Link

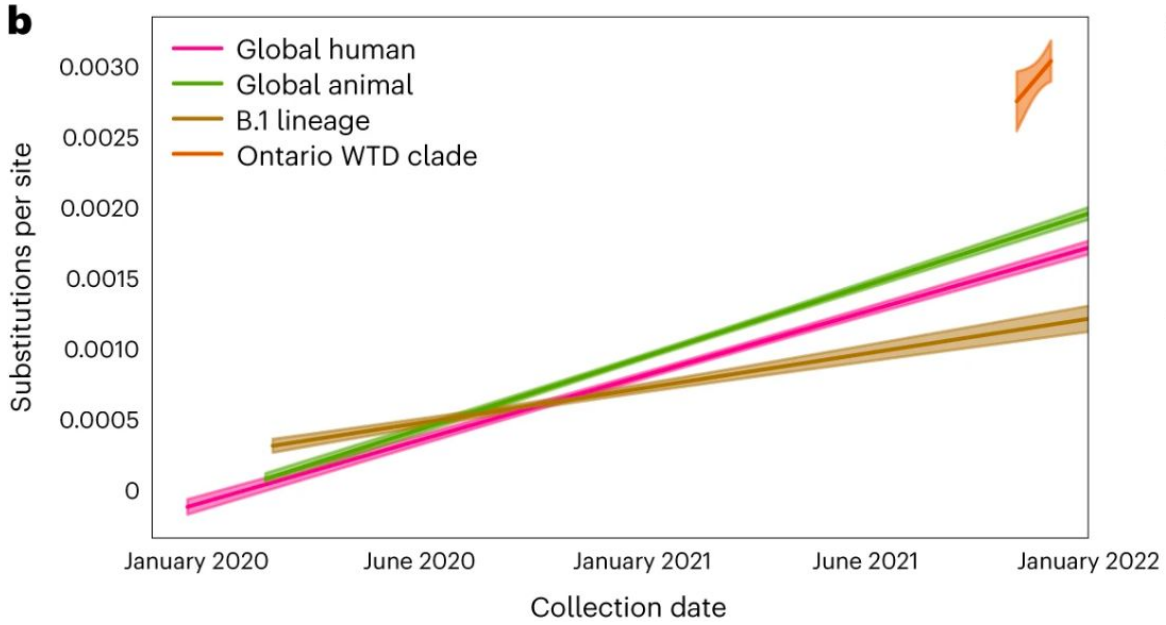
Convert genomic distance to time



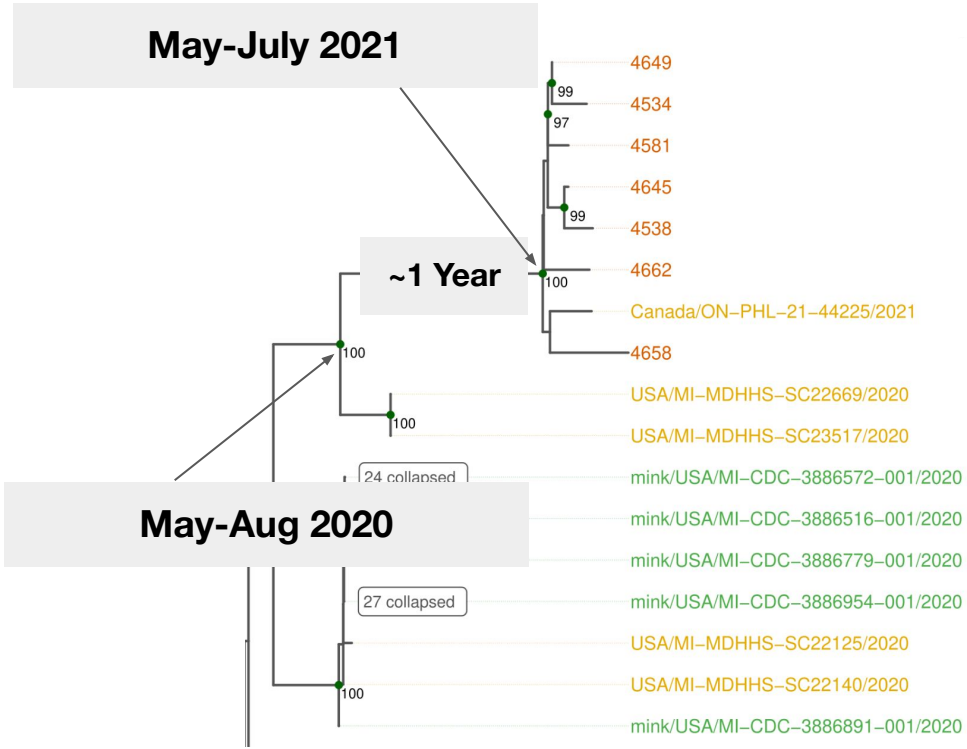
Convert genomic distance to time

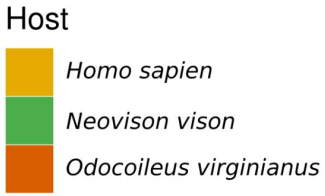


Mutation rates from Root to Tip Regression

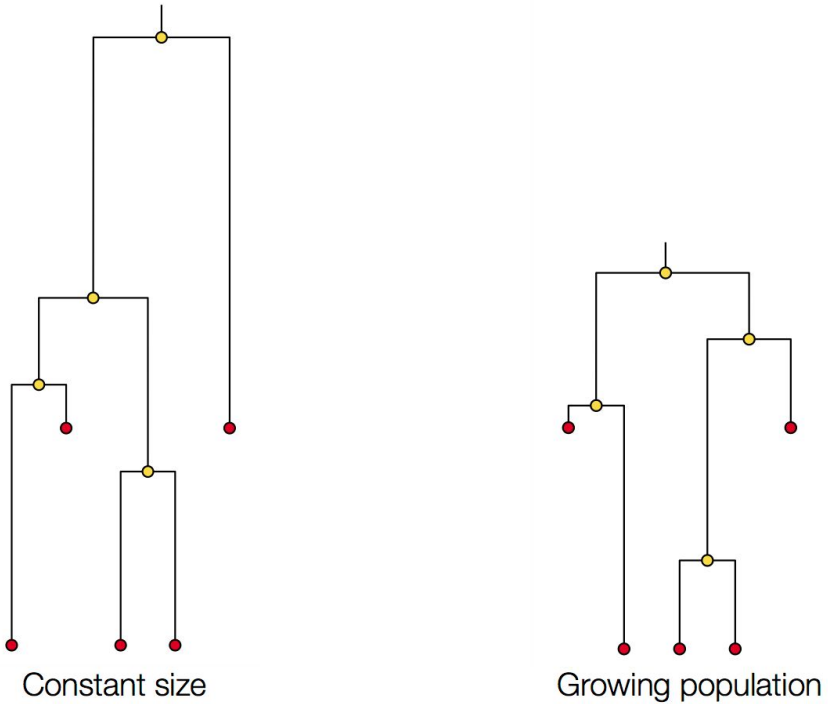


Mutations rates let us time of unobserved events



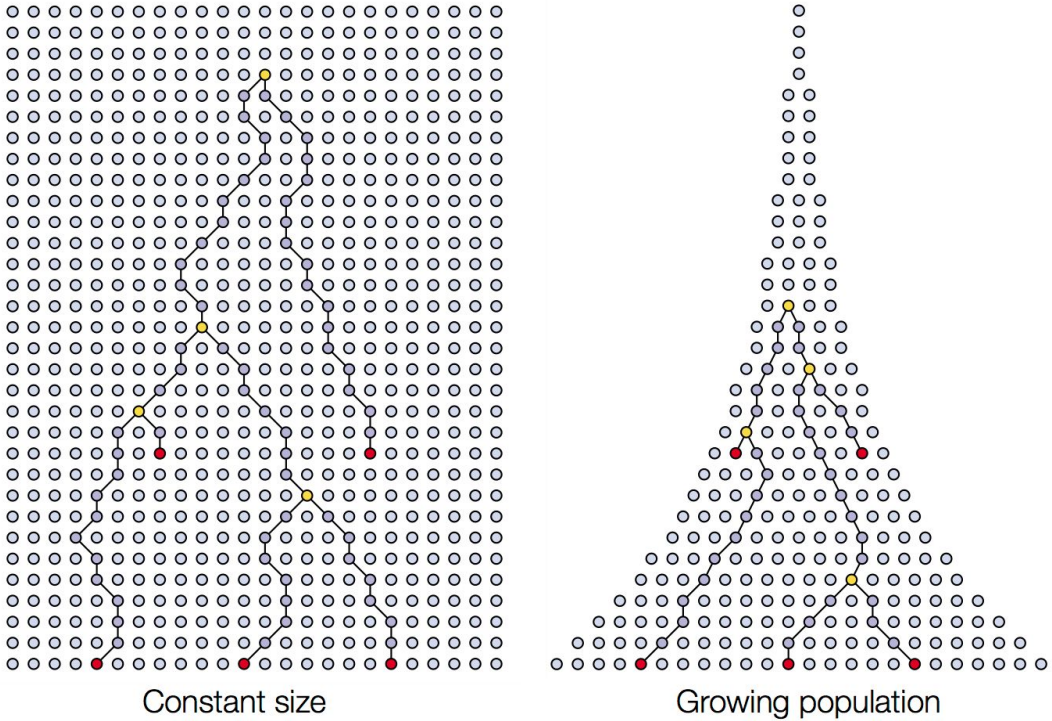


Tree shape tells us about population size



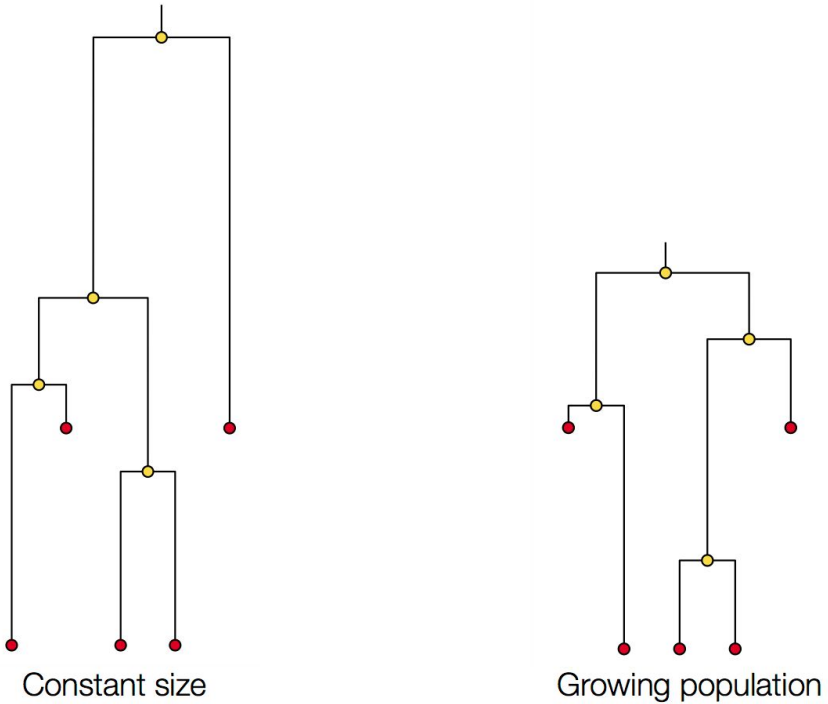
https://github.com/trvrb/gs541-phylodynamics

Tree shape tells us about population size



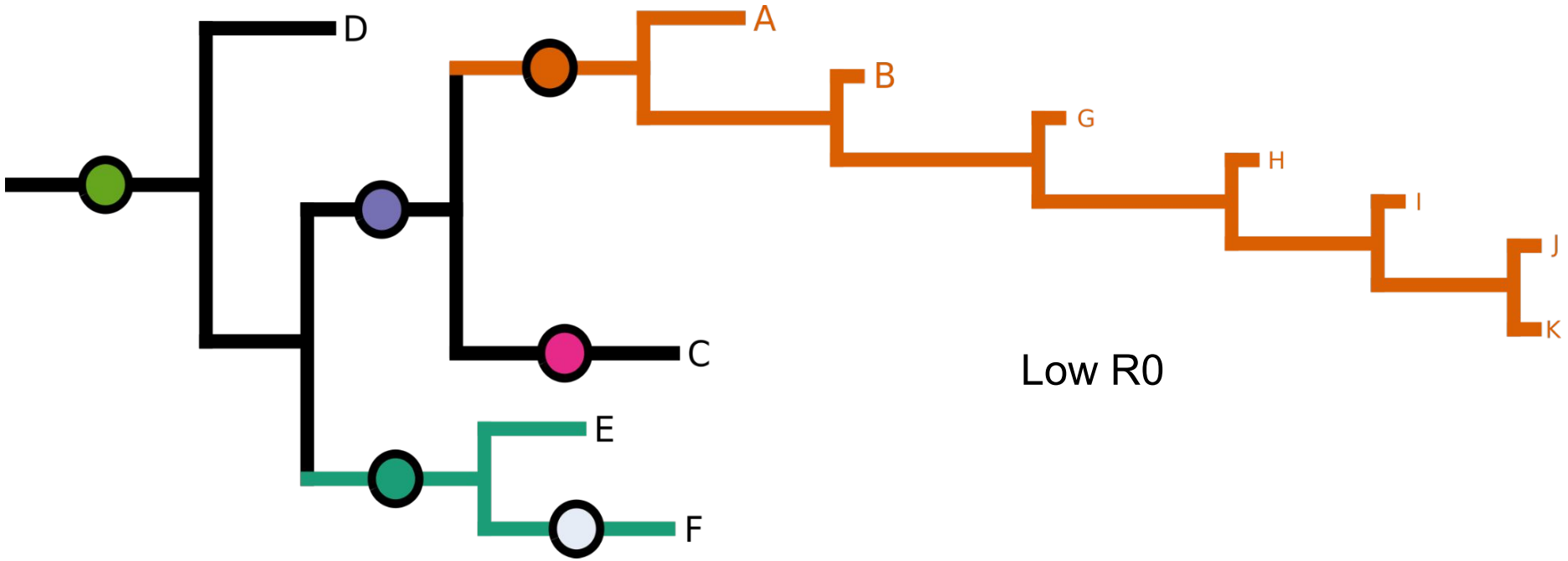
https://github.com/trvrb/gs541-phylodynamics

Tree shape tells us about population size

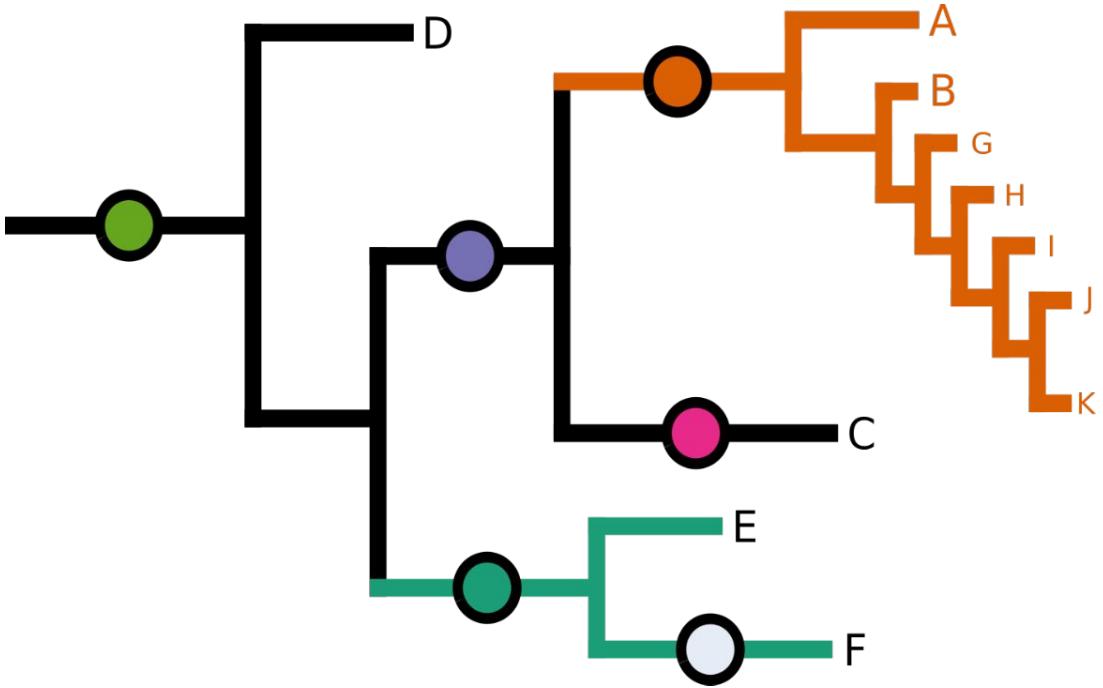


https://github.com/trvrb/gs541-phylodynamics

Can calculate epidemiological parameters from shape

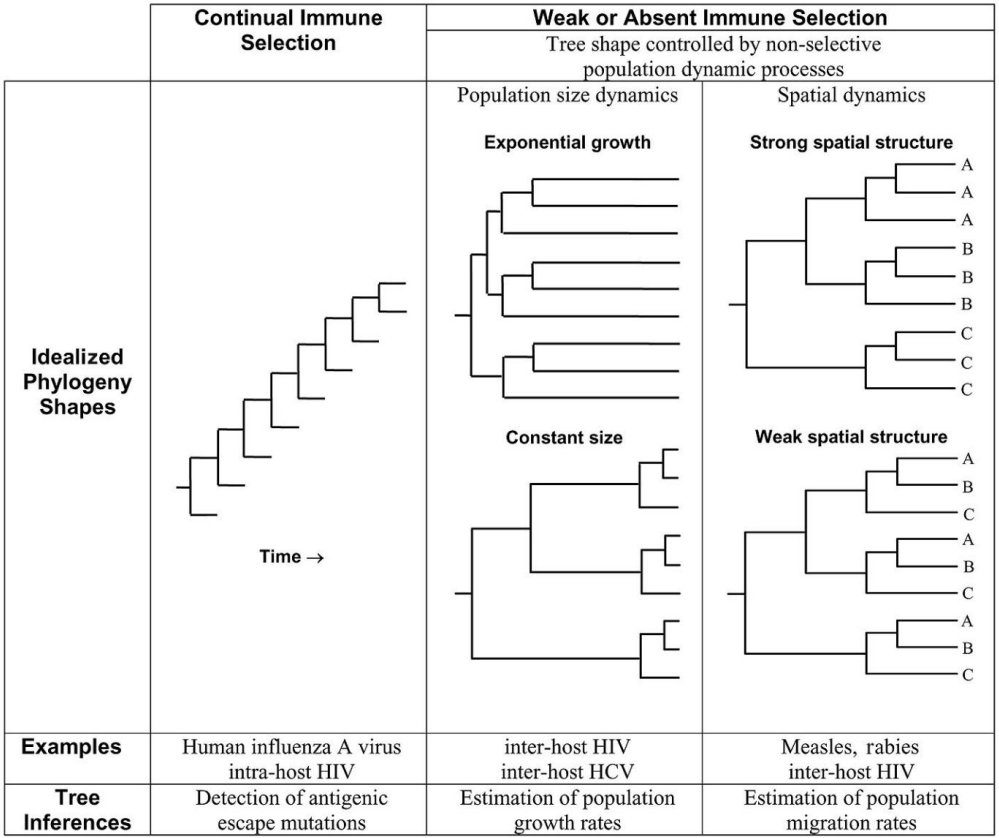


Can calculate epidemiological parameters from shape



High R0

Many other analyses are possible



Massive area:

- Birth-death models
- Coalescent models
- Bayesian skyline/skygrid models
- Spatiotemporal models (phylogeography)
- Recombination
- Inference of selection pressure

Grenfell, B. T. (2004). Unifying the Epidemiological and Evolutionary Dynamics of Pathogens. Science, 303(5656), 327–332. doi:10.1126/science.1090727

Summary

- Pathogen **evolution** and **epidemiology** are intrinsically linked
- Genomics provides insights into **evolution and unobserved events**
- Comparison of DNA sequences to databases can be used for **diagnostics**
- Pattern of mutations across genomes can be used to generate **phylogenies**
- Phylogenies are structured by **sampling**, **ecology, evolution, and epidemiology**
- Probabilistic **Bayesian phylogenetic inference** is a key tool
- Can use these approaches to do many things including:
  - Identify **lineages**
  - Surveille **evolution**
  - Infer **timing/location** of outbreaks/events
  - Determine **epidemiological parameters**