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Developing a genomic surveillance program for syphilis in Canada (and Ontario)

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April 4, 2024

PHO Rounds

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Objectives

- Describe the change in syphilis epidemiology in Canada and abroad
- Describe the *Treponema* genome and the value of a genomic epidemiology program for syphilis
- Describe challenges associated with whole genome sequencing of *Treponema spp.*
- Discuss approaches to sequencing a non-culturable bacterium

Genomics

- Genomics has a quite a few definitions
- A concise definition would be the study of an organisms full complement of genetic information.
- This can include study of genome structure and function, populations dynamics (think antimicrobial resistance)
- With the exception of RNA viruses, all genomes are DNA based

Metagenomics

- Metagenomics has a quite a few definitions and is now used to refer to a fairly broad sub discipline
- We will consider metagenomics to be the study of genetic information of samples containing multiple organisms and/or viruses
- Metagenomics can be used to study diversity within a sample (from species to metabolic pathways) or as commonly used in public health, the generation of a pathogen sequence from a patient sample
- I will refer the latter approach as targeted metagenomics for this talk.

Treponema spp.

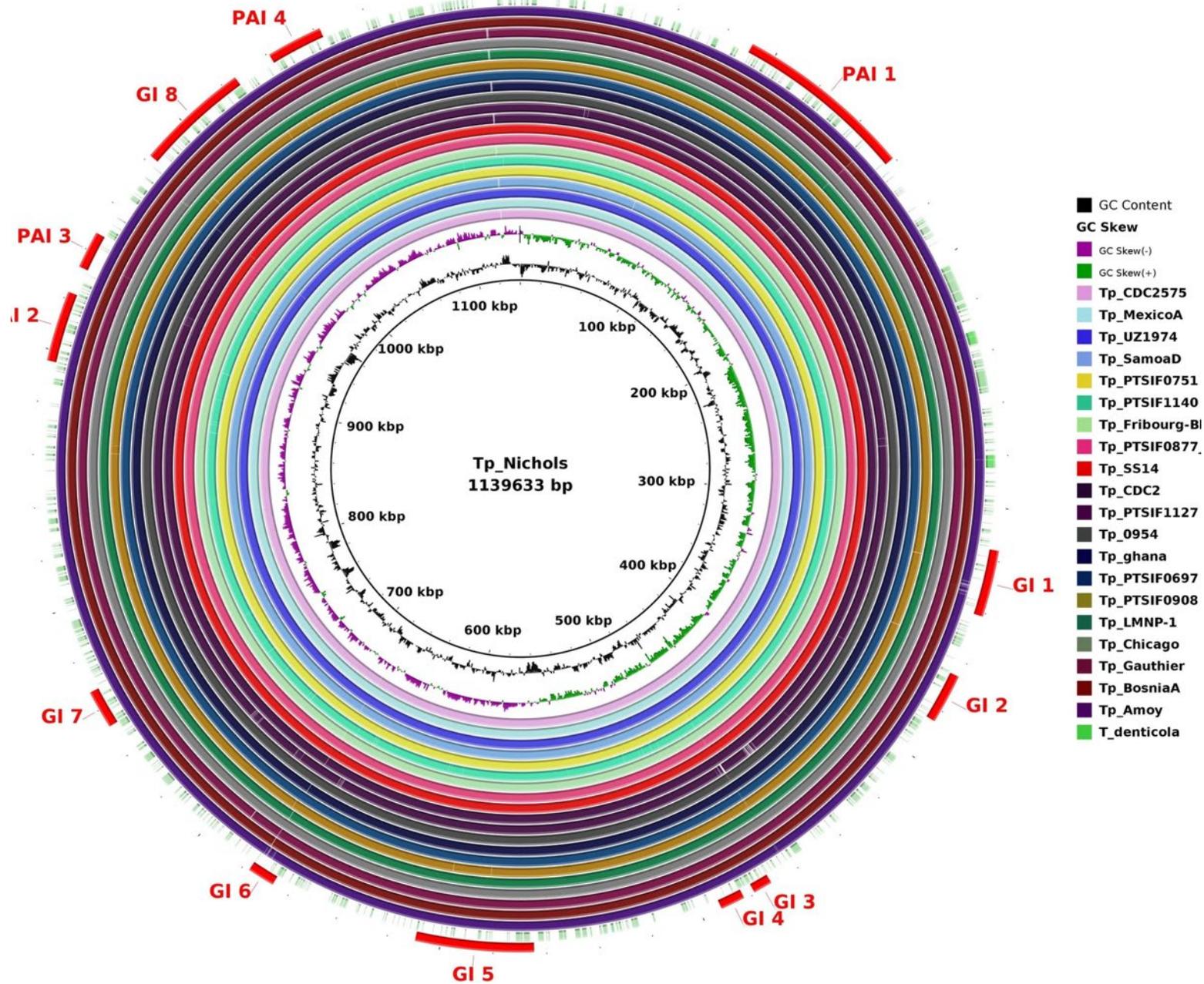
- Composed of pathogenic and nonpathogenic species
- Gram negative, motile, and spiral shaped
- *Treponema pallidum* (*Tp*) is a pathogenic species with four disease causing subspecies
 - *T. pallidum* subsp *endicum* is the causative agent of endemic syphilis (sometimes referred to as Bejel)
 - *T. pallidum* subsp *pertenue* is the causative agent of yaws
 - *T. pallidum* subsp *carateum* is the causative agent of pinta
 - *T. pallidum* subsp *pallidum* is the causative agent of venereal syphilis

Tp



- The different subspecies cause infections with some similarities but differ in epidemiology, clinical presentation, and geography
- Genomics can be challenging for *Treponema pallidum*

Reference 1



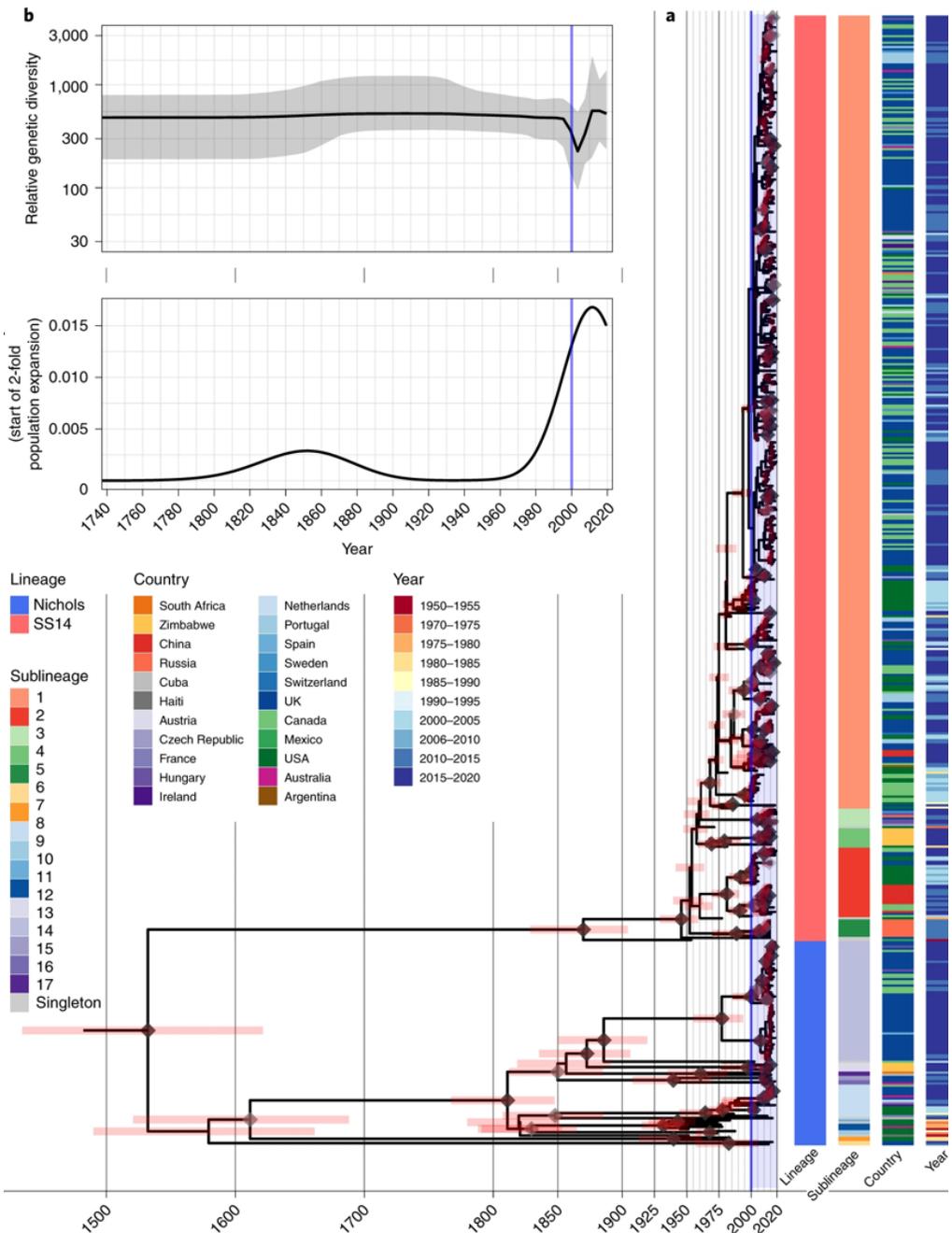
Reference 2

Tp Genomics

- Pathogenicity of *Tp* linked to a protein family named *Treponema pallidum* repeat (tpr) proteins
- These gene that are surface proteins (adhesions and porins) that vary in expression among closely related strains
- They are potential target for vaccine development because they offer potential (and stable antigen) sites

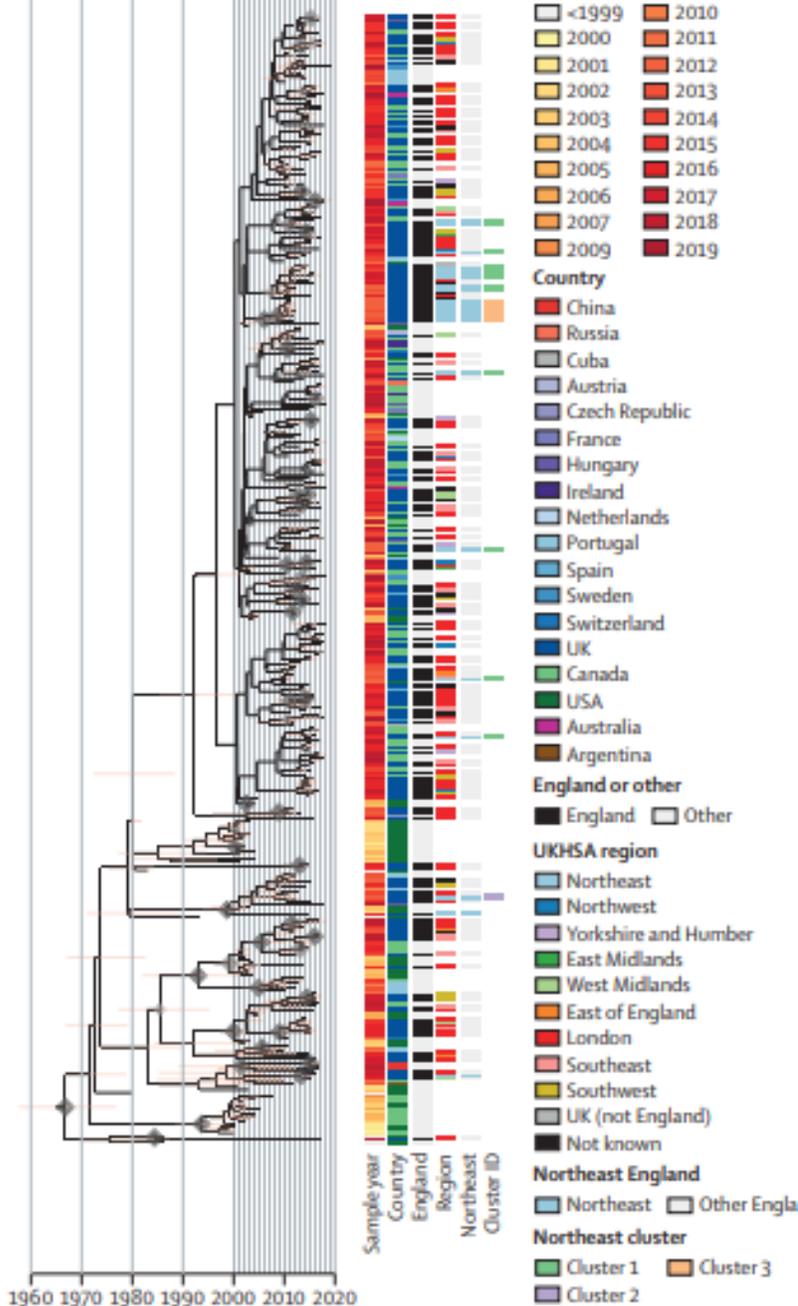
Tp Genomics

- Genomics can help understand the evolution and variability of the different *trp* genes (help guide vaccine development) or identify surface proteins that can be used for POTC
- Macrolide (class of antibiotics) resistance is common among syphilis genomes but penicillin is still an effective treatment!
- ** fun fact – *Treponema pallidum* is capable of coating its surface with host serum proteins or mucopolysaccharides to avoid immune response and immunosuppression



- *Tpp* is comprised of two lineages – Nichols and SS14
- SS14 has greater diversity than Nichols but both have undergone a recent expansion and are found globally
- Many sublineages are shared among multiple countries
- Genomic surveillance is needed to elucidate transmission patterns/networks

Reference 3

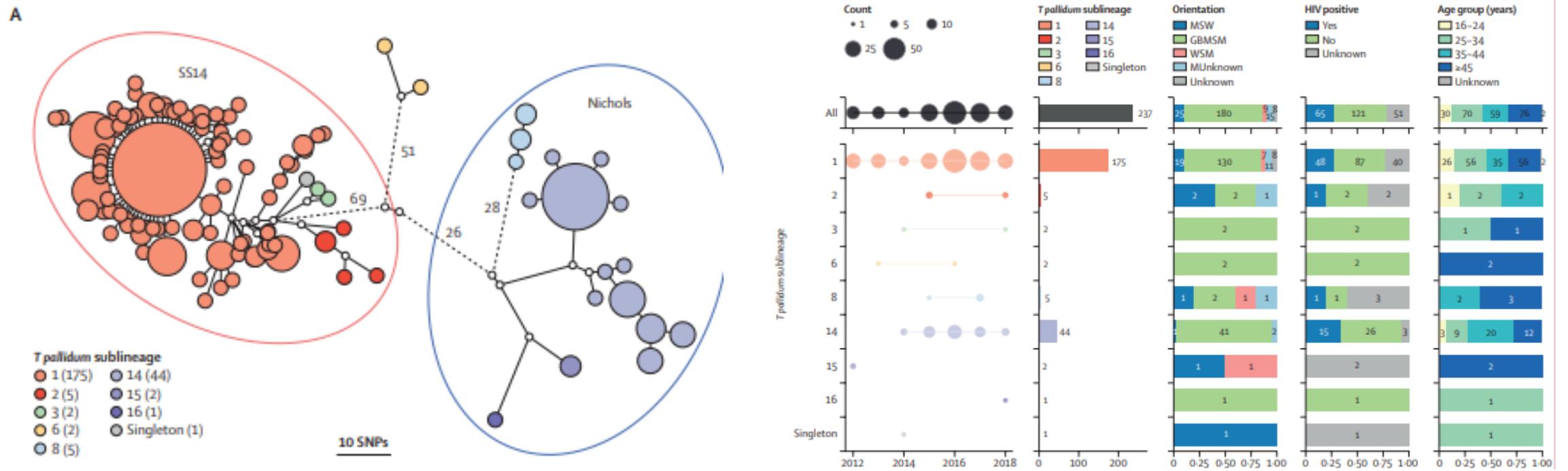


- 237 *Tpp* genomes were sequenced from samples between 2012 and 2018
- Strains circulating in the UK are also found globally
- This is true for the two predominant sublineages circulating in the UK
- These lineages also have widespread macrolide resistance

Reference 4

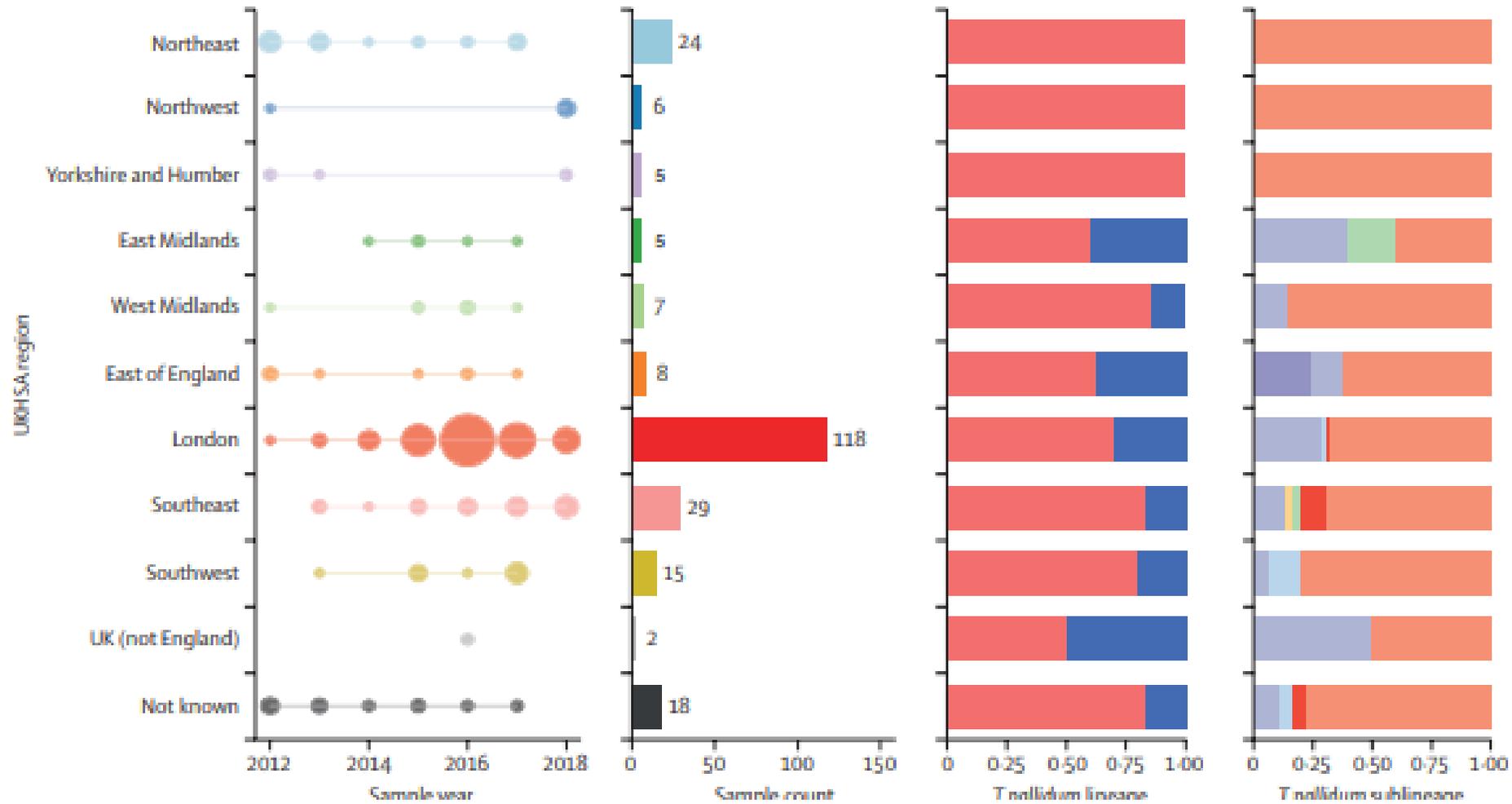
Tpp – UK example

- Two dominant clusters with one being SS14 and the other being Nichols.
- The SS14 cluster showing greater diversity in epidemiological factors including, age, sexual orientation, and gender.



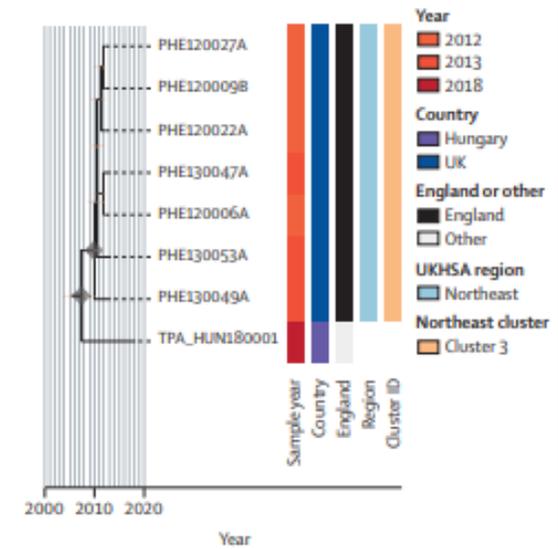
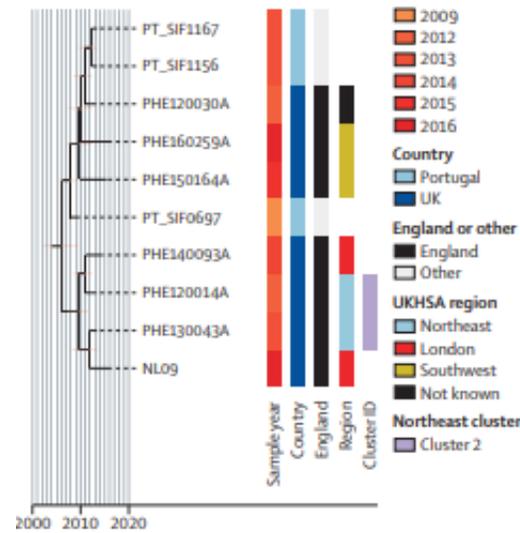
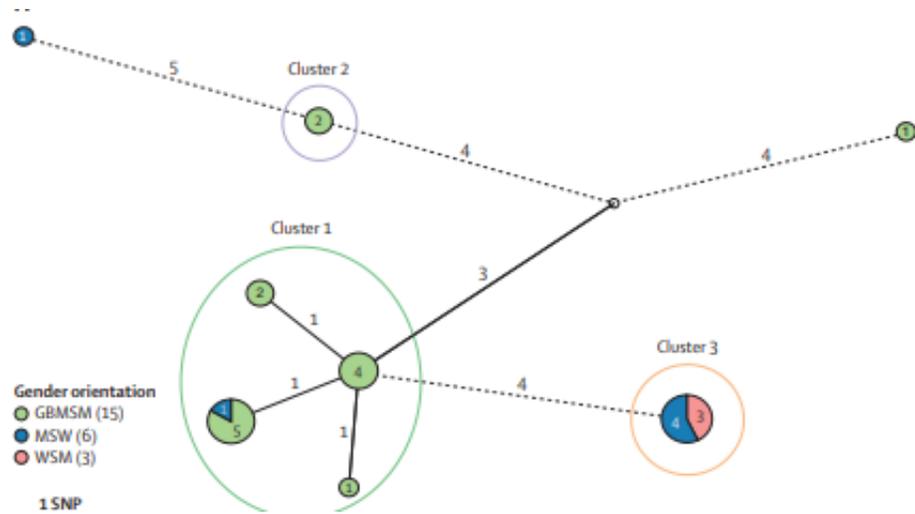
Reference 4

Tpp – UK example



Reference 4

Tpp – UK example

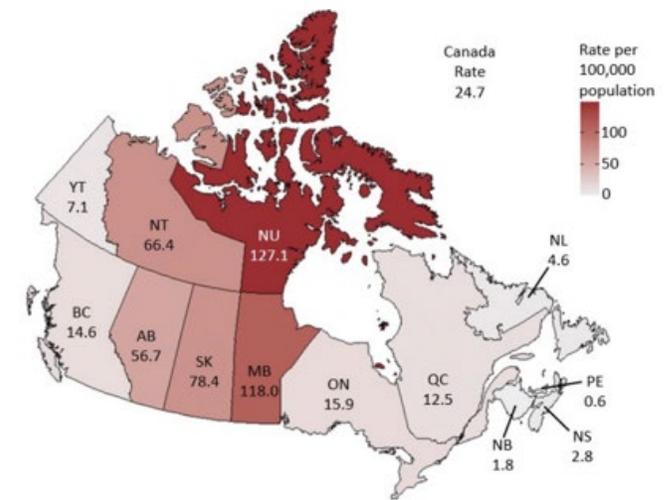


- Analysis of sequences from Northeast England cluster based on epidemiology
- Some of these clusters link more closely with sequences from outside the UK

Reference 4

Tpp – Canada

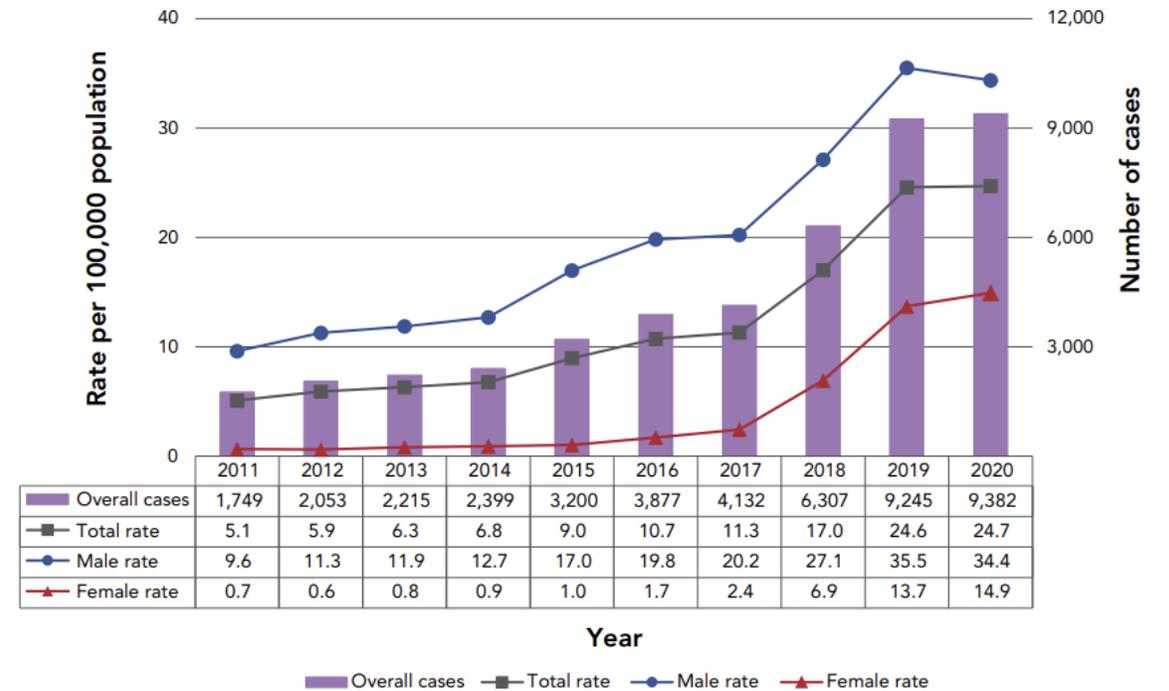
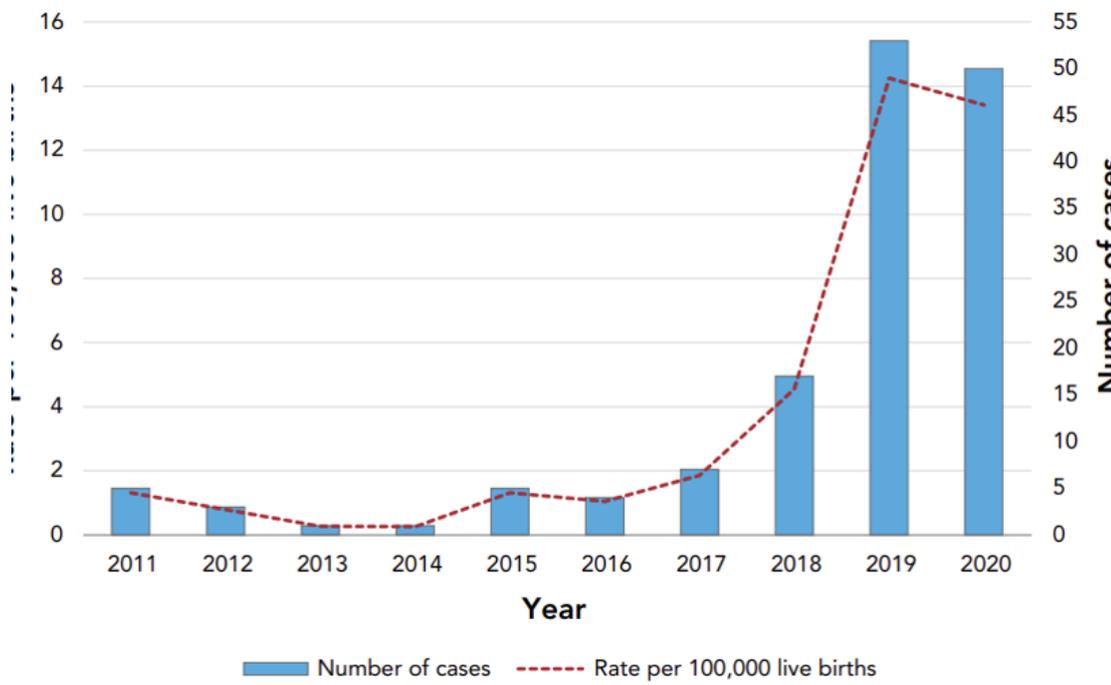
- *T. pallidum* subsp *pallidum* (*Tpp*) is an STI of increasing public health concern in Canada
- In 1998 national goal was to maintain rate at or below 0.5 cases per 100 000 population
- In 2020 national rate was 24.7 cases per 100 000 population with a 773% increase among females from 2016 to 2020



Reference 5

Tpp – Canada

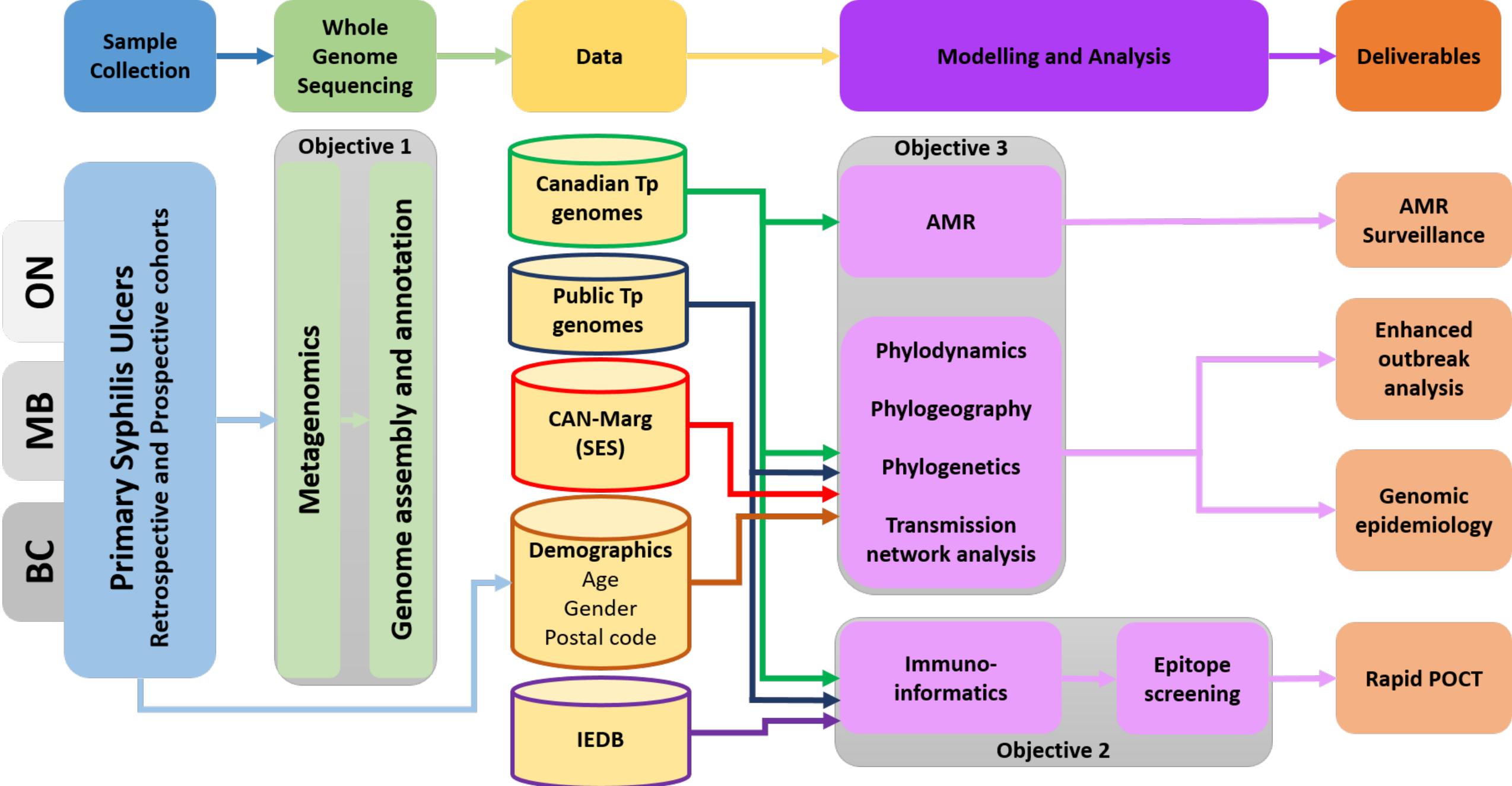
- In Ontario we are also seeing an increase in cases with 15.9 cases per 100 000 population in 2020 increasing to 19.9 cases per 100 000 population in 2021 (~25% increase)
- We need to understand the epidemiology of syphilis in Canada as it is becoming a crisis!

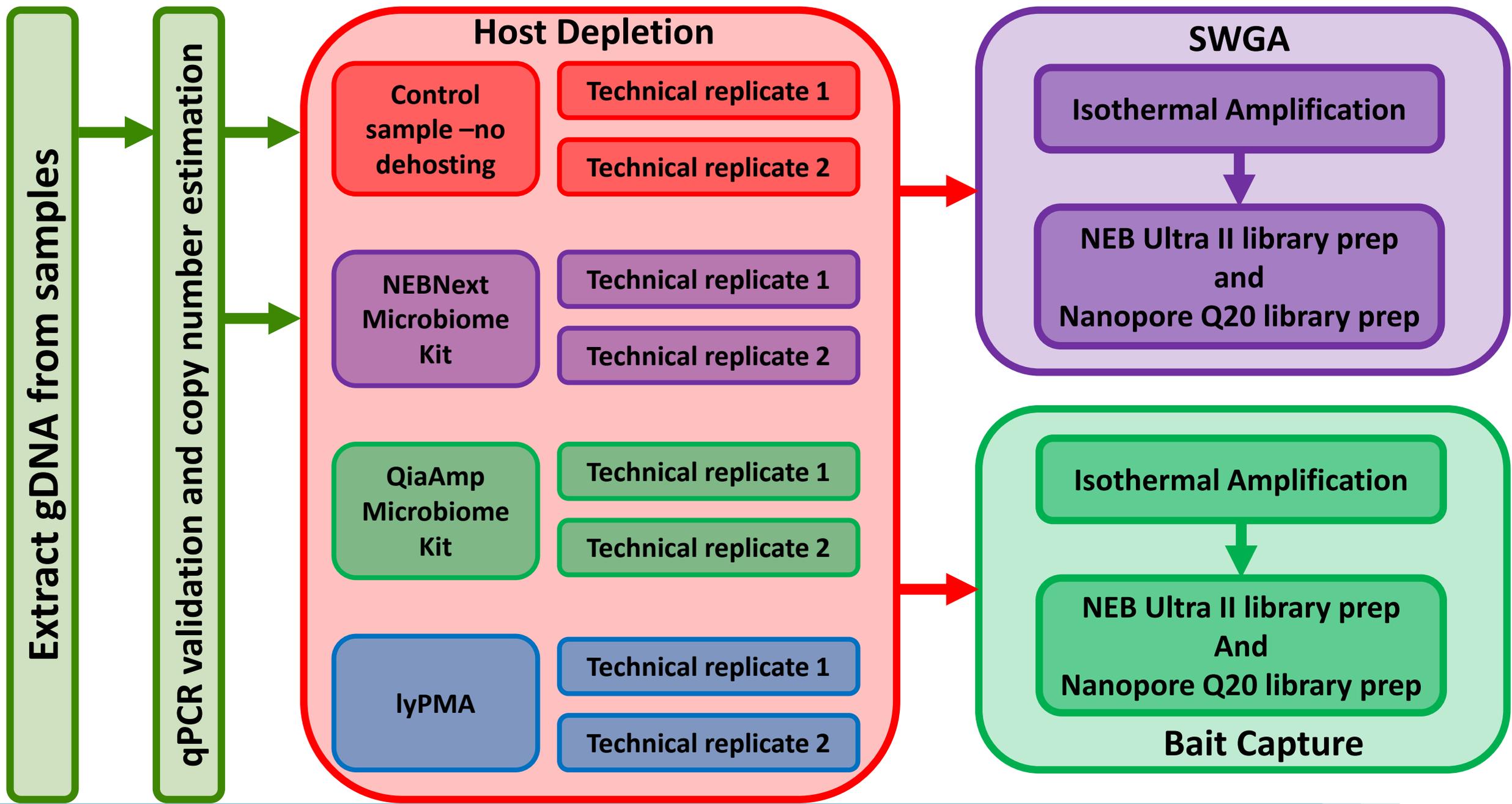


Reference 5

Tpp - Genomic Surveillance

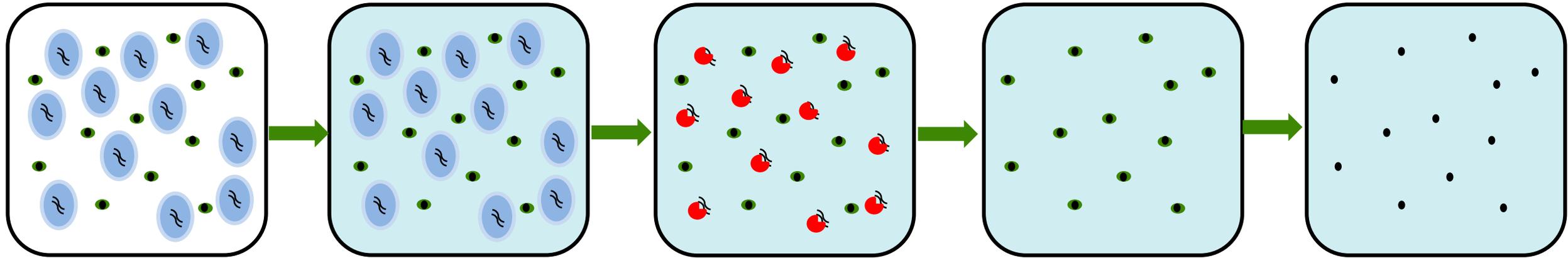
- 1) Develop and implement *Tpp* specific metagenomic analysis of clinical specimens to obtain standardized syphilis WGS data in Canada and to develop subsequent bioinformatic pipelines.
- 2) Analyse genomes of *Tpp* using immuno-informatics to identify novel antigens/epitopes that can be used to develop innovative rapid diagnostic platforms such as point-of-care tests (both rapid antigen and antibody detection tests).
- 3) *Tpp* genomes will be used to conduct molecular surveillance, outbreak potential and spatio-temporal dynamics; and to characterize and predict antibiotic susceptibility.



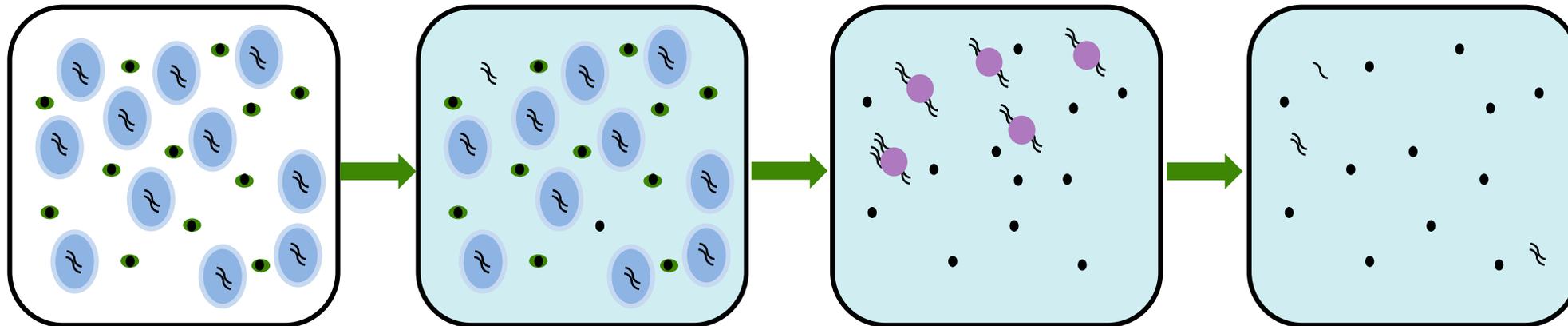


Sample Biasing Methods

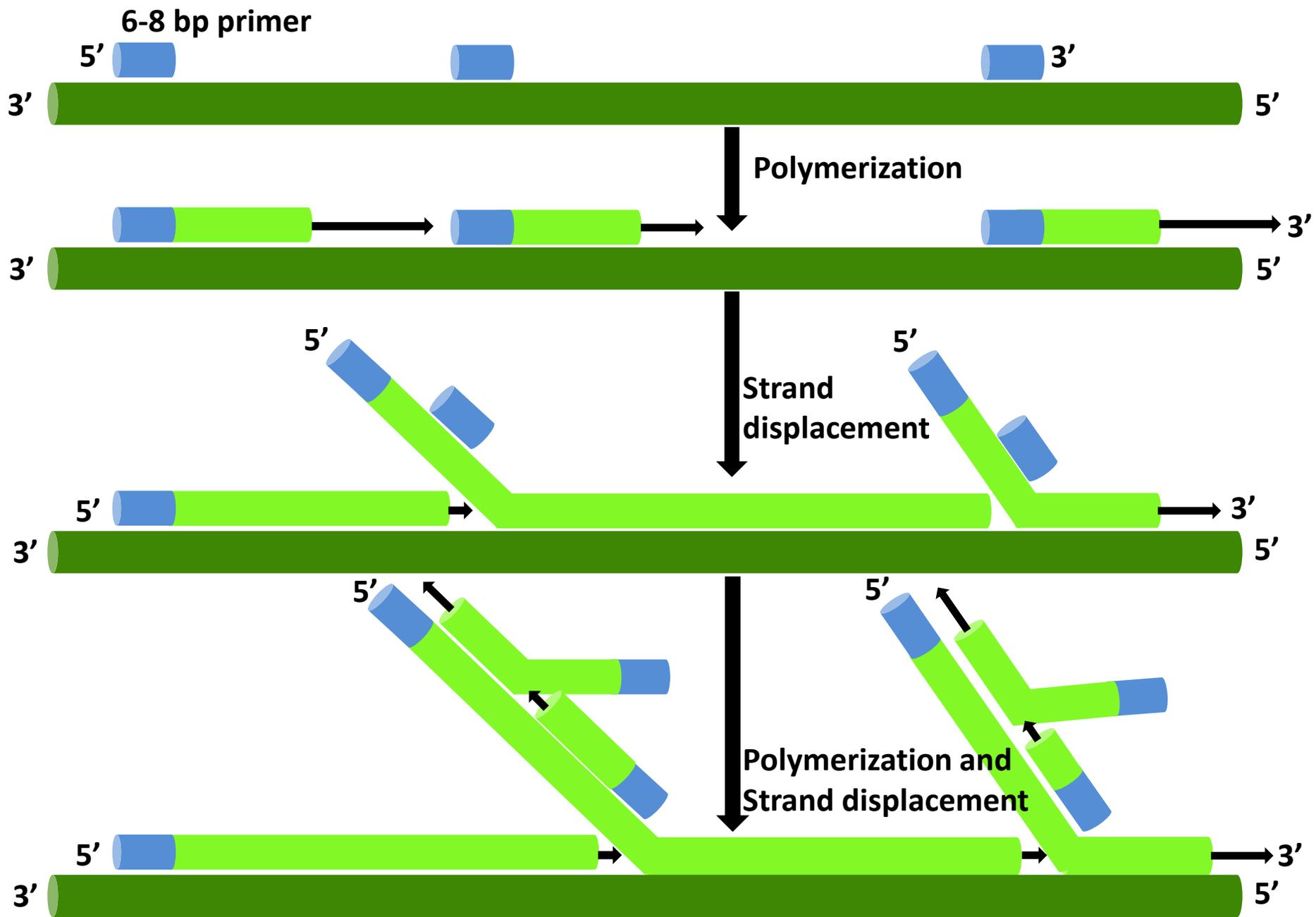
Differential lysis



Selective enrichment



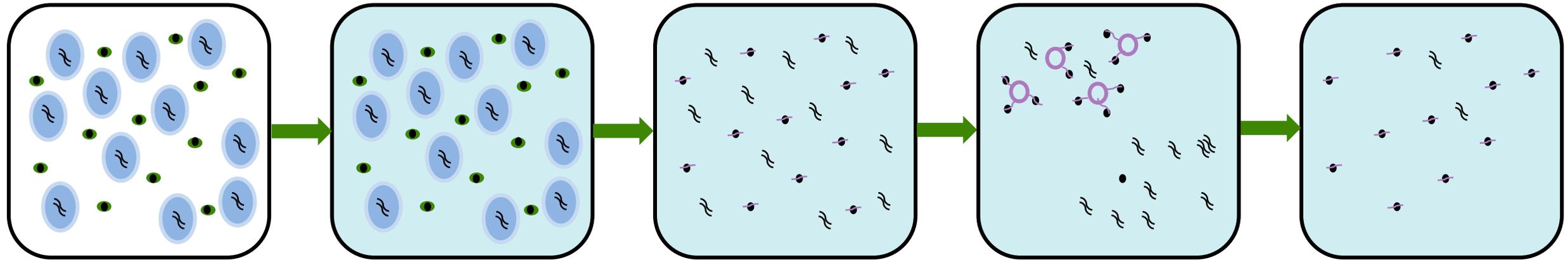
Selective Whole Genome Amplification

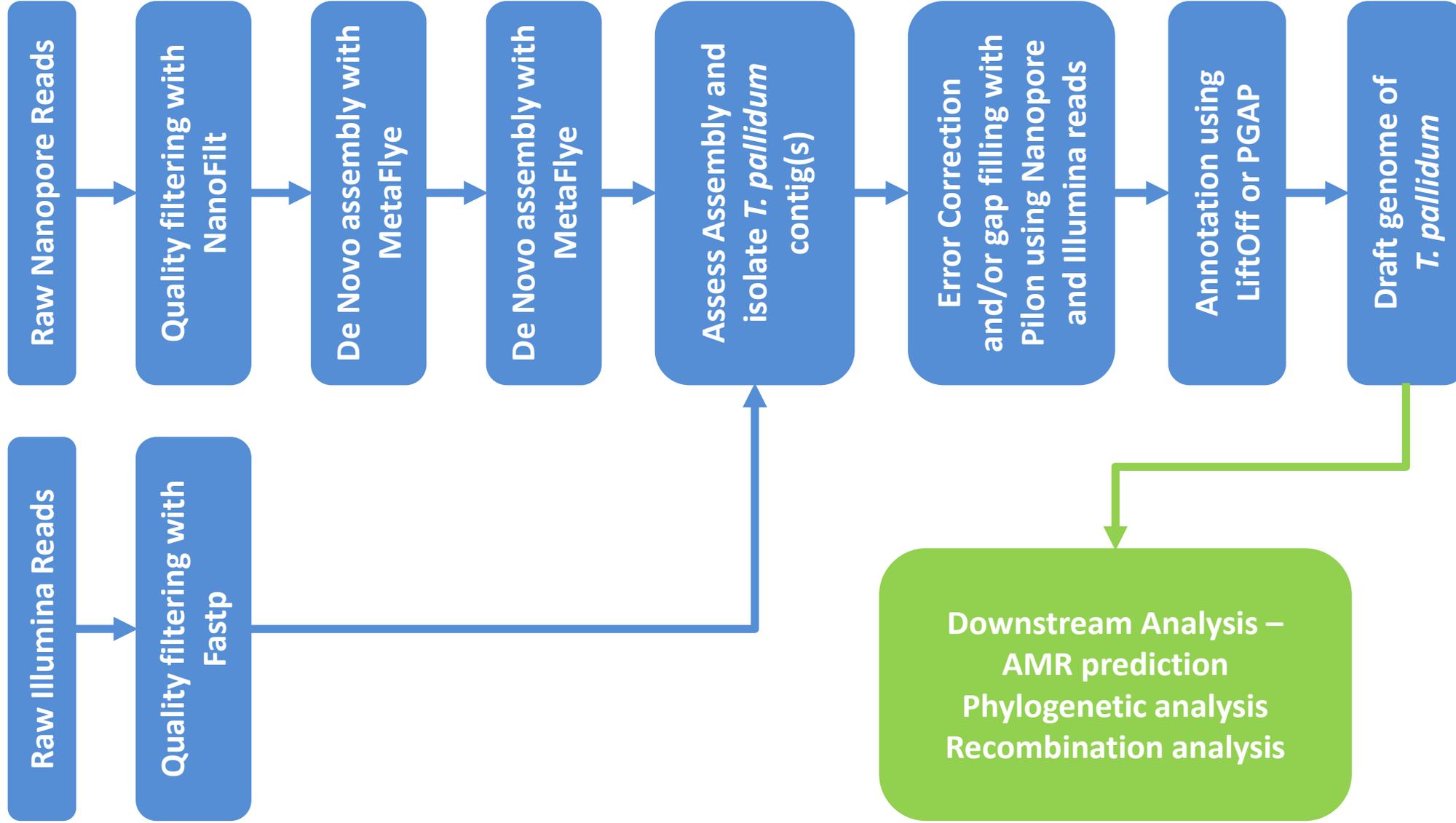


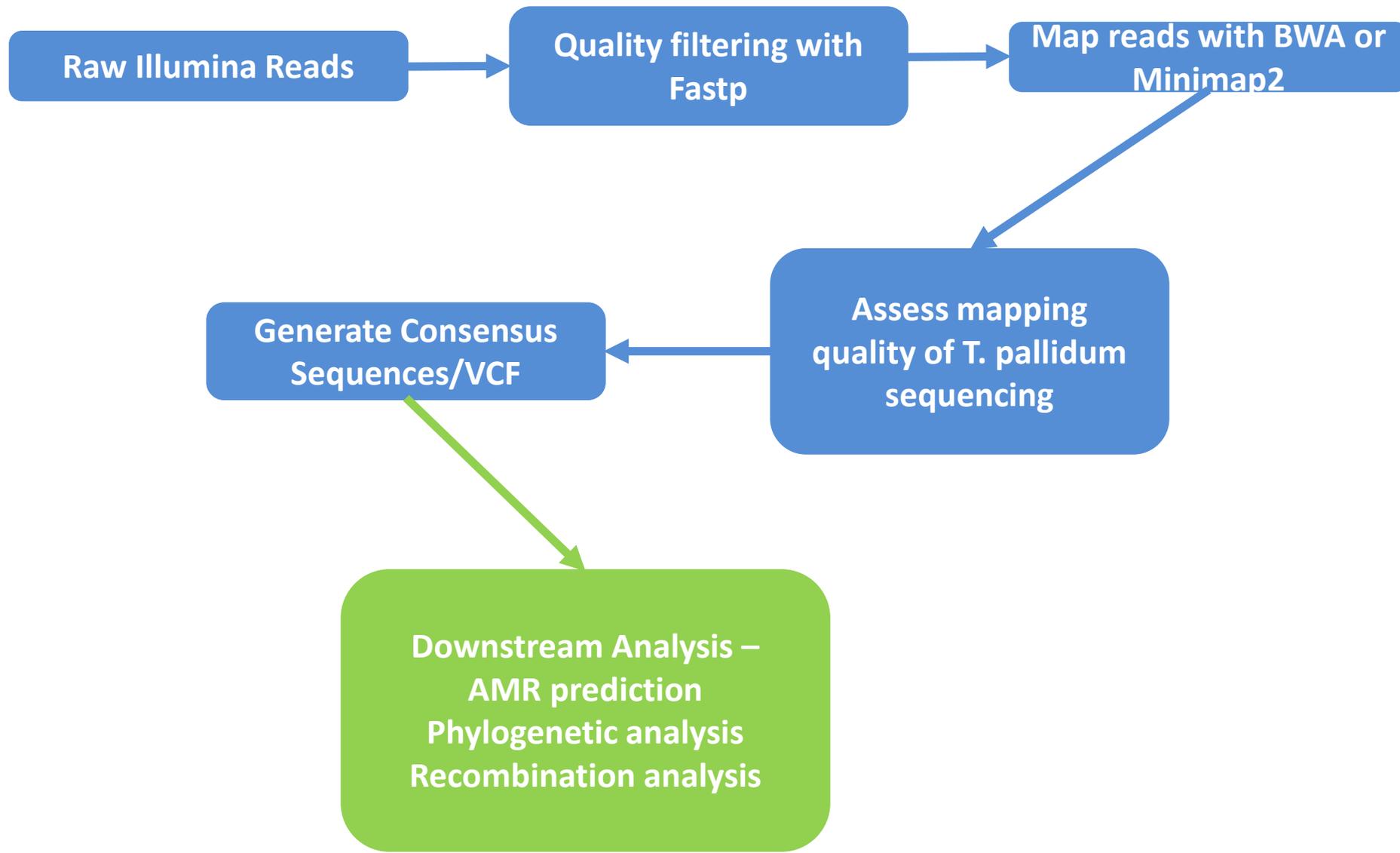
Reference 6

Sample Biasing Methods

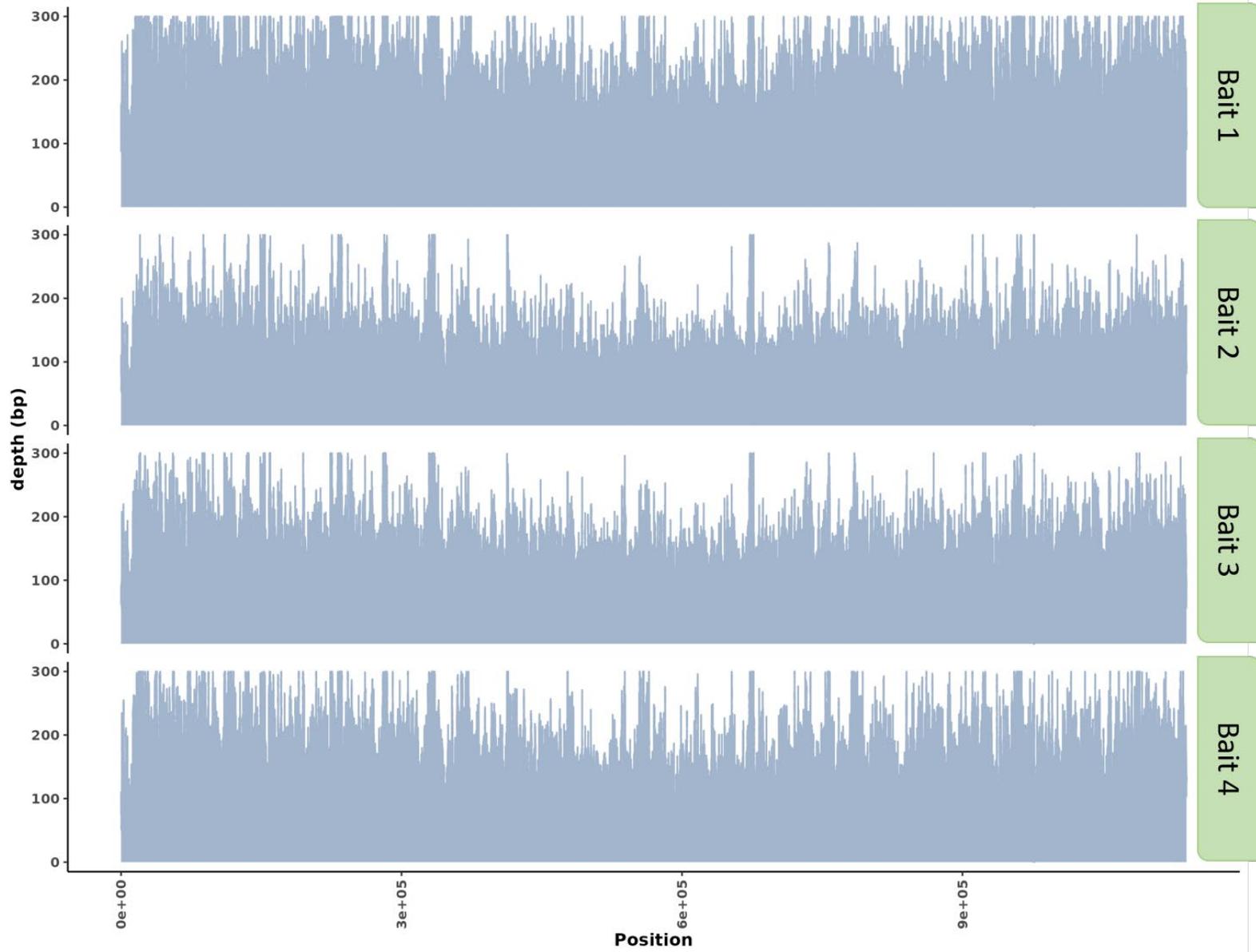
Bait capture

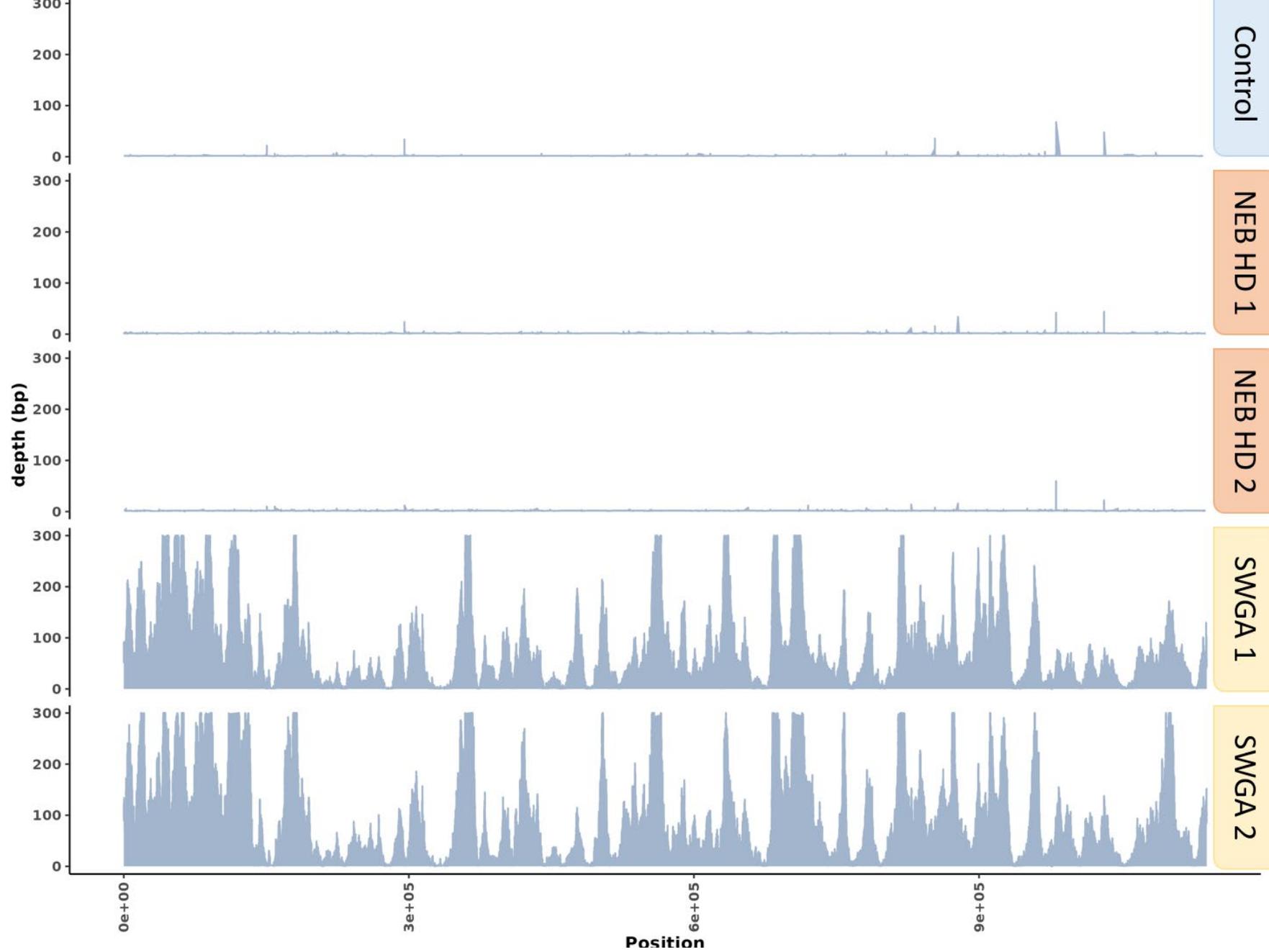


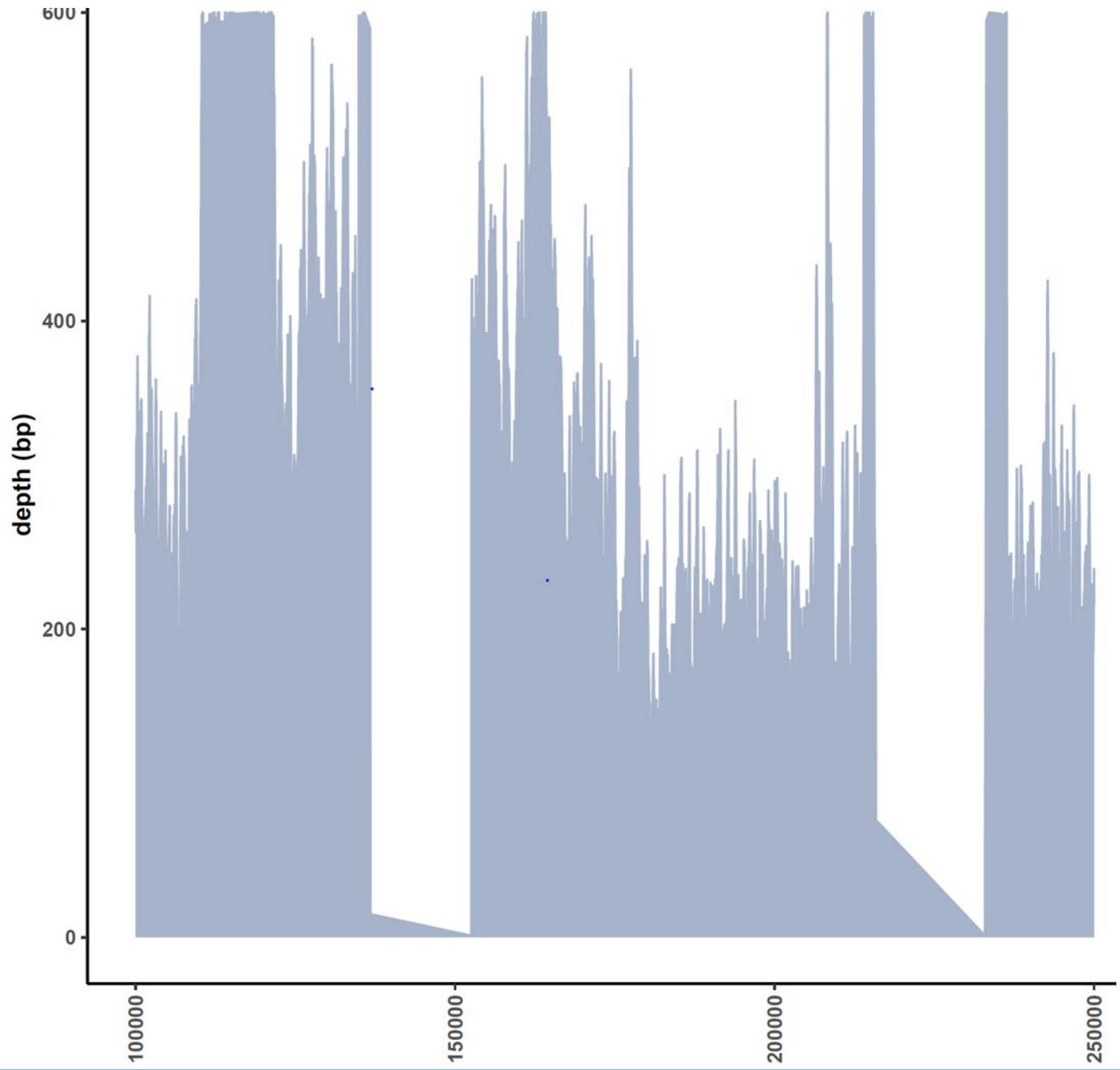




Sample	Clean Raw	Mapped	Mapped fraction	Coverage
Control	859820	1498	0.17%	4.78
Bait 1	1260110	1103112	87.54%	99.99
Bait 2	868562	730412	84.09%	99.99
Bait 3	918940	823556	89.62%	99.99
Bait 4	1039116	919719	88.51%	99.99
NEB HD 1	836296	1714	0.20%	12.74
NEB HD 2	740436	1464	0.20%	11.99
SWGA 1	587120	307255	52.33%	70.86
SWGA 2	731486	412854	56.44%	92.44







References

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5. Aho, J., Lybeck, C., Tetteh, A. *et al.* Rising Syphilis Rates in Canada, 2011-2020. *Can Commun Dis Rep* **23**, 52-60 (2022)
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