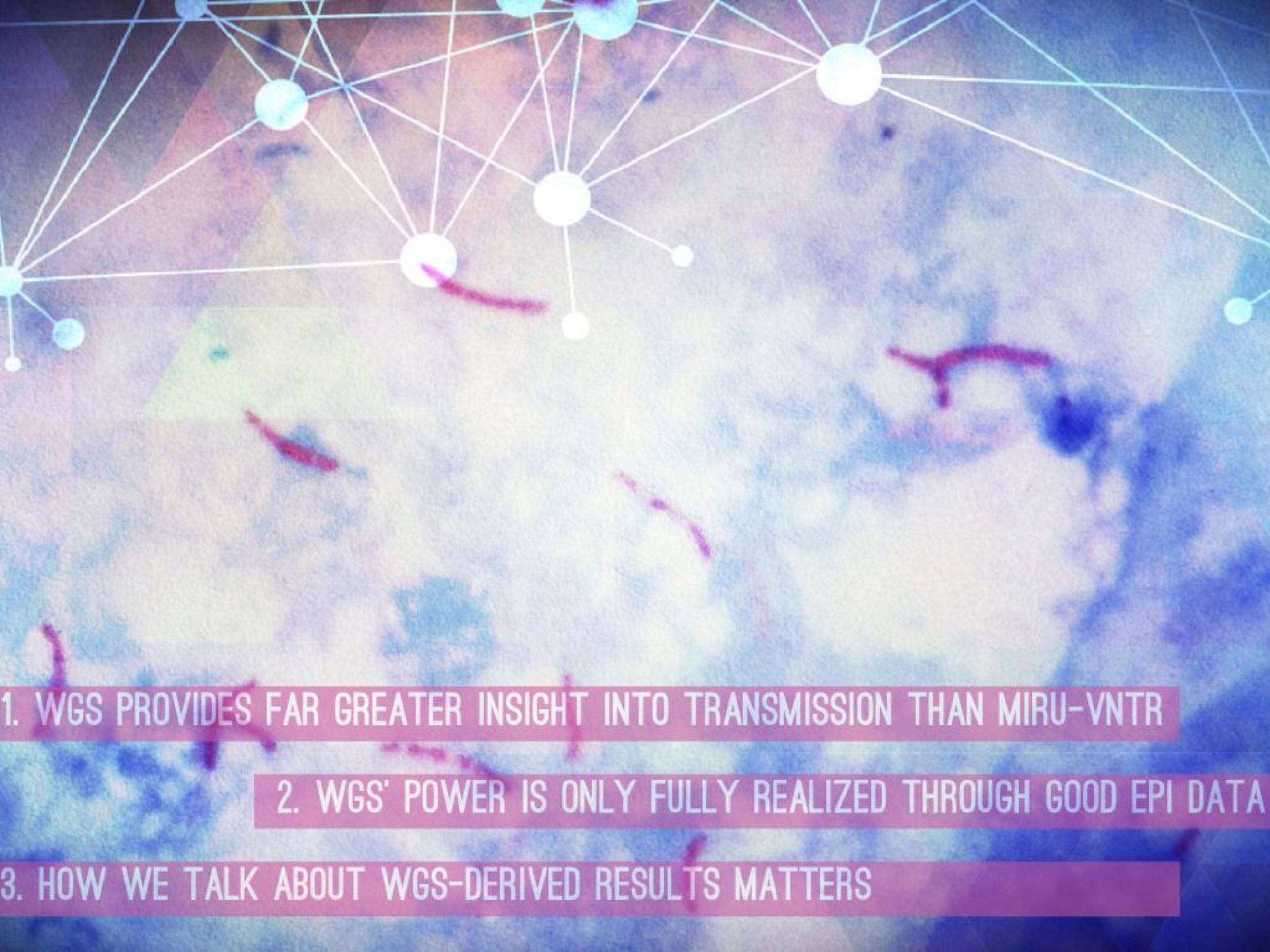
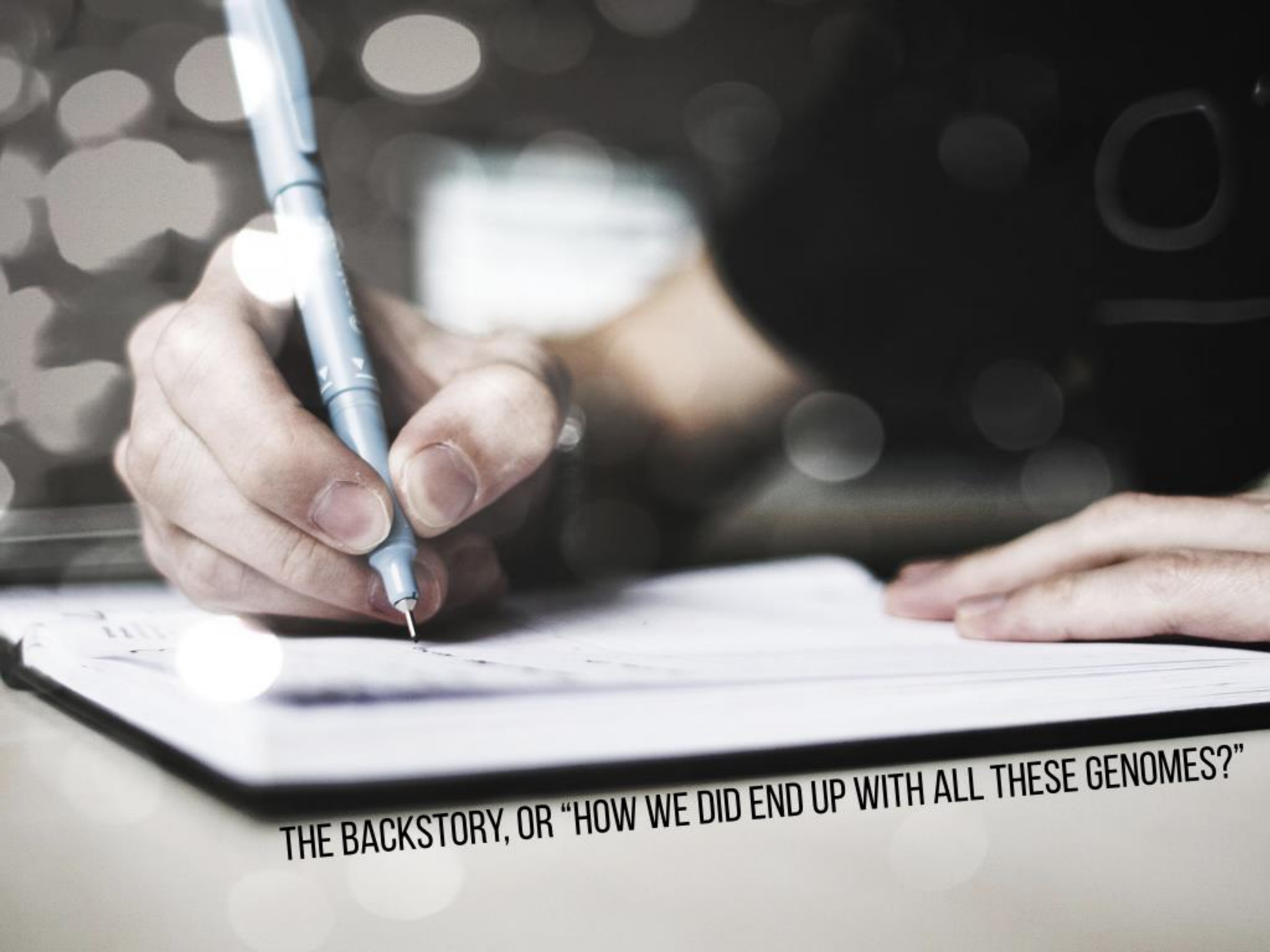
Using whole genome sequencing to drive TB elimination in a low-incidence setting

Jennifer Gardy, BC Centre for Disease Control



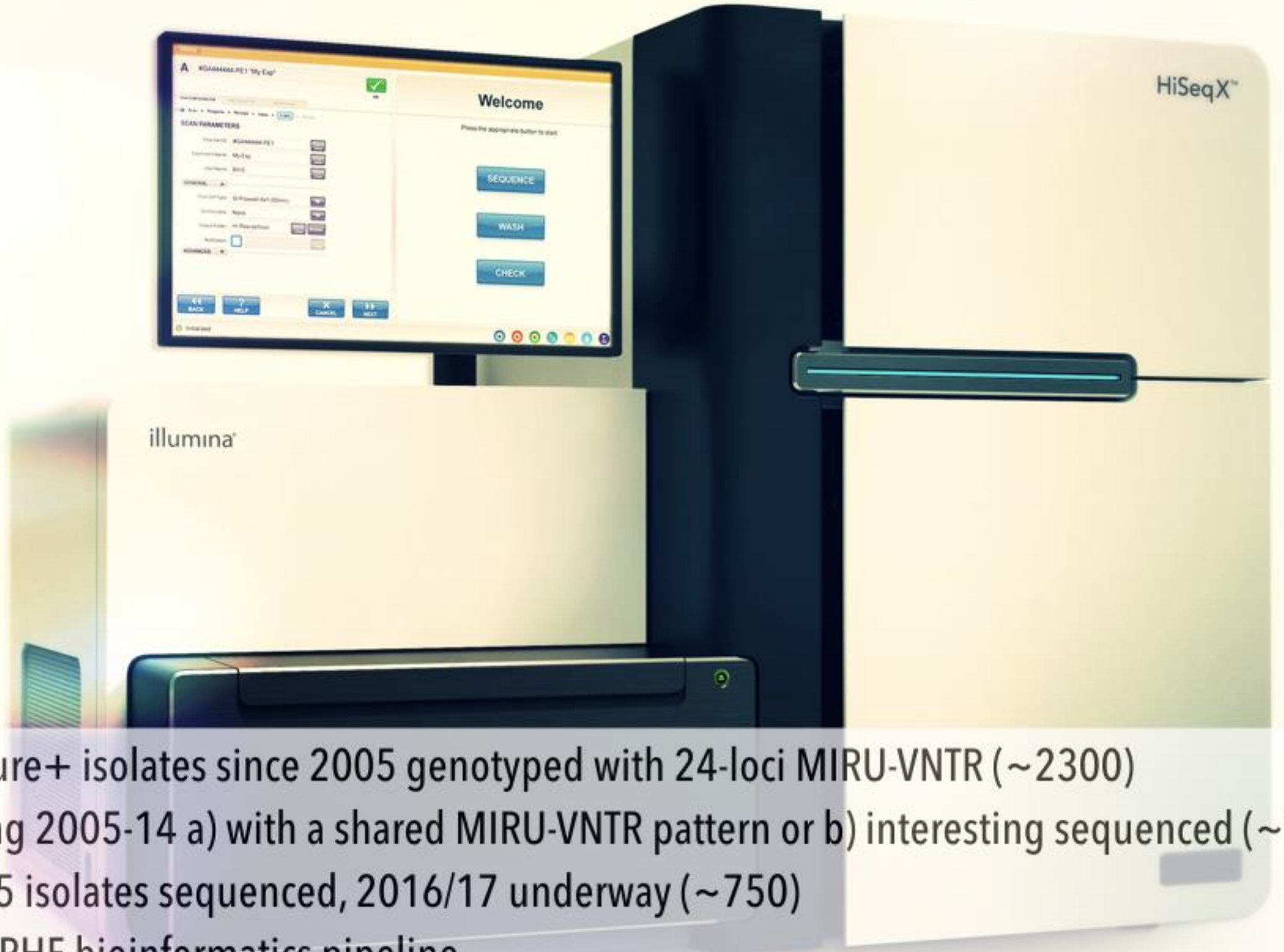
1. WGS PROVIDES FAR GREATER INSIGHT INTO TRANSMISSION THAN MIRU-VNTR
2. WGS' POWER IS ONLY FULLY REALIZED THROUGH GOOD EPI DATA
3. HOW WE TALK ABOUT WGS-DERIVED RESULTS MATTERS



THE BACKSTORY, OR "HOW WE DID END UP WITH ALL THESE GENOMES?"

MOST TB IN BC OCCURS IN PEOPLE BORN OUTSIDE CANADA

TB IN THE CANADIAN-BORN IS CONCENTRATED IN OUR MOST VULNERABLE POPULATIONS



- All culture+ isolates since 2005 genotyped with 24-loci MIRU-VNTR (~2300)
- Anything 2005-14 a) with a shared MIRU-VNTR pattern or b) interesting sequenced (~1400)
- All 2015 isolates sequenced, 2016/17 underway (~750)
- Oxford/PHE bioinformatics pipeline
- Genomes and resistance data in NCBI

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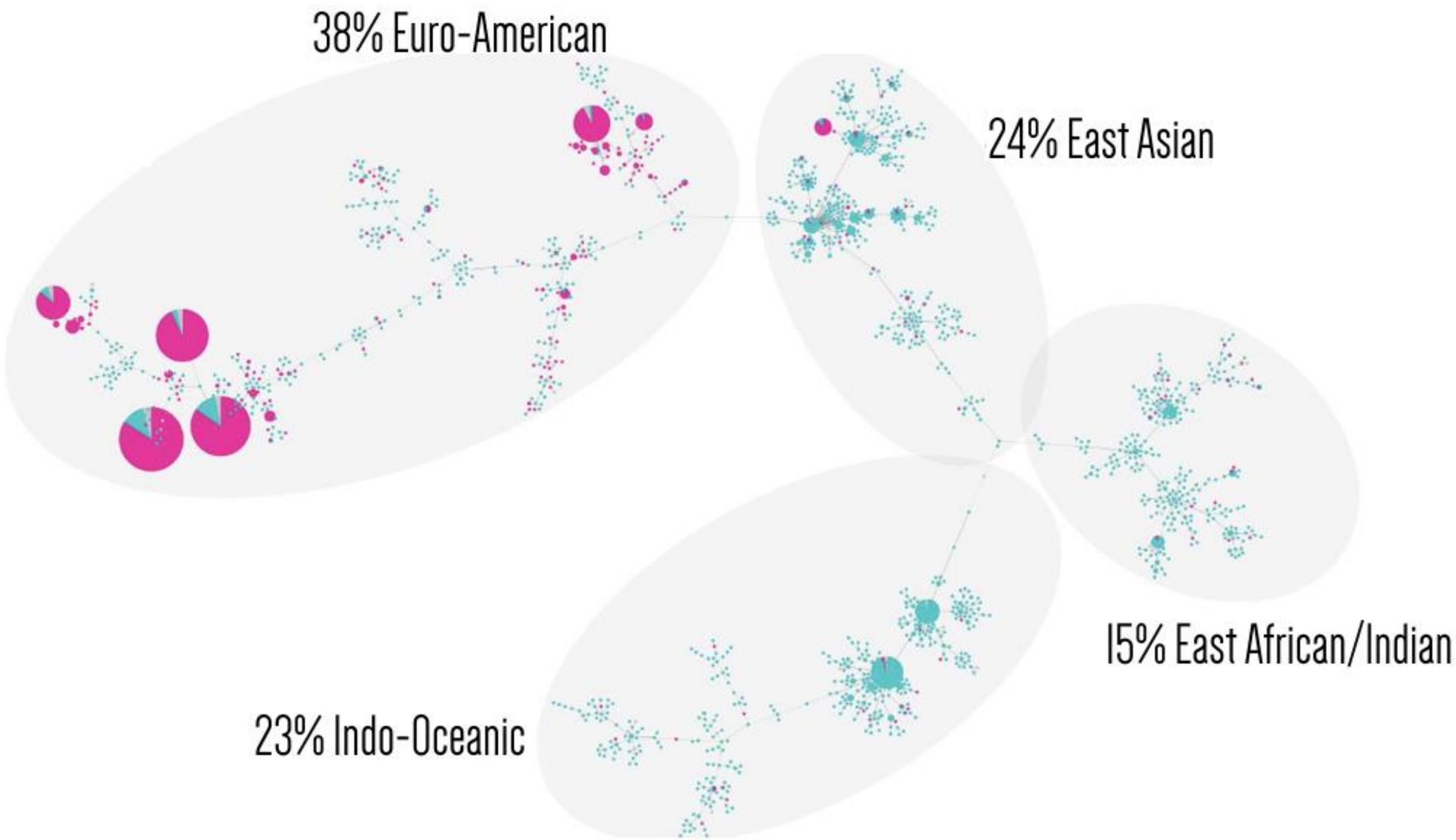
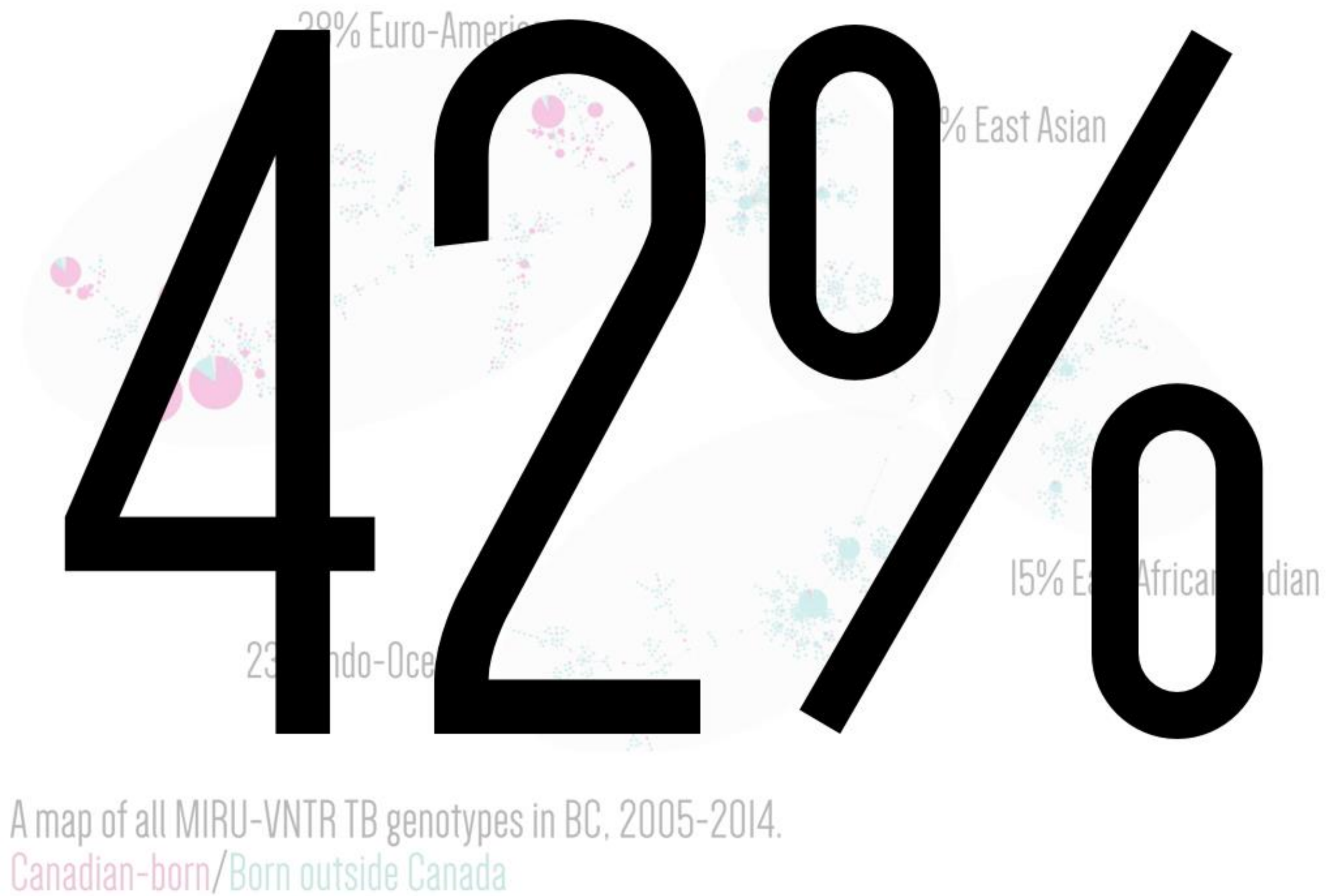


A map of all MIRU-VNTR TB genotypes in BC, 2005-2014.
Canadian-born/Born outside Canada



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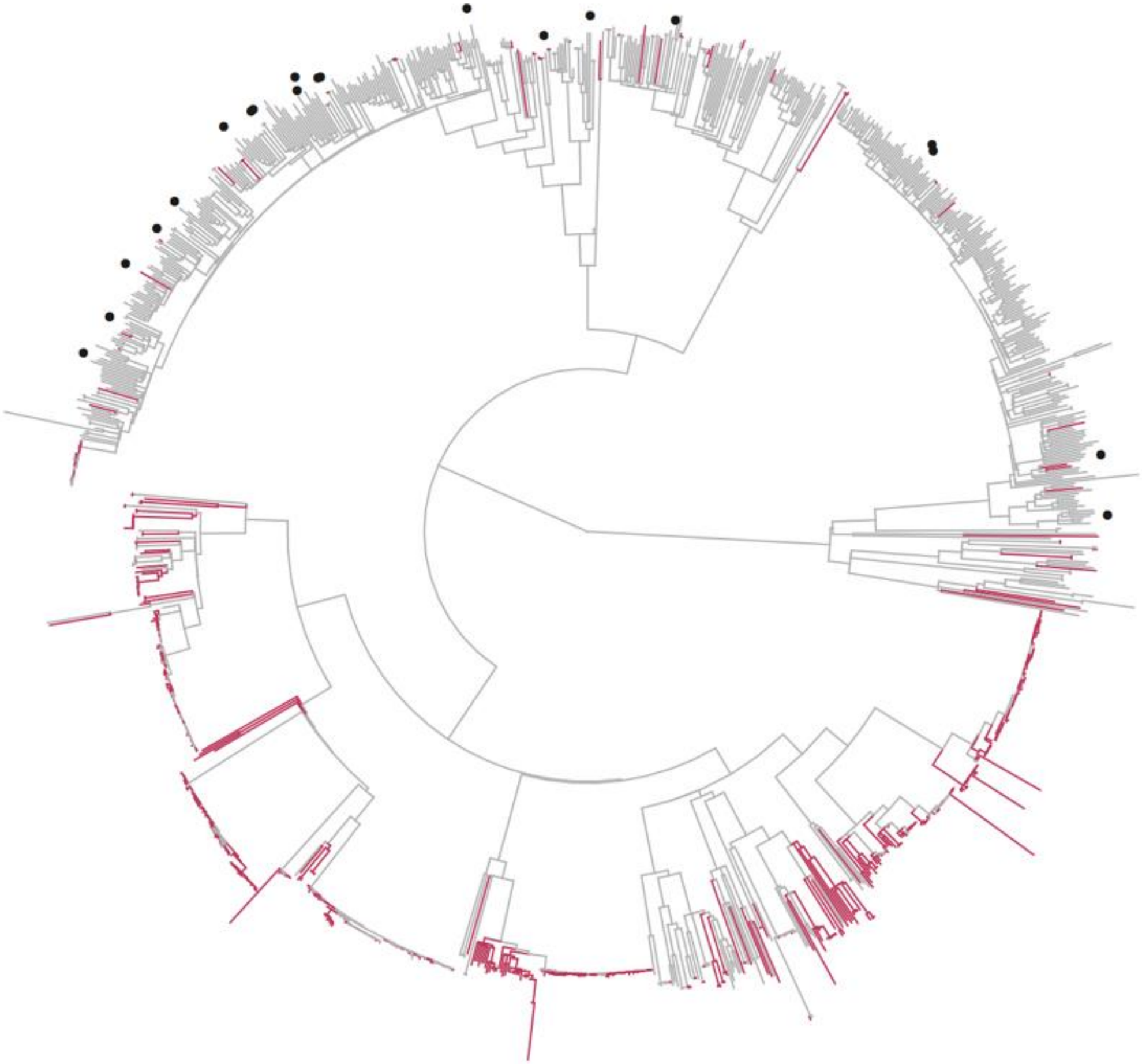
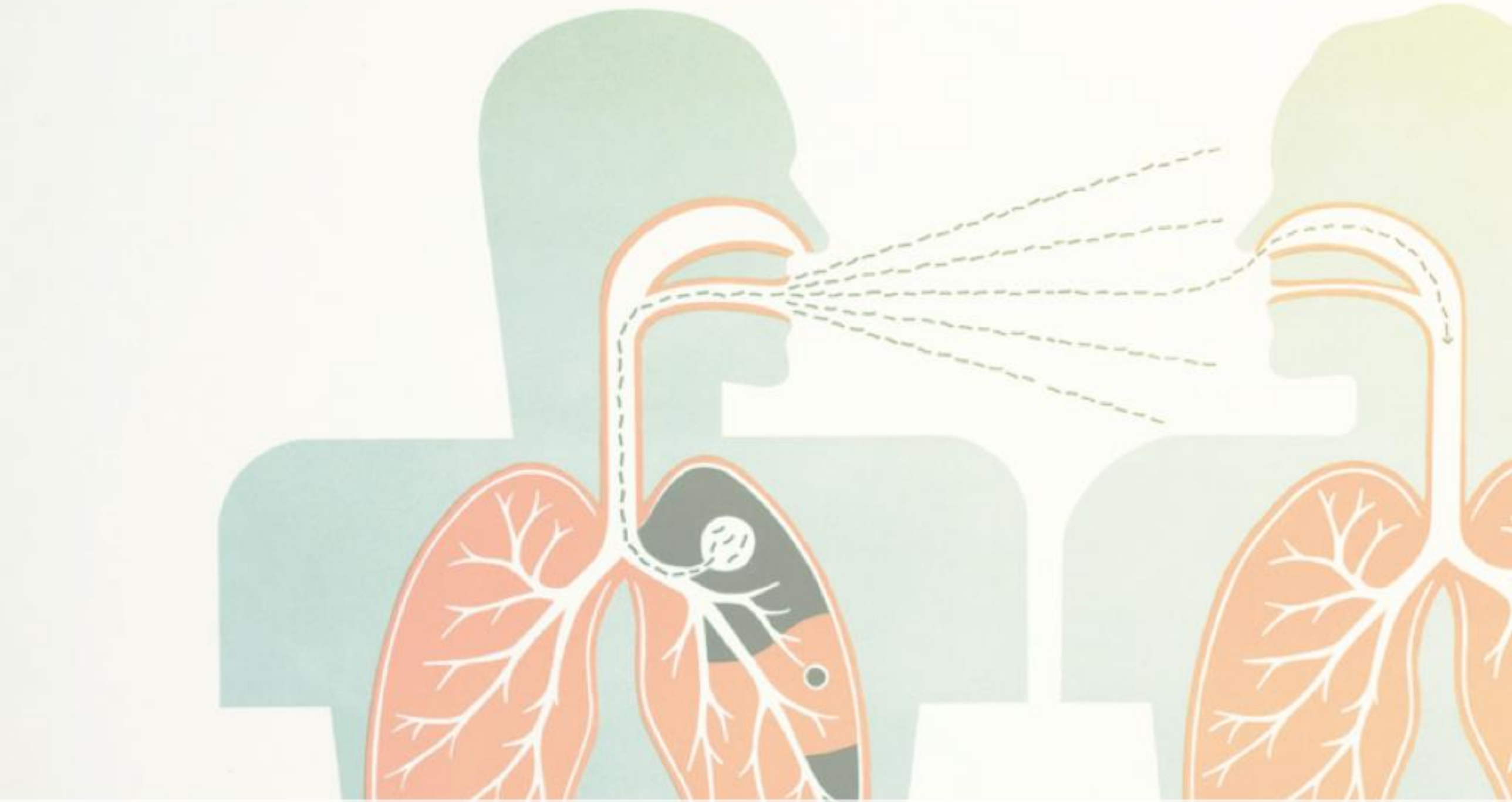


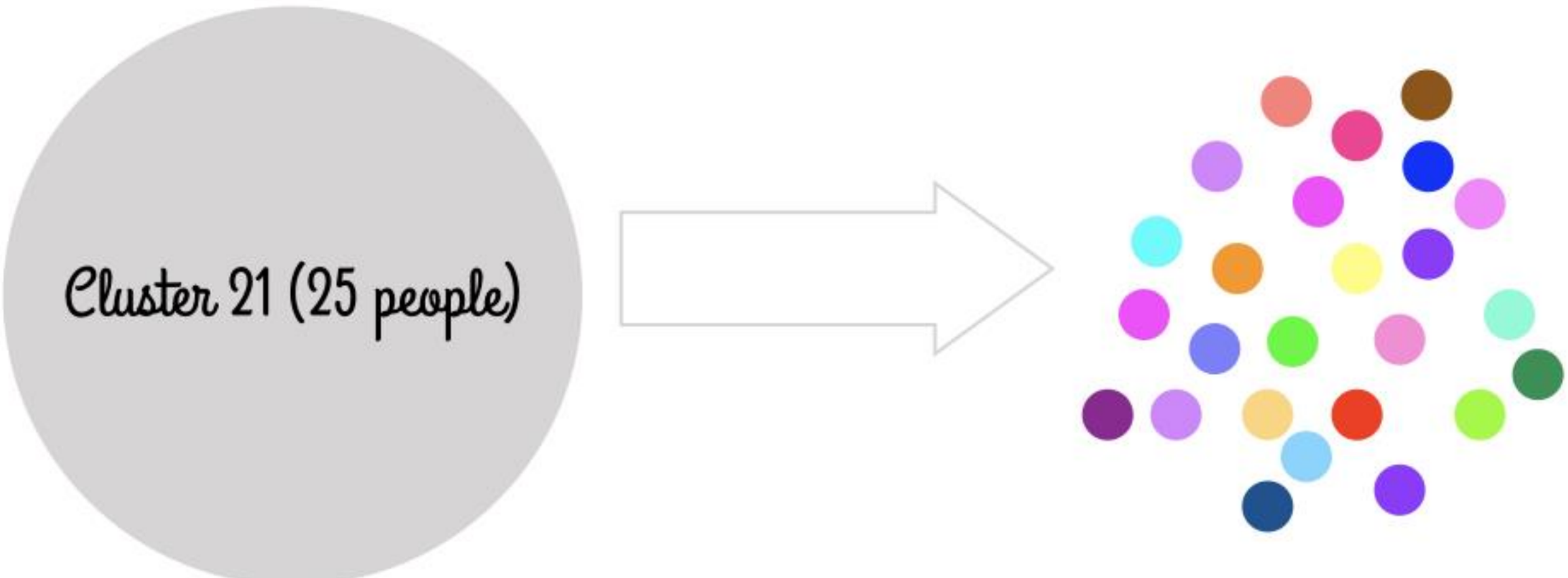
24%

Tuberculosis Germs Get from One Body into Another



ONE IN FOUR TB CASES IN BC IS DUE TO LOCAL TRANSMISSION

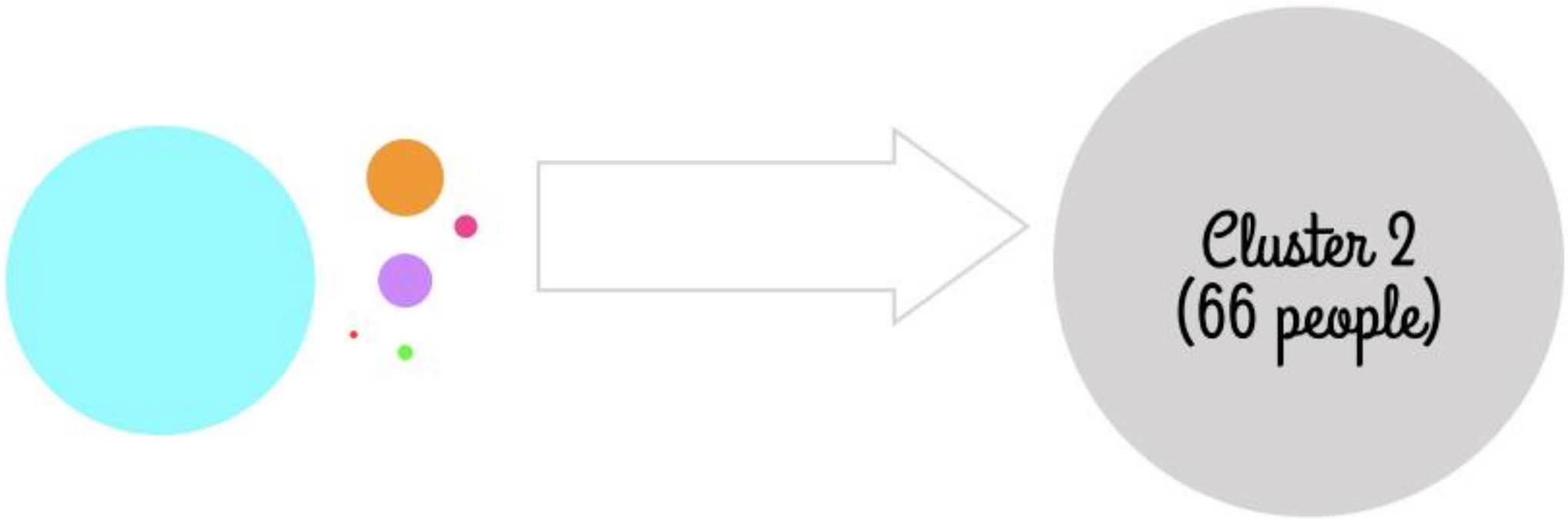
SOME MIRU-VNTR CLUSTERS DISINTEGRATE AFTER WGS



SOME MIRU-VNTR CLUSTERS DISINTEGRATE AFTER WGS

OF 195 UNIQUE MIRU-VNTR CLUSTERS, 100 COMPLETELY DISINTEGRATED AFTER WGS

95% OF THESE ISOLATES WERE NON EURO-AMERICAN LINEAGE STRAINS



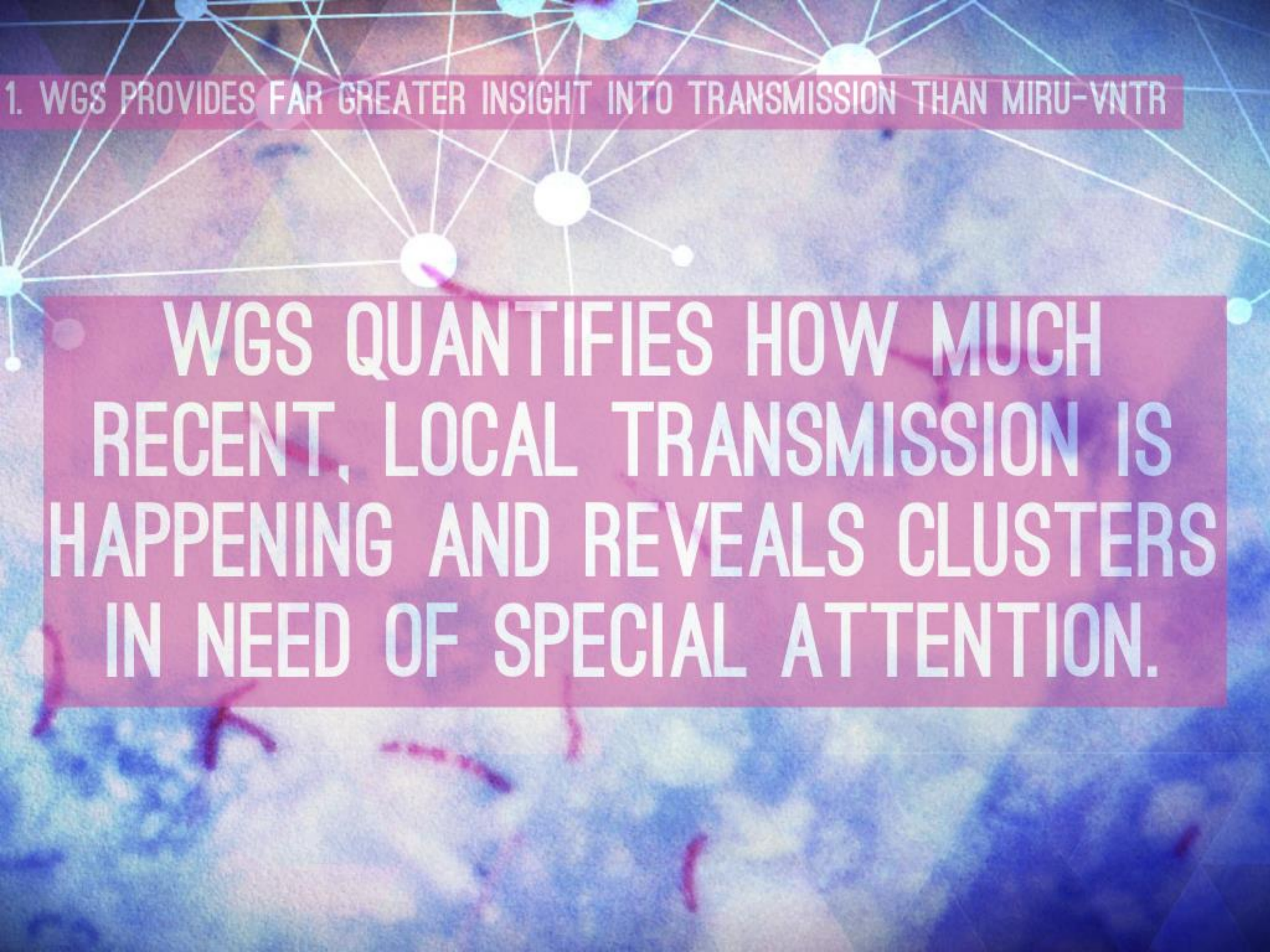
WGS LINKS MIRU-VNTR CLUSTERS

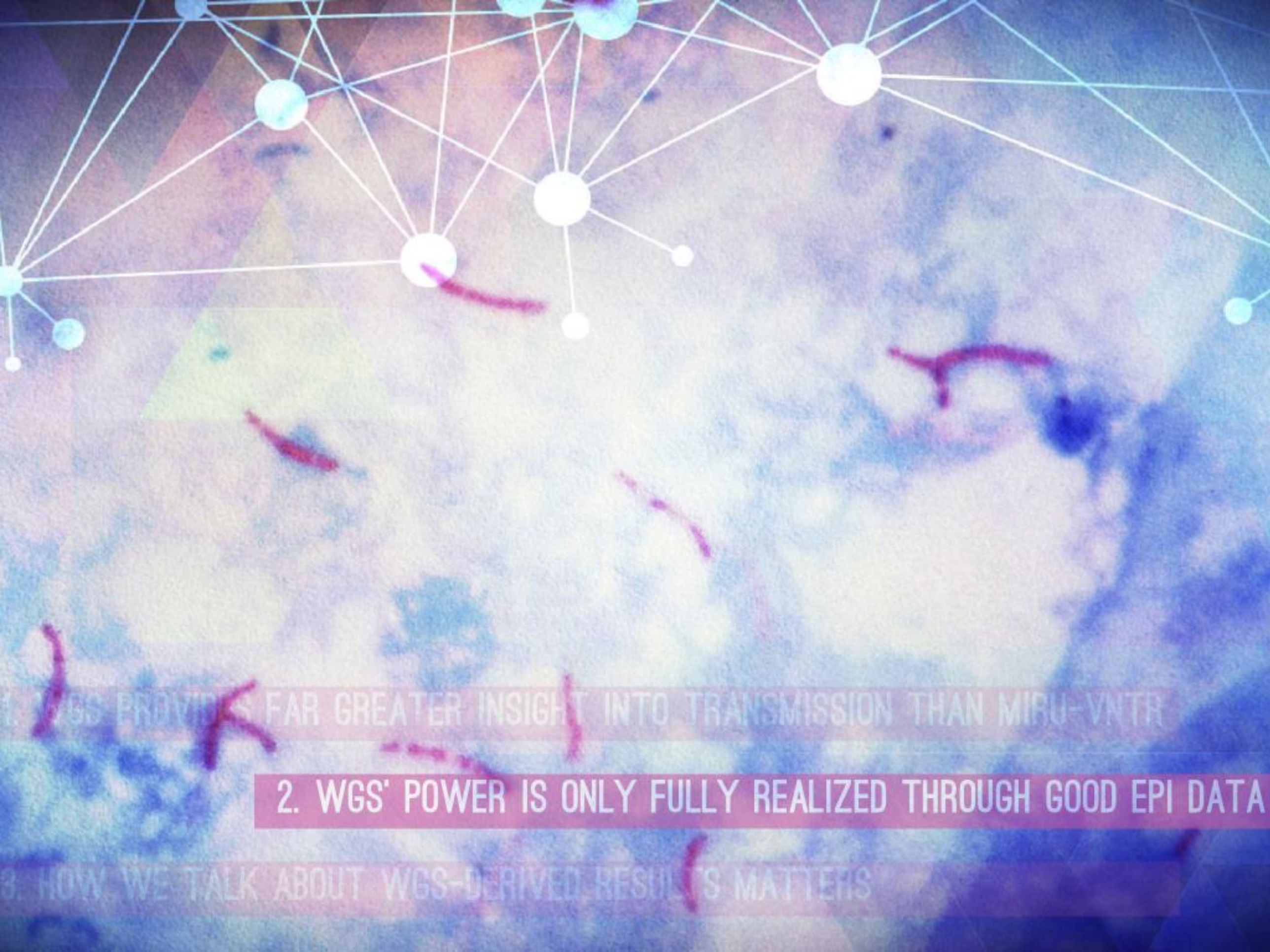
WGS RESOLUTION MATTERS

5.17

48 15 3 2

36 14 7 2 2 2 5


1. WGS PROVIDES FAR GREATER INSIGHT INTO TRANSMISSION THAN MIRU-VNTR
WGS QUANTIFIES HOW MUCH RECENT, LOCAL TRANSMISSION IS HAPPENING AND REVEALS CLUSTERS IN NEED OF SPECIAL ATTENTION.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```
GAGGCTCAATCAAGCCCCGCGAGGCCTTGCAAGGAGTGAAATACAGG
GAGGCTCAATTAAGCCTCGCGGGGCCTTGCAAGGAGTGAACTACAGG
GAGGCGCAGTCAAGCCCCACGGAGCCCCACAAGGAGTGCGATACARG
GAGGCGCAGACAAGCCCCACGGAGCCCCACAAGGAGGGCGATACAAG
GAGGCGCAGTCAGGCCCCACGGAGCCCCACCAGGAGTGCGATACAGG
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
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GAGGCTCAATCCAGCCCCACGGGGCCCCACACAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
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GAAGGTCAATCAAGCCCCACGGGGCCCCACAAGGAGTGCGATACGGA
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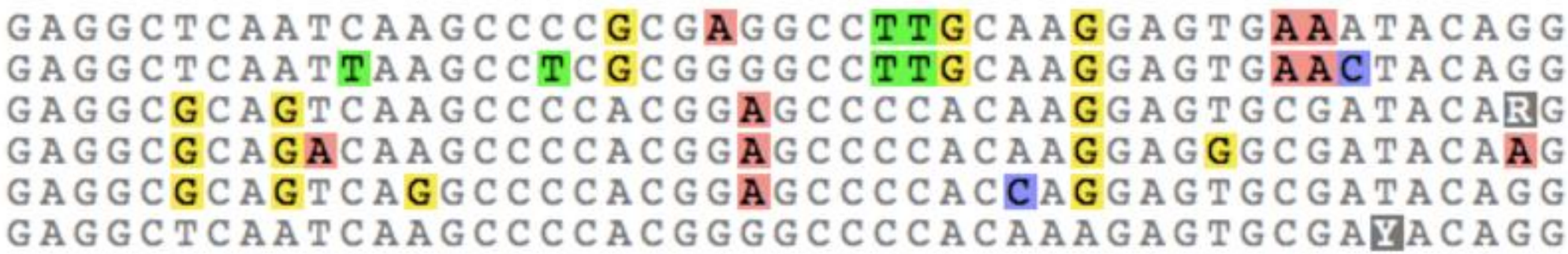

These isolates were picked up 2001-2004.

The level of diversity we see suggests this is an “old” strain.

These isolates came from one region.

```
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCAAGCCCCAYGGGGCCCCACAAAGAGTGCGAYATAGG
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCAAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
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GAGGCTCAATCMAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCGATCCAGCCCCAYGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCGCCACGGGGCCCCACAAAGAGTGCGAYACAGG
CAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACACAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGGCTCAATCCAGCCCCACGGGGCCCCACAAAGAGTGCGAYACAGG
GAGACTCAATCAAGCCCCACGGGGCCCCACAAAGGATGCGAYATAGG
GAAGGTCAATCAAGCCCCACGGGACCCCACAAGGAGTGCGATACGGG
```

These individuals were separated by thousands of kilometres and four years.

GAAGGTCAATCAAGCCCCACGGGACCCCACAAGGAGTGCGATACGGG
GAAGGTCAATCAAGCCCCACGGGGCCCCACAAGGAGTGCGATACGGA

2. WGS' POWER IS ONLY FULLY REALIZED THROUGH GOOD EPI DATA

UNDERSTANDING THE DRIVERS OF TRANSMISSION IS A TEAM EFFORT.

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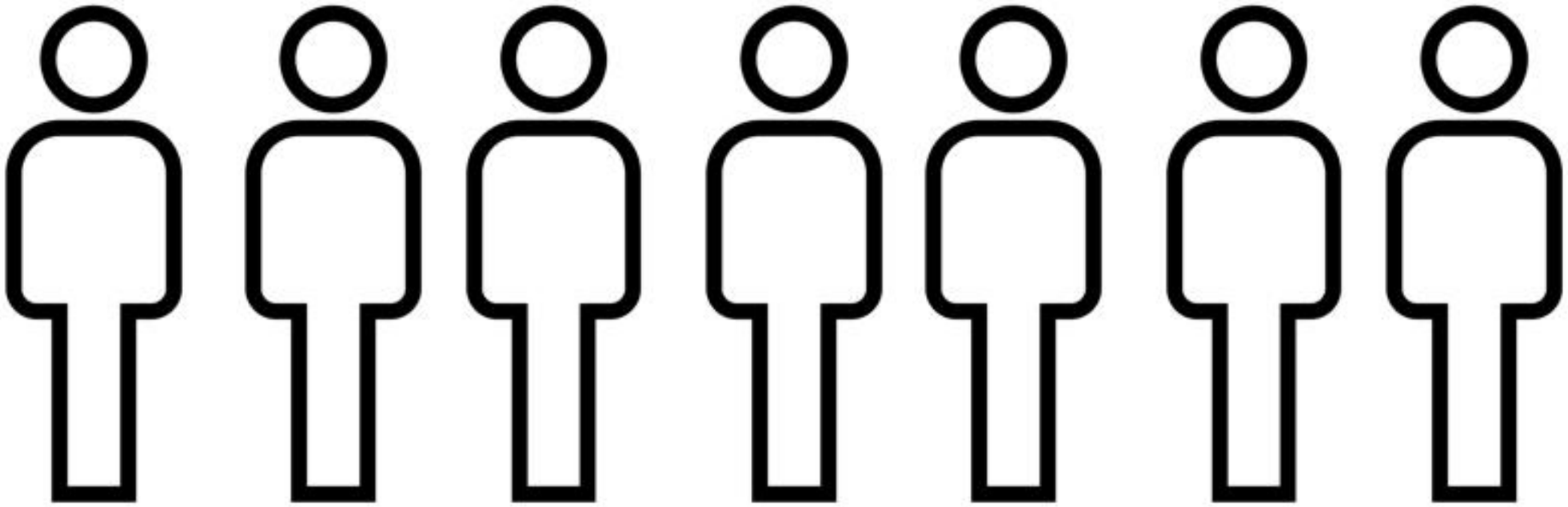
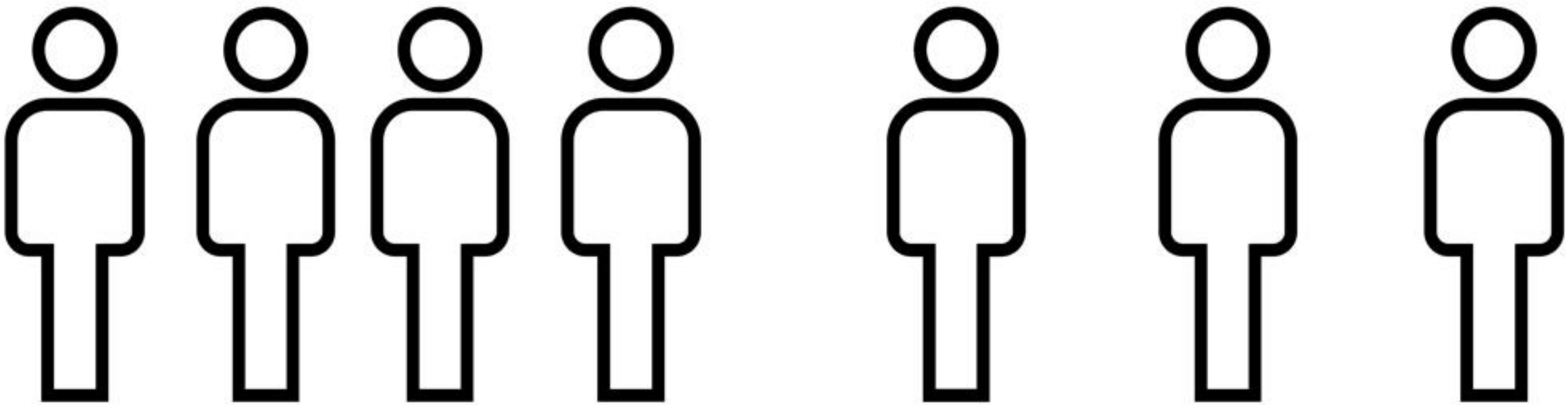
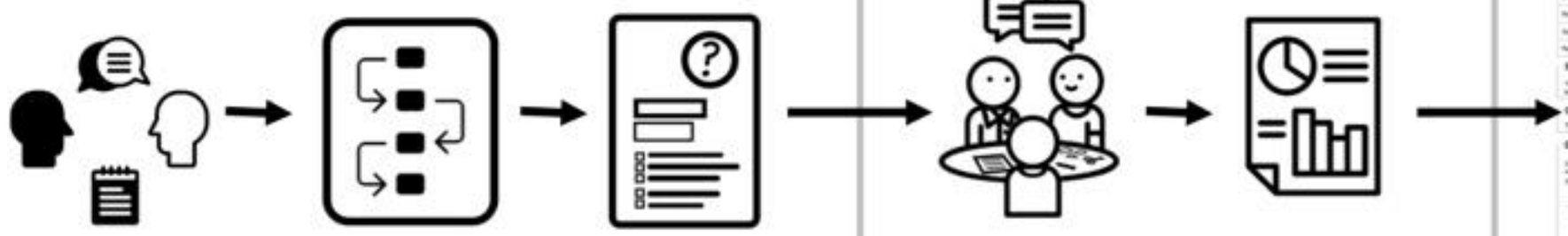




MIRU PATTERN 1 2 3 4

Design Study



Data Gathered						
Qualitative	○				○	
Quantitative			○		○	
Study Design	Exploratory Sequential Model			Embedded Model		

"Design isn't just what it looks and feels like – design is how it works" - Steve Jobs

HOW DO WE PRESENT SUSCEPTIBILITY RESULTS?

Basic table

Drug Susceptibility

INH	RIF	EMB	PZE
R	R	S	S

Sentence

Drug Susceptibility

The specimen is resistant to isoniazid, rifampin. It is sensitive to ethambutol and pyrazinamide.

By phenotype

Drug Susceptibility

Prediction	Drugs
Sensitive	Ethambutol, Pyrazinimide
Resistant	Isoniazid, Rifampin
Indeterminate	-

By drug

Drug Susceptibility

Drug	Prediction
Isoniazid	Resistant
Rifampin	Resistant
Ethambutol	Sensitive
Pyrazinimide	Sensitive

Drug Susceptibility

SUSCEPTIBLE	RESISTANT	INDETERMINATE
Ethambutol Pyrazinimide	Isoniazid Rifampin	

Binned by phenotype

MYCOBACTERIUM TUBERCULOSIS WHOLE GENOME SEQUENCING REPORT

NOT FOR DIAGNOSTIC USE

See `https://github.com/amcrisan/TB-WGS-MicroReport` for how to automatically fill the contents of this template

Patient Name	JOHN DOE	Patient ID	12345678910
Birth Date	2000-01-01	Location	SOMEPLACE
Sample Type	SPUTUM	Sample Date	2016-12-25
Reporting Lab	LAB NAME	Report Date/Time	2017-01-01, 15:36
Requested By	REQUESTER NAME	Requester Contact	REQUESTER@EMAIL.COM

Summary

The specimen was positive for **Mycobacterium tuberculosis**. It is **resistant to isoniaizd and rifampin**. It belongs to a cluster, suggesting **recent transmission**.

Organism

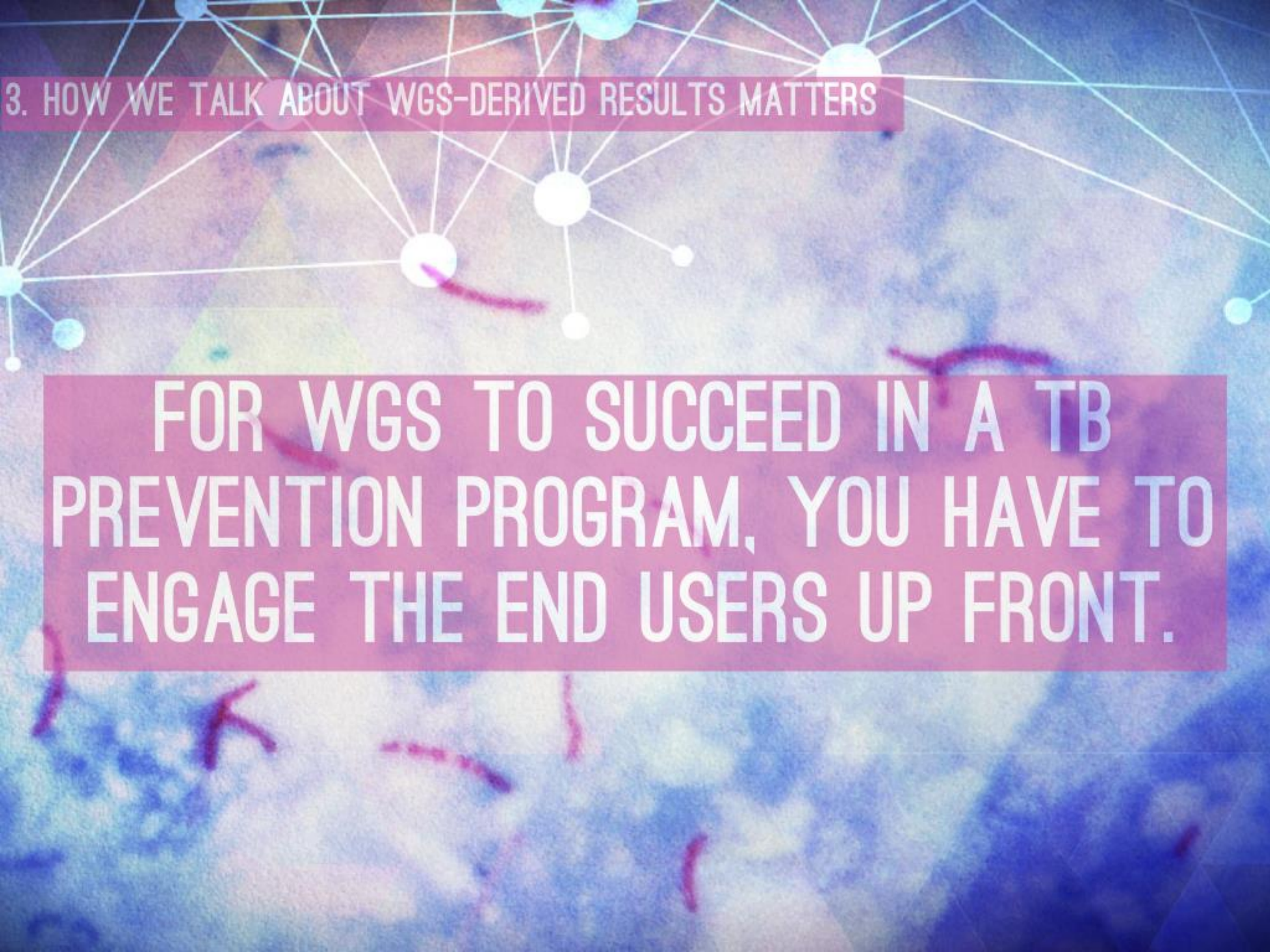
The specimen was positive for **Mycobacterium tuberculosis**

Drug Susceptibility

Drug susceptibility is predicted by the presence of mutations known to confer drug resistance in *M. tuberculosis*.

- ☐ No drug resistance predicted
- ☐ Mono-resistance predicted
- ☑ Multi-drug resistance predicted
- ☐ Extensive drug resistance predicted

Drug class	Prediction	Drug	Resistance Gene (Amino Acid Mutation)
First Line	Sensitive	Ethambutol	No resistance mutation detected
		Pyrazinimide	No resistance mutation detected
	Resistant	Isoniazid	katG (S315T)
		Rifampin	rpoB (S531L)
Second Line	Sensitive	Streptomycin	No resistance mutation detected
		Ciprofloxacin	No resistance mutation detected
		Ofloxacin	No resistance mutation detected
		Moxifloacin	No resistance mutation detected
		Amikacin	No resistance mutation detected
		Kanamycin	No resistance mutation detected
		Capreomycin	No resistance mutation detected



3. HOW WE TALK ABOUT WGS-DERIVED RESULTS MATTERS

FOR WGS TO SUCCEED IN A TB PREVENTION PROGRAM, YOU HAVE TO ENGAGE THE END USERS UP FRONT.

Jennifer Guthrie, Jay Johnston, Tori Cook, Danielle Jorgensen, Clare Kong, Mabel Rodrigues, David Roth, Fay Hutton, Tim Walker, Jeremy Swann, Lori Strudwick, Beth Roberts , Meadow Allen, Jan McFadzen, Brendan Hanley, Ana Crisan, Geoff McKee, and the entire team at the BCPHL Mycobacteriology lab.