

## AN INTRODUCTION TO GENOTYPE CLUSTER INVESTIGATIONS

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### LEARNING OBJECTIVES

- Describe the structure and purpose of the national genotyping network
- Name at least three ways that genotyping results can be used in TB control
- Name the basic steps in a genotype cluster investigation

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### SO WHAT IS GENOTYPING?

- Laboratory method to analyze the genetic material of the TB organism
- Specific sections of the organism are analyzed to identify genetic patterns
- These patterns distinguish different strains of the TB organism

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## NATIONAL TB GENOTYPING SURVEILLANCE NETWORK

- Each result is assigned a “name” so that isolates can be compared across jurisdictions
- PCRTYPE based on spoligotype and MIRU-12
- GENTYPE based on spoligotype and MIRU-24
- Web based data collection system implemented in March 2010
  - Compare aggregate data for a PCR or Genotype
  - Approximately 71,000 isolates have been genotyped

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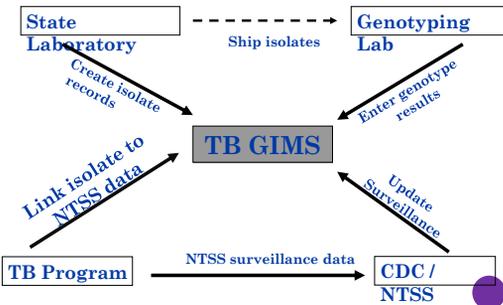
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### TB GIMS DATA FLOW




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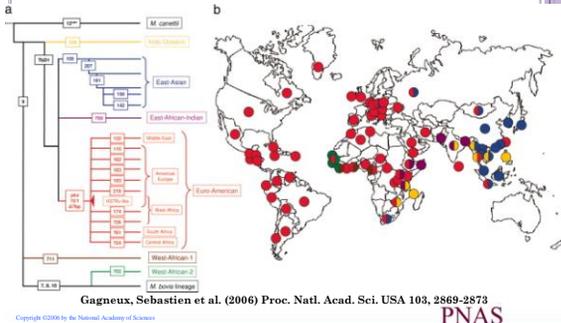
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## The global population structure and geographical distribution of *M. tuberculosis*




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UNITED STATES AND MEXICO

Lineage-family	Mexico	United States
Indo-Oceanic Manila	7%	2%
Indo-Oceanic Mexico	2%	
East Asian	3%	10%
East African Indian		1%
Euro-American LAM	19%	12%
Euro-American Harlem	12%	11%
Euro-American X	19%	27%
Euro-American S	2%	4%
Euro-American undefined	28%	30%
<i>M. bovis</i>	7%	1%

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SO WHAT IS A GENOTYPE CLUSTER?

- When TB isolates match on spoligotype and MIRU-VNTR they are said to “cluster. So a cluster is two or more isolates with identical genotypes
  - This may represent recent transmission

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WHAT IF THE GENOTYPE DOES NOT MATCH?

- When the a new TB isolate does not match, it is called “unique”
- Typically 20-40% of isolates will be unique, that is they will not match any other isolate in the library
- In Virginia, 45% of the isolates in our library are unique
- When suspect transmission or false positive the lack of a match will rule out your suspicion

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### THE PROMISE OF TB GENOTYPING FOR TB CONTROL PROGRAMS

- Identify ongoing chain of transmission
  - Identify high risk groups or areas where transmission is ongoing
  - Confirm or rule out suspected epi links between cases
- Distinguish reactivation from exogenous transmission
- Identify false positive cultures



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### IDENTIFY CHAIN OF TRANSMISSION

- Refine contact and outbreak investigations
  - Confirm or refute suspected links between patients
    - e.g., family members infected with different strains
    - e.g., casual contacts infected with the same strain
  - Define magnitude of an outbreak
    - e.g., is a new case part of an on-going outbreak?



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### IDENTIFY REACTIVATION FROM NEW INFECTION

- If a person has TB at different times and they have culture results, the genotype may help distinguish break down of old disease
- In practice, we have not had any experience of this finding in Virginia



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### IDENTIFY FALSE POSITIVE CULTURES

- Estimated 2-3% of positive cultures for MTB are actually cross contamination
  
- Suspicious for contamination
  - Negative sputum smear and only one positive specimen
  - Clinically the patient does not exhibit expected TB signs and symptoms
  - Possibility of exposure has been explored and ruled out



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### IDENTIFY FALSE POSITIVES, CONTINUED

- If you suspect cross contamination or misidentification has occurred: CALL TB Control for assistance
  
- Common causes of false positive cultures
  - Mislabeled specimens
  - Lab cross-contamination
  - Clinical device contamination



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### INVESTIGATIONS

- Genotype investigations are a collaboration and can be initiated several ways:
  - Public health nurse case managers suspects a link between cases
  - TB epidemiologist reviews genotype results and identifies a new or expanding cluster



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SO A GENOTYPE MATCHES, NOW WHAT?

- The genotype match is just a starting point.
- It suggests that recent transmission has occurred, but does not prove it.



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SHOE LEATHER EPI

- Person, place, time
- What are the epi links between the cases in the cluster?



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GENOTYPE CLUSTER INVESTIGATION

- Multiple steps
- Multiple information sources
- Examine existing information on persons in cluster to look for commonalities or links
  - Talk with case managers, outreach workers, physicians etc



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**STEP ONE: GATHER EVERYTHING WE KNOW**

- TB epidemiologist will review the national data to see if any other TB cases have the same genotype
  - If there are matches other places, once more is know about the Virginia cluster may consider calling other states
- If this is a new isolate in an existing cluster, consider whether it is an outbreak

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**State List of GENTypes**

State: VIRGINIA  
 Date Type: Count Date  
 Date Range: 11/04/2010 - 11/04/2013      Number of GENTypes: 394

GENType	PCRTYPE	ClusterName2	Spoligotype	MIRU	MIRU2	Total No. of Cases	Total No. of Cases in Rest of US
G03079	PCR02778	VA_0192_001	577777803720771	222325133322	243234213328	7	1
G19076	PCR00369	VA_0174_002	67400003413771	254326223432	148143253218	5	0
G10531	PCR00015	VA_0019_001	7777776777780901	224325153323	443234423337	4	0
G02381	PCR00795	VA_0118_002	376177607760771	224326133223	443324221127	4	11
G13527	PCR00071	VA_0055_002	777777714020771	225325153323	233454223335	3	1
G09777	PCR00600	VA_0016_001	7777760007760771	124325153224	323224122326	3	2
G13031	PCR00255	VA_0191_001	77777780000611	224325141323	434232413223	3	10

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**Cluster Snapshot for G03079**

**Cluster Definition**

GENType: G03079  
 PCRTYPE: PCR02778  
 Date Range: 10/28/2010 - 10/28/2013  
 State/County/Region: VIRGINIA

Lineage: EuroAmerican (L4)  
 Date Type: Count Date  
 State Cluster Name2: VA\_0192\_001  
 # cases in cluster: 7

**Data Completeness**

Genotype Coverage: 90.5%      #Patients with PCRTYPE but no MIRU2 result: 0  
 #Isolates with no linked surveillance record: 0  
 Genotype report date of most recent isolate without surveillance record:

**Cluster Detection**

Alert Level: N/A      Recent change in alert level:  
 Alert level and LLR are only available for single county areas.

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CONTINUE TO GATHER INFORMATION...

- Discuss the match with the nurses, outreach workers and physicians who manage the cases
- Review medical records and contact investigations
- Establish precise period of infectiousness for each case
- Search for possible locations of transmission
- Are there any clues of an epi-link between the cases in the clusters?



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STEP TWO

- Medical chart abstraction with a standardized locations questionnaire
- Summarize the data and brainstorm
  - Consider re-interviewing the clients
  - Develop some additional questions based on the investigation to combine with the locations questionnaire



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THINGS TO CONSIDER....

- Did any of the cases name the other in the contact investigation?
- Did any of the cases spend time in the same location during the infectious period
- Are there other characteristics that may link them: e.g. substance abuse, chronic medical issues, public transit, same neighborhood....



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STEP THREE

- If warranted, re-interview the client

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IS THERE AN OPPORTUNITY FOR INTERVENTION?

- Do you need to expand the contact investigation based on the genotype cluster investigation?
- Are there additional evaluation criteria for the contact investigations?

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CONCLUSIONS

- TB genotyping is a powerful tool for TB control and can help identify ongoing transmission
- Genotyping can identify false positive cultures
  - Prevent unnecessary treatment and use of resources
- Genotyping suggests avenues of investigation, a focus on *where* as opposed to *who*, that traditional contact investigations may miss

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## RESOURCES

- Great presentation that summarizes genotyping and epidemiological information.  
<http://sntc.medicine.ufl.edu/Files/Haiti/Module%2011%20%20Genotyping%20ENGLISH.pdf>
- Scholarly review article on molecular epidemiology of TB.  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1592690/pdf/0061-05.pdf>
- CDC website about genotyping.  
<http://www.cdc.gov/tb/publications/factsheets/statistics/genotyping.htm>

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## ACKNOWLEDGEMENTS FOR SLIDES FROM THE PRESENTATIONS BELOW

- Lauren Cowan, CDC “What can a spoligotype tell us?”
- Thomas Shinnick, CDC “Genotyping of Mycobacterium Tuberculosis Isolates.”
- Smita Ghosh, CDC “TB GIMS Data Flow.”

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## THANK YOU

- Questions

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