



## Practical Applications of Genotyping

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## Overview

- What is your strategy?
  - Selective
  - Universal
- Data management
- Specific uses
  - False positive laboratory tests
  - Assessment of transmission
  - Program evaluation



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## Definitions

- Selective strategy: genotype SOME isolates when there are questions
- Universal strategy: attempt to genotype ALL isolates
  - Variability in the proportion submitted
  - The more you submit the more useful the data



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Strategy	Selective	Universal
Links identified	—suspected	—suspected —unsuspected
Pros	—less data management —fewer logistics	—easier to go back in time —easier to find links across jurisdictions —more uses for data




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### How Do the Data Arrive?

Name	RVCT	Date shipped	County	Spoligotype	MIRU	Cluster ID
A	7990004	11/10/07	A	775777757760771	223326153324	CA_822
B	7990003	11/10/07	A	775777757760771	223326153324	CA_822
C		9/5/07	A	677770057703771	351226743234	CA_674
D		8/23/07	A	677770057703771	351226743234	CA_674
E	6990015	2/2/07	A	777777706777370	225514263213	CA_754
E		12/21/06	A	777777706777370	225514263213	CA_754
F	6990011	11/15/06	A	677077777770060	354235235423	
G	6990007	8/7/06	A	000000000003771	433424565231	CA_003
H	6990005	6/13/06	A	677000357770170	432243443212	CA_504
I		3/4/06	A	677770057703771	351226743234	CA_674
J	5990021	1/12/06	A	677770057703771	351226743234	CA_674

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- ### Data Management
- Lab output
    - Specific patients can be identified if you already know something about them
    - Sufficient for already suspected events
  - Making the data more useful
    - Remove duplicates
    - Link genotype data to epi. data
    - State TB programs may be doing this
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## Cluster Investigation

- Multiple cases in a high-risk setting
  - Healthcare facility
  - Prison
  - Homeless shelter
- Did transmission occur?
  - Implications for infection control
  - Need for expanded preventive efforts
- May not be possible with selective genotyping unless isolates saved




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## Example

- Foreign born acute care nurse develops TB
  - Previous TST positive
  - Never took LTBI treatment
- TB patient recently on ward, but cared for by other nurses
- Was there transmission?
  - Maybe not—nurse at risk for TB (foreign birth)
  - Maybe!
    - Implies a lapse in infection control
    - Large contact investigation may be needed




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## Do the Genotypes Support Transmission?

RVCT	Date shipped	County	Spoligotype	MIRU	Cluster ID	Epi. Data
7990004	11/10/07	A	775777757760771	223326153324	CA_822	
7990003	11/10/07	A	775777757760771	223326153324	CA_822	
	9/5/07	A	677770057703771	351226743234	CA_674	
	8/23/07	A	677770057703771	351226743234	CA_674	
6990015	2/2/07	A	77777706777375	225514263213	CA_754	Hispanic USB child
	12/21/06	A	77777706777375	225514263213	CA_754	Sm+ FB Hispanic adult
6990011	11/15/06	A	677077777770067	354235235423		
6990007	8/7/06	A	000000000003771	433424565231	CA_003	
6990005	6/13/06	A	677000357770177	432243443212	CA_504	
	3/4/06	A	677770057703771	351226743234	CA_674	
5990021	1/12/06	A	677770057703771	351226743234	CA_674	

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## Outbreak Investigation—Rare Strain

- Rare genotype match + epidemiologic link = likely transmission
- Confirm epidemiologic linkages
  - Some epi. linkages may not be associated with transmission (genotypes do not match)
  - Could lead unnecessary investigations or prevention efforts
- Identify unsuspected cases (universal genotyping)
  - 20-40% of linked cases not identified by contact investigation
  - Transmission in “non-traditional” settings common
  - May be important for prevention/control




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## Hypothetical Rare Strain

RVCT	Date shipped	County	Spoligotype	MIRU	Cluster ID	Epi. Data
7990004	11/10/07	A	775777757760771	223326153324	CA_822	
7990003	11/10/07	A	775777757760771	223326153324	CA_822	
	9/5/07	A	677770057703771	351226743234	CA_674	AA child
	8/23/07	A	677770057703771	351226743234	CA_674	AA adult
6990015	2/2/07	A	777777706777370	225514263213	CA_754	Hispanic USB child
	12/21/06	A	777777706777370	225514263213	CA_754	Sm+ FB Hispanic adult
6990011	11/15/06	A	67707777770060	354235235423		
6990007	8/7/06	A	000000000003771	433424565231	CA_003	
6990005	6/13/06	A	677000357770170	432243443212	CA_504	
	3/4/06	A	677770057703771	351226743234	CA_674	Asian USB
5990021	1/12/06	A	677770057703771	351226743234	CA_674	AA sm+

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## What Now?

- Reinterview cases
  - Infectious periods
  - Undisclosed contacts?
  - Settings where exposure possible (clubs, bars, churches, etc.)
- Look further back? (universal genotyping)
- Check other jurisdictions




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	RVCT	Date shipped	County	Spoligotype	MIRU	Cluster ID	Epi. Data
6		9/5/07	A	67770057703771	351226743234	CA_674	AA child
5		8/23/07	A	67770057703771	351226743234	CA_674	AA adult
4		3/4/06	A	67770057703771	351226743234	CA_674	Asian USB
3	5990021	1/12/06	A	67770057703771	351226743234	CA_674	AA sm+
2	4990007	9/5/04	A	67770057703771	351226743234	CA_674	AA sm+
1	4980025	3/7/04	B	67770057703771	351226743234	CA_674	Asian FB sm+

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### The Three Largest Clusters in California, 2004-Present

	CA_021	CA_006	CA_038
% of CA cases	7.5%	4.9%	2.2%
% Foreign-born	88%	81%	57%
Major FB group	Asian	Asian	Hispanic
Genotype family	Manila	Beijing	LAM

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### Outbreak Investigation — Common Strain

- Common genotype match + epidemiologic link = ??
- Difficult to identify local transmission from background
- Clues to local transmission
  - U.S. born
  - Children
  - Healthcare workers
  - Susceptibility
  - Time in U.S.
  - Setting (family, club, etc.) cluster
- RFLP can be used to further assess transmission

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## A Word About Outbreak Surveillance

- Value of genotype in suspected cluster/outbreak clear
- Surveillance in low incidence settings
  - Fewer cases >> analysis less complicated
  - All clusters can be assessed
- Surveillance in high incidence settings challenging
  - Many clusters
  - Common strains
  - Analytic tools needed to prioritize




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## Program Evaluation

- Laboratory
  - False positive cultures
  - Errors in susceptibility testing
- Contact investigation
  - Cases with matching genotype with new links identified
  - Focus on place/setting in addition to person
- Specific control efforts
  - Outbreak
  - Endemic strains
- Overall program
  - Proportion of cases clustering




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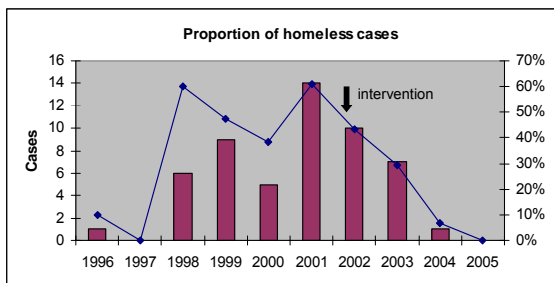
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### Number of Outbreak Strain Cases and Proportion of Homeless Cases, Rotterdam, 1996-2005

(de Vries G et al. Am J Respir Crit Car Med 2007;176:201-7.)




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## Summary

- Genotyping has many practical applications for TB control
- Universal genotyping allows more applications
- The more you submit, the more you can do with the data!
- Challenges
  - Data management
  - Analytic tools for surveillance
  - Still learning how to use genotyping most effectively



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## Thank You

- For your attention
- Martin Cilnis
- Steven Yu
- Ed Desmond
- Wendy Cronin
- Patrick Moonan



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