

California's Experiences Using Tuberculosis Whole Genome Sequencing

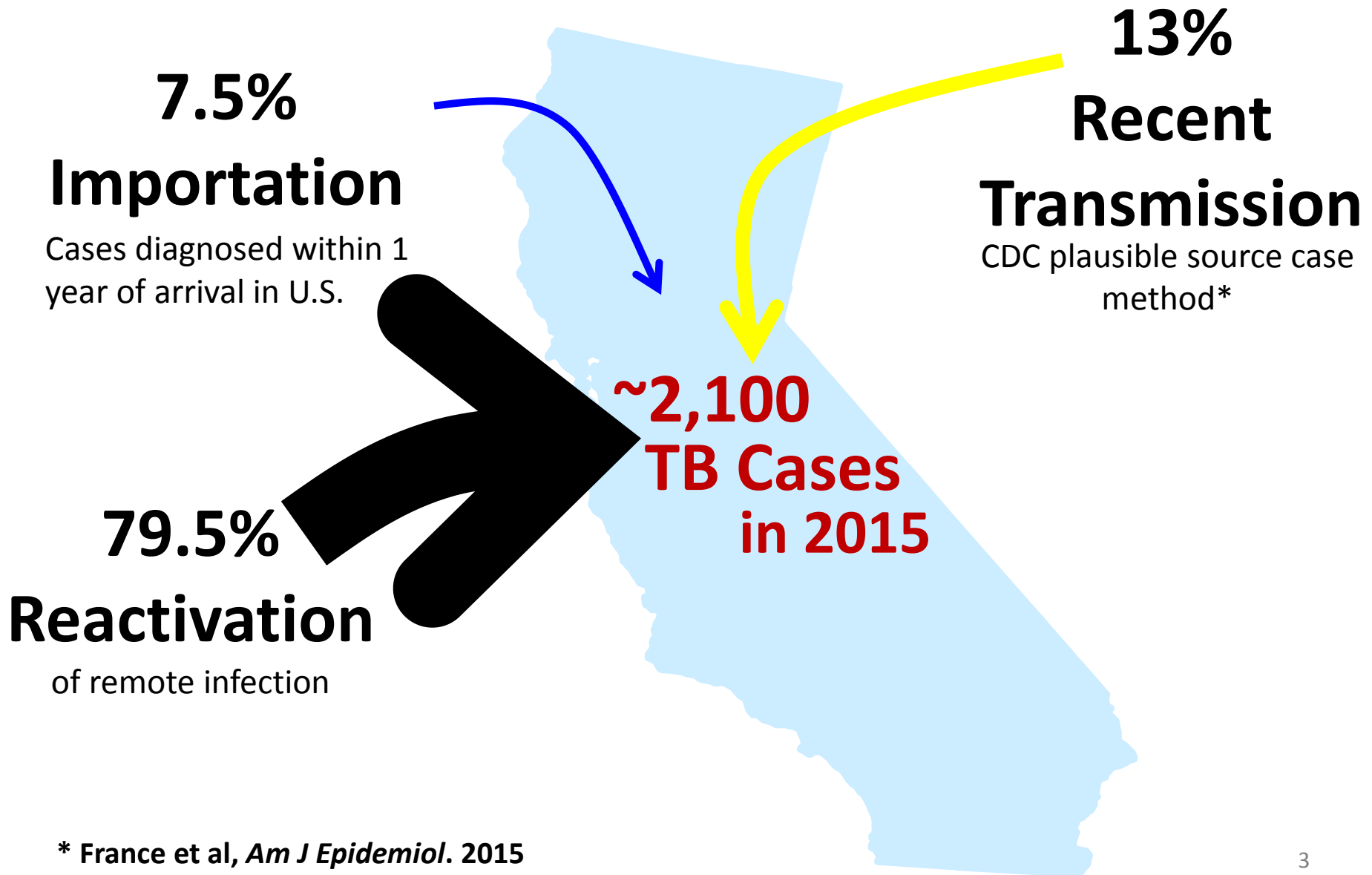
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Objective

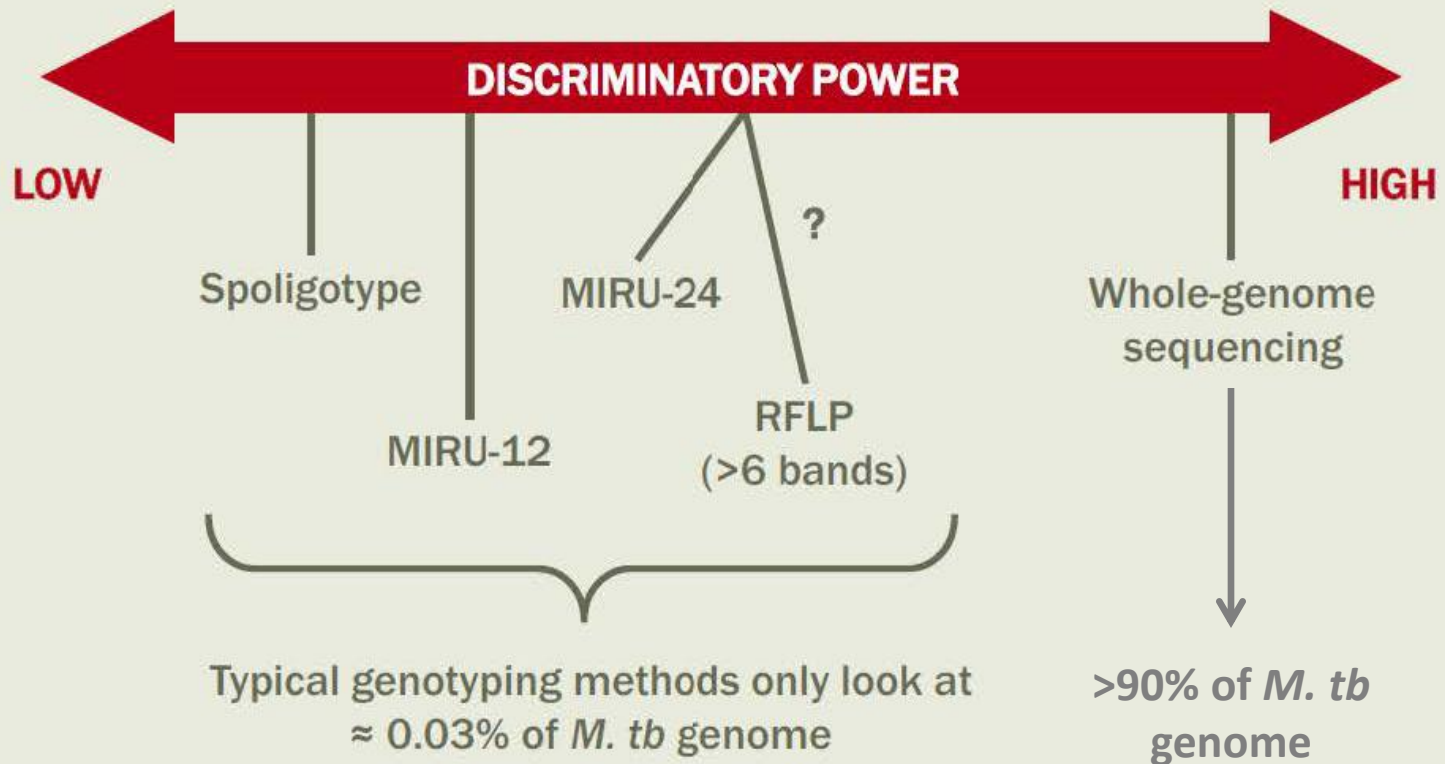
Describe how whole-genome sequencing (WGS) data has been used to better understand outbreak-related tuberculosis (TB) transmission dynamics and focus public health action

Tuberculosis in California



* France et al, *Am J Epidemiol.* 2015

Discriminatory Power of Molecular Methods

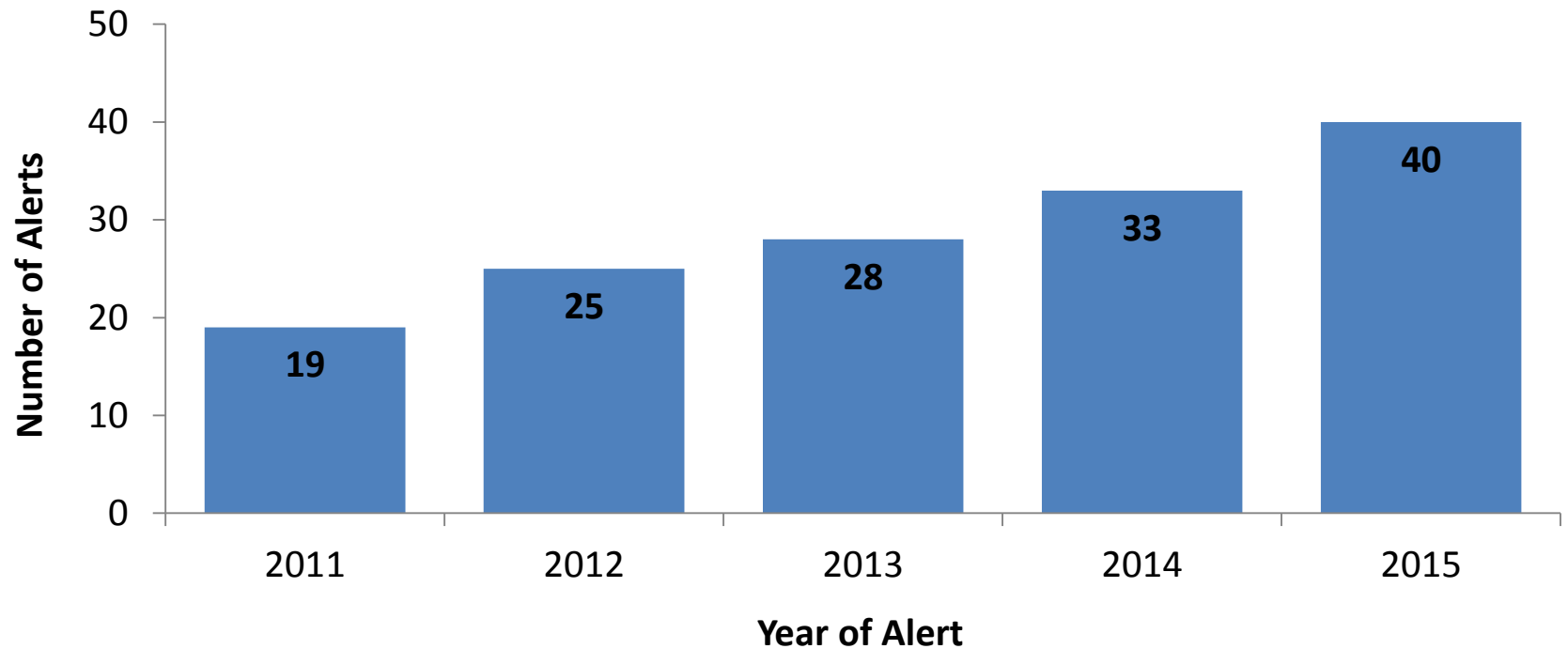


CDC Outbreak Detection Using TB Genotyping*

- TB genotype cluster alerts:
 - Generated when a genotype has a higher than expected concentration within a county compared to other counties in the US in a 3-year window
- Large outbreak surveillance:
 - ≥ 10 TB cases in a 3-year period related by recent transmission

*Spoligotype and MIRU-24

CDC TB Genotype Cluster Alerts in CA, 2011-2015

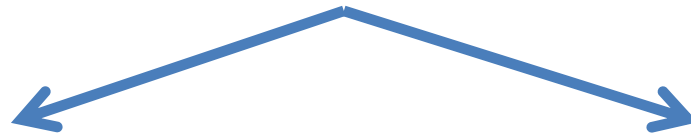


Steps of a TB Genotype Cluster Investigation

TB genotype cluster alert received by TB outbreak team



Prioritize genotype clusters



Higher priority

Lower/no priority

Notify local health departments

Monitor genotype



Investigation

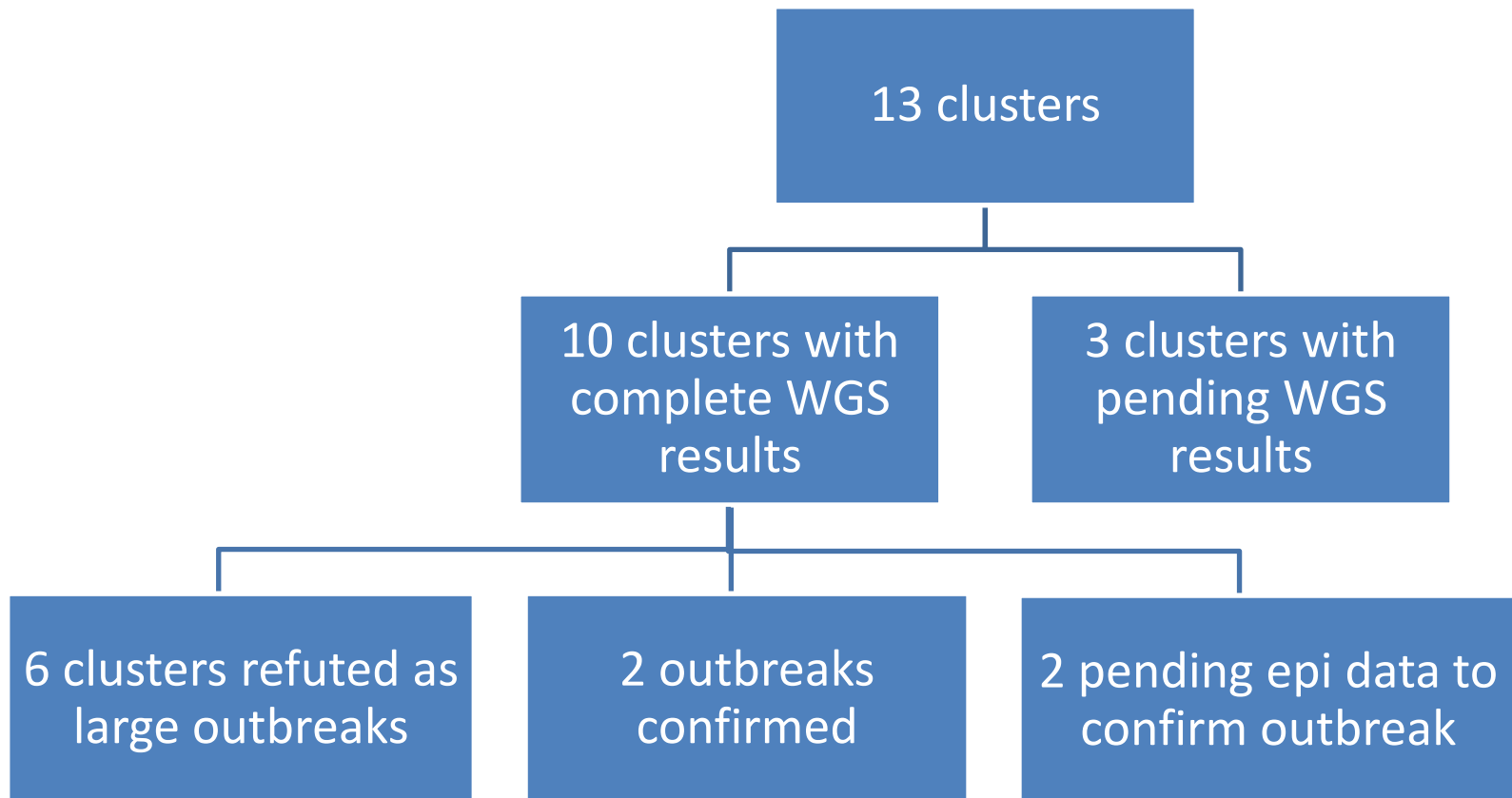


Implement interventions

CA's Criteria for Requesting TB WGS

- Inform decisions on where to focus public health action
- Help confirm or refute that a genotype cluster is an outbreak
- Confirm transmission hypotheses
- Determine which cases are due to recent versus remote transmission in large multi-year outbreaks

TB WGS in California, 2013-2015



Example 1: Suspected TB Outbreak Refuted By WGS

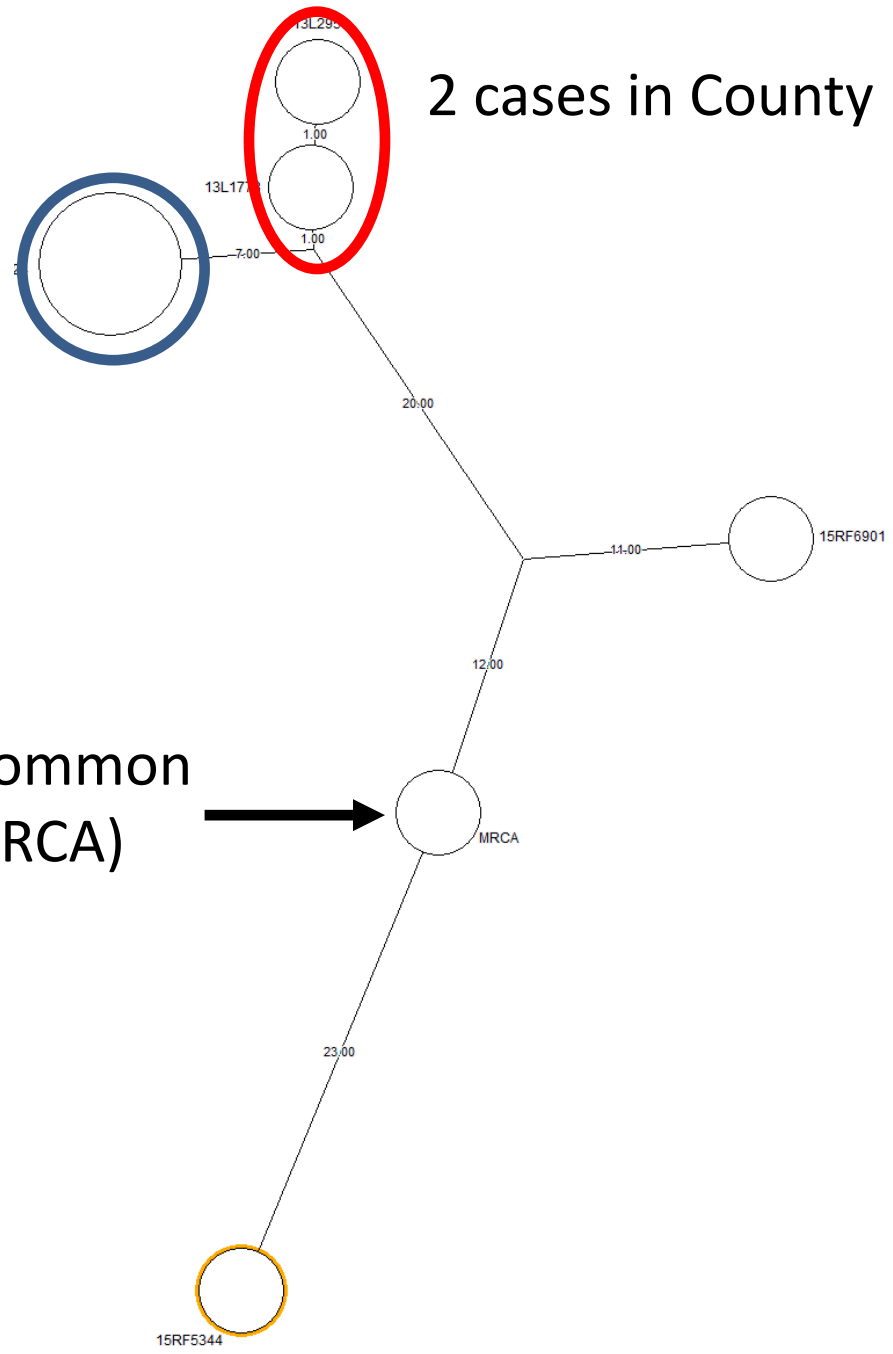
- Preliminary epidemiologic investigation findings:
 - 2 likely transmission groups in 3 different counties
- WGS confirmed findings
- Background:
 - CDC alert, higher priority cluster
 - 10 cases in 5 central CA counties reported since 2013
 - Mostly Asian-born cases, one US-born child
 - Majority had infectious TB
 - Rare genotype: only one other TB case outside of CA

Example 1

2 cases in County B and C

4 cases in County A

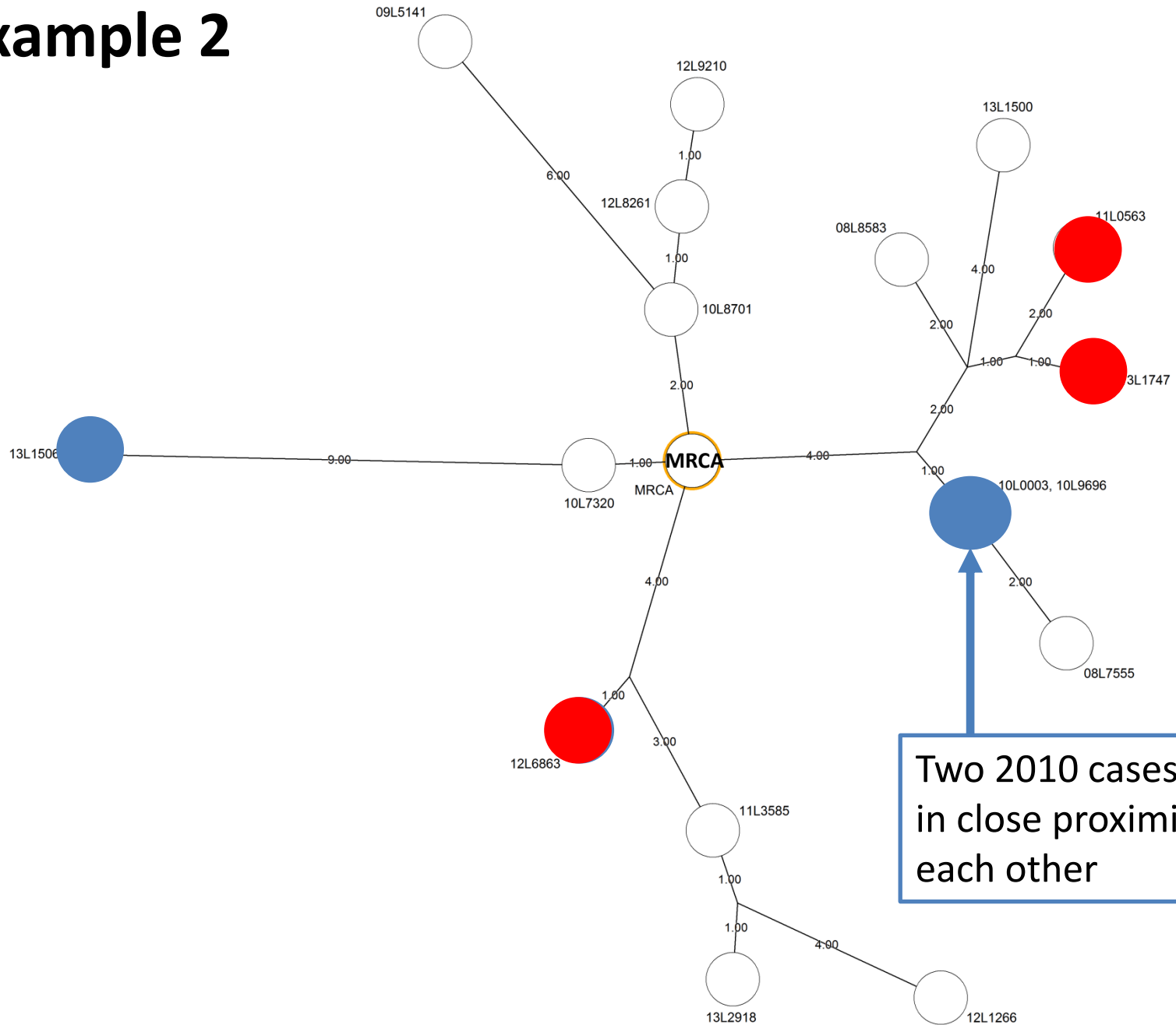
Most Recent Common Ancestor (MRCA)



Example 2: TB Genotype Cluster Refuted as a Large Outbreak by WGS

- Investigation identified epidemiologic links among a small subset of cases in the large cluster
 - Epi links were confirmed and refuted by WGS
- Background: higher priority cluster
 - Genotype primarily found in one CA county
 - High percentage of US-born blacks

Example 2



Example 3: TB Genotype Cluster Confirmed as a Large Outbreak by WGS

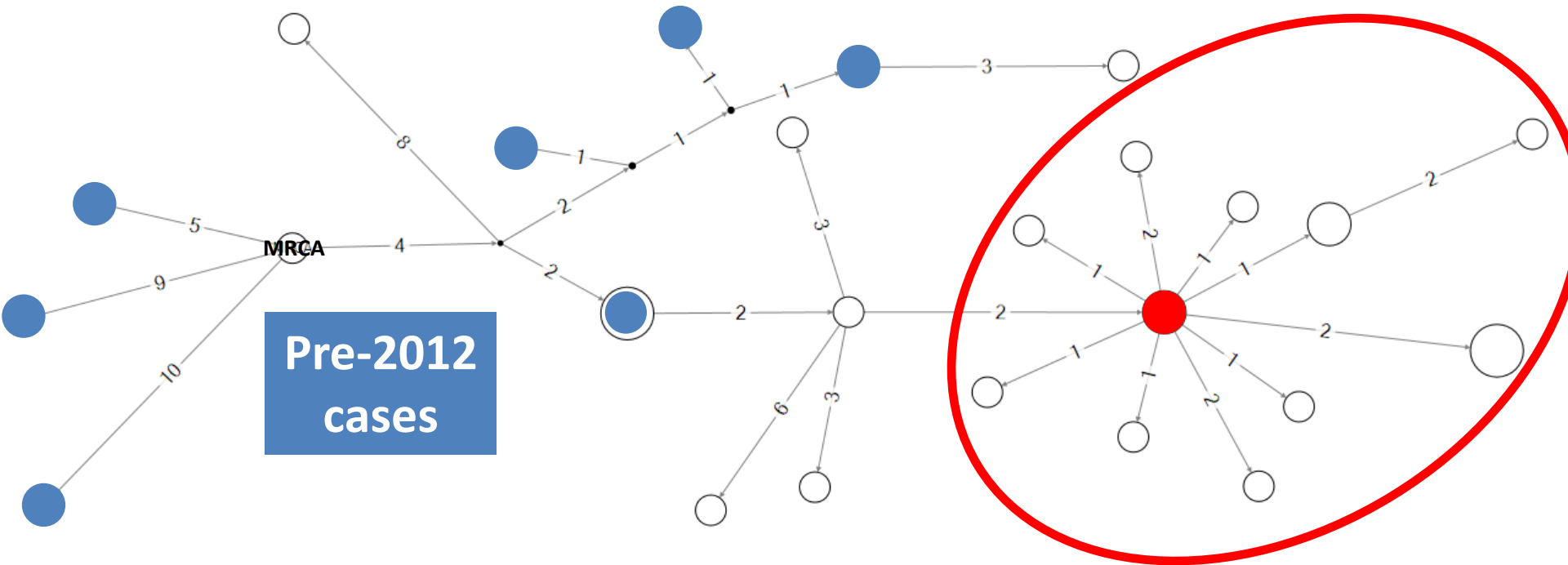
WGS helped to:

- Confirm outbreak transmission hypotheses
- Determine which cases are due to recent versus remote transmission in large multi-year outbreaks
- Identify previously unsuspected transmission links

Background

- Large confirmed outbreak of 26 cases 2012-2015
- Investigation priorities based largely on hypothesis of a single patient identified as most likely source case for 15 secondary cases
- 7 TB cases with the same genotype diagnosed before 2012, some in other CA counties or States

Example 3



Summary of California's Experiences Using Tuberculosis WGS

- Save resources
 - Refute large outbreaks before launching an investigation
- Improve efficacy of outbreak investigations
 - Focus investigations on small sub-clusters of cases that may be linked by recent transmission
 - Distinguish which cases are due to recent vs. remote transmission in large multi-year outbreaks
 - Test outbreak transmission hypotheses

Next Steps

- Build TB program capacity to interpret and apply WGS to outbreak investigations:
 - Training
 - Visual analysis tools
- Evaluation of WGS results to inform which clusters should be selected for sequencing
- Continue collaboration in the CDC/APHL WGS project

Acknowledgements

- County
 - Local health department partners
- State
 - California TB Control Branch
 - California Microbial Diseases Laboratory
- Federal:
 - CDC Division of TB Elimination
 - APHL

Thank You!