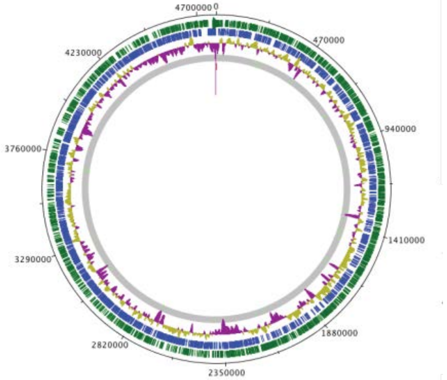
National Jewish Health®

Genomic Analysis of Nontuberculous Mycobacteria (NTM)



Presented by:
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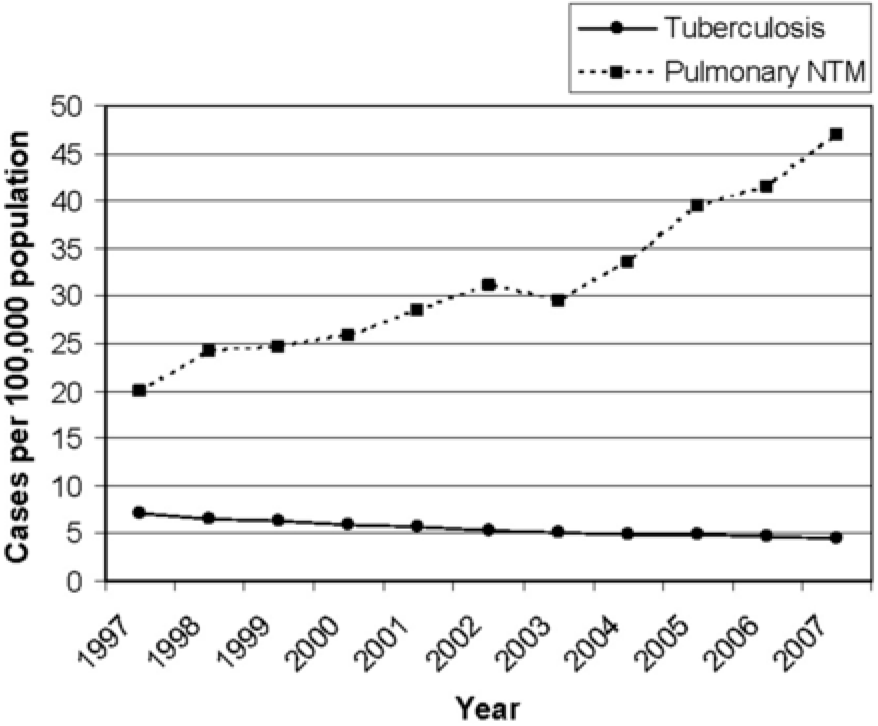
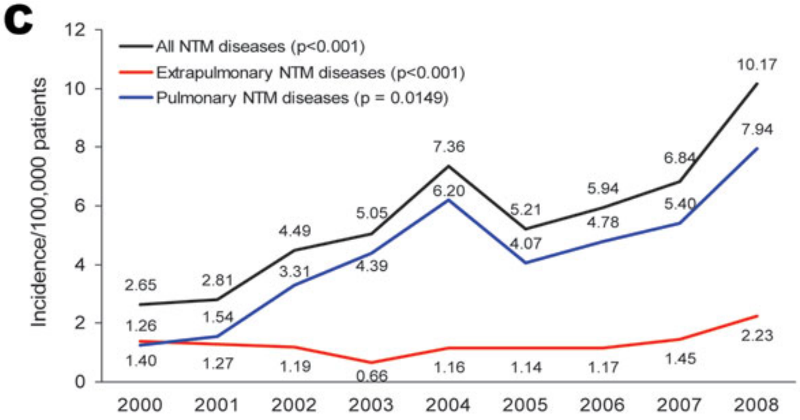
National Jewish Health
Center for Genes, Environment, and Health
Denver, CO

Presented at: FDA Circulatory System Devices Panel Meeting
Gaithersburg, MD
June 2-3, 2016

NTM – Increasing Prevalence



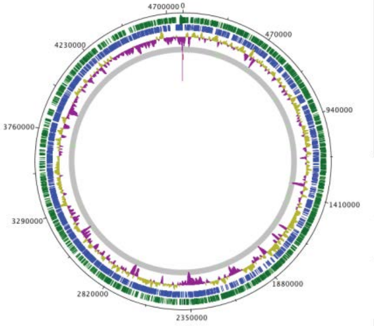
Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. **Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries**. *Am J Respir Crit Care Med* 2012;185:881-6.



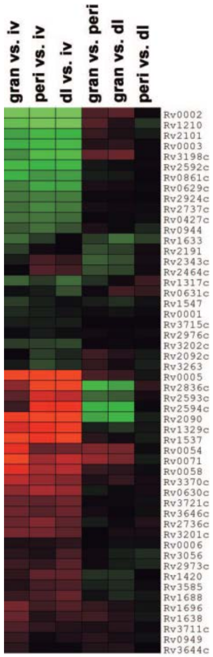
Increasing Incidence of Nontuberculous Mycobacteria, Taiwan, 2000–2008 Chih-Cheng Lai, Che-Kim Tan, Chien-Hong Chou, Hsiao-Leng Hsu, Chun-Hsing Liao, Yu-Tsung Huang, Chuan-Liang Kao, Kwen-Tay Luh, and Po-Ren Hsueh. *Emerging Infectious Diseases*

Genomic and Computational Approaches to Nontuberculous myocobacteria

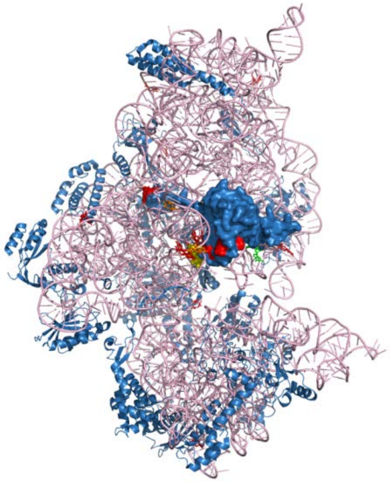
Genome



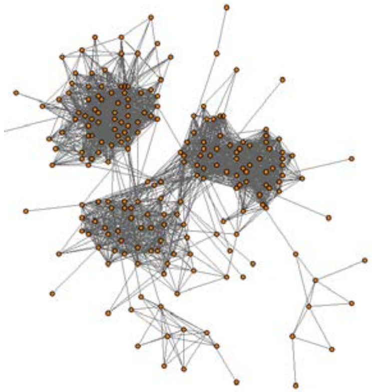
Transcriptome



Proteome

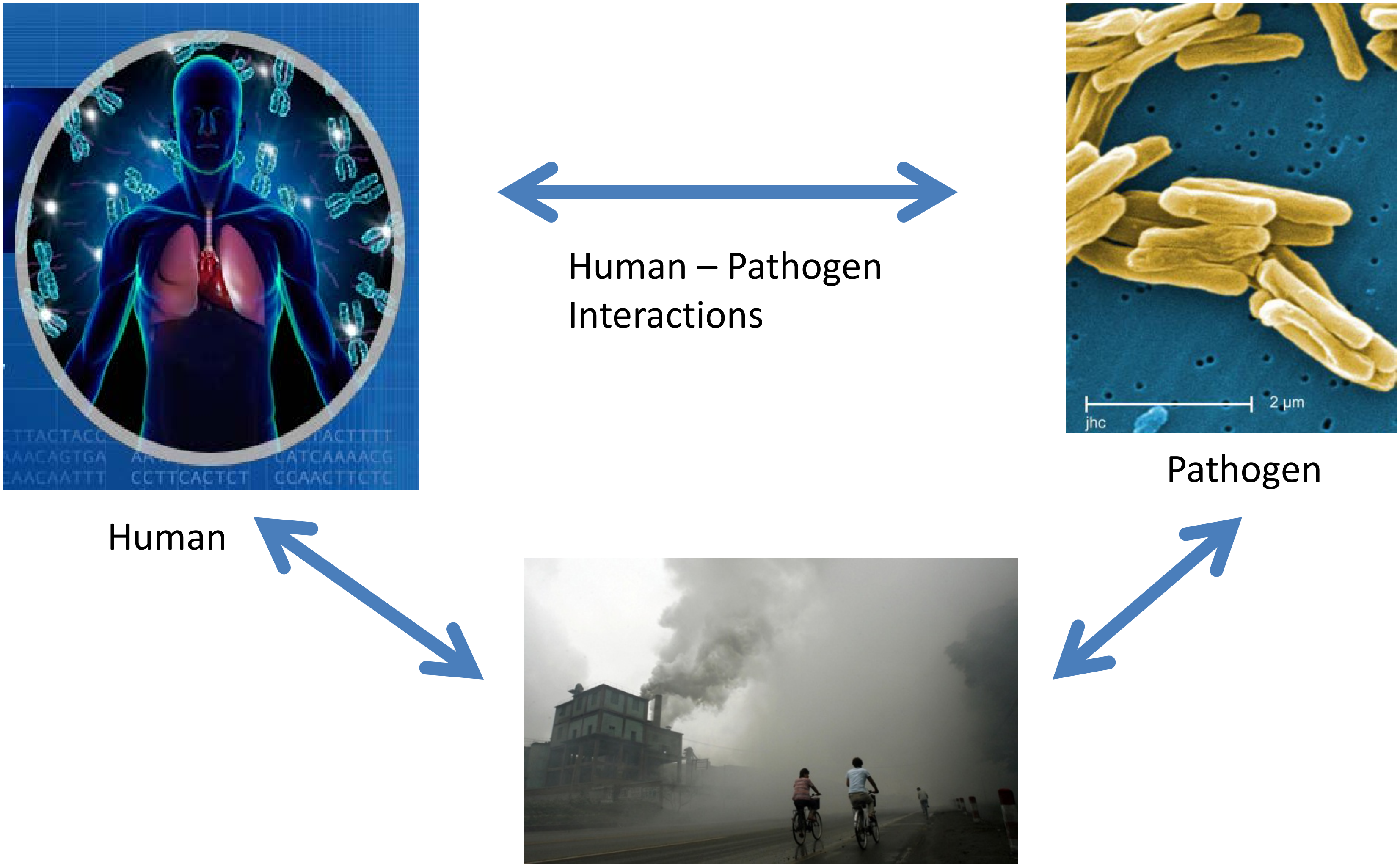


Interactome



Microbiome/
Virome

Host-Pathogen-Environment Interactions



Human – Pathogen Interactions

Human

Pathogen

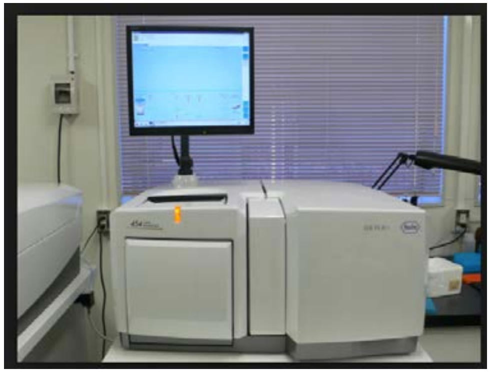
Environment

Next Generation Sequencing

PacBio

Illumina MiSeq and HiSeq

Life Technologies Ion and Proton



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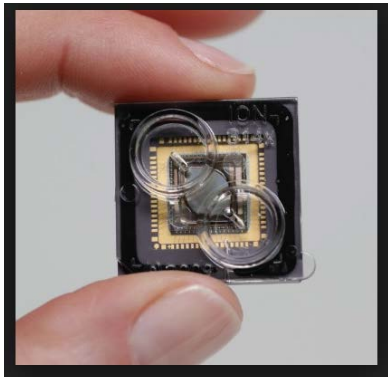


Ion Sequencing Chip

Next Generation sequencing enables the rapid and robust sequencing of whole bacterial genomes.

Genomic Analysis Pipeline

Bacterial Preparation

↓

Genomic DNA isolation

↓

Genomic Library Construction

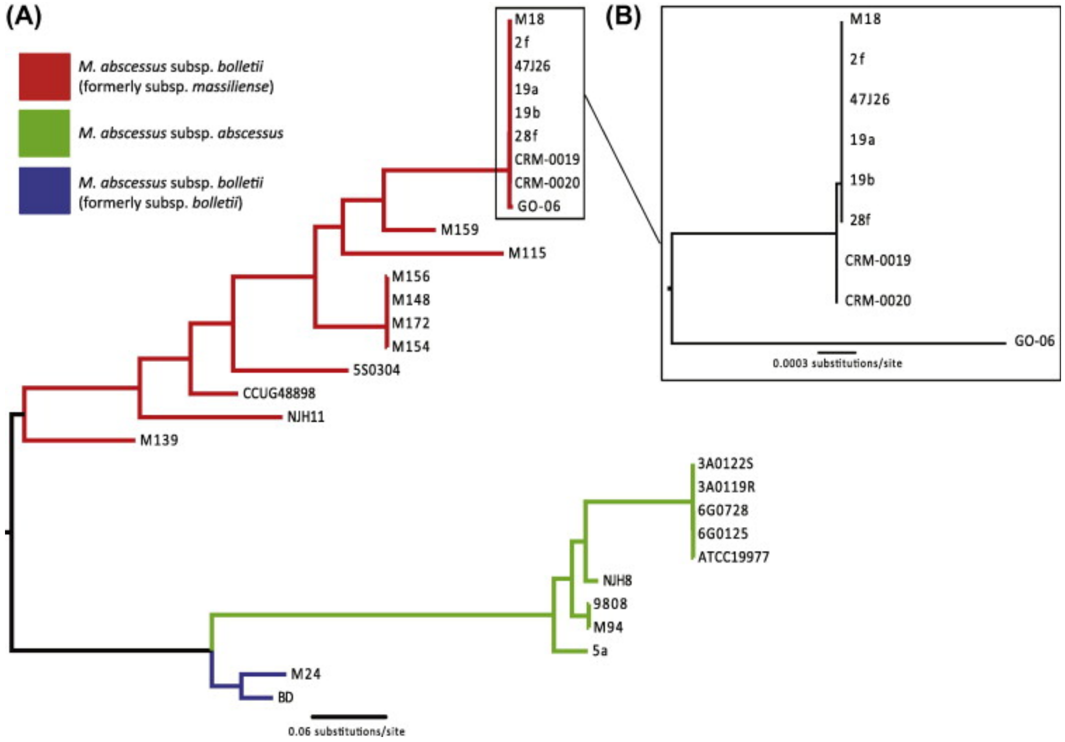
↓

Next Generation Sequencing and Genomic Analysis

↓

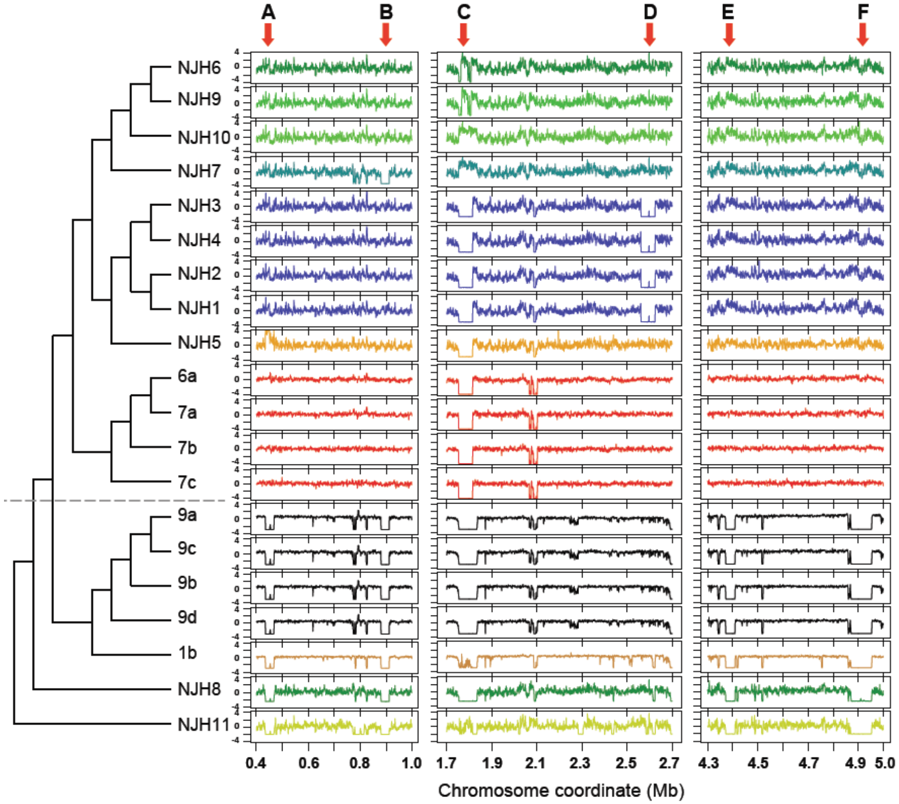
We release and make sequence data available to the public through the National Center for Biotechnology Information (NCBI Bioproject)

NTM Phylogenomics – based on whole genome sequence polymorphisms



Phylogenomics of Brazilian epidemic isolates of Mycobacterium abscessus subsp. bolletii reveals relationships of global outbreak strains.
Davidson RM, Hasan NA, de Moura VC, Duarte RS, Jackson M, **Strong M.**
Infection Genetics and Evolution Sep 18;20C:292-297. 2013

Genomic Comparisons

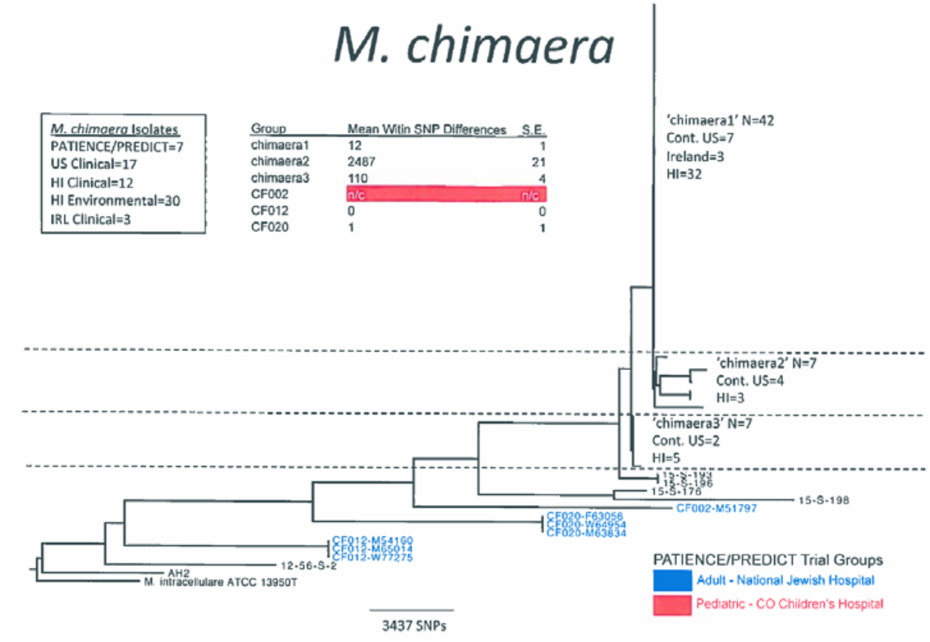


Genome sequencing of *Mycobacterium abscessus* isolates from patients in the United States and comparisons to globally diverse clinical strains.
Rebecca M. Davidson, Nabeeh A. Hasan, Paul R. Reynolds, Sarah Totten, Benjamin Garcia, Adrah Levin, Preveen Ramamoorthy, Leonid Heifets, **Charles L. Daley**, and **Michael Strong**. *Journal of Clinical Microbiology*, (2014).

NTM Whole Genome Sequencing vs. Other Genotyping Methods

In cases of limited genomic diversity among species (as appears to be the case for *M. chimaera*), WGS will enable much more precise and accurate comparisons, where other methods would not provide adequate resolution.

Other typing approaches: MLST – Multilocus sequence typing, PFGE- pulse field gel electrophoresis, VNTR – Variable Number Tandem Repeat, RAPD – Randomly Amplified polymorphic genotyping, Rep-PCR – repetitive sequence PCR, MST - multispacer sequence typing



M. chimaera

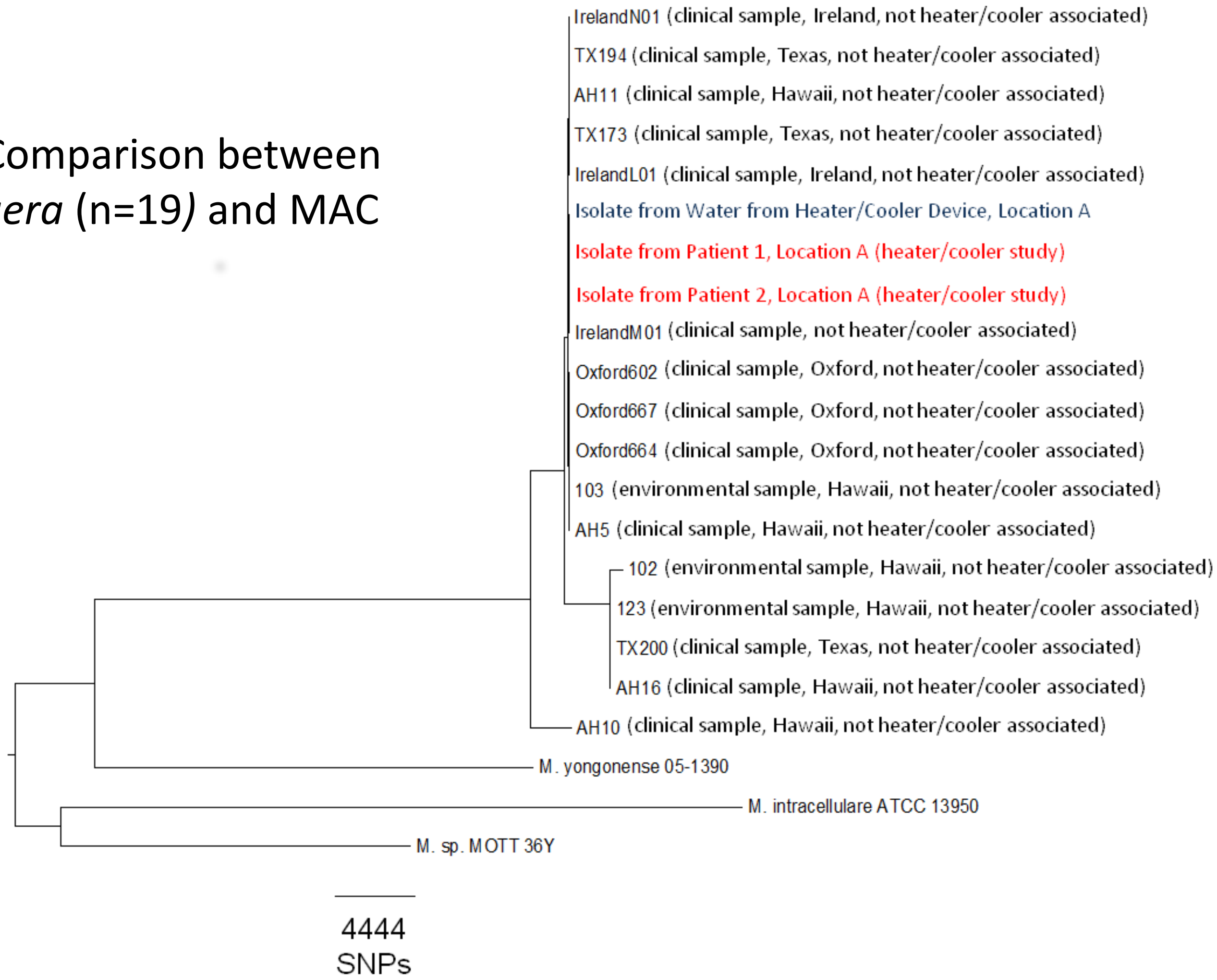
M. chimaera Isolates
PATIENCE/PREDICT=7
US Clinical=17
HI Clinical=12
HI Environmental=30
IRL Clinical=3

Group	Mean Witin SNP Differences	S.E.
chimaera1	12	1
chimaera2	2487	21
chimaera3	110	4
CF002	n/c	n/c
CF012	0	0
CF020	1	1

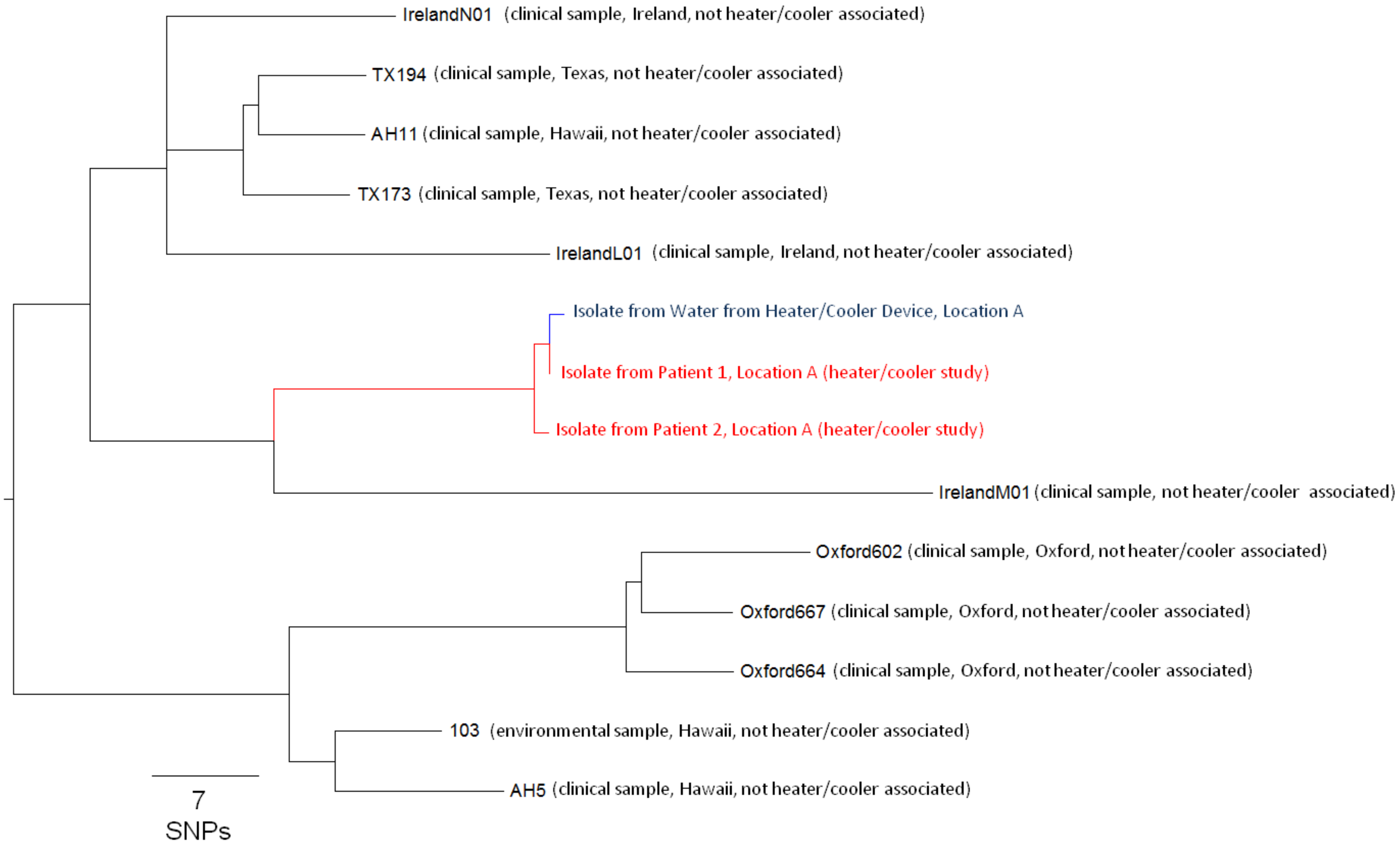
PATIENCE/PREDICT Trial Groups
🟦 Adult - National Jewish Hospital
🟥 Pediatric - CO Children's Hospital

2 tiered phylogenomic comparison of *M. chimaera*

Phylogenomic Comparison between select *M. chimaera* (n=19*)* and MAC isolates (n=3).



2 tiered phylogenomic comparison of *M. chimaera*



Genomic Relatedness of Strains

	Mean SNPs	N
Within Heater/Cooler Study (HC) *M. chimaera*	2.67	3
Between HC and non-HC *M. chimaera*	867	48

Perform Whole Genome Sequencing (WGS) and compare sequence information from *M. chimaera* isolates in the US, Canada, and Europe, including environmental, hospital, patient, and non-related strains (to assess genomic diversity, refine genomic interpretation, and identify putative markers)

We at National Jewish Health welcome referral of clinical and environmental isolates of NTM, specifically *M. chimaera,* to populate this project and further aid the FDA and CDC to get to the bottom of this public health issue