

Whole Genome Sequencing and Machine Learning to **Modernize AMR Diagnostics**

PACCARB – July 10, 2019



JONG LEE, MBA
DAY ZERO DIAGNOSTICS
CEO & CO-FOUNDER

Day Zero Corporate Overview



Jong Lee, MBA
CEO

- Harvard & Harvard Business School
- Experienced MedTech exec & consultant



Miriam Huntley, PhD
CTO

- MIT & Harvard
- Expert in genomics, computational biology

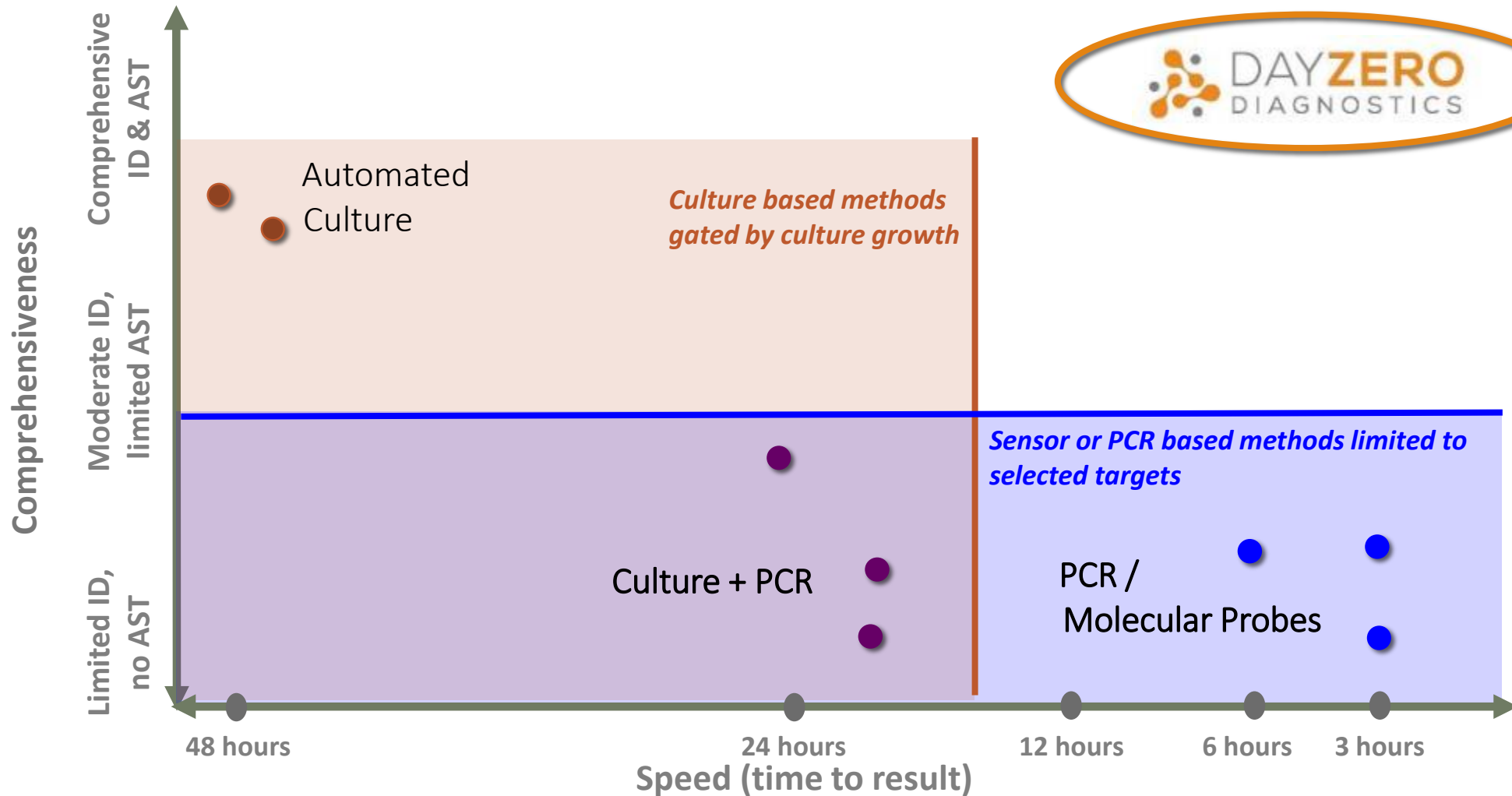


Doug Kwon, MD PhD
CSO

- Harvard & NYU
- Infectious Disease MD and Research Lab Director

- Founded in 2016, spin-off from Kwon Lab at MGH
- Based in Boston, MA
- Developing sequencing-based diagnostic for AMR/S direct from clinical samples
- Providing rapid sequencing based services for HAI outbreak control & hospital epidemiology

Rapid vs. Comprehensive Tradeoff: DZD Will Deliver Both



Our Mission: Diagnose Infections on Day Zero



Clinical Samples
(e.g., Whole Blood)



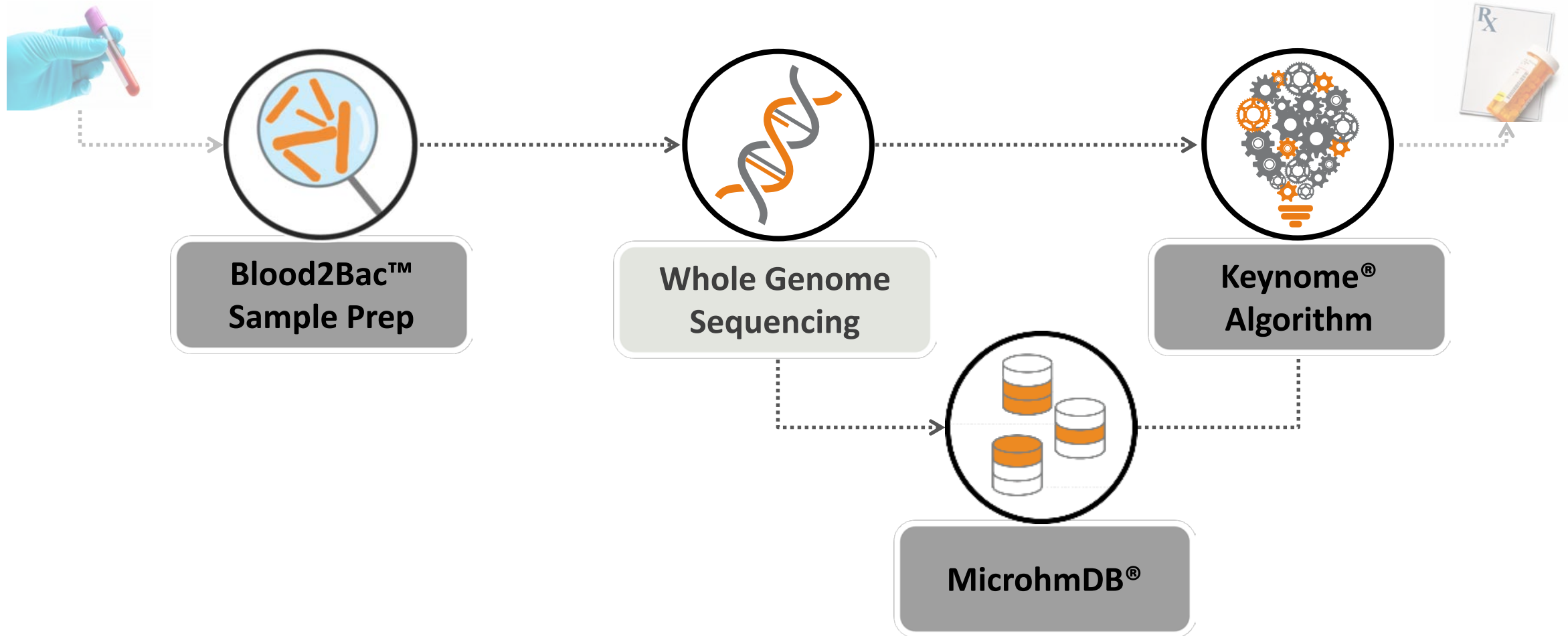
Species ID &
AMR/S Profiles



6 Hours



Technology Required to Enable Clinical Use

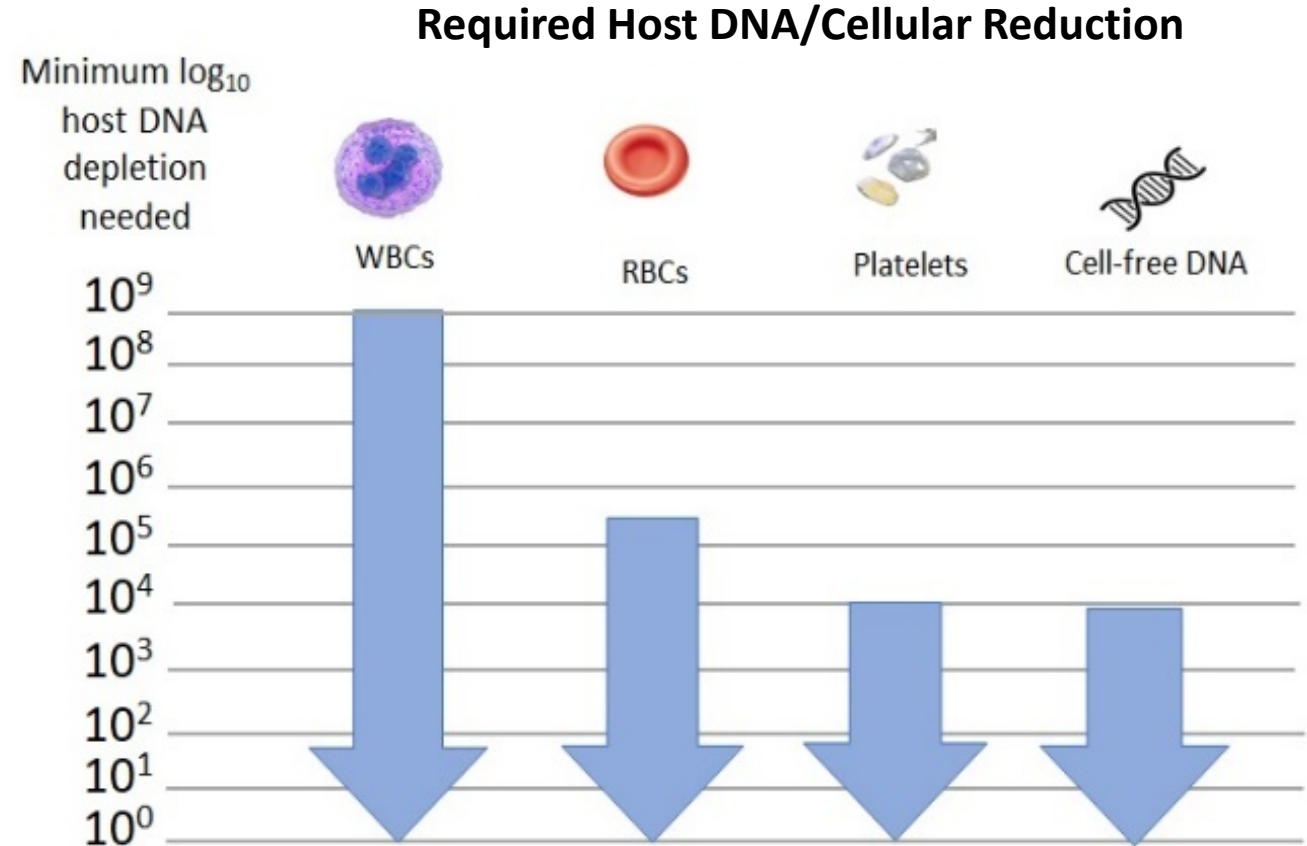




Major Challenges to Culture-Free Pathogen Sequencing from Clinical Blood

At 1 CFU/mL, must solve:

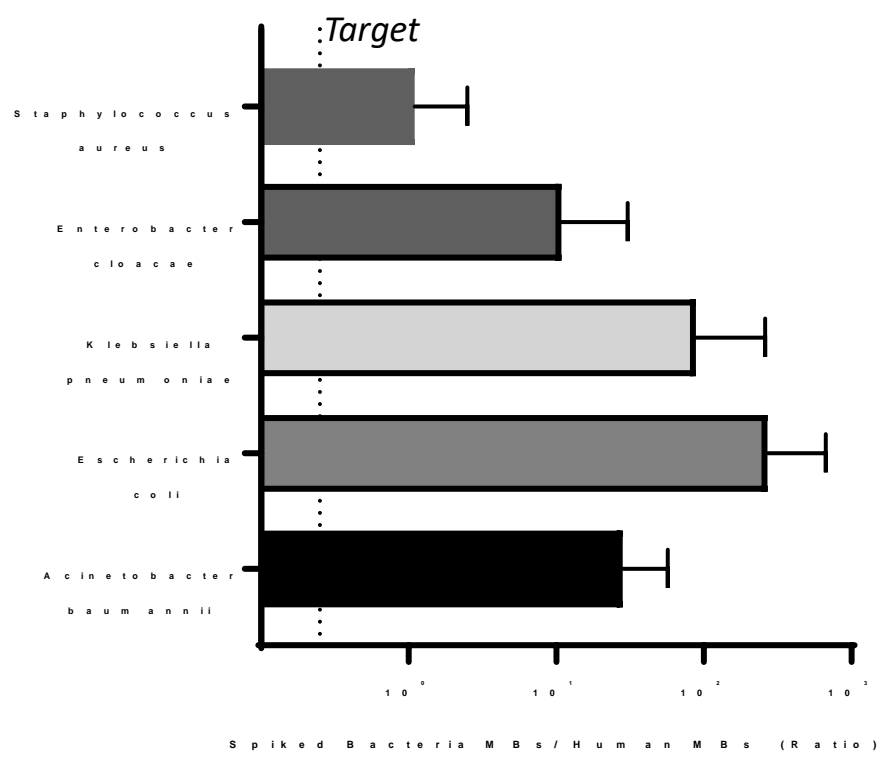
- 1. Relative abundance:** human DNA outnumbers bacterial DNA by 8-9 orders of magnitude
- 2. Absolute abundance:** there is only 10's of femtograms of bacterial DNA
- 3. Amplification inhibitors:** Blood and blood collection containers carry amplification inhibitors



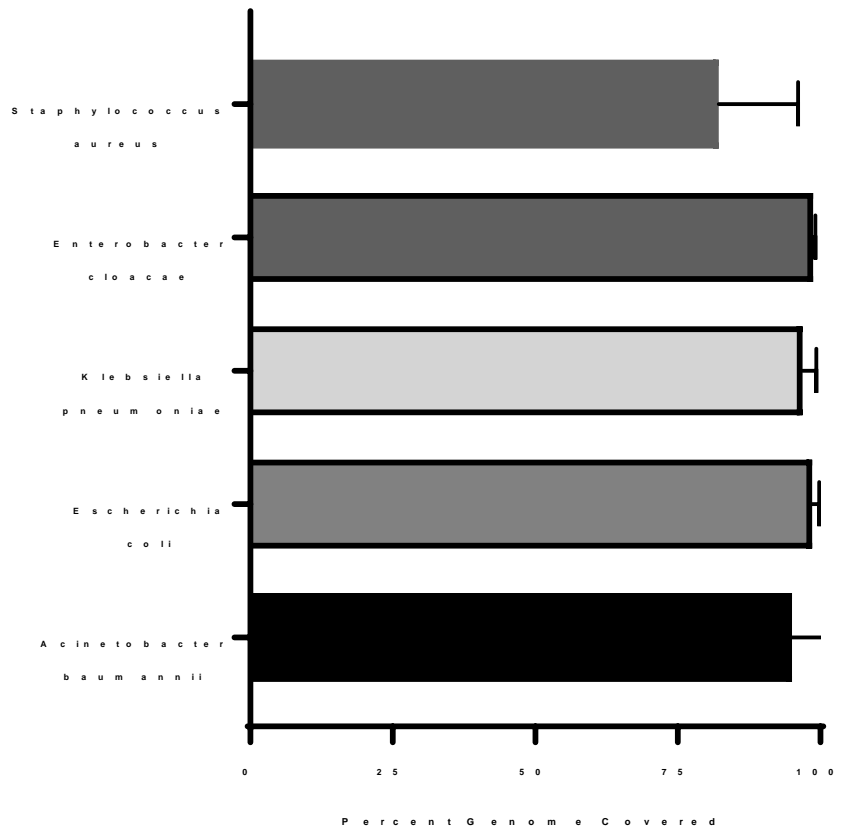


Blood2Bac: Agnostic Detection of Bacteria in Blood Down to 1 cfu/ml

Ratio of bacterial DNA / human DNA reads from 1 CFU



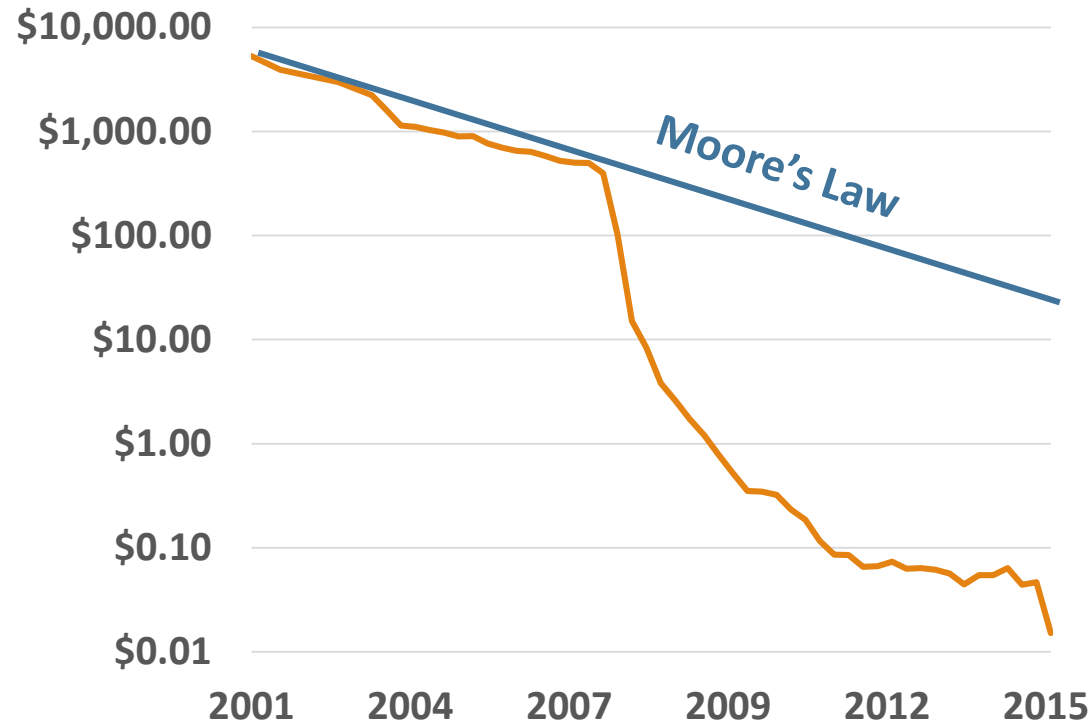
Genome coverage achieved



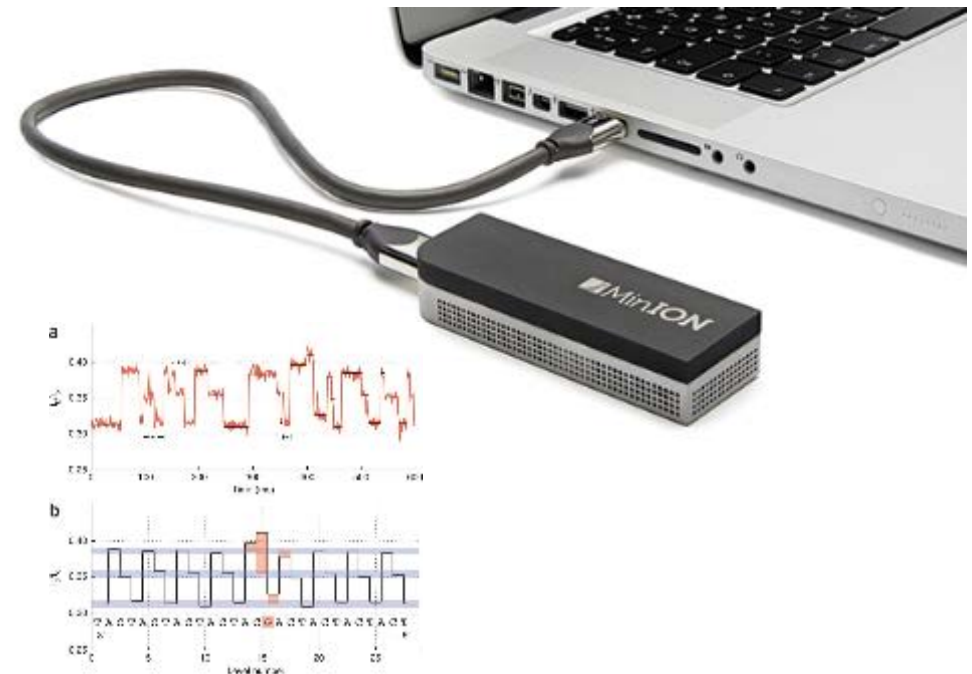


Thesis: Sequencing Will Be A Diagnostic Utility

SEQUENCING COST PER MB OF DATA DROPPING DRAMATICALLY



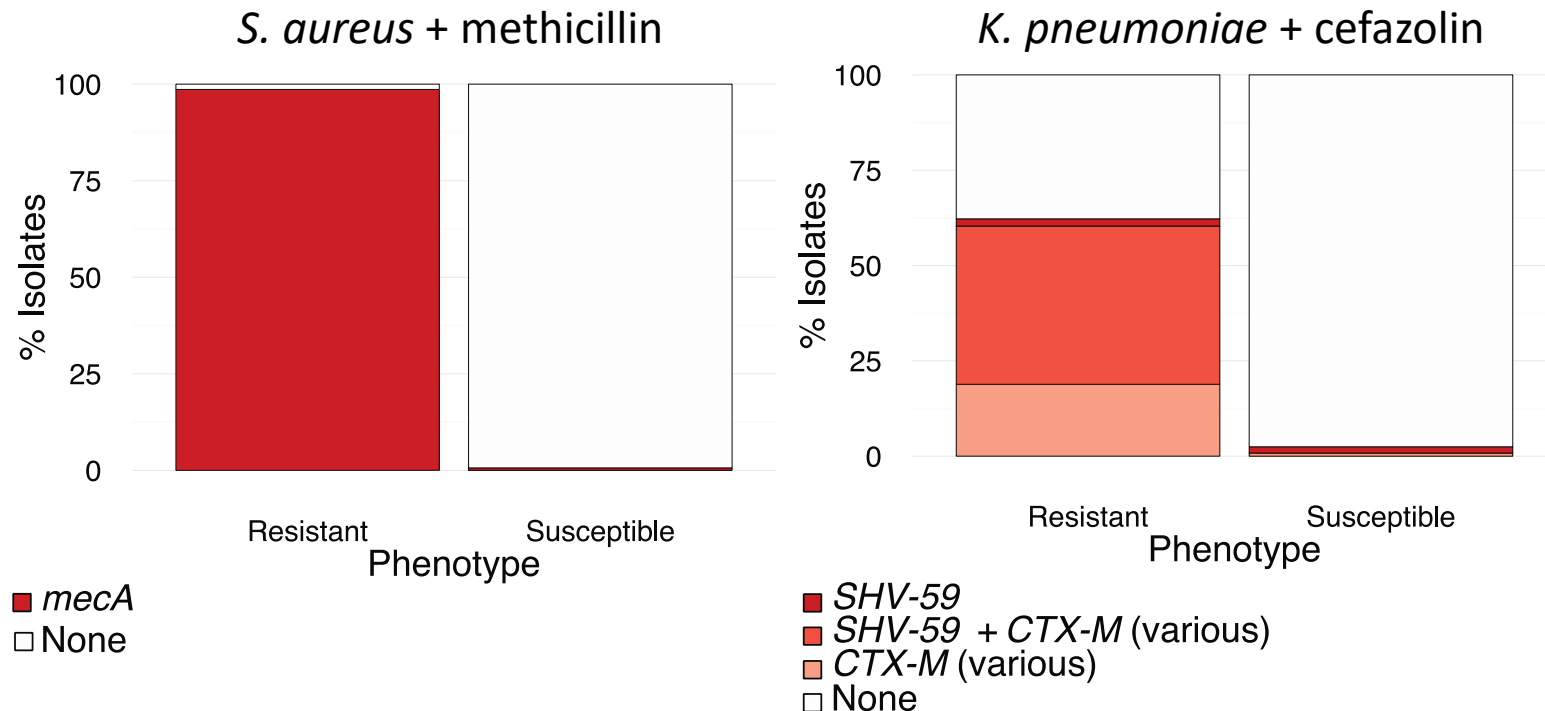
NEW GENERATIONS ENABLE RAPID, SINGLE SAMPLE SEQUENCING





Traditional AMR Prediction: Resistance Gene Lookup

Percent of Isolates Containing Relevant AMR Genes

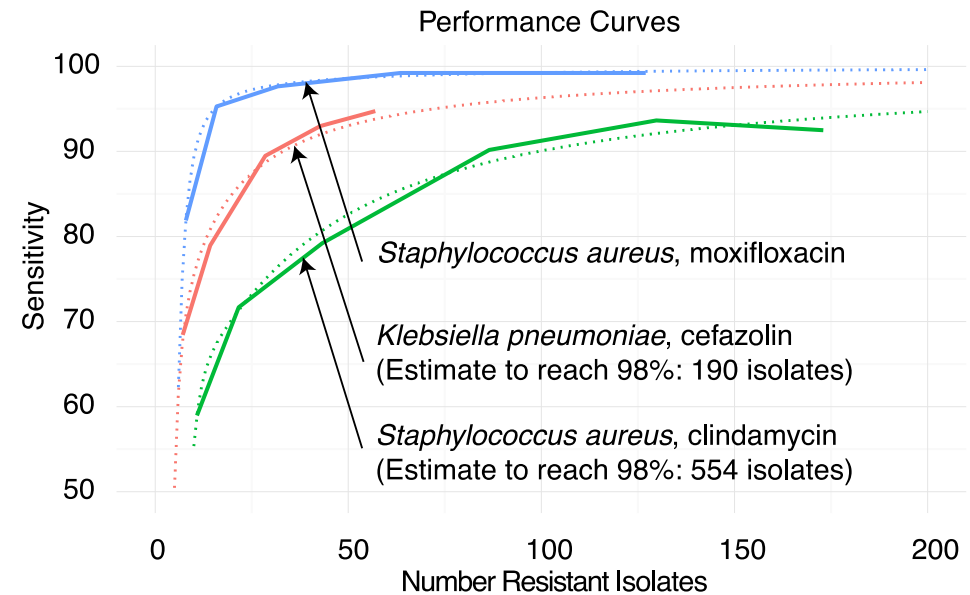
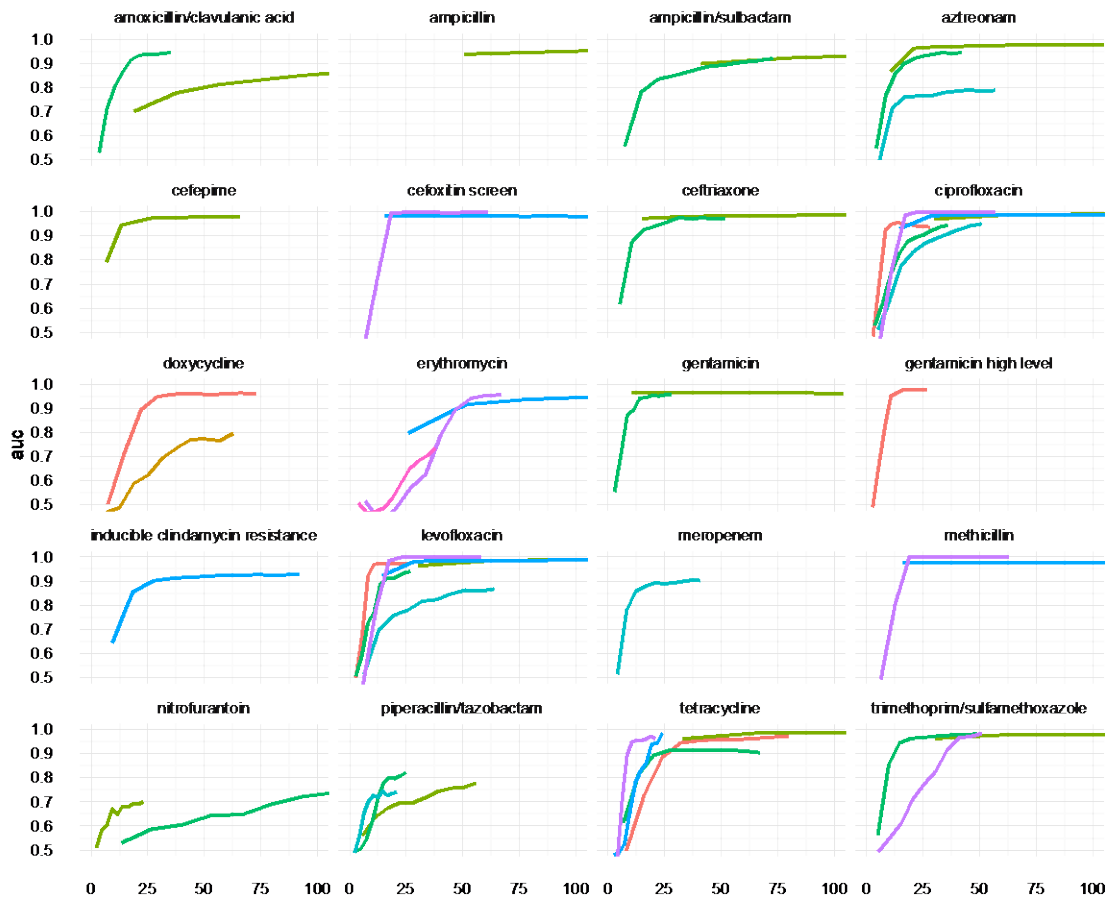


WGS data from Earle, S. G., et al. (2016). *Nature microbiology*, 1, 16041.
Spades + BLAST of ArgANNOT resistance genes

- Highly interpretable, backed by scientific understanding
- **Limited** to a small subset of validated resistance genes
 - Not all mechanisms of resistance are well characterized or known
 - Complex mechanisms difficult to characterize with presence / absence of genes
- Not comprehensive enough to predict susceptibility



Keynome Accuracy Improves With Amount of Training Data in MicrohmDB



- Keynome performance improves with data
- Performance curves differ between species/drug combinations



MicrohmDB: Large Scale Dataset of Pathogen Genomes and AMR Profiles

Collect Clinical Isolates



45,000 samples collected to date from multiple hospital microbiology labs

Sequence Genomes



High throughput whole genome sequencing (NextSeq, HiSeq) – 25,000 thus far

Link AMR Data

Sample

	Ampicillin	Ciprofloxacin	Tetracycline	..
AGTTGACTCACTCGATC...	R	R	S	
GATGATGTAGCTGCAAT...	S	R	S	
AGTAGTCGATCGTACGA...	R	R	R	
CGCGTTAGCTAGCTATC...	S	S	S	
GCTAGCTACTCGATCGT...	S	S	R	
AAAGCTATCGTGAGCTC...	R	R	R	
TTTCTACTACGGCTGCT...	R	R	R	
GCTACTCGATCGTAGCT...	S	S	R	
...				

Link genomes with phenotypic AMR data
Bioinformatic annotations



DZD Vision: WGS Diagnostics Enable Large Scale Data Opportunity

