Overview of CIDT – Challenges and Opportunities

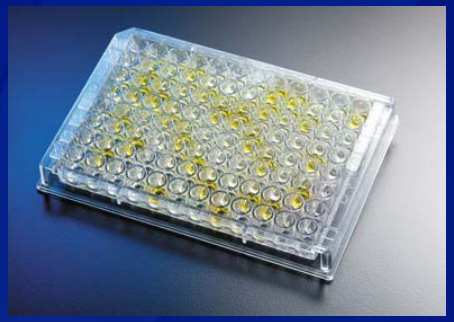
Enteric Diseases Laboratory Branch

InFORM II
Phoenix, AZ, 19 November 2015

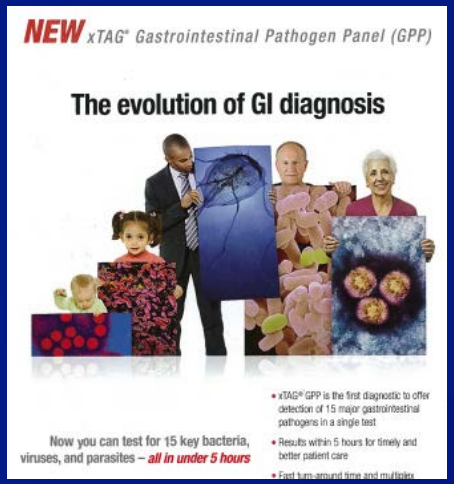
National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases

CIDT's

- Enzyme immunoassays



- Molecular analytical panels



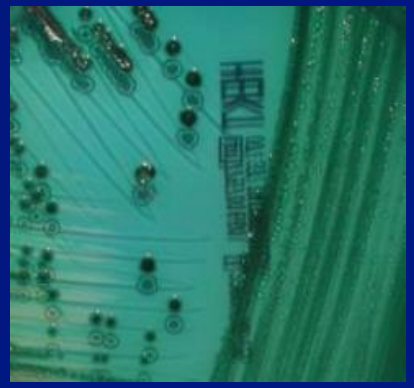
July 28, 2015

World's Most Portable Molecular Diagnostics System Unveiled at AACC

GeneXpert Omni to Further Decentralize Critical TB, Virology and Ebola Tests

SUNNYVALE, Calif. and GENEVA, July 28, 2015 /PRNewswire/ -- Cepheid (Nasdaq: CPHD) and FIND today unveiled the GeneXpert® Omni, the world's most portable molecular diagnostics system enabling unprecedented access to accurate, fast and potentially life-saving diagnosis for patients suspected of TB, HIV and Ebola in even the most remote areas of the world.

CIDT Opportunities & Challenges



- Patient care
- Accurate case counting
- Maintaining isolate-based surveillance

CIDT's are developed to aid clinicians

- Fast diagnosis to guide treatment

CIDT Challenges To Clinicians

- **EIA's**
  - Developed to detect one pathogen at a time
  - Sensitivity and specificity issues
- **Molecular diagnostic panels**
  - Up to 22 bacteria, virus, parasites
  - Sensitivity issues
    - Stx2f not detected
    - Norovirus targets change
      - Even though it works today, it might not tomorrow
  - Specificity issues
    - Are they detecting what they claim?
      - EPEC, EAEC, ETEC
  - How to interpret mixed infections?

Opportunities Of CIDT's To Public Health

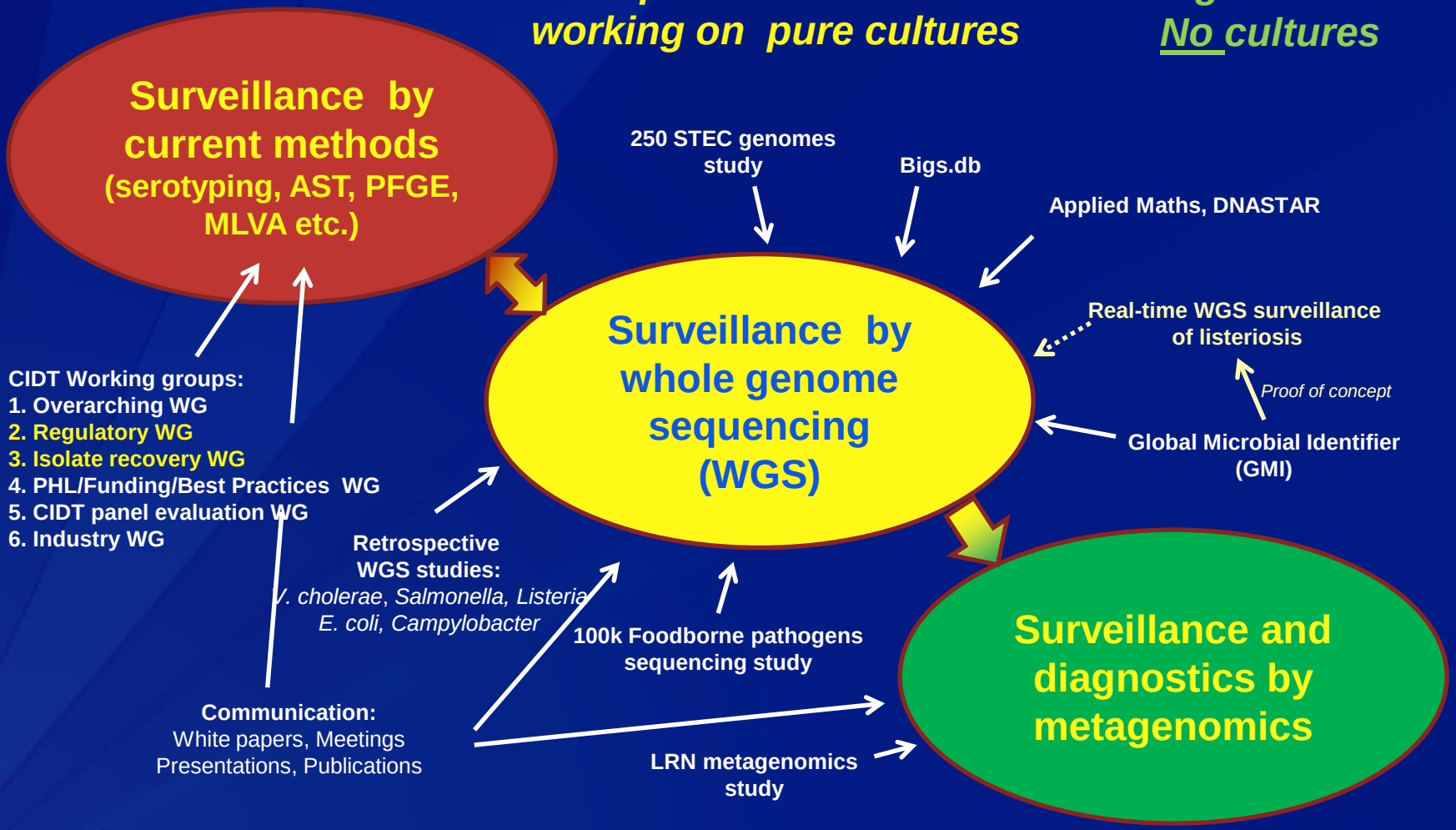
- Better case counting of pathogens rarely looked for by traditional methods
  - *Yersinia,* DEC, *Plesiomonas, Vibrio,* virus, parasites

But……

- Panels vary widely in pathogens they diagnose
  - Both the number of pathogens and the targets used
- Suffer from sensitivity and specificity issues
- Critical for public health to know what CIDT was used to diagnose each patient

CIDT's Are A Threat To Laboratory Surveillance Because We Lose The Cultures Critically Important For Our Surveillance

Laboratory Strategy to Meet The Challenge of Culture Independent Diagnostic Methods (CIDT)



Regulatory Workgroup

- Charter: Identify barriers and make recommendations/develop strategies to assure continued flow of specimens and isolates to public health
- Members:
  - CDC, APHL, ASM, FDA (Microbiology Devices), AdvaMed, Joint Commission, CAP, IDSA
- Issues discussed:
  - Laboratory regulation
  - Test regulation
  - Test coding, coverage, reimbursement & compliance
  - Case reporting rules, state isolate/specimen submission requirement
  - Diagnostic test development

Isolate Recovery

- **The Culture Preservation Workgroup:**
  - Public Health Labs (CO, IA, LA County (CA), MN, and TN), APHL, and CDC
- **Generate data to formulate recommendations for the efficient recovery of *Salmonella* and STEC (Shiga toxin-producing *E. coli*) from CIDT-positive specimens.**
  - Media Study
  - Seeded Stool Study

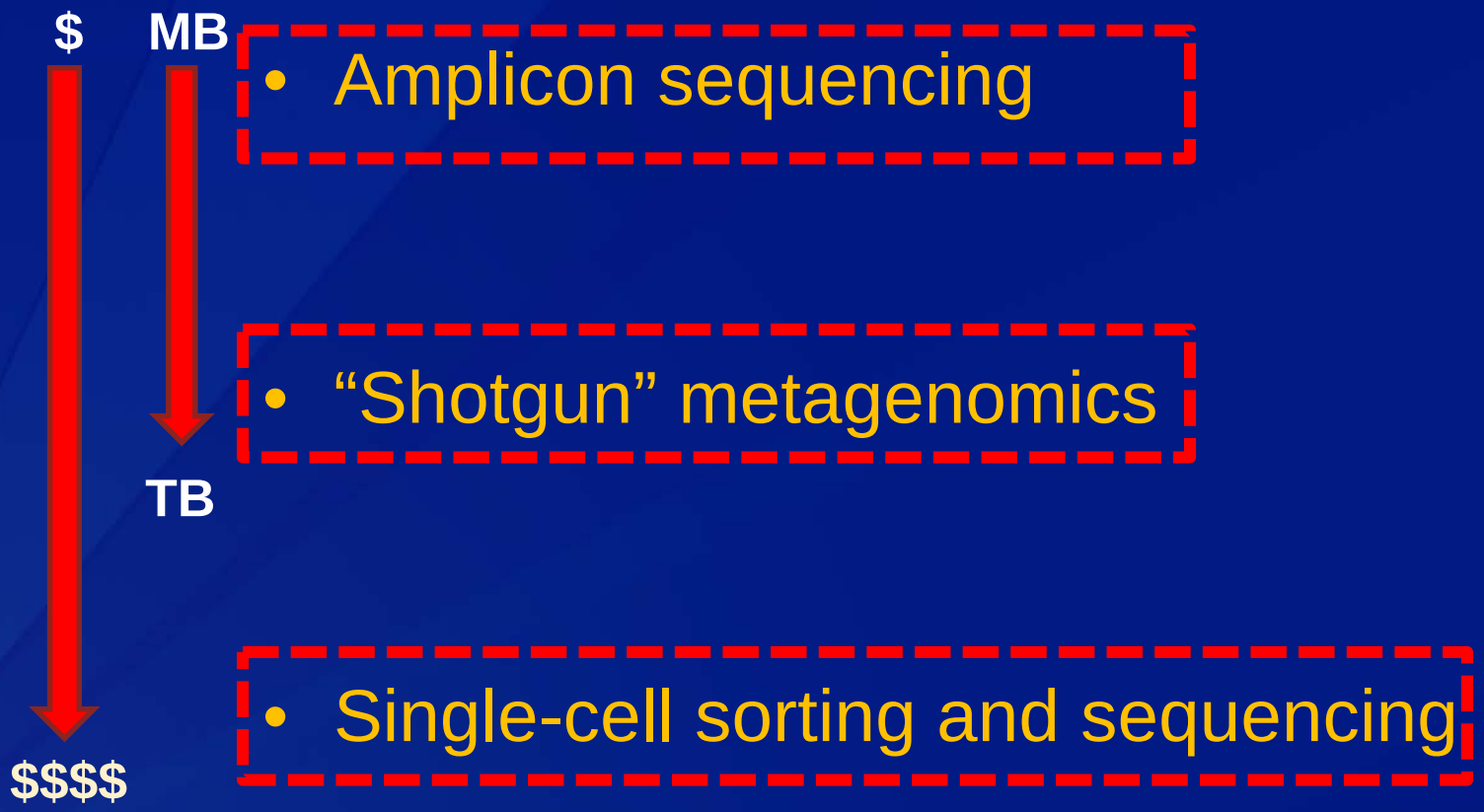
Culture Preservation Study Final Steps

- **CIDT Steering Committee meeting for Oct 2015**
  - Review results of CIDT media and stool studies
  - Develop science based recommendations for recovery of STEC and *Salmonella* isolates
- **Disseminate results to scientific community**
  - INFORM meeting (Nov 2015)
  - MMWR guidance document
- Bio-stability of specimens for metagenomics analyses

The Promise Of Metagenomics

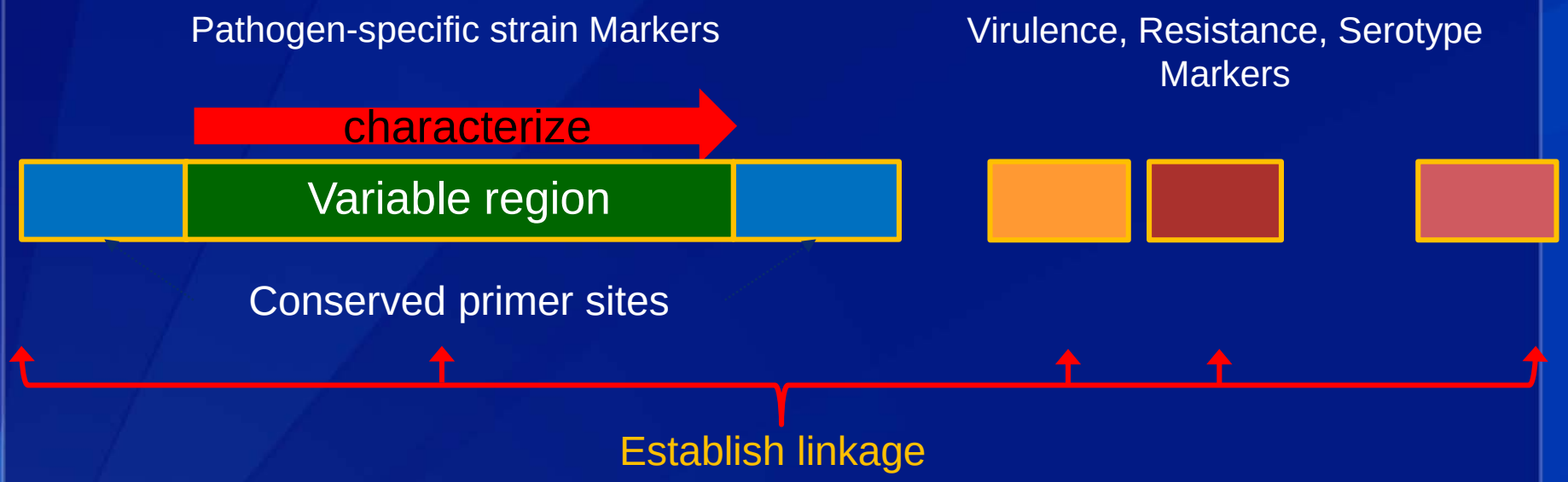
- **More pathogens will be detected**
- **More paradigm shifts are possible/likely:**
  - **Pathogen interaction/complementation**
    - Virulence factors from different pathogens may interact and thereby enhance/ reduce the virulence of one or both pathogens
  - **Virulence complementation/enhancement/inhibition by normal flora**
    - Virulence factors in a commensal could complement the virulence gene repertoire of a pathogen
    - A commensal may compete for receptors for a pathogen thereby rendering it less pathogenic
  - **Host ~ Pathogen associations**
    - The host genotype may be determined
    - Non-secretors and resistance to norovirus infection
  - But technology, bioinformatics and ethics are not there, yet

Three Public Health Approches To Metagenomics



Development of Organism-specific Strain Markers Through Amplicon Sequencing

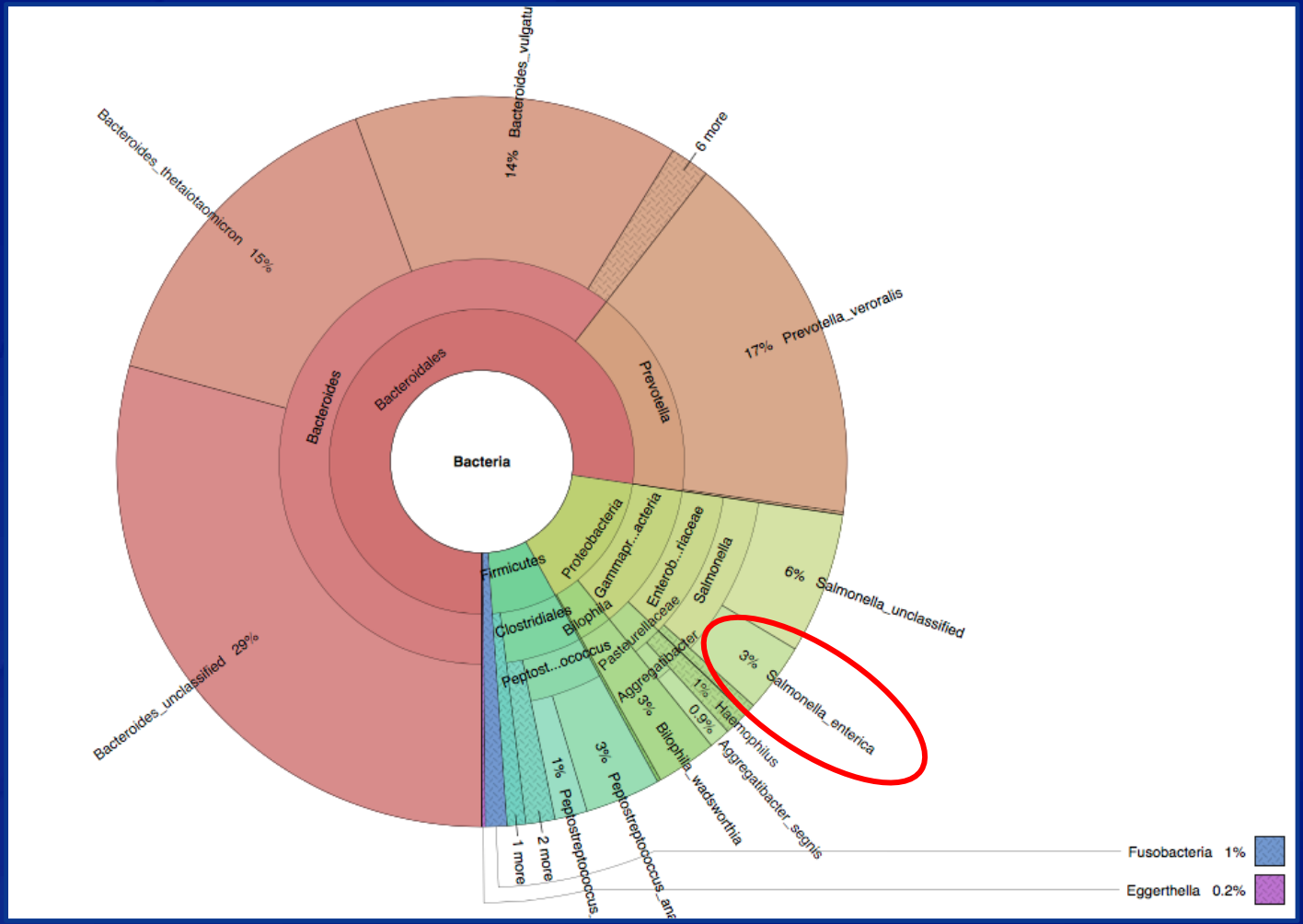
1. Identify suitable markers:



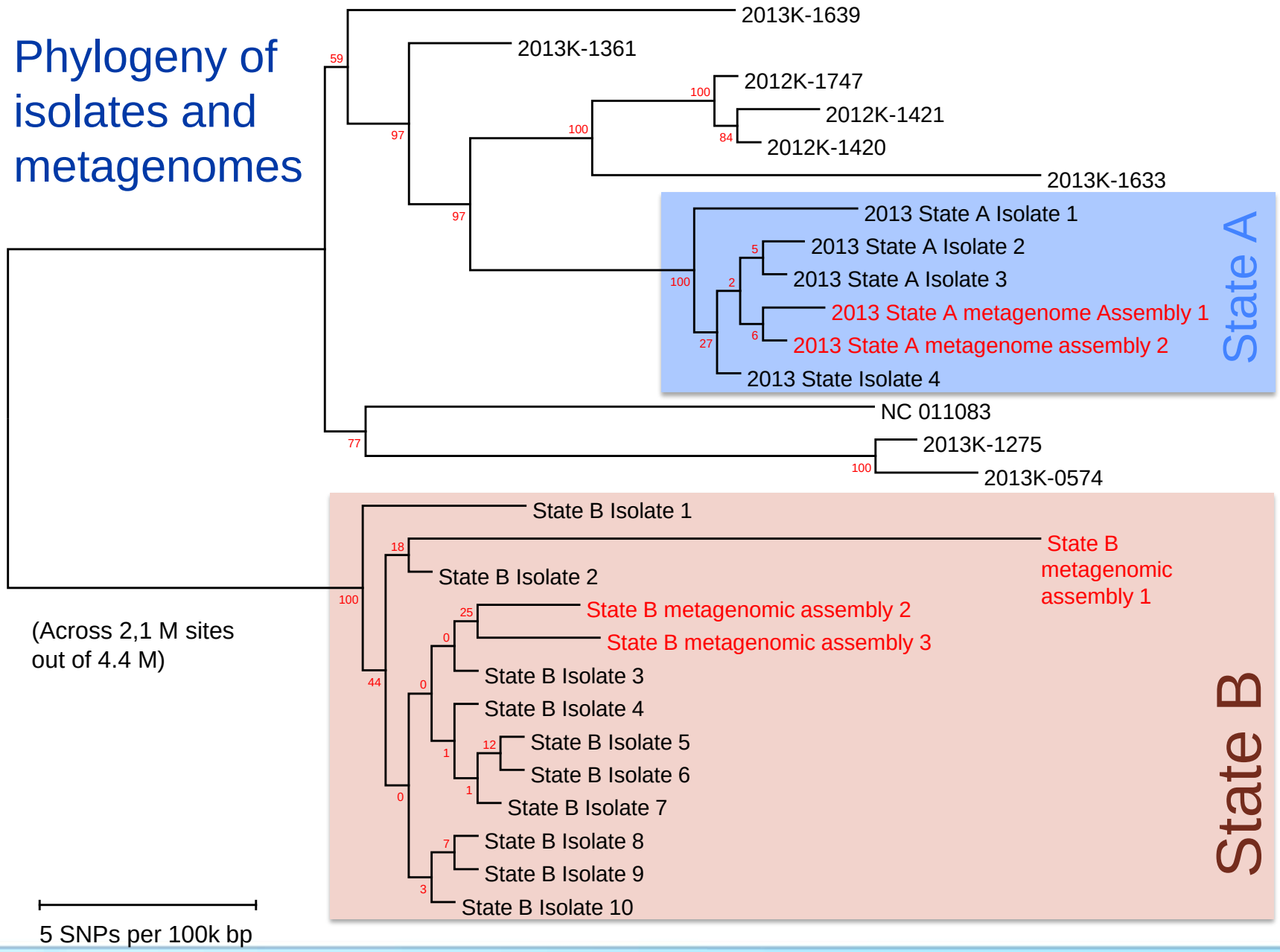
2. Test markers against stool metagenomic data sets

3. Conduct field trial

Metagenomics By Shotgun Sequencing



Phylogeny of isolates and metagenomes



(Across 2,1 M sites out of 4.4 M)

5 SNPs per 100k bp

Metagenomics: Limiting Factors

Factor	Limitation	
	Amplicon Sequencing	Shotgun
Need for *a priori* hypothesis	Yes	No
Cost	No	Yes
Sequencing read length (and error rate)	No	Yes
Metagenomic-specific software, pipelines	No	Yes
Computing processing power, bandwidth	No	Yes
Signal to noise	No	Yes

Metagenomics: Timeline

- Outbreaks of undetermined etiology: 2016[1] – 2018
- PulseNet: 2019[2] (per John) – 2025 (per Peter)

[1] With limitations

[2] Assuming key technological advancements

Acknowledgements

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University of Oxford, M. Maiden

Disclaimers:

"The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention"

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