The Future of Culture-Independent AMR Detection





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Agenda

01 AMR Surveillance in NARMS

02 Current Metagenomic Methods and Limitations

03 Emerging Methods in Host-Association

04 Conclusions & Next Steps



AMR Surveillance in NARMS

National Antimicrobial Resistance Monitoring System



Partners in antimicrobial resistance and food safety

National Antimicrobial Resistance Monitoring System



phenotype
antimicrobial susceptibility testing

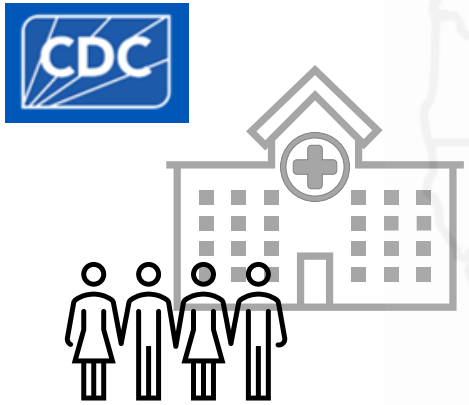
+

genotype
whole genome sequencing

=

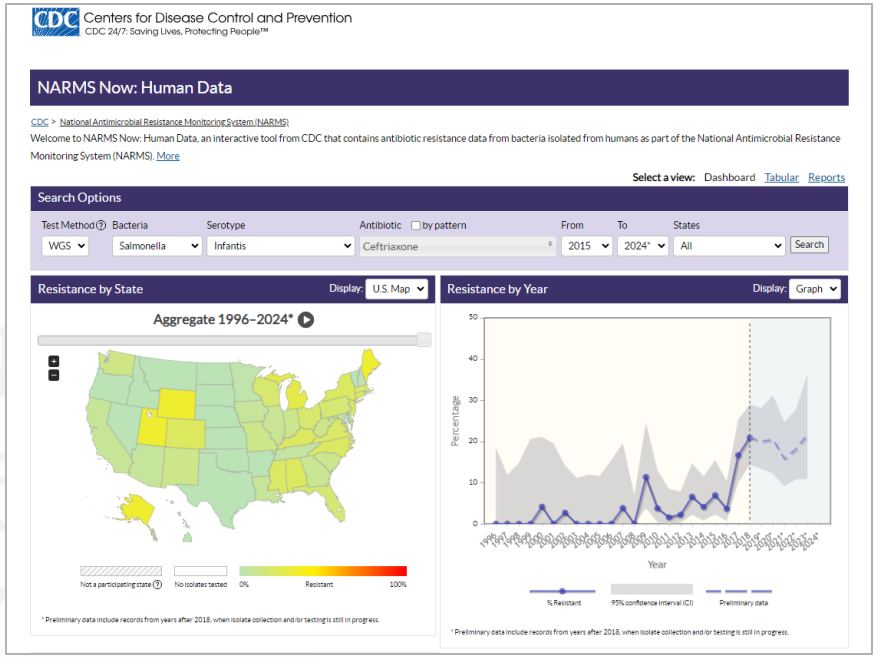
predicted
phenotype + genotype

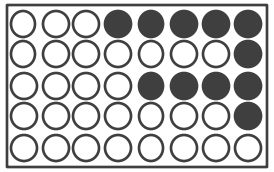
National Antimicrobial Resistance Monitoring System



PulseNet USA™
The National Molecular Subtyping Network for Foodborne Disease Surveillance

NIH National Library of Medicine
National Center for Biotechnology Information





5%
phenotype

\+



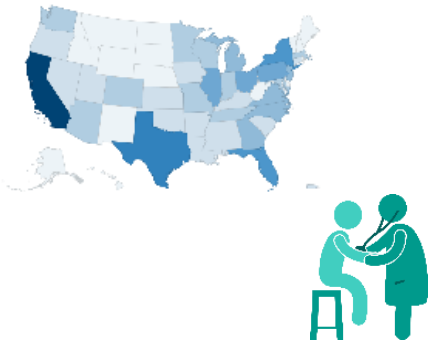
100%
genotype

\+



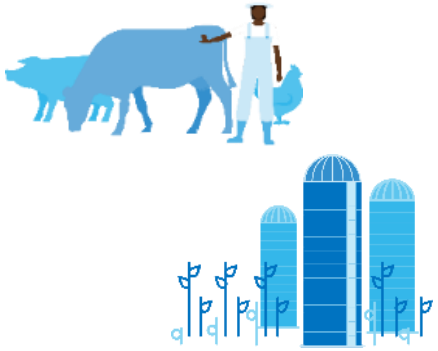
demographic
patient questionnaires

NARMS-CDC uses WGS for AR surveillance and outbreak response: by the numbers for 2024



68,169

Human clinical sequences submitted by 80+ Federal/State/Local PHLs



20,262

Food/animal/environmental sequences submitted by USDA/FDA/PHLs



0 delays

Real-time detection and response to emerging AR



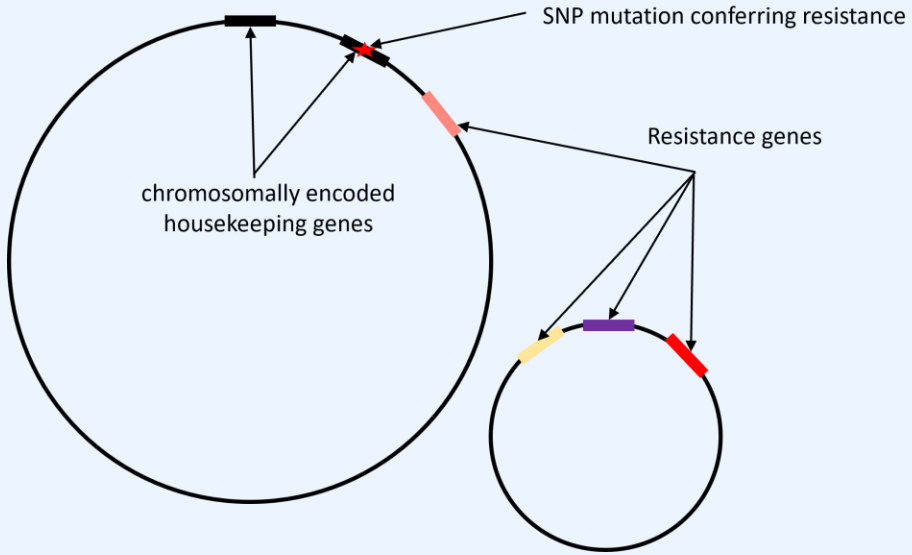
150

Number of clusters or outbreaks analyzed for AR

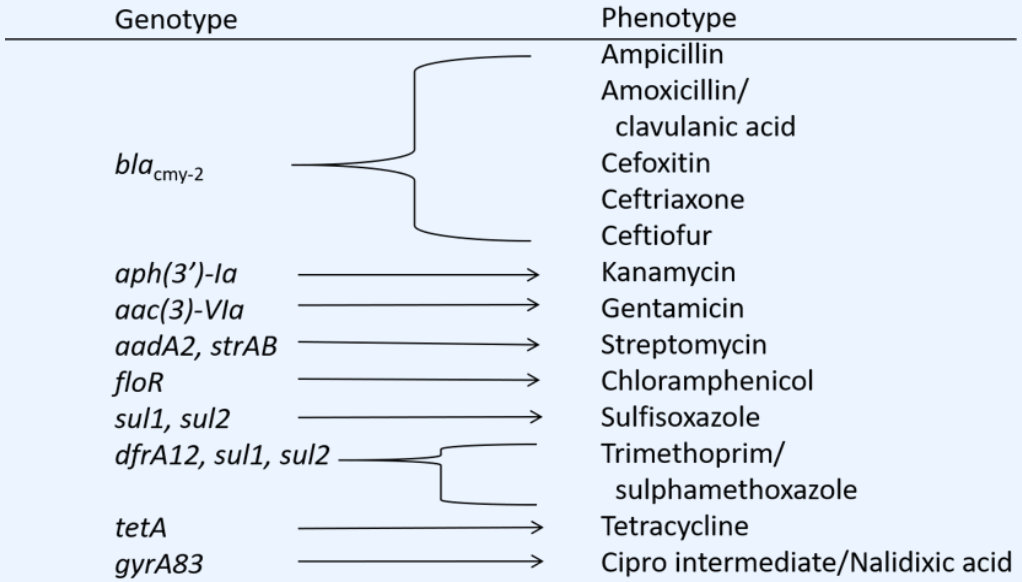
** genomic data also used for emerging and concerning resistance and special studies*

Genotypic Surveillance of AMR

- Isolate sequences are submitted by PHLs to PulseNet 2.0 for analysis.
- All isolates submitted to PulseNet are screened for resistance determinants using AMRFinder.



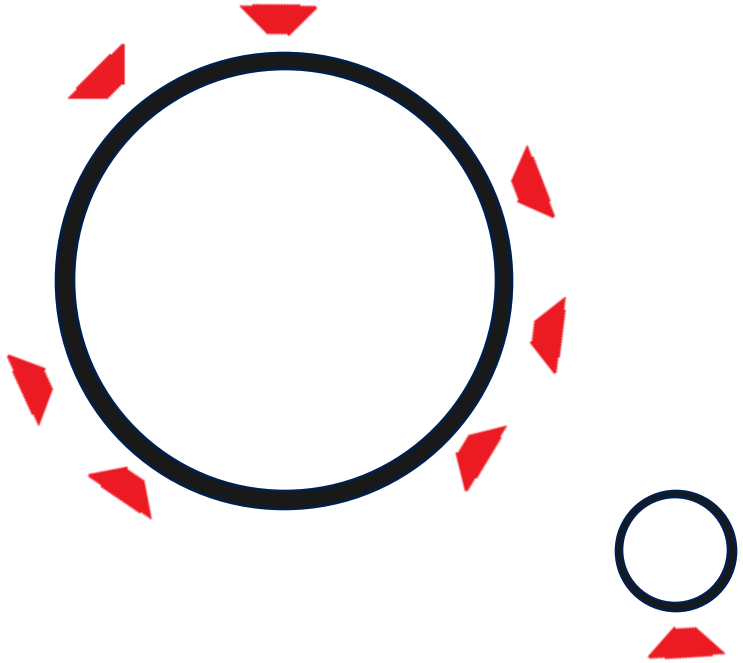
- Resistance determinants are translated into a predicted resistance profile by NARMS.





Current Metagenomic Methods and Limitations

Targeted Sequencing



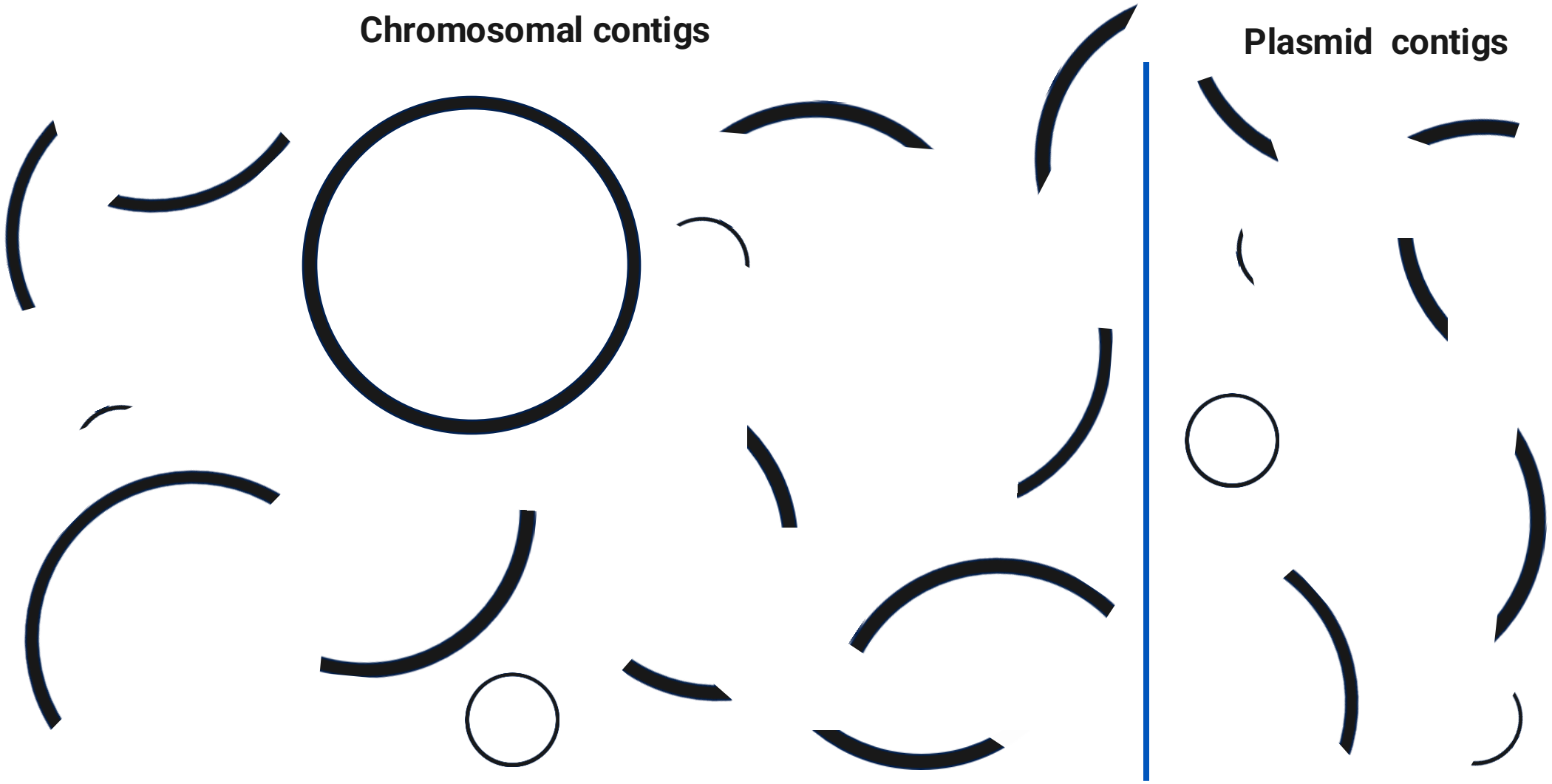
- PCR or probes targets regions of interest
  - Pathogen loci
  - AMR genes
  - Virulence genes
- Strengths
  - Ability to capture low-abundance targets
  - Increases signal from complex matrices
- Weaknesses
  - Can add considerable amount of cost and/or time to a procedure
  - Cannot capture emerging or novel targets
  - Recovers only a limited amount of genome

Shotgun Sequencing

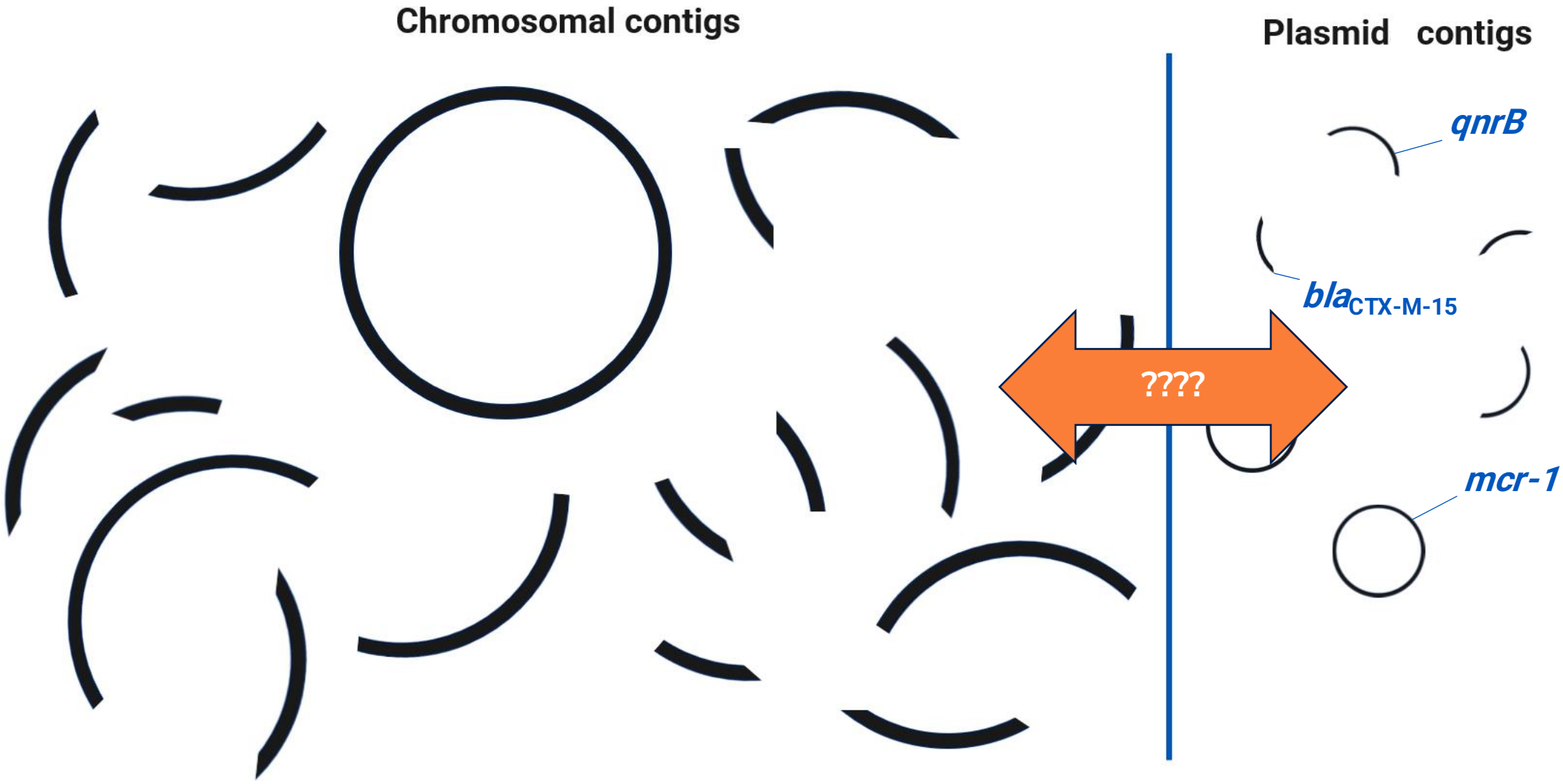
- Can sequences all nucleic acids within a sample
- Strengths
  - Provides a more complete picture of a community
  - Simpler workflow
- Weaknesses
  - Capturing low abundance targets may require very high depths
  - Metagenome-assembly may not be able to reconstruct full genomes



Common Problem Threatens AMR Surveillance



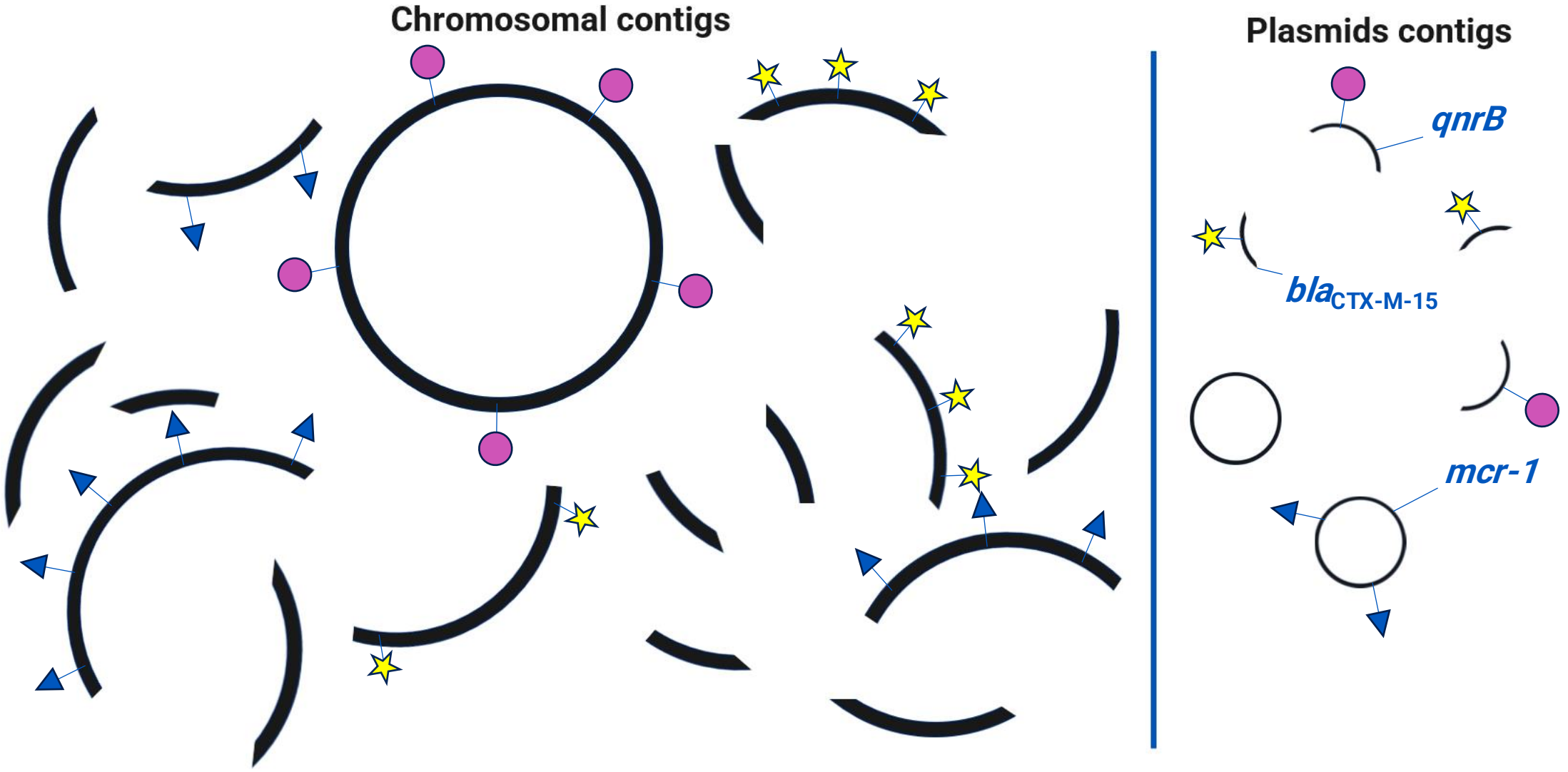
Common Problem Threatens AMR Surveillance





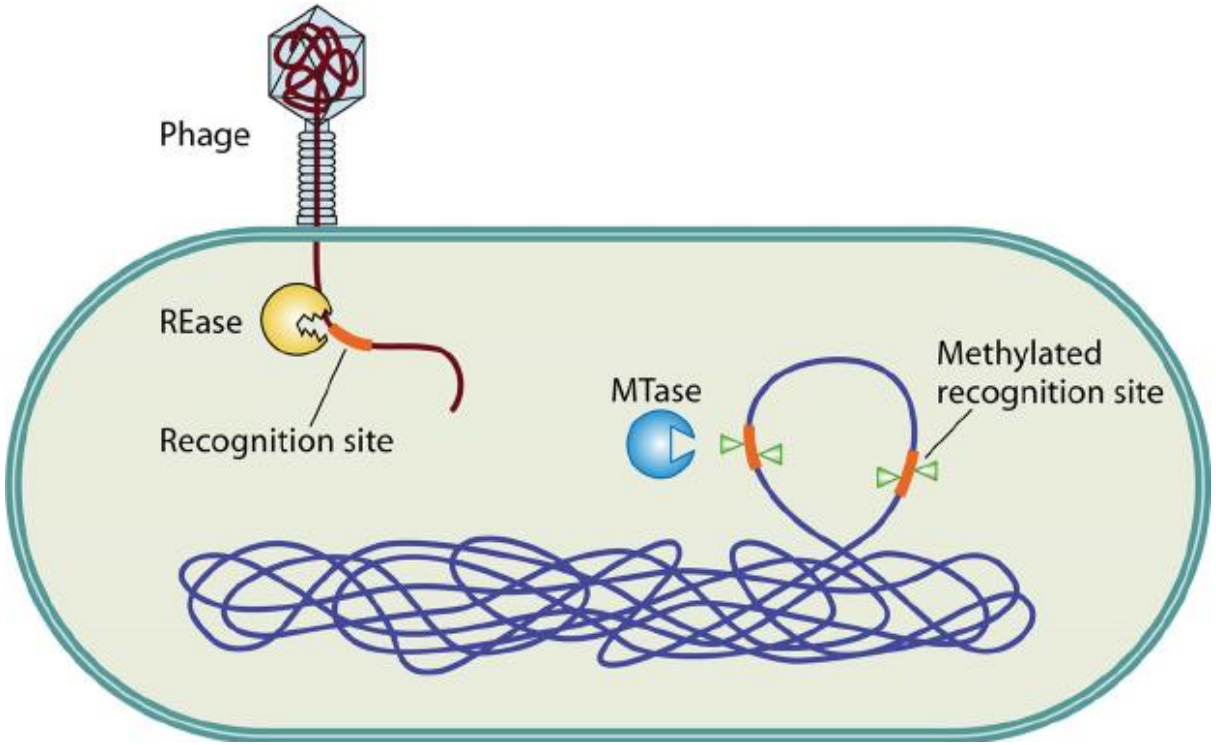
Emerging Methods in Host-Association

Strain-Specific DNA Modification Profiles



Bacterial Restriction Modification Systems

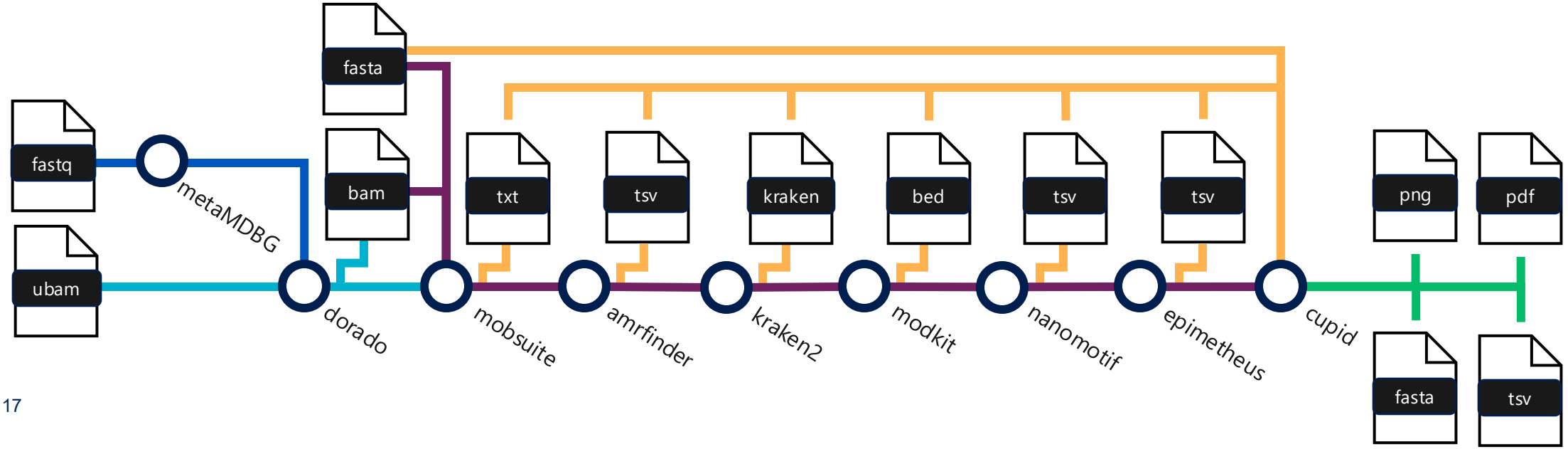
- A bacterial defense system to protected against foreign DNA.
  - DNA restriction endonucleases which cleave DNA at specific recognition sites.
  - DNA methyl transferases which methylate host DNA at those specific sites, protecting it.



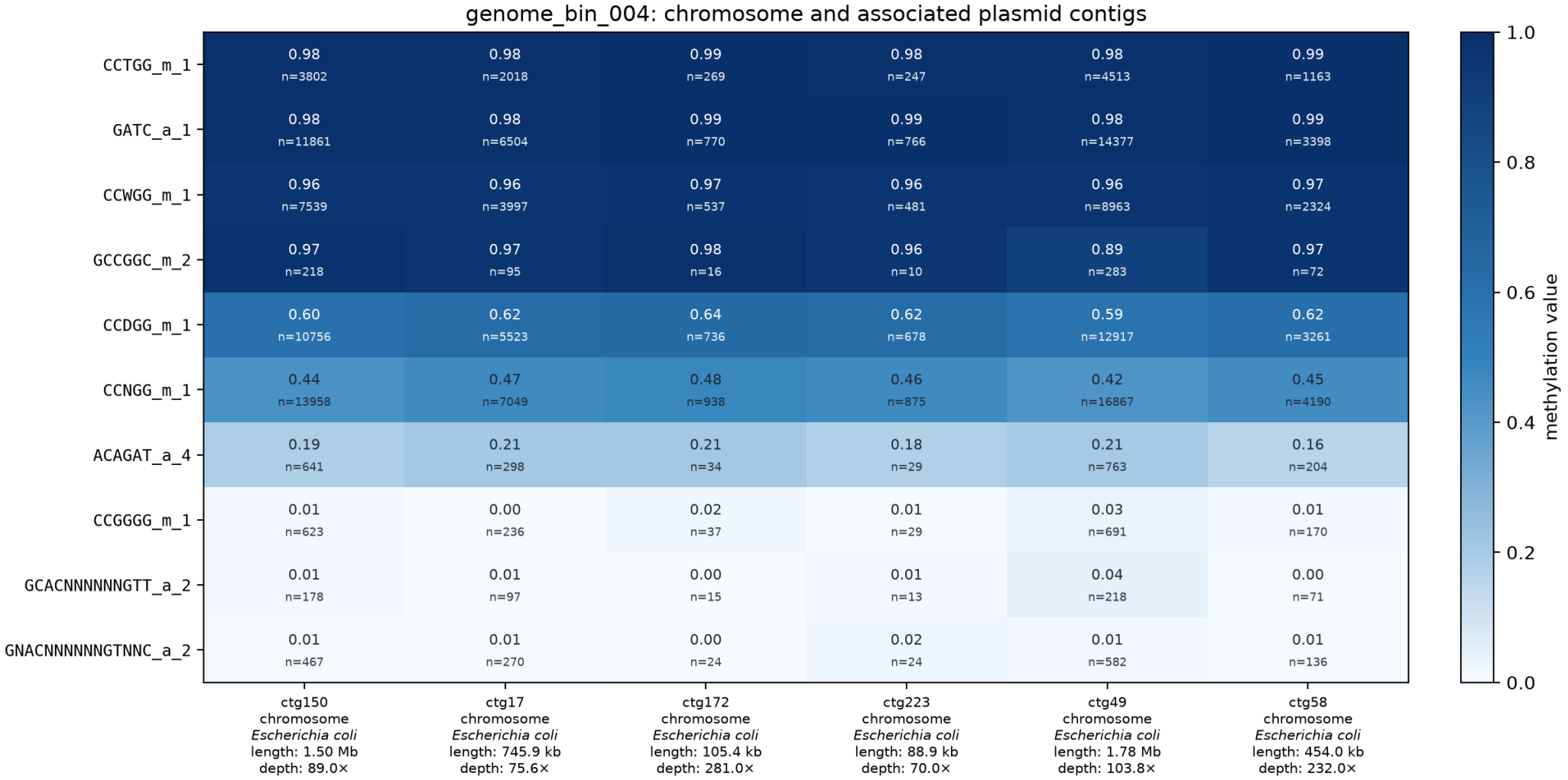
Can Epigenetic Profiles & MAGs be Used for Host-Association?

Sequenced quasi-metagenomic samples

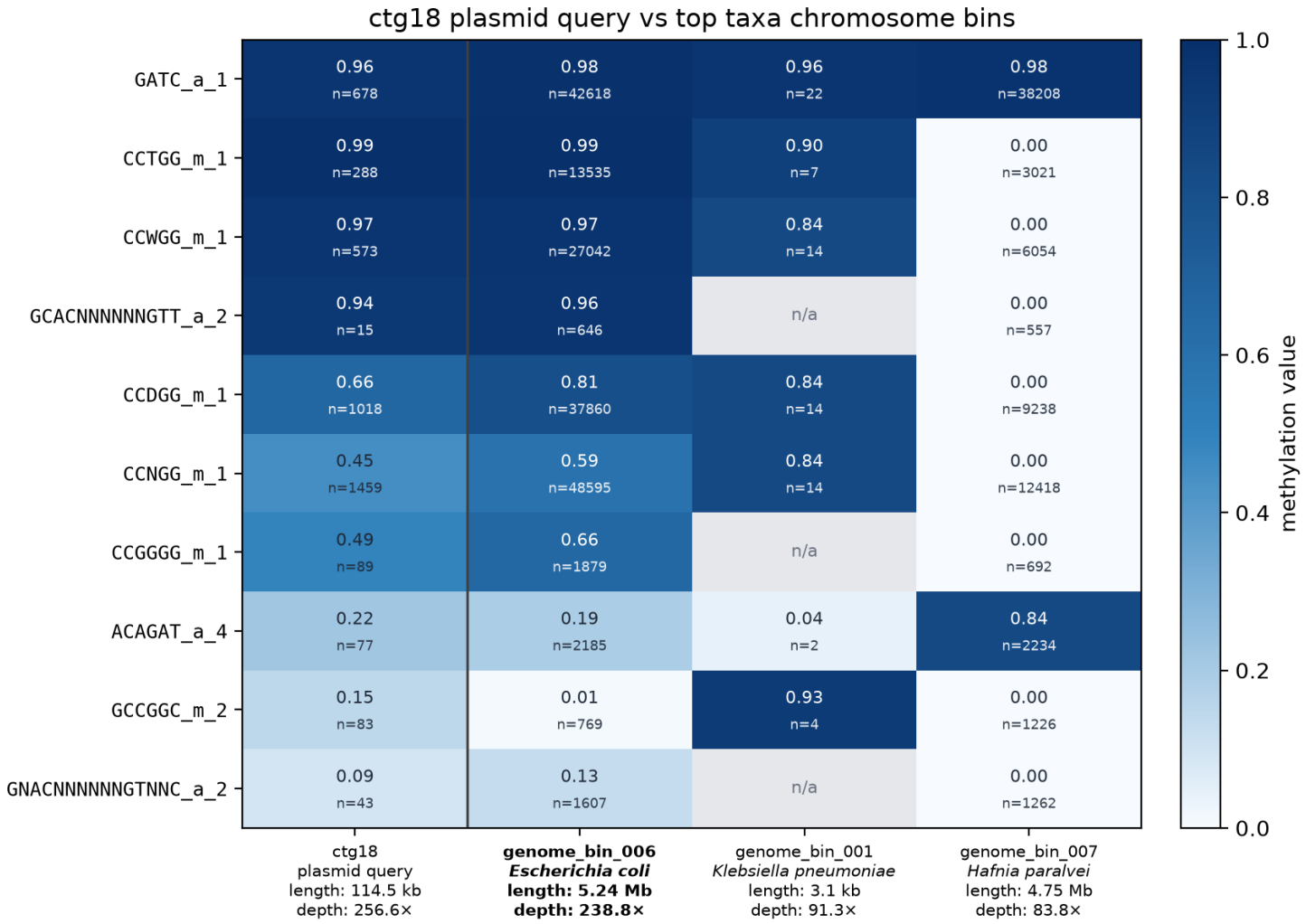
- Known AMR-carrying plasmids
- Multi-pathogen primary specimens
- Closely-related samples (multiple pathotypes of *E. coli*)

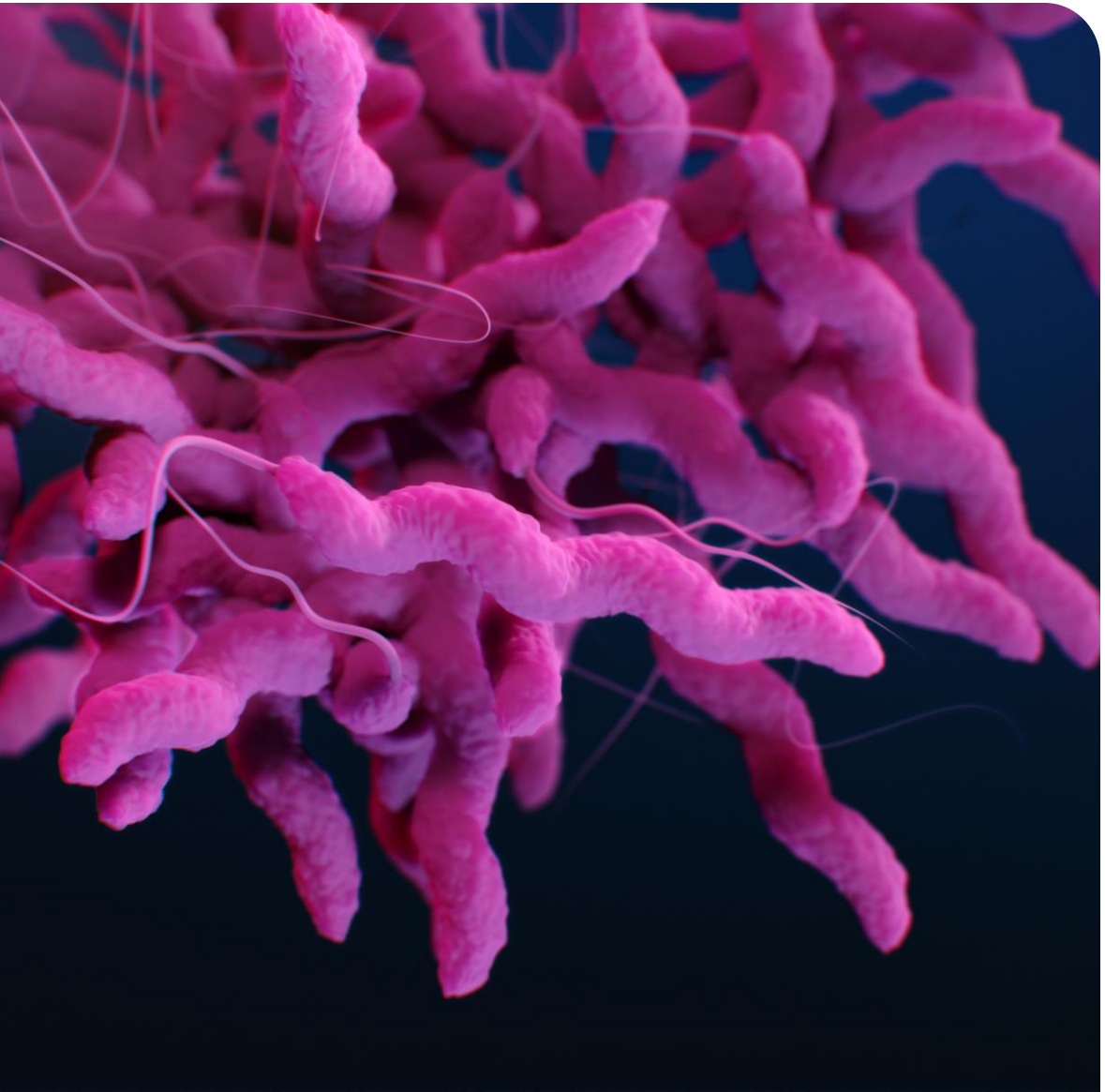


Reconstruction of Bacterial Genomes through Binning Chromosomal Contigs by Epigenetic Profile



Attribution of AMR-Carrying Plasmid to Host by Epigenetic Profile





Conclusions & Next Steps

Conclusions

- Continuity of AMR surveillance, through programs like NARMS, is key for understanding trends in AMR prevalence and emerging AMR threats in foodborne pathogens
- Current metagenomics methods have limitations in attributing plasmid-borne AMR genes to a bacterial host
- Epigenetic profiles can be used for binning metagenome-assembled genome contigs, improving genome completeness and attributing plasmids to their respective host

Next Steps for Exploring Culture-Independent AMR Surveillance

- Further testing will be needed to evaluate
  - Limit of detection and depth requirements
  - Applicability to more complex matrices
  - Whether enrichment is necessary and/or efficient
- Interested in methods like these or have other ideas? Connect with NARMS to continue the conversation!



Acknowledgements

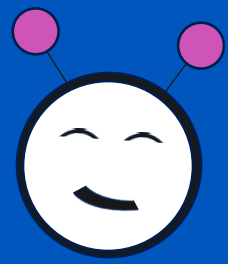
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