Clinical Metagenomics for Drug-Resistant Infections: Ethical Issues

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Imagine a case…

A patient has arrived at the emergency department with a fever, respiratory symptoms and indications of sepsis. A sputum sample is sent for culture and metagenomic analysis. Meanwhile, the patient is started on first-line broad-spectrum antibiotics. Before other testing is completed, metagenomic results identify Klebsiella pneumoniae *as the pathogen responsible*, *with a gene associated with drug resistance. Clinicians increase infection control precautions and switch antibiotics. The metagenomics results are also positive for another pathogen,* Tropheryma whipplei*, which appears to be unrelated to the disease symptoms.*

Based on Charalampous et al. 2024.

Outline

- Background
  - *Pathogen metagenomics*
- Ethical considerations
  - *Rationing and cost-effectiveness*
  - *Diagnostic benefit*
  - *Tailoring treatment*
  - *Incidental findings*
  - *Other uses of the data*
  - *Addressing AMR*
- Conclusion

Credit: American Society for Microbiology

Background

Pathogen Metagenomics

- Method of sequencing pathogen DNA that analyses the whole sample
- Allows for picking up novel or unexpected pathogens in the sample
- Clinical and public health advantages over other methods (PCR, microbial culture…)
  - Fast turn-around times
  - Possible better identification of resistance genes
  - Addressing diseases of unknown aetiology
  - Addressing unexplained disease outbreaks

Ethical Considerations

Rationing and cost-effectiveness

Some level of resource rationing is required in all healthcare settings, because all are resource-limited.

- Is it best for the clinician to use limited metagenomics testing capacity for *this patient?*
- Does costly metagenomics produce better results than culturing and resistance testing?
- Will treatment be rendered much more cost-effective if changed in response to metagenomics findings?

Details:

Rationing principles might include (Doyal 1994):

- Allocating resources according to distribution of health care needs within the population
- Allocation of resources according to extremity of need within disease areas
- Allocation of resources only according to effective (non-futile) treatment
- Otherwise equal allocation to resources

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- Allocating resources according to distribution of health care needs within the population
  - Some infectious diseases affect populations uniformly, some affect particular groups; metagenomics is pathogen-agnostic; could/should appropriate use be set according to suspected pathogen/disease?

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Rationing principles might include (Doyal 1994):

- Allocation of resources according to extremity of need within disease areas
  - It seems intuitive that patients with worse symptoms (who will also likely be in more urgent need of diagnosis and effective treatment) should be prioritised for metagenomic diagnosis access.

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Rationing principles might include (Doyal 1994):

- Allocation of resources only according to effective (non-futile) treatment
  - If pathogen metagenomics is likely to be used when clinicians are presented with novel diseases or syndromes, this may be difficult to achieve compared to non-futile allocation of other diagnostic methods.

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Rationing principles might include (Doyal 1994):

- Otherwise equal allocation to resources
  - Are there any new issues raised by metagenomics that alter the resource allocation principles that should be used?
  - How should cost-effectiveness get weighed against other principles of resource allocation where there are other effective diagnostic options like PCR and culturing?

Ethical Considerations

Diagnostic benefit and tailoring treatment

- Reduced turnaround time can contribute to diagnostic benefit. Metagenomic testing can result in same-day diagnosis for up to 86% of samples, and in one study resulted in changes to antimicrobial treatment in nearly half of all same-day diagnoses (48%, n=53) (Charalampous et al. 2024).
- This avoids ineffective treatment and may prevent the patient condition worsening.
- Culturing and sensitivity testing may be needed for confirmation.

Details:

- Pathogen genomics (broader than metagenomics) has been hailed as facilitating precision medicine and precision public health (Leguia et al. 2019).

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- Achieving clinical benefit from diagnosis should be considered in comparison to existing methods (e.g., drug susceptibility testing using culturing may also be effective for tailoring treatment)
- If achieving comparative benefit comes down to the timeliness, this should be acknowledged, especially if benefit is limited by the need for confirmation from other less timely methods.

Ethical Considerations

Incidental findings

- Might occur when: (i) clinicians were not searching for the organism that was discovered, and (ii) clinicians receive a positive result for the type of organism they were searching for, but they are uncertain as to the significance.
- *T. whipplei* is frequently carried asymptomatically (Keita, Raoult & Fenollar 2013). Should clinicians be concerned or not? Does the additional information create an unnecessary burden of worry for patient or clinician? Would treatment be a waste of resources?

Details:

- Incidental findings have been thoroughly discussed in ethics literature on human genetics. We might be guided by principles here including:
  - Fostering resilience in patients through clinical interactions and preparing them for 'genomic uncertainty' (Newson et al. 2016)

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  - Additional consideration might be needed in relation to the return of incidental findings from children's samples (Kleiderman et al. 2014)

Ethical Considerations

Other uses of data

- It is unlikely that this patient's case is relevant for public health. However, the results of pathogen genomics for resistance testing in other settings may be important for national surveillance of communicable diseases, and has informed public health responses (Poon et al. 2016).
- In what situations should data be shared for non-clinical uses? When ought the patient be informed of this? What interventions are acceptably developed on the basis of population-scale metagenomic surveillance?

Details:

- Physicians have ethical obligations to promote population health as well as patient health which may justify some forms of data sharing (Jamrozik et al. forthcoming) on top of reporting that is legally required for notifiable diseases. Yet—

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- Potential for population health benefit from sharing genomic data must be weighed against risks of privacy infringement and harm suffered by the individual (Faber et al. 2025).
- Forensic uses of metagenomic data raise questions in jurisdictions where their use may facilitate rights violations, e.g., to freedom of association or expression of sexual orientation.

Ethical Considerations

Addressing AMR

- Genomic drug resistance testing is recommended for HIV and TB. But with targeted testing, certainty of the association between gene and phenotype (of the target infection) is higher.
- With metagenomics, the certainty of association between ESBL gene and *K. pneumoniae* may be lower. This means:
  1. First-line treatment may have been clinically effective after all
  2. Risk of AMR contribution from first-line treatment may have been lower than metagenomics indicated

Details:

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- This may mean that confirmation is *always* needed, which reduces the marginal benefit of metagenomic testing over conventional methods.
- For infections spreading within hospitals, if metagenomic testing does indicate resistance, and this is confirmed, this may make a stronger case for infection prevention and control methods and may help to address infection spread and AMR within wards.

Ethical Considerations – further work needed!

- *Rationing and cost-effectiveness*
- *Diagnostic benefit*
- *Tailoring treatment*
- *Incidental findings*
- *Other uses of the data*
- *Addressing AMR*

Ethics research lags far behind technological development for pathogen (meta)genomics. With countries like Australia starting to implement it within public health systems for routine surveillance and outbreak response (AusCDC 2025), ethical guidance is urgently needed.

Credit: American Society for Microbiology

Conclusion

There are many ethical considerations that need to be accounted for in using metagenomic testing for diagnosis in clinical settings, particularly for the diagnosis of resistant infections.

Implications for patient burdens, extensions of clinicians' and microbiologists' obligations, and public health/AMR may be significant.

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This article is part of the Pathogen Genomics in Clinical Practice collection.

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