Clinical Utility of Routine Whole Genome Sequencing of AMR Pathogens in Healthcare Settings

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Abstract

The estimated number of annual deaths that might have been prevented by effective antimicrobial therapy has grown to 1.27M deaths [1]. Healthcare-associated infections (HAIs) with antimicrobial resistant (AMR) pathogens are widespread and are a common cause of complications among hospitalized patients. AMR can negatively impact patient outcomes, and the economic burden associated with HAI infections due to longer hospital stays, higher treatment costs, and a reduced availability of intensive care unit beds exceeds $ 4.6 billion US annually [2].

Whole Genome Sequencing (WGS) coupled with bioinformatic solutions can comprehensively characterize AMR pathogens and is increasingly adopted for epidemiological analysis. In healthcare settings, it can identify AMR outbreaks, distinguish between hospital-acquired and community-acquired infections, and thus help to curb or even prevent transmissions. Broad-scale adoption of WGS in healthcare settings has not yet occurred.

This poster explores the utility of WGS of AMR pathogens in healthcare settings with a focus on the benefits to patients and healthcare economics. We survey advances in WGS and introduce solutions designed to facilitate a broad-scale adoption.

Background

Recent studies demonstrate the high clinical utility potential of routine WGS of critical AMR pathogens isolated in healthcare settings.

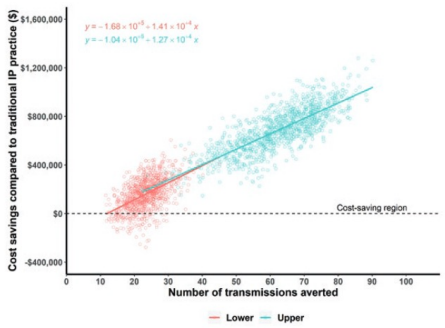


Figure 1 (Sundermann et al. 2021): projected cost savings as function of averted transmission events.

Clinical utility of routine WGS

Clinical utility corresponds to the ratio of patient outcome by total cost of care, i.e. …

(patient benefit / economic benefit).

WGS to inform local or regional IPC action is highly net cost-saving while saving patient lives.

The Local Perspective

A 2021 study published by Alexander Sundermann *et al.* [3] retrospectively investigated the economical and patient benefit from WGS of 3165 clinical isolates and the subsequent bioinformatic outbreak analysis to inform infection prevention and control action at a local US hospital.

The authors estimated that based on these isolate data up to 63 transmission events could have been avoided (patient benefit) by routine WGS, leading in this case to net savings (economic benefit) of up to $ 0.69M US for a single hospital.

The Regional Perspective

A 2021 study by Louisa Gordon *et al.* [4] compared WGS vs. the standard of care interventions for six common MDR pathogens. The impact of WGS on patient care and economics was modelled based on isolate WGS data collected from 27 hospitals during a data 2 Year research demonstration project involving prospective WGS for isolates of suspected outbreaks. A model for cost and patient benefit at the regional level was developed based on reported AMR incidents during hospitalization, the national point prevalence for HAI and the multidrug resistance rates. The end points were hospital costs and avoided infections/colonizations & deaths.

The model clearly demonstrated the benefit of routine isolate WGS, leading to > $ 18M US in savings (economic benefit) and 650 avoided patient deaths (patient benefit).

Benefits & Challenges

Benefits of routine WGS in healthcare settings:
If deployed routinely for critical AMR pathogens, WGS of isolates and isolate-like materials, such as rapid blood cultures, from nosocomial infective agents can deliver the following benefits to healthcare professionals:

- Reduction of transmission events: Pathogen typing and clustering can enable near real-time outbreak detection and monitoring informing IPC measures and preventing transmission events.
- Pathogen ID: can confirm SOC diagnoses.
- WGS-AST: Rapid antibiotic susceptibility prediction from genomic data can complement culture-based AST.
- Informed guidelines and patient care: Full genomic characterization of virulence and AMR markers, AMR mechanisms and their transmission can help pathologists and ID specialists to establish the disease etiology and to better inform patient care.

Challenges:

Despite proven clinical utility and well understood technical benefits, the adoption of WGS into the clinical routine is hampered by:

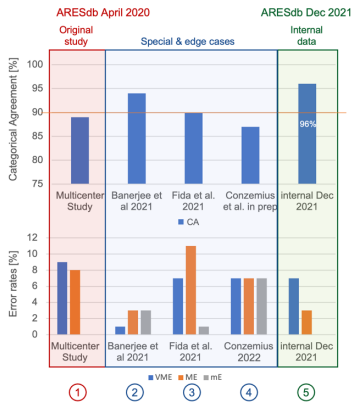
- Cost
- lack of local NGS capacity
- turnaround time
- lack of bioinformatics expertise

Rapid WGS solutions

OpGen laboratories offer cost-effective end-to-end WGS of clinical isolates at rapid turnaround times. The ARES isolate sequencing assay (**ARESiss**) has been validated following CLIA guidelines and provides 100% accuracy for pathogen ID and typing and AMR marker detection with a sensitivity and specificity of >95% and >99%, respectively [5].

Data are processed by **ARES**cloud, a stand-alone web application that automates bioinformatic data analysis, reporting and outbreak analysis.
AREScloud uses machine learning models to predict phenotypic susceptibility and resistance from genomic data (WGS-AST) [6] enabling users to generate individual and cumulative antibiograms for a broad range of pathogen drug combinations.
WGS-AST has been evaluated in numerous evaluation studies and under clinical routine settings.

Figure 2: Evaluation of WGS-AST categorical agreement (CA), very major, major and minor error rates relative to AST.



① ***WGS-AST multicenter evaluation:*** *Ferreira, I. et al. Species Identification and Antibiotic Resistance Prediction by Analysis of Whole-Genome Sequence Data by Use of ARESdb: an Analysis of Isolates from the Unyvero Lower Respiratory Tract Infection Trial. J Clin Microbiol* ***58****, (2020).*

② **Bloodstream infections:** *Banerjee, R. et al. Core Genome Multi-Locus Sequence Typing and Prediction of Antimicrobial Susceptibility Using Whole Genome Sequences of Escherichia coli Bloodstream Infection Isolates. Antimicrob Agents Ch AAC0113921 (2021).*

③ **A.baumannii:** *Fida, M. et al. Acinetobacter baumannii Genomic Sequence-Based Core Genome Multilocus Sequence Typing Using Ridom SeqSphere+ and Antimicrobial Susceptibility Prediction in ARESdb. J Clin Microbiol e00533-22 (2022).*

④ **CP and non-CP CREs:** *Conzemius, R. et al. Automated antimicrobial susceptibility testing and antimicrobial resistance genotyping using Illumina and Oxford Nanopore Technologies sequencing data among Enterobacteriaceae. Front Microbiol 13, 973605 (2022).*

⑤ ***internal benchmark:*** *model training & test performance metrics*

To further unlock the potential for low cost, rapid turnaround sequencing, WGS-AST models have been trained and validated to support nanopore long read data. A 2022 study performed in collaboration with the Johns Hopkins University School of Medicine [7] highlighted the potential of nanopore sequencing for clinical microbiology applications and demonstrated that combining AMR genotypes (Table 1 A) with AI-based WGS-AST prediction (Table 1 B) can help guide effective therapeutic management decisions.

A

Marker class	Accuracy	Sensitivity	Specificity	FNR	FPR	TP	FP	FN	TN	*n*
ESBL	78%	95%	70%	5%	30%	79	29	4	69	181
pAmpC	96%	70%	91%	30%	9%	16	0	7	158	181
CP	99%	98%	100%	2%	0%	99	0	2	80	181
KPC	98%	96%	100%	4%	0%	74	0	3	104	181
MBL	100%	100%	100%	0%	0%	15	0	0	166	181
OXA-48	99%	93%	100%	7%	0%	13	0	1	167	181

CA: Categorical agreement, FNR: False-negative rate, FPR: False-positive rate, TP: True positive, FP: False positive, FN: False negative, TN: True negative, and *n*: number of evaluated samples.

B

Platform	CA	VME	ME	TP	FP	FN	TN	*n*
Illumina	90%	10%	11%	1,646	161	178	1,315	3,300
ONT	88%	11%	13%	1,619	194	205	1,282	3,300

CA: Categorical agreement, VME: Very major error, ME: Major error, TP: True positive, FP: False positive, FN: False negative, TN: True negative, and *n*: number of evaluated species-antimicrobial pairs.

Table 1 A: Performance metrics of the AMR marker identification on ONT data, which is compared to the markers identified on the Illumina data (reference). **B:** Overall performance of the WGS-AST models across all antimicrobials, broken down by sequencing platform.

References

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Poster 113