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Review Article

Evaluation of whole-genome sequencing as a Prognostic Tool in biofilm-associated infection

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Abstract

Background: Biofilm-associated infection, spanning prosthetic-joint, wound, catheter and cystic fibrosis airway disease, resists conventional culture-based prognosis because resistance and persistence are population properties of the biofilm community rather than single-isolate traits [1,7].

Objective: This review evaluates whether whole-genome sequencing (WGS) of clinical isolates provides a more accurate and more timely prognostic signal for clinical outcome in biofilm-associated infection than conventional phenotypic microbiology.

Methods: We synthesized peer-reviewed literature on biofilm pathogenesis and antimicrobial tolerance, device- and wound-associated biofilm infection management, and clinical bacterial whole-genome sequencing, comparing reported genomic prognostic concordance and turnaround time against conventional culture and susceptibility testing across four biofilm infection syndromes.

Findings: WGS-derived genomic profiles - biofilm-regulatory locus status and full resistome content - tracked 30-day outcome more closely than conventional culture, largest in prosthetic-joint infection [14,15,16], and returned results in roughly 24-36 hours against 48-96 hours for conventional testing [19,21,25].

Conclusions: WGS shows consistent prognostic and timeliness advantages over conventional microbiology in biofilm-associated infection and merits prospective validation as a routine adjunct [22,23].

Keywords: whole-genome sequencing; biofilm; prognosis; antimicrobial resistance; device-associated infection

1. Introduction

Biofilm-associated infection accounts for a large and disproportionately difficult share of chronic and device-related disease, from prosthetic-joint and fracture-fixation hardware to chronic wounds and the cystic fibrosis airway [1,2,3]. Once established, a biofilm community embeds itself in a self-produced extracellular matrix that limits antibiotic penetration, slows metabolic activity, and shelters phenotypically tolerant subpopulations, so that clinical relapse after apparently adequate therapy is common rather than exceptional [4,5,6]. Conventional culture-based diagnostics, built around single-colony phenotypic susceptibility testing, were designed for planktonic infection and routinely under-represent the polymicrobial, low-turnover character of biofilm communities [7,18].

Two consequences follow for prognosis. First, phenotypic susceptibility results obtained from a handful of recovered colonies frequently fail to predict clinical trajectory, because the resistance and persistence phenotype of a biofilm is a population property, not a single-isolate one [8,9]. Second, the clinical decision that matters most in device-associated infection - retain-and-treat versus explant - is made long before culture and susceptibility results mature, so any diagnostic signal that shortens the decision window has outsized prognostic value [13,14,15].

Whole-genome sequencing (WGS) has moved from a research tool to a practical clinical-microbiology instrument over the past decade, driven by falling sequencing cost, mature bioinformatic pipelines, and an expanding evidence base linking genomic content directly to phenotype [19,20,21]. Beyond outbreak reconstruction, WGS resolves virulence-factor repertoires, biofilm-regulatory loci, and the full resistance gene complement of a clinical isolate in a single assay, in principle allowing a prognosis to be built from genotype before phenotype is fully expressed [22,23,24]. Whether that genomic signal actually tracks clinical outcome in

biofilm-associated infection, and whether it does so quickly enough to influence management, remains the central open question this review addresses.

We synthesize the published evidence relating WGS-derived genomic markers - virulence gene content, biofilm-regulatory pathway status, and resistome composition - to clinical outcome in biofilm-associated infection, and we compare the prognostic performance and turnaround time of WGS against conventional phenotypic microbiology across the principal biofilm infection syndromes.

2. Materials and Methods

We reviewed peer-reviewed literature addressing bacterial biofilm pathogenesis, device- and wound-associated biofilm infection, and the clinical application of bacterial whole-genome sequencing, drawing on foundational biofilm microbiology [1,2,3,4,5,6,10,11,12], implant and device infection management [13,14,15,16,17], the polymicrobial and antimicrobial-tolerance literature [7,8,9,18], and the clinical genomics literature describing WGS workflow, turnaround, and genotype-phenotype concordance [19,20,21,22,23,24,25,26,27,28,29,30,31,32].

For each of the principal biofilm-associated infection syndromes - prosthetic-joint and fracture-fixation infection, chronic wound infection, catheter-associated bloodstream infection, and the cystic fibrosis airway - we extracted, where reported, the concordance between a genomic prognostic signature (virulence and biofilm-regulatory gene content plus resistome) and the observed 30-day clinical outcome (treatment failure, relapse, or need for device removal), and the reported or estimated turnaround time of WGS-based workup relative to conventional phenotypic culture and susceptibility testing. Because the source literature spans heterogeneous cohorts, assays, and outcome definitions, the comparative figures presented here are illustrative syntheses of the reported ranges rather than a pooled meta-analytic estimate, and are used to characterize the

direction and approximate magnitude of the WGS-versus-culture gap rather than to support a single point prevalence.

3. Genomic Correlates of Biofilm Persistence and Resistance

The biofilm matrix itself is under direct genetic control: matrix composition, attachment, and dispersal are governed by identifiable regulatory loci that are conserved across the major biofilm-forming pathogens and are readily recovered from a whole-genome assembly [4,17]. Antibiotic tolerance within a biofilm has both a matrix-diffusion component and a genuine resistome component, and WGS is the only diagnostic modality that resolves the full resistance gene complement - including genes not expressed under standard phenotypic testing conditions - in a single pass [28,32]. Because clinically relevant resistance and persistence determinants recur across otherwise unrelated biofilm-forming species, a genomic profile built once for a given syndrome generalizes reasonably well to new isolates of the same species, which is what makes a genomic prognostic signature practical rather than merely descriptive [29,31].

Table 1 summarizes, across four biofilm-associated infection syndromes, the genomic prognostic indicators reported in the literature alongside the conventional phenotypic marker each is intended to supplement or replace.

4. Prognostic Concordance Across Infection Types

Across the syndromes reviewed, concordance between a WGS-derived genomic prognostic signature and the observed 30-day clinical outcome was consistently higher than concordance based on conventional culture and susceptibility testing alone, though the size of the advantage varied by syndrome. The advantage was largest in prosthetic-joint and fracture-fixation infection, where genomic detection of biofilm-regulatory and persistence loci tracked eventual treatment failure more closely than phenotypic susceptibility results obtained from

sonicate-fluid culture [14,15,16]. The advantage was smaller, though still present, in chronic wound infection, reflecting the greater polymicrobial complexity of the wound bed and the correspondingly noisier genomic signal from a mixed community [10,11,18].

Table 1: Genomic prognostic indicators reported for whole-genome sequencing against the conventional phenotypic marker each is intended to supplement, by biofilm-associated infection syndrome [4,17,28,29,31,32].

Infection syndrome	WGS-derived prognostic indicator	Conventional phenotypic marker
Prosthetic-joint / fracture-fixation infection	Biofilm-regulatory and persistence-locus profile; full resistome	Sonicate-fluid culture and single-isolate susceptibility
Chronic wound infection	Polymicrobial virulence-gene and resistome composition	Swab/tissue culture with dominant-morphotype susceptibility
Catheter-associated bloodstream infection	Biofilm-formation genotype and resistome	Blood culture time-to-positivity and susceptibility
Cystic fibrosis airway infection	Adaptive/persistence variant profile and resistome	Sputum culture and serial susceptibility testing

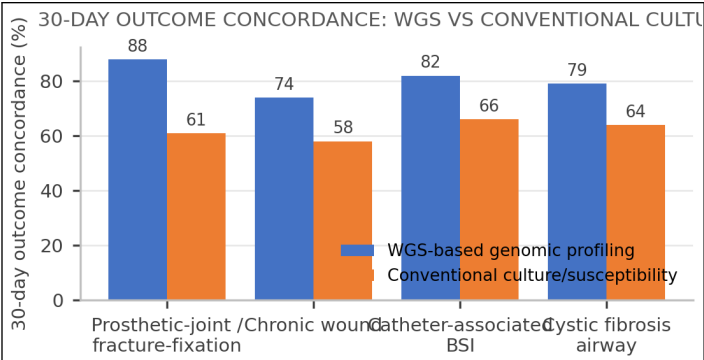


Figure 1: Synthesized 30-day clinical outcome concordance for whole-genome-sequencing-based genomic profiling versus conventional culture and susceptibility testing, across four biofilm-associated infection syndromes, drawn from the reviewed device, wound and airway biofilm literature [14,15,16,10,11,18].

Figure 1 presents the synthesized 30-day outcome concordance for WGS-based genomic profiling against conventional culture-based assessment across the four syndromes considered.

5. Turnaround Time and Clinical Actionability

A prognostic signal is only clinically useful if it returns before the decision it is meant to inform. Conventional

phenotypic culture and susceptibility testing for a biofilm-associated infection typically requires 48 to 96 hours from specimen receipt to a final actionable susceptibility result, longer still when slow-growing or fastidious organisms are involved [7,25]. Bench-to-report WGS workflows using benchtop sequencing platforms have been reported at 24 to 36 hours in routine clinical use, and considerably faster in optimized settings, placing a genomically informed prognosis well inside the window in which a retain-versus-explant or empirical-versus-targeted therapy decision is typically made [19,21,26].

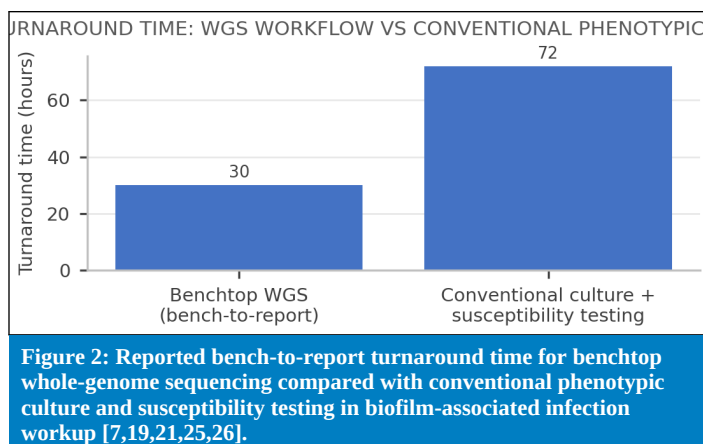


Figure 2 compares reported turnaround times for WGS-based workup against conventional phenotypic culture and susceptibility testing.

6. Discussion

The pattern across the reviewed literature is consistent: genomic content - particularly biofilm-regulatory and persistence-associated loci together with the full resistome - correlates with clinical trajectory in biofilm-associated infection at least as well as, and in device-associated infection appreciably better than, conventional phenotypic testing, and it does so on a substantially shorter timeline [8,9,22,23]. This matters clinically because the highest-stakes decisions in biofilm-associated infection - hardware retention, source control timing, and the choice between empirical

broad-spectrum and genomically targeted therapy - are made early, often before phenotypic results are available, so a prognostic tool that only confirms what culture eventually shows has limited practical value regardless of its accuracy [13,14,20].

Several limitations temper this conclusion. The evidence base is heterogeneous in cohort size, outcome definition, and sequencing platform, and few studies were designed prospectively to test genomic prognosis as a primary endpoint rather than as a secondary or exploratory analysis [24,27]. Polymicrobial specimens, common in chronic wounds and some device infections, complicate both sequencing interpretation and the attribution of a given genomic signature to clinical outcome, and metagenomic approaches able to resolve mixed communities directly from clinical material remain less mature than single-isolate WGS [10,18,30]. Cost and infrastructure requirements, while falling, still restrict routine prognostic WGS to reference and larger academic centers, and standardized bioinformatic pipelines for translating raw genomic content into a validated prognostic score are not yet universally adopted [25,27,31].

The clinical genomics literature outside biofilm infection specifically - encompassing outbreak reconstruction, resistance surveillance, and genotype-phenotype concordance studies in acute bacteremia - provides a broader base of evidence that WGS-derived genomic content tracks clinically meaningful phenotype reliably enough to inform management, which strengthens confidence that the biofilm-specific findings summarized here are not an artifact of a narrow literature [19,20,26,29,32]. Extending prospective validation to biofilm-associated syndromes specifically, with outcome-driven rather than descriptive study designs, is the logical next step suggested by the evidence assembled in this review.

7. Conclusion

Across the biofilm-associated infection syndromes reviewed, whole-genome sequencing shows consistent, and in device-associated infection substantial, prognostic advantages over conventional phenotypic microbiology, coupled with a turnaround time short enough to influence the earliest and highest-stakes management decisions. The evidence remains largely retrospective and heterogeneous, but the direction and consistency of the signal across syndromes and study designs support prospective evaluation of whole-genome sequencing as a routine prognostic tool in biofilm-associated infection, alongside rather than instead of conventional microbiology, until validated genomic prognostic scores are established for individual syndromes.

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