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Rapid Antimicrobial Susceptibility Testing in Bloodstream Infections: Current Landscape and Emerging Technologies

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ABSTRACT

Rapid bloodstream infection diagnosis is essential to enable timely targeted therapy, to reduce the risk of progression to sepsis, to limit unnecessary antimicrobial exposure, and to support effective antimicrobial stewardship. However, conventional culture-based workflows in routine practice often require 48–72 hours to deliver organism identification and antimicrobial susceptibility testing (AST) results. This review summarises rapid AST analytical technologies for bloodstream infections, including commercial systems and emerging phenotypic and molecular methods that aim to shorten time to actionable susceptibility information to less than 8 hours from a positive blood culture. Phenotypic platforms are to be preferred, and they are compared and reviewed according to their dominant analytical principle, while the role of genotypic assays for early identification and resistance inference is discussed as a complementary strategy. Across approaches, sample preparation, including bacterial enrichment and matrix removal, emerges as the dominant limitation, while speed and organism-antibiotic coverage shape clinical utility and implementation. Progress of rapid AST platforms toward routine adoption will require streamlined sample preparation, broader panels, and robust evidence of clinical benefit and cost-effectiveness.

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INTRODUCTION

Bloodstream infections (BSI) pose a significant healthcare and economic burden due to their high mortality rates, prolonged hospital stays, and frequent association with sepsis and septic shock. Recent cohort studies report substantial hospital costs per patient, with median total care costs ranging from €2,530-€4,388 in Europe to $12,939 in the US[1, 2]. Globally, BSI are associated with nearly 3 million deaths each year[3], with reported 30-day mortality rates varying from 17% to almost 40%, depending on the geographical region and the causative pathogen[4-6]. *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are among the most frequently isolated pathogens, while *Staphylococcus aureus* accounts for the highest number of fatal bloodstream infections[5-7]. Importantly, although BSI reflect invasive infection and may lead to pathogen dissemination to distant sites, mortality is primarily driven by sepsis, a dysregulated host response to infection that results in life-threatening organ dysfunction[8], and its progression to septic shock.

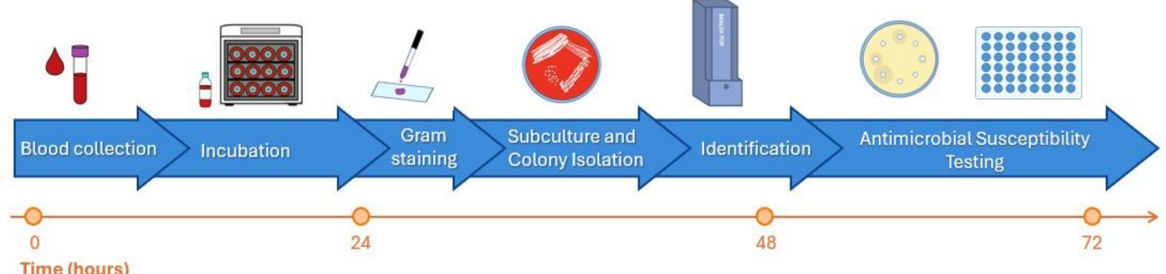

Figure 1: Clinical workflow for identification and antimicrobial susceptibility testing of bloodstream infections.

Blood culture remains the reference standard for the diagnosis of bloodstream infections, bacteraemia and sepsis. The pathogen concentrations in whole blood are typically very low, often between 1 and 100 colony-forming units per mL (CFU/mL)[9], and these numbers are masked by abundant host cells. Automated blood culture systems allow pathogen detection and enrichment, typically requiring 10-19 hours to signal positivity, and up to 5 days to confirm a negative finding[10]. Time to positivity is dependent on the growth rate of the microorganism. While blood culture enables reliable downstream identification and susceptibility testing, it introduces a significant delay between sampling and actionable results (Figure 1), during which patients are commonly managed with empirical broad-spectrum therapy.

Following blood culture positivity, bacterial identification is typically performed using Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS)[11, 12]. This method has been shown to reduce turnaround time significantly, the time to effective antibiotic administration, and the length of hospitalisation compared to conventional phenotypic testing[13], and therefore represents a cost-effective solution in high-volume settings such as microbiological laboratories within secondary care centres. Despite its advantages, MALDI-TOF-MS presents some limitations in its ability to identify polymicrobial cultures and anaerobic bacteria, as well as showing limited identification below bacterial species level[14]. Consequently, complementary approaches such as molecular methods and biochemical tests are still commonly employed in routine diagnostics, as well as in low-resource settings.

Antimicrobial Susceptibility Testing (AST) plays a crucial role in guiding clinicians on the appropriate antimicrobial treatment of bloodstream infections, improving patient outcomes and limiting the emergence of antimicrobial resistance. AST is traditionally performed using culture-based methods, such as disk diffusion and broth microdilution. While these tests are considered the gold standard for accuracy and reliability, they are labour-intensive and time-

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consuming, often requiring 24 hours or more after blood culture positivity to deliver results. In recent years, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) introduced guidelines for performing rapid disk diffusion methods directly from positive blood cultures (PBC)[15, 16]. These methods shorten the time to results to approximately 8 hours but are restricted to a limited number of bacterial species and antibiotics and often require multiple manual readings. Nevertheless, rapid disk diffusion methods rely on routinely available equipment and consumables and, given their low cost and simplicity, remain a useful option for low-resource settings.

As an alternative to manual methods, automated platforms such as the VITEK 2 (bioMérieux), BD Phoenix (Becton Dickinson), and Microscan WalkAway (Beckman Coulter) have dominated the AST technology landscape in routine clinical testing over the last few decades. These platforms rely on biochemical reactions (colorimetric or fluorescent) and turbidimetric measurements to identify a broad range of organisms and determine their antimicrobial susceptibility. They have shown good reliability, are easily integrated in the laboratory workflow, and although a standardised inoculum is usually needed, studies have shown that they can provide identification and susceptibility profiles directly from a positive blood culture for a range of organisms and antimicrobials[17-19]. However, their time to results often ranges from 8 to 24 hours, which limits their utility in the management of bloodstream infections and sepsis, where early targeted intervention is critical.

	PHENOTYPIC AST	GENOTYPIC AST
PRINCIPLE	Measures bacterial growth/metabolism in the presence of antibiotics.	Detects known resistance genes.
OUTPUT	Quantitative (MIC) or qualitative (S/I/R). 0.50 0.25 0.12 0.06 0.03 0.00 Result S I R	Presence/absence of resistance genes. Resistance genes: bla_{CTX-M} Detected; *mecA* Not detected; *vanA* Not Detected
TIME TO RESULTS	Hours to Days.	Minutes to Hours.
ADVANTAGES	• Detects resistance regardless of underlying mechanisms. • Detects novel or emerging resistance mechanisms. • Provides direct prediction of antimicrobial susceptibility.	• Rapid turnaround time. • Does not require viable bacteria. • Requires minimal sample volume.
LIMITATIONS	• Slow turnaround time. • Requires viable bacteria. • May require high sample volumes.	• Limited to targets included in the assay panel. • Does not detect novel, or emerging mutations. • Gene presence may not correlate to phenotypic resistance.

Figure 2: Key characteristics of Phenotypic and Genotypic Antimicrobial Susceptibility Testing methods.

An ideal AST platform would deliver actionable results within a clinically meaningful time window, enabling early therapy optimisation. The emphasis on speed is supported by sepsis /septic shock data showing that each hour of delay in effective antibiotic administration after the onset of hypotension is associated with a 7.6% decrease in survival[20]. Beyond rapid turnaround, an optimal test would have high sensitivity at low pathogen concentration, cover a wide range of organisms and antimicrobials, and perform reliably in cases of polymicrobial infection. Equally important are ease of use (minimal handling, streamlined workflow, and compatibility with laboratory practice) and clear interpretability of the results. Finally, balancing

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initial costs with downstream savings from reduced broad-spectrum antibiotic use and shorter hospital stays would support widespread adoption.

Delayed initiation of effective antimicrobial therapy in bloodstream infection and sepsis has consistently been associated with increased mortality and poorer clinical outcomes[21, 22]. In addition, prolonged broad-spectrum antibiotic exposure is associated with increased selection pressure and the emergence of antimicrobial resistance (AMR). Recent global estimates suggest that bacterial AMR was directly responsible for 1.27 million deaths and associated with 4.95 million deaths in 2019[23]. Reducing the time to effective antibiotic administration is therefore critical. Despite advances in automation and rapid identification, progress in the development of rapid AST platforms has been slower. Two main diagnostic strategies, phenotypic and genotypic AST, have been developed to guide antimicrobial therapy, each with distinct advantages and limitations (Figure 2). This review summarises commercial and emerging AST technologies for bloodstream infections, describes their underlying principles (Figure 3), and highlights key advantages, limitations, and implementation challenges.

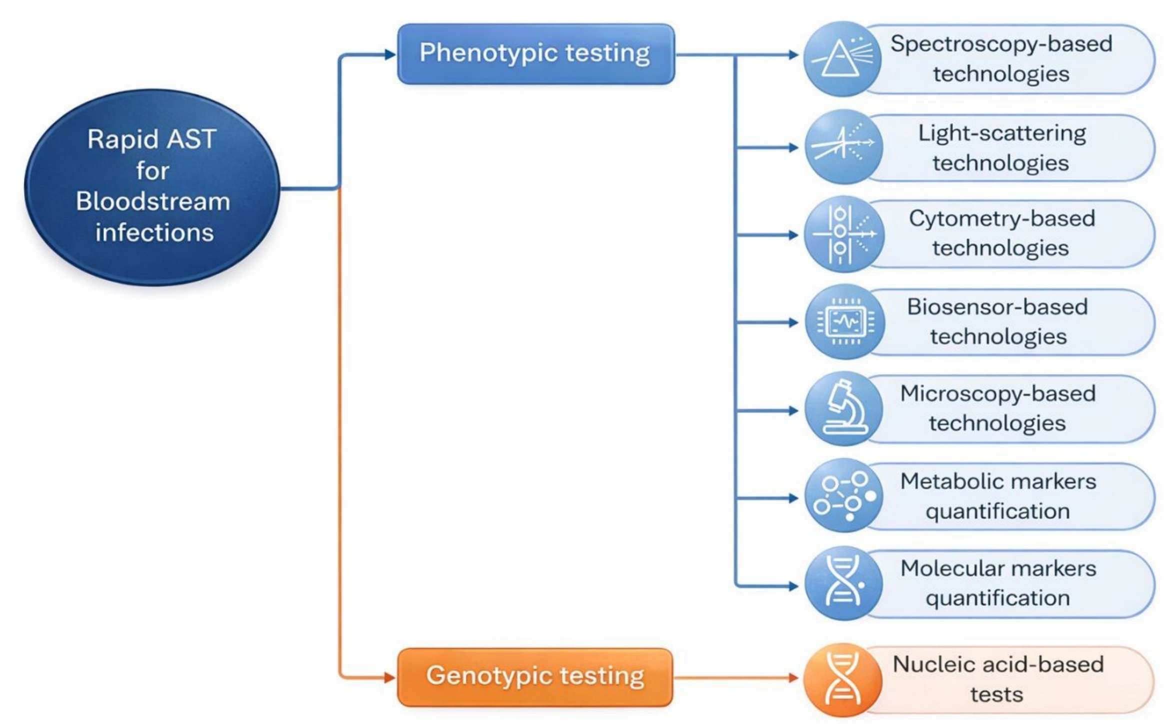

Figure 3: Overview of rapid AST approaches for bloodstream infections. Schematic diagram illustrating the two main diagnostic strategies (phenotypic and genotypic testing) and the principal analytical categories discussed in this review.

METHODS

Literature searches were performed on PubMed between August and September 2025 using the Medical Subject Headings (MeSH) “Microbial Sensitivity Test”, “Sepsis”, and “Rapid Diagnostics”, as well as the terms “bloodstream infection”, “rapid”, and “antimicrobial susceptibility”. Searches were restricted to articles published in the last 10 years. Additional technologies were identified through expert consultations (Figure 4).

Diagnostic technologies were categorised into two groups: Commercial Platforms, defined as technologies that have received regulatory clearance or authorisation through the U.S. Food and Drug Administration or a CE mark for use in the European Economic Area; and Emerging

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Technologies, which include platforms currently in development or under clinical evaluation but not yet cleared for clinical use, proof-of-concept studies, and literature-described methodologies with preliminary validation.

Studies were excluded if they: addressed pathogen detection and identification only; were not designed as a rapid AST workflow (defined here as Time to Result (TTR) ≤ 8 hours from a positive blood culture); described protocols developed by clinical laboratories; evaluated fluorogenic probes as standalone assays; or discussed platforms that have been discontinued or withdrawn from the market. Literature articles evaluating lateral flow tests, addressing fungal or mycobacterial AST, or discussing AST or resistance marker detection only as a potential future extension were also excluded from this review.

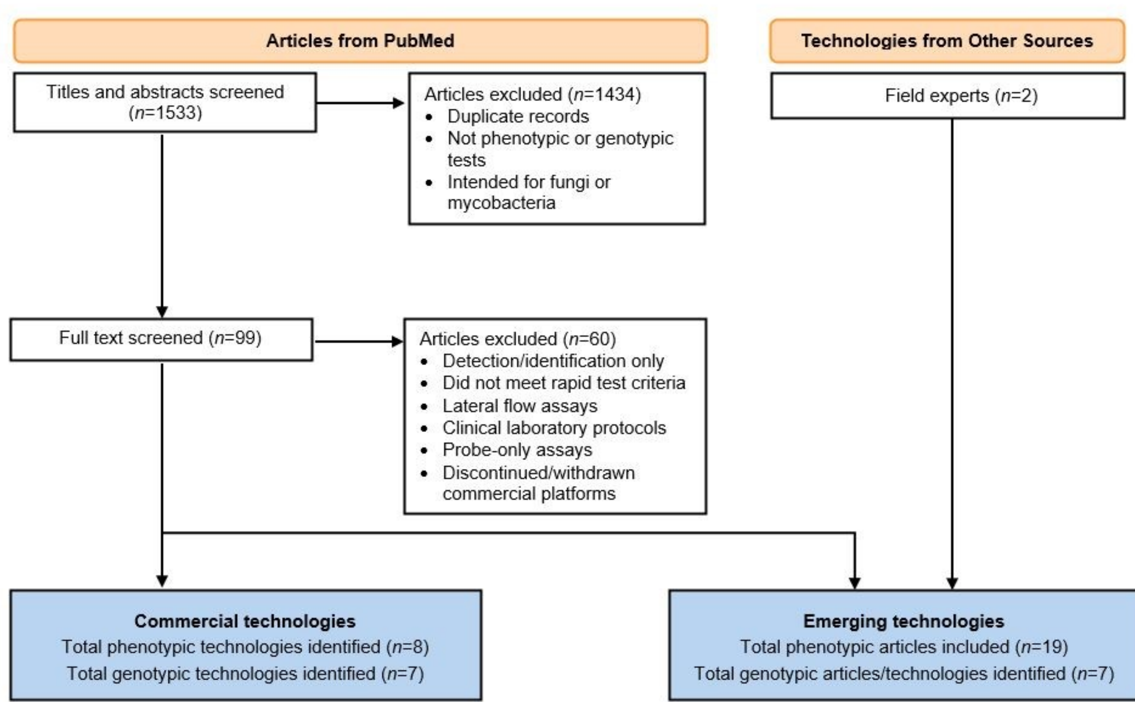

Figure 4: PRISMA-style flow diagram of the search and study selection (adapted from Page et al. [24]).

RESULTS AND DISCUSSION

Commercial Phenotypic Platforms

In recent years, several rapid phenotypic AST technologies, able to provide results within 8 hours from a PBC, have received regulatory clearance for clinical use (Table 1). These platforms rely on different methodologies to determine antimicrobial susceptibility, including time-lapse microscopy, light scattering, flow cytometry, fluorescence intensity measurements, or volatile organic compounds detection.

Platform	Company	Principle	Average TTR	Gram-positive panel	Reference
FASTinov AST	FASTinov	Flow cytometry coupled with fluorescent probes to detect bacterial cell damage	2 h	✓	[25]
QuickMIC	Gradientech	Real-time imaging of bacteria exposed to a linear antibiotic gradient	3 h	NA	[26]

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LifeScale	Affinity Biosensors	Microfluidic sensor and mechanical resonator measure the mass of individual microbes	4.5 h	NA	27
ALFRED^AST 60	Alifax	Broth microdilution coupled with light-scattering technology	5 h	✓	28
Selux NGP system	Selux Diagnostics	Fluorescence-based viability and surface area growth assay	5.5 h	✓	29
VITEK REVEAL	bioMérieux	Broth microdilution coupled with volatile organic compounds detection sensors.	5.5 h	NA	30
dRAST	QuantaMatrix	Microbial growth monitored via time-lapse microscopy	6 h	✓	31
ASTar	Q-linea	Broth microdilution coupled with Time-lapse microscopy	6 h	NA	32

Table 1: Commercial Phenotypic Rapid AST Technologies. All platforms listed provide Gram-negative testing. Platforms providing Gram-positive testing are indicated in the table.
NA: Not available.

FASTinov (FASTinov SA) and QuickMIC (Gradientech AB) provide results within 2 to 3 hours, making them promising tools for early sepsis intervention. However, their integration into the laboratory workflow presents practical limitations, due to the need for labour-intensive sample pre-processing (FASTinov) and limited organism-antibiotic panel coverage (QuickMIC). Other systems, including dRAST (Quantamatrix Inc.) and ASTar (Q-linea AB) offer a more balanced solution, with an average TTR of 5-6 hours and comprehensive organism-antibiotic coverage. Accelerate Pheno (Accelerate Diagnostics, Inc.) was the only integrated system that provided both identification and AST results for a broad panel of organisms and antibiotics, reducing the overall time to results by approximately 40h compared to traditional automated systems and culture-based methods[33, 34]. However, the platform has recently been withdrawn from the market following the manufacturer's liquidation [35].

Emerging Phenotypic Technologies

As commercial platforms continue to be optimised to improve their diagnostic potential and integration, a number of rapid technologies are currently in development or undergoing clinical validation, while several workflows allowing rapid AST have been described in the literature in recent years (Table 2, Figure 5). These emerging approaches are discussed below according to their dominant analytical principle or measured analyte.

Main Method	Reference	Principle	Clinical sample type [a]	Average TTR [b]	Gram-positive	Gram-negative	Category Agreement [c]	Maturity Stage [d]
Spectroscopy-based technologies	Dekter *et al.*, 2017 [36]	Classical Raman Spectroscopy measurements of bacterial metabolic activity.	PBC	5 h	✓	✓	*n*=13 100%	Proof-of-concept
	Zhu *et al.*, 2022 [37]	Raman Microspectroscopy measurements of D_2O metabolism.	PBC	3 h	✓	✓	*n*=86 93%	Analytical validation
	Zhang *et al.*, 2020 [38]	Stimulated Raman Scattering measurements of D_2O metabolism.	PBC	2.5 h	✓	✓	ND	Proof-of-concept
	Han *et al.*, 2023 [39]	Surface-Enhanced Raman Spectroscopy measurements of bacterial metabolic activity.	PBC	5 h	✓	✓	*n*=401 96%	Analytical validation

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Light-scattering technologies	Idelevich *et al.*, 2018 [40]	Forward-angle laser light-scattering and OD measurements of bacterial growth.	PBC	5 h	ND	✓	*n*=19 ≥90%	Analytical validation
	Falconer *et al.*, 2024 [41]	Scattered-light integrated collection (SLIC) measurements of bacterial growth.	PBC	2 h	ND	✓	*n*=505 95.5%	Clinical validation
Cytometry-based technologies	Filbrun *et al.*, 2022 [42]	Sucrose separation of bacteria coupled with label-free flow cytometry.	PBC	5-10 h	✓	✓	*n*=49 90%	Analytical validation
	Edgar *et al.*, 2021 [43]	Acoustic signals generated by dye-labelled phage-bound bacteria measured via photoacoustic cytometry	PBC	4 h	✓	ND	ND	Proof-of-concept
	Hornsey *et al.*, 2026[44]	Electrical and morphological properties of bacteria measured via microfluidic impedance cytometry.	PBC	4 h	ND	✓	*n*=4,947 97.7%	Clinical validation
Microscopy-based technologies	Zhu *et al.*, 2023 [45]	Integrated microfluidic chip combining separator gel and AST chambers for optical imaging.	PBC	3.5 h	ND	✓	*n*=60 93.3%	Analytical validation
	Forsyth *et al.*, 2021 [46]	Dextran separation of bacteria coupled with optical imaging of single cells trapped in a microfluidic device.	WB	2 h	ND	✓	ND	Proof-of-concept
	Kim *et al.*, 2024 [47]	Bacterial recovery via functionalised magnetic particles; multiplex DNA hybridisation for ID; optical imaging of bacteria immobilised in agarose matrix.	WB	13 h	✓	✓	*n*=98 94.9%	Analytical validation
Biosensor-based technologies	Sturm *et al.*, 2024 [48]	Metabolic activity-induced oscillations measured via nanomechanical sensors.	PBC	4 h	ND	✓	*n*=85 97.6%	Analytical validation
	Xu & Ren, 2023 [49]	Wireless LC sensor detection of bacterial growth-induced permittivity changes.	PBC	30 min	✓	✓	ND	Proof-of-concept
	Shi *et al.*, 2018 [50]	Immuno-electrochemical detection of bacterial growth using enzyme-labelled antibody sandwich complexes.	WB	3.5 h	ND	✓	ND	Proof-of-concept
Metabolic markers quantification	Matsui *et al.*, 2019 [51]	Intracellular ATP levels measured via bioluminescence as a marker of metabolic activity.	PBC	6 h	✓	✓	ND	Proof-of-concept
	Rydzak *et al.*, 2022 [52]	Liquid chromatography–mass spectrometry quantification of multiple metabolic markers as a measure of bacterial growth.	PBC	6 h	✓	✓	ND	Proof-of-concept
Molecular markers quantification	Maxson *et al.*, 2018 [53]	Quantitative PCR measurements of 16S rRNA as a marker of bacterial growth.	PBC	4 h	✓	✓	*n*=432 96.3%	Analytical validation
	Young *et al.*, 2024 [54]	Multiplexed RNA hybridisation-based quantification of antibiotic-induced gene expression signatures.	PBC	4 h	ND	✓	*n*=387 95%	Clinical validation

Table 2: Emerging Rapid Phenotypic AST technologies.

[a] Clinical sample type: Intended clinical sample matrix for application.
WB: Whole Blood.
PBC: Positive Blood Culture.

[b] Average Time to Results (TTR): Time to Results reported from the starting sample type used in the study.

[c] Category agreement (CA): Agreement with reference methods (broth microdilution or disk diffusion) or conventional automated systems.
Only studies evaluating CA on the intended clinical sample type were included.
n: indicates the total number of organisms–antibiotic combinations.
ND: No Data.

[d] Maturity stage: Validation stage reflects readiness for application in bloodstream infection workflows. Classification was guided by the intended clinical use of each technology.
Studies targeting direct-from-blood detection were considered analytically validated when evaluated in whole blood at clinically relevant bacterial concentrations (≈1–100 CFU/mL) and supported by quantitative performance metrics against a reference method.
Studies intended for positive blood culture workflows but evaluated only using isolates grown in culture media, spiked whole blood samples, or lacking quantitative performance metrics, were classified as proof-of-concept.

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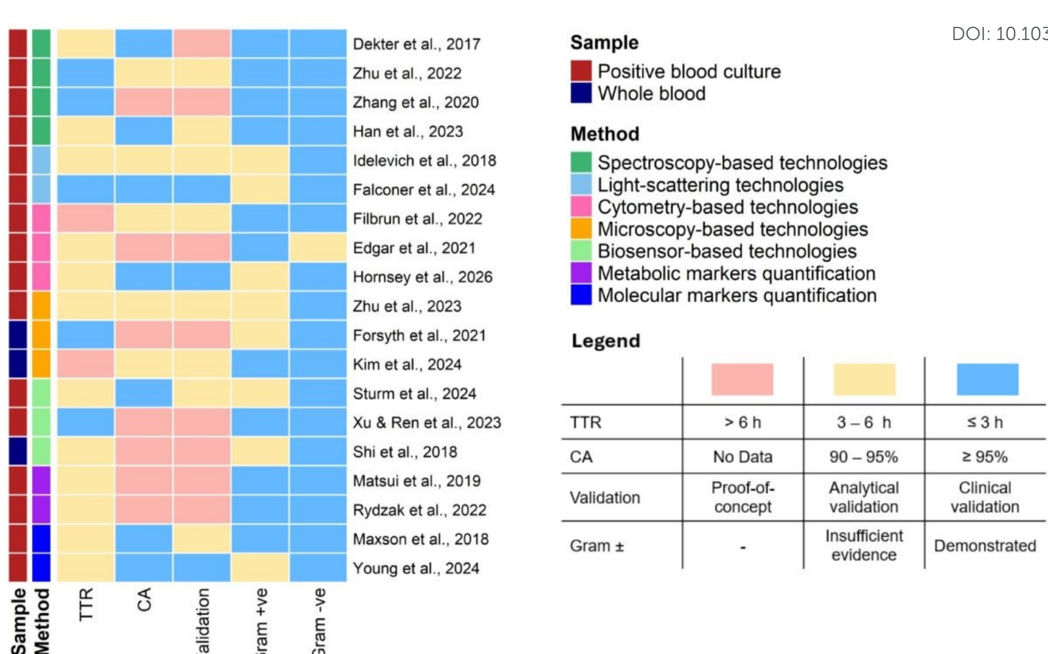

Figure 5: Comparative overview of rapid phenotypic AST technologies applied to bloodstream infections. Studies are grouped according to the underlying technological approach and the type of clinical sample investigated. Heatmap cells summarise the reported time to results (TTR), category agreement (CA), validation stage, and evidence supporting applicability to Gram-positive and Gram-negative organisms. Colour coding was applied independently for each characteristic according to the categories shown in the embedded legend.

Spectroscopy-based technologies

Vibrational spectroscopy encompasses techniques that probe the molecular composition of bacterial cells by measuring energy shifts of photons interacting with (bio)chemical bonds. These techniques have been extensively investigated for whole organism fingerprinting and bacterial characterisation[55, 56], and can detect molecular changes in bacterial metabolism and physiology in response to antibiotics, providing rapid, label-free assessment of susceptibility. However, blood components can interfere with spectral acquisition and complicate interpretation, often requiring labour intensive sample preparation to isolate bacterial cells.

Raman spectroscopy measures the *inelastic* scattering of photons, generating spectra that reflect certain kinds of vibrational modes of chemical bonds (functional groups) within a sample. While Raman spectroscopy can provide rapid AST directly from positive blood culture bottles within 5 hours[36], its low sensitivity and prolonged spectral acquisition limit throughput. Enhanced techniques, like Raman Microspectroscopy, Stimulated Raman Spectroscopy (SRS) and Surface-Enhanced Raman Scattering (SERS) have been investigated in an effort to address these limitations. Raman Microspectroscopy combines classical Raman measurements with microscopy to improve laser focusing and signal collection, with typical interrogation areas of ~1x1 µm (the typical dimensions of an individual bacterium range from 1 to 2 µm, and these weigh ~1 pg, and are therefore well within Raman spectroscopy's single cell analysis capabilities). Zhu *et al.*[37] used Raman Microspectroscopy coupled with the metabolic incorporation of deuterium oxide (D_2O, heavy water) to determine the antimicrobial susceptibility of bacteria, and developed an automated system integrating sample preparation with spectra acquisition and analysis. In this approach, D_2O served as a marker of metabolic activity, enabling detection of newly synthesised biomolecules through the incorporation of deuterium into C-D bonds. The resulting platform, named CAST-R (Clinical Antimicrobial

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Susceptibility Test Ramanometry), reduced the labour-intensive sample preparation, delivered results within 3 hours from PBC, and achieved a 93% CA when compared to broth microdilution. Similarly, Zhang *et al.*[38] used D_2O-probed SRS, a technique in which two synchronised laser beams are used to obtain a stronger Raman signal, to measure the MIC of common clinical isolates in 2.5 hours. The method was tested on spiked whole blood, demonstrating feasibility in this matrix, but validation on positive blood cultures remains to be demonstrated.

Whereas Raman Microspectroscopy and SRS improve signal collection through optical approaches, SERS addresses the sensitivity limitation by amplifying Raman signals using plasmonic nanostructured metallic surfaces[57]. Incident light excites surface plasmons on these substrates, generating strong local electromagnetic fields that enhance Raman signals from nearby analytes. SERS allows the generation of AST results within 5 hours from a PBC and achieved high agreement (>95%) compared with conventional automated systems[39]. Moreover, coupling this technique with microfluidics or deep learning analysis has been reported to improve accuracy, reproducibility, and turnaround times[58, 59].

Light-scattering technologies

Multi-angle (elastic) light scattering provides for a significant improvement in microbial detection [60]. The clinical utility of laser light-scattering technology for rapid AST directly from positive blood cultures has been established with the commercial platform ALFRED^{AST} (Alifax, Italy), which monitors bacterial growth in liquid culture by analysing the scattering signals collected by two photodetectors positioned at 30° and 90° relative to the incident laser beam [28, 61]. Recent studies have explored variations of this principle to improve sensitivity and shorten the time to results. In Forward Laser Light-Scattering (FLLS), detectors are positioned at low angles relative to the incident beam, where most of the scattered light is concentrated, thereby improving signal capture efficiency compared with conventional methods. This approach was applied to determine the Carbapenem susceptibility profile of *Enterobacteriaceae* and *P. aeruginosa* strains within 5 hours from a PBC, achieving 100% sensitivity and specificity in a small sample set (n=13)[40]. In the study, the authors compared two sample preparation methods, lysis/centrifugation and filtration/dilution, and found that the former produced cleaner samples and enabled rapid detection, while the latter, although simpler, introduced optical interference that delayed detection.

More recently, scattered-light integrated collection (SLIC) was developed as an alternative light-scattering technique. SLIC employs an integrated detection space and a phase lock signal to collect and quantify the total scattering output while disregarding absorbed light. The method demonstrated high sensitivity, enabling the detection of bacterial concentrations as low as 100 CFU/mL[62]. A proof-of-concept study evaluated the ability of SLIC to perform rapid AST on Gram-negative bacteria isolated from PBC and achieved a 95.5% category agreement (CA) compared to VITEK 2, with minimal sample processing (dilution only) and an average TTR of 2 hours[41]. While the authors reported a high rate of major and very major errors (4.1% and 7.1% respectively), the discrepancy may partly be attributable to the use of Tryptic Soy broth in place of the standard Mueller Hinton Broth (MHB) in their validation study.

Flow Cytometry-based technologies

Flow cytometry-based technologies analyse single cells passing through a detection system in a fluid stream, providing morphological, biochemical, and physiological information [63-65]. Depending on the platform, cytometry can exploit light scattering and fluorescence,

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photoacoustic signals, or electrical impedance, enabling detection of early phenotypic responses at the single-cell level, potentially shortening the time to results.

In flow cytometry, heterogeneous cell populations are quantified and sorted based on light scattering and fluorescence signals as they flow through a laser-based detection system. Similarly to spectroscopy-based techniques, the effective implementation of flow-cytometry for rapid AST is dependent on the preparation of a pure bacterial suspension directly from blood cultures, as residual blood components can significantly interfere with signal detection.

The commercial platform FASTinov (Portugal) employs fluorescence flow-cytometry to determine the susceptibility profile of a broad range of Gram-positive and Gram-negative bacteria in approximately 2 hours, and achieved >95% agreement when compared to disk diffusion[66]. However, fluorescent dye uptake can vary in antibiotic-stressed bacteria. To address this, Filbrun *et al.*[42] developed a label-free approach, which included bacterial separation via centrifugation through a sucrose cushion, and MIC determination based on both count rates and morphological changes. The method produced MIC values rather than susceptibility categories, but TTR was significantly longer (≈ 5 to 10 hours depending on the species), and accuracy was lower (≈73% *vs*. broth microdilution), though category agreement remained close to 90%.

Alternative cytometry methods have been explored to overcome the limitations imposed by optical scatter and uptake of fluorescent dyes in complex biological specimens. In photoacoustic flow cytometry, bacteria bound to fluorescently labelled bacteriophages pass through a pulsed laser light, where the dye absorbs energy and generates a transient acoustic wave via thermoelastic expansion. This method was used to detect and differentiate daptomycin-resistant from -sensitive *S. aureus* strains in under 4 hours and identified heterogenous resistance within clonal populations[43]. While the approach could be applied to other bacterial species and multiple antibiotics, its reliance on fluorescently labelled phages adds complexity and cost.

Unlike optical or photoacoustic methods, impedance cytometry offers a label-free assessment of antimicrobial susceptibility. By measuring the electrical properties of cells (resistance and capacitance) as they flow through a multi-frequency electric field, impedance cytometry provides information on cell size, morphology and membrane properties. This principle underlies the iFAST (impedance-based Fast Antimicrobial Susceptibility Test) platform, which uses microfluidic single-cell impedance measurements to detect the phenotypic responses of bacteria to antibiotics in 3 to 5 hours[67, 68]. Preliminary multi-site clinical evaluation data suggest that this approach may achieve high agreement with reference methods when applied to bloodstream infection isolates[44].

Microscopy-based technologies

Microscopy-based techniques, defined here as approaches that rely on optical imaging of bacterial growth dynamics rather than vibrational spectroscopy measurements, have been extensively employed for rapid antimicrobial susceptibility testing in recent years. Several commercial platforms, including QuickMIC, Selux NGP, dRAST, ASTar, and Accelerate Pheno, utilise microscopy to monitor changes in cellular morphology, growth, or division at the single-cell or microcolony level, allowing the detection of antibiotic-induced phenotypic effects over short incubation periods.

Effective microscopy analysis relies on stable bacteria immobilisation and reduced background interference. Although separation of bacteria from blood components improves

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signal clarity, a pure bacterial pellet is not always required, as computational methods can distinguish bacteria from complex matrices. However, this is dependent on the platform: a higher degree of bacterial separation may be necessary for systems incorporating microfluidic confinement, such as single-cell trapping, where residual blood components can interfere with cell capture and imaging. For instance, Zhu *et al.*[45] developed a bacteria separation integrated AST (BSI-AST) chip enabling rapid phenotypic AST directly from PBC in 3.5 hours. The microfluidic platform incorporated a separator gel for bacterial extraction and multiple antibiotic-preloaded downstream chambers, thus providing integrated sample preparation. Centrifugation and vacuum-assisted fluid handling were used to concentrate and distribute cells for optical imaging, steps which could potentially be automated. However, the method was not applicable to Gram-positive bacteria, and the impact of bacterial motility on imaging performance was not addressed.

Similarly, a proof-of-concept study combined bacterial separation via dextran sedimentation with microfluidic single-cell trapping, allowing individual cells to be spatially confined within narrow channels and imaged under antibiotic exposure. The workflow was completed directly on whole blood within 2 hours, significantly shortening the time to results[46]. However, MIC determination was limited to *E. coli* with a single antibiotic (ampicillin), and efficient bacterial recovery was demonstrated only at relatively high concentrations (10-100 CFU/mL), despite evidence that pathogen concentration in BSI commonly fall within the range of 0.01–10 CFU/mL[69].

More recently, a culture-independent platform, named uRAST (Ultra-Rapid AST), was announced by QuantaMatrix (based in South Korea)[70]. The system employs magnetic particles coated with synthetic beta-2-glycoprotein I (sβ2GPI) peptides, short fragments of an innate immune response protein capable of binding to common pathogen-associated molecular patterns, to recover bacteria directly from whole blood at clinically relevant concentrations (≈1–10 CFU/mL). A multiplex DNA hybridisation assay, termed quick-mapping ID (QmapID), is subsequently used for pathogen identification, while phenotypic AST is performed on bacteria immobilised within an agarose matrix. This study demonstrated clinical feasibility for pathogen identification directly from blood and reported an average TTR of 13 hours from initial blood processing to susceptibility results. However, although the QmapID assay was evaluated using patient samples, AST performance metrics were derived retrospectively from spiked blood samples, showing 94.9% CA with the broth microdilution method[47]. Prospective clinical AST validation remains therefore to be demonstrated.

Biosensor-based technologies

Biosensor-based technologies have recently emerged as promising platforms for rapid antimicrobial susceptibility testing. Biosensors allow the direct transduction of bacterial responses to antibiotics into physical or electrical signals, thereby enabling the detection of early morphological or physiological changes without the need for prolonged incubation.

Nanomechanical sensors include a range of mechanical transducers, including cantilever beams and other resonator geometries. These sensors can be functionalised to promote bacterial attachment and operated in either static mode, where surface deflection is used to measure the oscillatory nanomotion of metabolically active bacteria (growth-independent AST), or dynamic mode, where resonant-frequency shifts are monitored to quantify mass changes associated with bacterial growth (growth-dependent AST)[71]. In practice, these systems require the preparation of a sufficiently clean and standardised bacterial suspension,

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typically achieved through selective blood cells lysis or centrifugation followed by dilution, as residual blood components and uncontrolled inoculum levels can interfere with sensor performance.

One example of a dynamic, growth-dependent approach is the commercial LifeScale platform (Affinity Biosensors), which uses microchannel resonators to measure the mass and number of individual cells, and provide MIC results within 4-5 hours[27]. However, growth-independent nanomechanical sensing has the potential to provide even faster results. In this context, Resistell (Switzerland) is developing Phenotech Multistar, a system that combines cantilever-based nanomotion detection with machine learning signal-analysis to detect and classify different bacterial susceptibility phenotypes in 2 to 4 hours[48]. Whilst initial results are positive, the current scope of nanomechanical sensing AST remains narrow: studies are primarily focused on *Enterobacterales*, whereas certain Gram-positive organisms present additional challenges due to their tendency to form aggregates in blood, considerably complicating surface attachment and signal interpretation. Measurements are also sensitive to environmental factors, such as temperature, vibration, and fluid viscosity, and signal interpretation often requires advanced data analysis.

The passive electrical properties of bacteria differ substantially from those of aqueous media [72-75]. Inductor-capacitor (LC) sensors are an alternative class of biosensors that use electrical resonance to detect changes in their environment. As bacteria grow and respond to antibiotics, their intrinsic dielectric properties alter the effective capacitance of the sensor, producing a measurable shift in resonance frequency.

In a recent study, wireless LC sensors were placed in bacterial cultures with or without antibiotics to produce MIC results in as little as 30 minutes[49]. The technology did not require surface functionalisation and can be readily integrated into standard multi-well formats. However, measurements were performed in low-salt Lysogen Broth rather than conventional MHB to minimise background conductivity and optimise sensitivity, which may complicate direct translation to guideline-compliant AST conditions.

Beyond mechanical and resonance-based biosensors, a recent study developed an immuno-electrochemical sensing platform capable of detecting fewer than 10 CFU/mL directly from blood in under 4 hours. The platform uses a working electrode functionalised with species-specific antibodies and enzyme-labelled antibodies. Formation of the immune sandwich complex positions the redox enzyme within the electric field at the electrode interface, generating a measurable electrochemical signal that increases with bacterial growth[50]. Notably, the assay operates directly on unprocessed whole blood, simplifying the workflow and reducing sample preparation. However, the use of small sample volumes (~200 µL) at ultra-low bacterial concentrations means that bacterial cells may not always be present in the sample, a limitation that is not fully addressed.

Metabolic marker quantification

The quantification of metabolic markers enables antimicrobial susceptibility to be inferred from bacterial physiological activity rather than from cellular division, growth or morphological changes. Existing approaches vary in both the number of biomarkers interrogated and the technologies employed for their detection.

Adenosine triphosphate (ATP) bioluminescence has been proposed as a possible marker for the detection of antibiotic resistance, due to the positive correlation between bacterial counts and ATP level[76]. A recent study investigated a rapid ATP bioluminescence-based AST workflow performed on positive blood cultures to detect levofloxacin resistance. The protocol

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involved centrifugation through a serum separator gel to remove blood components, followed by sample dilution and treatment to reduce extracellular ATP prior to antibiotic exposure. Intracellular ATP was then released and converted into a luminescent signal via a luciferase-based reaction, quantified using a luminometer. When compared with broth microdilution, ATP-derived MICs showed only partial concordance, with several samples showing higher MIC values. The authors attributed this discrepancy to antibiotic-induced bacterial filamentation, which increases cellular ATP content despite inhibited cell division [51].

Overall, these findings indicate that reliance on a single metabolic maker may limit the reliability of the method for routine clinical implementation. In contrast, multi-marker strategies may improve the robustness of metabolic phenotypic susceptibility testing.

One such approach was described by Rydzak *et al.*[52], who identified a panel of biomarkers capable of differentiating seven of the most common pathogens causing BSI, along with a set of metabolic flux markers that can be measured to infer antimicrobial susceptibility. Metabolic markers were measured via Liquid Chromatography-Mass Spectrometry, and the assay achieved a 95.2% agreement compared with the VITEK2 platform. While this strategy shows strong potential, advances in this field should prioritize reducing analytical complexity to enable clinical scalability.

Molecular marker quantification

Similarly to metabolic markers quantification, nucleic acid amplification strategies can be used to determine antimicrobial susceptibility by measuring changes in nucleic acid abundance or by monitoring transcriptional changes in response to antibiotics exposure. These approaches typically involve multiple sample processing steps, including centrifugation, cell lysis, nucleic acid extraction, and in some cases, amplification or hybridisation.

The 16S ribosomal RNA (rRNA), a component of the small subunit (30S) of bacterial ribosomes, is a common target in PCR diagnostic assays for the detection and identification of bacterial species, particularly in culture-negative samples[77-79]. As rRNA is rapidly produced in metabolically active bacteria, changes in its concentration following antibiotic exposure can serve as an early indicator of antimicrobial susceptibility. Following this principle, Maxson *et al.*[53] developed the RAMAST (RApid Molecular Antibiotic Susceptibility Testing) assay, which used quantitative PCR (qPCR) to measure changes in 16S rRNA levels. The assay achieved 96.3% CA with broth microdilution and produced results in under 4 hours. However, the authors reported relatively high major error and very major error rates, which were attributed to operator errors, sample processing issues, or incorrect qPCR readings. Variations in the culture media used may also have contributed to the observed discrepancies.

Rather than relying on a single target, the analysis of antibiotic-induced transcriptional signatures across multiple genes can be employed to assess antimicrobial susceptibility. The GoPhAST-R (Genotypic and Phenotypic AST through RNA detection) platform represents an example of this strategy. Following blood culture positivity, bacterial cells are diluted, exposed to antibiotics, and then lysed. RNA transcripts are quantified using a multiplexed hybridisation-based assay (NanoString), enabling the quantification of selected mRNA targets without nucleic acid amplification. Susceptibility is determined by comparing the transcriptional response signatures between treated and untreated samples, and key resistance genes are also reported[80]. In a recent clinical study including Gram-negative organisms, the platform reported 95% CA compared to conventional automated systems. For most antibiotics,

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transcriptional changes were detectable within 4 hours, although longer exposure (up to 16 hours) was required for slower-acting drugs or specific organism-antibiotic combinations[54].

Commercial Genotypic Platforms

Genotypic platforms complement the bloodstream infection diagnostic landscape by enabling rapid pathogen identification and, in some cases, detection of selected antimicrobial resistance determinants. Several molecular systems, developed for use directly from positive blood cultures, are currently available on the market (Table 4), and provide rapid information on critical resistance markers while conventional phenotypic AST results are pending. Most of these platforms consist of closed, cartridge-based systems that integrate nucleic acid extraction, amplification, and amplicon detection via melt-curve analysis, fluorescence signals, or microarray-based probe hybridisation.

Platform	Panel/Assay	Company	Principle	Average TTR	Regulatory status	References
Biofire Film Array	BCID2	bioMérieux	Nested multiplex PCR with amplicon-specific DNA melt analysis.	1 h	CE-IVD FDA 510(k)	81
Verigene	BC-GP BC GN	DiaSorin Molecular	Multiplex microarray-based PCR with gold nanoparticles-labelled probes and silver-mediated signal amplification.	2.5 h	CE-IVD FDA 510(k)	82, 83
ePlex	BCID-GP BCID-GN	Roche Diagnostics	Multiplex microarray-based PCR with ferrocene-labelled probes and electrochemical signal detection.	1.5 h	CE-IVD FDA 510(k)	84
Unyvero	BCU	Curetis	Multiplex PCR with amplicon detection via hybridisation on microarray probe membranes.	5 h	CE-IVD	85, 86
Molecular Mouse	Sepsis Panel	Alifax	Multiplex real-time PCR.	1 h	CE-IVD	87
eazyplex	BloodScreen GP BloodScreen GN	Amplex Diagnostics	Loop-mediated isothermal amplification with real-time fluorescence detection.	20 min	CE-IVD	88
iC-System	iC-GPC Assay iC-GN Assay	iCubate	Amplicon-Rescue Multiplex PCR with microarray hybridisation.	4 h	CE-IVD FDA 510(k)	89

Table 3: Commercial Genotypic platforms providing both identification and resistance marker detection.

Genotypic platforms offer short turnaround times and automated, standardised workflows which can be easily integrated into routine clinical practice. Nevertheless, they cannot replace phenotypic susceptibility testing, as the presence of known resistance genes does not necessarily indicate phenotypic resistance, and *vice versa*. Phenotypic expression may be modulated by the bacterial strain's genetic background and environmental conditions[90], and targeted panels may fail to detect resistance mediated by mechanisms not captured by the assay, including porin loss, efflux upregulation, and target-site alterations. Despite these limitations, evidence suggests that these tests can improve patient outcomes by reducing time to effective therapy and hospital length of stay, particularly when implemented together with antibiotic stewardship programmes[91, 92].

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Emerging Genotypic Technologies

Emerging genotypic platforms follow two parallel directions: expansion of multiplex panels designed for positive blood cultures (Table 5), and direct-from-blood testing to bypass blood culture and further reduce turnaround times (Table 6). One of the key challenges for PCR-based testing is recovering and enriching very low concentrations of bacteria while removing blood components (e.g. haemoglobin, Immunoglobulin G, and lactoferrin) that can inhibit amplification. Accordingly, recent studies have focused on physically separating bacteria from blood components, or isolating inhibitors prior to amplification. For instance, a spinning hollow disk was developed to separate blood cells from the bacteria-containing plasma fraction by dynamic sedimentation[93]. This workflow was later coupled with a single-tube pentaplex real-time PCR protocol targeting major β-lactamase genes (KPC, NDM, CTX, CMY, and OXA-48), enabling rapid resistance-marker identification in under 2 hours with reported detection limits of 4-8 CFU/mL[94]. In contrast, rather than separating the bacteria, a culture-free "biphasic" approach was developed in which whole blood is dried into a solid matrix and then overlaid with amplification reagents in a liquid phase. Using this configuration, inhibitory blood components are retained within the dried sample and amplification can be performed without the need for extraction or purification. When paired with loop-mediated isothermal amplification (LAMP), this workflow enables the rapid detection of pathogens and resistance markers in under 2.5 h, with detection limits equivalent to 1.2 CFU/mL[95].
While encouraging, the methods above targeted a very limited number of pathogens and resistance markers. As efforts shift toward multiplex detection, established technologies are being adapted into new assay platforms. For instance, droplet digital PCR (ddPCR) has been employed for whole blood testing in a high-throughput microfluidic format. In this approach, inhibitor-resistant PCR reagents are mixed with whole blood and partitioned into oil-in-water droplets via flow-focusing microfluidics. Following thermal cycling, the signal from fluorescent droplets containing the target gene is quantified, enabling results within 1 hour, with a reported detection limit of 10 CFU/mL[96]. However, a clinical validation study evaluating ddPCR performance against blood culture reported concordant results in 63.9% of the cases. Among discordant results, 12.9% were deemed presumptive false positives, whilst the remainder were classified as either probable or possible BSI cases[97].

Platform/Test	Company	Principle	Clinical sample type [a]	Average TTR [b]	Reference
QIAstat-Dx	Qiagen	Multiplex real-time PCR with fluorescence-based detection of amplification signals.	PBC	NA	Ng *et al.*, 2024 [98]
XGEN Multi Sepsis Flow Chip	Mobius Life Science	Multiplex microarray-based PCR with biotinylated primers and colorimetric immunoenzymatic signal detection.	PBC	3 h	Maluf *et al.*, 2023 [99]
Omix-AMP	Omix labs	Loop-mediated isothermal amplification with real-time fluorescence detection.	PBC	4 h	Maheshwarappa *et al.*, 2021 [100]

Table 5: Genotypic tests evaluated in clinical studies that have not yet received regulatory approval.

[a] *Clinical sample type: Intended clinical sample matrix for application.*
PBC: Positive Blood Culture.

[b] *Average Time to Results (TTR): Time to Results reported from the starting sample type used in the study.*

Direct-from-blood assays that omit bacterial separation inherently measure both DNA derived from intact bacterial cells and microbial cell-free DNA (cfDNA). Whilst total microbial DNA is

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being employed for the development of new molecular assays, such as Deepull Diagnostics' UIICORE BSI test[101], the diagnostic value of cfDNA remains debated[102-104]. Cell-free DNA does not necessarily indicate a viable bloodstream infection, as it may reflect background DNAemia, colonisation, or contamination. Nevertheless, it has been proposed as a complementary marker in culture-negative cases, in patients with mild or non-specific symptoms, or for the detection of polymicrobial infections and slow-growing organisms[105, 106]. Sequencing-based approaches using cfDNA or total microbial DNA have been widely explored as a diagnostic tool for early infection identification, and in some cases, detection of resistance genes[107-110]. However, these methods present several limitations, including long turnaround times (>8 hours), complex workflows, high costs, and uncertain clinical impact.

Reference	Principle	Clinical sample type [a]	Average TTR [b]	Maturity Stage [c]
Deepull Diagnostics - UIICORE [101]	Multiplex real-time PCR on total microbial DNA extracted from whole blood.	WB	1 h	Clinical validation*
Hoj *et al.*, 2021 [94]	Bacterial separation via a spinning hollow disk coupled with Pentaplex PCR.	WB	2 h	Analytical validation
Ganguli *et al.*, 2022 [95]	Biphasic blood drying method coupled with loop-mediated isothermal amplification.	WB	2.5 h	Clinical validation
Abram *et al.*, 2020 [96]	Droplet digital PCR in a microfluidic format with fluorescence-based detection of amplification signals.	WB	1 h	Analytical validation

Table 6: Emerging genotypic methods for pathogen identification and resistance detection.

[a] Clinical sample type: Intended clinical sample matrix for application.
WB: Whole Blood.

[b] Average Time to Results (TTR): Time to Results reported from the starting sample type used in the study.

[c] Maturity stage: Validation stage reflects readiness for application in bloodstream infection workflows.

** Clinical validation status based on information reported on the developer website.*

CONCLUSIONS AND FUTURE PERSPECTIVES

Rapid diagnostic AST platforms for bloodstream infections have evolved considerably over the past decade, with both phenotypic and genotypic approaches delivering meaningful reductions in turnaround time compared with traditional culture-based methods. However, the integration of these systems into routine laboratory workflows presents practical challenges.

A consistent theme emerging from this review is that sample preparation remains a key limitation across platforms. Most rapid technologies require the effective separation of bacteria from blood to reduce signal interference. Different strategies, including centrifugation, selective lysis, dilution, affinity capture, and density-based separation (e.g. sucrose cushioning or dextran sedimentation), present distinct trade-offs in sensitivity, turnaround time, automation potential, and workflow complexity. For instance, dilution-based workflows simplify processing but reduce the bacterial concentration, potentially increasing detection limits and time to results. As such, they are most useful in technologies requiring a positive blood culture, as well as in those which do not require a purified bacterial pellet. In contrast, some separation strategies can improve detection limits and provide a clean bacterial pellet but introduce complexity and additional handlings steps. The optimisation, standardisation, and automation

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of sample preparation workflows will therefore be critical to facilitate large-scale routine implementation.

Emerging platforms would also benefit from balancing speed with wider organism-antibiotic coverage. Given the high costs associated with these systems, platforms offering moderate turnaround times, but comprehensive coverage are likely to offer greater clinical utility than ultra rapid systems (TTR < 3 hours) with limited panels. While time to result is critical, particularly in light of data suggesting that each hour of delay in effective therapy is associated with a decrease in survival, speed alone is insufficient if the causative pathogen or resistance determinant falls outside the test's scope. Broader coverage, even at the expense of slightly longer turnaround times, may therefore translate into improved outcomes across a wider range of clinical scenarios.
Collectively, these findings suggest that the primary barrier to widespread adoption is not the ability to generate rapid signals, but the challenge of integrating streamlined sample processing with broad pathogen–antimicrobial coverage.

In recent years, direct-from-blood testing has become a central focus, particularly for molecular approaches. As detailed in the review, most phenotypic AST approaches require sufficient, and often substantial, numbers of viable organisms to generate robust signals, making broad direct-from-blood testing significantly more challenging. In contrast, molecular tests do not require organism preservation and overcome low pathogen concentrations through nucleic acid amplification and are therefore more likely to be integrated into fully automated, whole blood testing systems in the near future.
While molecular approaches cannot replace AST testing, rapid identification and resistance marker detection have the potential to support earlier therapeutic optimisation and reduce unnecessary broad-spectrum antibiotic use. In this context, although sequencing-based approaches are not yet routinely compatible with the rapid turnaround times required for early clinical decision-making, ongoing technological advances, including improvements in sequencing chemistry, library preparation, and bioinformatic pipelines, may allow them to achieve comparable clinical impact. When combined with established resistance databases such as the Comprehensive Antibiotic Resistance Database (CARD), sequencing-based strategies could expand resistance detection beyond predefined molecular panels, ultimately providing more comprehensive resistance profiling.

Comparative clinical trials and cost-effectiveness analyses will be essential to determine which technologies provide sustainable clinical benefits in terms of costs and patient outcomes. Ultimately, the success of next-generation diagnostics will depend not only on technical innovation but also on their capacity to easily integrate into existing clinical workflows and meaningfully influence therapeutic-decision making.

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Author Contributions

D. Nicoletti conceptualized the review, conducted the literature search, and wrote the original draft. D. B. Kell and R. Goodacre provided guidance, critically reviewed, and edited the

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Declarations

Ethics:

This study is a literature-based review and did not involve human participants or animals; ethical approval was not required. All data reviewed were obtained from publicly available sources.

Competing Interests:

D. Nicoletti's PhD is funded by Innotive Diagnostics, a company currently developing technologies related to antimicrobial susceptibility testing for bloodstream infections and sepsis. D. B. Kell serves on the Board of Directors, and S. Jindal is the Chief Scientific Officer of Innotive Diagnostics. All three authors hold equity in the company. The funder had no role in the design, analysis, interpretation, or writing of this manuscript.

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Data availability statement

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review. All information discussed in this article is derived from previously published literature cited within the manuscript.

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