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Availability and Access of Bacterial Infection Diagnostics in the United States

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KEY POINTS

- Bacterial infection diagnostics, such as phenotypic methods, genotypic methods, rapid point-of-care diagnostics, and companion diagnostics, are available across a variety of U.S. healthcare facilities. No single diagnostic technology is superior to others across all healthcare settings.
- No current data source adequately tracks the availability and use of novel bacterial infection diagnostics, though evaluation through a combination of public and proprietary sources may provide evidence to enhance infection disease management. Nonetheless, gaps in data remain.
- Barriers to uptake of novel bacterial infection diagnostics include cost, reimbursement variability, turnaround time, delays in clinical guideline development and implementation, clinical practices such as outdated diagnostic workflows that providers have historically relied on, technological limitations of available diagnostics, and clinician training and expertise in diagnostic technologies.

INTRODUCTION

Bacterial infection diagnostics are crucial for ensuring accurate and prompt determination of patient infection status, identifying the infection-causing pathogen, and are critical to the fight against antimicrobial resistance (AMR). When a bacterial infection is suspected, but suitable diagnostic tools are delayed or unavailable, clinicians often resort to empiric prescriptions of broad-spectrum antimicrobials,[1,2] which may be less effective, unnecessary, and can contribute to AMR and poorer patient outcomes. Diagnostics are particularly important for the appropriate use of newer antimicrobial agents. Clinicians may hesitate to prescribe newer agents, even when they are highly effective, due to a lack of susceptibility information.[3] Diagnostic limitations can undermine the marketability of new antimicrobial products, leading to hesitation to invest in the next generation of necessary therapeutics.[4]

Advanced diagnostics that use molecular, genetic, or novel detection technologies provide faster, more accurate identification of bacterial infections than traditional, culture-based methods and are becoming more available.[5] But access to these diagnostics is still limited and may vary by healthcare setting. The primary objective of this study was to survey the published literature regarding the availability and use of diagnostics for managing bacterial infections in the United States, and the barriers to deployment and uptake of diagnostic testing in various healthcare settings. Another aim of the study was to investigate available data sources that can be used to quantify the extent of use and gaps in adoption of bacterial infection diagnostics.

METHODS

To review the literature, we queried PubMed, Scopus, and Google Scholar, limiting our search to meta-analyses, reviews, and systematic reviews published in English from 2018-2024. Our search criteria were written to return: (1) data sources to track diagnostic product availability and usage; (2) evidence on whether patients have access to the diagnostic products that they need; (3) barriers to the use of novel diagnostic products; and (4) studies that mention the United States. We also investigated types and specific examples of bacterial infection diagnostics available to U.S. healthcare facilities and summarized them in the appendix of this report. The search yielded 55 studies. We then screened their titles and abstracts for relevance to the research questions. Our screening produced 27 studies that qualified for full-text review. During the full-text review, we excluded three studies as irrelevant to the research questions, leaving 24 in-scope studies. We also employed a snowball approach to identify additional relevant studies that were not captured in the initial search. Snowballing produced 16 additional studies, including reports from the National Institutes of Health (NIH) and National Academies of Sciences, Engineering, and Medicine (NASEM), for inclusion in the review.

ADOPTION AND USE OF DIAGNOSTICS IN BACTERIAL INFECTION MANAGEMENT AND CONTROL AT U.S. HEALTHCARE SETTINGS

Our literature review did not identify any studies with specific quantitative information on the use of diagnostics in infection management and control in U.S. healthcare facilities (e.g., number of diagnostic tests ordered/used, by healthcare setting and geographical region, over time, numbers of laboratories with technology for performing each type of diagnostic test). However, we found two studies that examined diagnostics use in individual hospitals.[6,7] Many studies also reported valuable qualitative information regarding general trends in the uptake of diagnostics in various healthcare settings. The most notable takeaway from the literature review is that there is no single diagnostic technology that is consistently superior to others across all healthcare settings, and many are used on a case-by-case basis while weighing tradeoffs and needs.[8,9,10] For example, whole genome sequencing (WGS) is not possible at all facilities because it requires a reference database of known antibiotic resistance genes, expensive sequencing machines, and a highly-trained staff.[11] Meanwhile, polymerase chain reaction (PCR) tests are more accessible and simple overall, but can only detect previously identified pathogens and antibiotic resistance genes.[12]

Public and proprietary data sources have the potential to offer valuable insights into the use of diagnostics for infection management and control in the United States. Thus, to quantify the extent of use and gaps in adoption of bacterial infection diagnostics, it may be possible to use a combination of public databases that includes, for example, the Centers for Disease Control and Prevention's (CDCs) National Healthcare Safety Network (NHSN) and the College of American Pathologists (CAP) Accredited Laboratory and Biorepository Directory, results from surveys like the National Ambulatory Medical Care Survey (NAMCS), and/or claims data from the Centers for Medicare & Medicaid Services (CMS). Merging data from these and similar resources may help us to analyze trends in the use of diagnostic testing by patient demographics, region of the country (e.g., rural versus urban), and healthcare setting (e.g., hospitals, physicians' offices, clinics, etc.). Proprietary sources, such as commercial laboratory data from

providers like Quest Diagnostics and selected electronic health records (EHRs) from the Health Care Cost Institute (HCCI) or the National Patient-Centered Clinical Research Network (PCORnet), provide more detailed information on the types of diagnostics used, their frequency of use, and patient outcomes.* Table 1 below outlines the various data sources, their availability, and the types of variables they report for analysis.

Additionally, market research reports could also provide information on diagnostic uptake. These reports, often produced by industry analysts and market research firms (Markets and Markets,[13] Grand View Research,[14] and Research and Markets[15]), may offer a broader view of diagnostic use trends, technology adoption, and industry dynamics that may not be fully captured by the above data sources.† This information may also help better contextualize the data available from those listed in Table 1.

Table 1. Secondary Data Sources for Estimating Use of Diagnostic Tests for Bacterial Infections

Data Source	Public or Proprietary	Types of Variables Available [c]
CDC National Healthcare Safety Network (NHSN) [a]	Public	Facility characteristics, infection data, antimicrobial use, patient demographics
National Ambulatory Medical Care Survey (NAMCS)	Public	Visit characteristics, diagnostic tests ordered, patient demographics, insurance information
Medicare Claims Data (CMS) [b]	Public	Claims data, ICD-10 and CPT codes, beneficiary demographics, healthcare utilization, costs, and reimbursement
Medical Expenditure Panel Survey (MEPS)	Public	Patient-reported data on demographics, healthcare utilization, insurance data, limited diagnostic test data [e], medical conditions
College of American Pathologists (CAP) Accredited Laboratory and Biorepository Directory	Public	Directory of all CAP accredited laboratories. CAP accreditation requires the publication of a menu of diagnostic tests provided at the facility
Commercial Lab Data (e.g., LabCorp, Quest Diagnostics) [d]	Proprietary	Test volume, test types, turnaround time, geographic distribution, patient demographics
EHR Data [d]	Proprietary	Clinical information, diagnostic codes, lab results, patient demographics, utilization metrics

[a] While the NHSN does not directly track the number of specific diagnostic tests used for infection management (such as blood cultures or PCR tests), the antimicrobial use and resistance (AUR) module could provide indirect insights into diagnostic utilization. It is unclear if NHSN data are accessible through a special data use agreement with CDC.
[b] Diagnostic use rates would be visible in Medicare Part B claims data, as this part of Medicare involves fee-for-service (FFS) reimbursement for outpatient diagnostic tests. In Part B, diagnostic tests (e.g., blood tests, cultures, imaging) are separately itemized and billed using CPT/HCPCS codes, which can provide detailed insights into the specific types and frequencies of diagnostic tests ordered and performed. This allows for direct analysis of the utilization of different types of diagnostic tests.
[c] These do not comprise the full list of variables available from a given source.
[d] There are fees associated with the acquisition and use of proprietary sources.
[e] Data are not likely to be sufficiently granular.

* Based on our preliminary review of publicly available data descriptions for these databases.
† Typically, these reports provide estimates of market share by different types of diagnostic technologies and projections of sales for different market segments, which may serve as one proxy, albeit a limited one, for uptake.

GAPS IN DIAGNOSTIC USE DATA

While we could estimate use patterns using the data sources listed in Table 1, gauging gaps in diagnostic usage for infection management is more challenging. One option for estimating gaps in use may involve comparing usage data from sources like Medicare Part B claims (which provide detailed information on tests performed in outpatient settings) against established clinical guidelines from authorities, such as the Infectious Diseases Society of America (IDSA). In theory, one could identify gaps by analyzing the expected use of diagnostics based on these guidelines and comparing those outcomes with the actual diagnostic rates calculated from one or more of the data sources in Table 1. For example, if guidelines recommend diagnostic testing for sepsis or pneumonia, but claims data show low diagnostic test utilization, a gap in diagnostic use may be inferred. This type of data-driven comparison could provide insights into situations when a diagnostic should have been used but was not and may help pinpoint gaps in diagnostic adoption. However, despite the availability of these data sources, a robust assessment of gaps in diagnostic usage would be challenging for several reasons. First, the databases in Table 1 are incomplete in the sense that they do not capture those tests that should have been ordered but were not.[‡] Moreover, comparing actual usage to clinical guidelines can be difficult because guidelines may not always be strictly followed due to clinically appropriate reasons. Finally, using a proxy such as antibiotic prescriptions to infer underuse of diagnostics can be unreliable because empirical treatments are sometimes appropriate (e.g., for severe infections, for critically ill patients, for patients with certain co-morbidities). Combined, these factors might make it hard to definitively pinpoint gaps in diagnostic uptake and use.

As an alternative to or in support of analyses using secondary data sources, surveys or interviews with healthcare providers designed to gather qualitative data on why diagnostics may not be used when indicated could also be helpful. Such qualitative data may uncover common barriers to adoption, such as lack of insurance coverage (see Reimbursement Variability), insufficient training of staff on newer technologies and methods (see Clinician Training and Expertise Requirements), and cost (see Capital Cost), providing insights into systemic gaps in diagnostic use. Interviews may also point to additional secondary data sources and innovative methods for quantifying the magnitude of the problem.

BARRIERS TO UPTAKE

We identified several barriers to uptake of novel bacterial infection diagnostics that have been cited in published literature. Select barriers to uptake included cost, reimbursement variability, turnaround time, delays in clinical guideline development and implementation, clinical practices (e.g., outdated diagnostic workflows that providers have historically relied on, or variation in providers' decision making during the diagnostic process), technological limitations of available diagnostics, and clinician education and expertise requirements, each of which is discussed in more detail below.

[‡] These would need to be estimated by reviewing those claims in which an antimicrobial was prescribed and reimbursed without an accompanying diagnostic test reimbursement.

Capital Cost

The literature frequently cites the capital cost associated with implementing and using new diagnostic tools. In fact, some tests are not commercially available because the perceived value of the test does not outweigh costs of adoption.[9] Additionally, high costs associated with using diagnostic technologies for precision treatment may be a deterrent for third party payer reimbursement,[16] which can affect diagnostic uptake (see Reimbursement Variability). The equipment itself is expensive, as in the case of single-cell-based antimicrobial susceptibility testing (AST) systems, PCR, and enzyme-linked immunosorbent assay (ELISA).[8,17] Equipment costs can vary depending on specifications such as throughput, data quality, and portability (i.e., benchtop *versus* larger high-throughput sequencers). For instance, in 2018, Illumina launched a benchtop sequencer called the iSeq Sequencing system for approximately $20,000 and Illumina high-throughput sequencers approached $1 million at that time.[18] If the cost of installing new testing equipment is too high, healthcare facilities may choose to outsource diagnostic testing to commercial clinical laboratories, which may cause transportation challenges.[2] Additionally, there are costs associated with running tests for patients after the diagnostic platform is installed. Per test costs vary depending on the specific technology and necessary reagents. For example, it costs $9.98 per GeneXpert test cartridge for a tuberculosis diagnostic test,[19] an AcceleratePheno test was reportedly about $277 per sample,[20] and metagenomic next generation sequencing (mNGS) is approximately $2,500 per sample.[2] Additionally, molecular diagnostic platforms such as WGS tests generally have a higher cost per test compared to phenotypic tests.[11] Studies we reviewed specifically mentioned that Illumina sequencing, RNA-seq, and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) are all particularly costly diagnostic technologies.[12,20,9] Given the high costs often associated with novel diagnostic implementation and use, further research may be needed to develop cost-effective implementation strategies, especially in resource constrained healthcare settings.[10]

Reimbursement Variability

Variable reimbursement coverage for diagnostic testing also affects uptake of bacterial infection diagnostics. If healthcare providers do not get reimbursed fully for diagnostic testing, or if they are uncertain about reimbursement, they might choose not to perform certain tests or types of tests. Similarly, if a diagnostic test is not fully covered by their insurance, patients may decline the test. According to experts who participated in an October 2022 workshop on "Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance," payer coverage is not standardized across geographic regions nor across different healthcare settings (i.e., inpatient versus outpatient).[2] Health insurance in the United States is provided by a mix of public and private payers, including Medicaid, Medicare, and numerous private insurers. Each of these payers can have different coverage policies based on regional factors like local healthcare costs, state regulations, and outcomes of payer-provider negotiations. For instance, Medicaid programs vary by state, and coverage policies for diagnostic tests might differ based on what each state chooses to include as essential services. Meanwhile, Medicare patients in particular may be subject to local coverage determinations about reimbursement for diagnostic testing.[2,21]

Payer coverage also varies between inpatient and outpatient settings because faster and often more expensive diagnostics are often needed in inpatient settings, especially for patients requiring urgent care,

while less costly, traditional methods are preferred for outpatient settings. Therefore, the cost of the same diagnostic test could vary widely for different patients and providers. Industry stakeholders maintain that third-party payers are ethically obligated to reimburse for diagnostic testing for all patients regardless of their ability to pay for services. This is especially important for low-income communities and for novel diagnostics that are usually more expensive than conventional tests.[2] Furthermore, insurance companies typically classify rapid diagnostics as diagnostic services and not as routine services (which are often fully covered by insurance). Classification is often based on the test's purpose and frequency of use, and rapid diagnostics are often needed for specific reasons in cases of acute symptom onset, rather than for routine monitoring such as cancer screening.[22] Experts suggest that to overcome these issues, rapid diagnostics could be classified as routine tests to guarantee reimbursement coverage, and payers should be educated on the long-term cost-effectiveness of diagnostics reimbursement.[2] Reimbursement variability creates a barrier to diagnostic accessibility, and therefore affects diagnostic uptake and use.

Turnaround Time

The time it takes for a diagnostic to produce results, or turnaround time, varies across different types of diagnostics and affects how and when they are used. Providers that need to diagnose patients quickly will be more likely to use tests that return results within a few hours rather than days, sometimes at the expense of other factors such as test sensitivity, accuracy, or scope of tested conditions. Providers also consider the likelihood that patients' infections may worsen and be transmitted to others while waiting for results.[17] Therefore, balancing the need for quick diagnostic results with other important factors is a constant challenge and requires accurate turnaround time information. Culture-based diagnostics have historically been the gold standard for testing AMR and are currently recommended by the Clinical Laboratory Standards Institute (CLSI).[11] Culture-based diagnostics like disk diffusion have turnaround times of 24 – 48 hours, but they offer important advantages, such as providing antimicrobial susceptibility data, established validation methods, and lower cost.[11] Diagnostic tests that require cultured microbes, such as WGS (2.5-3 days turnaround time[23]), are not ideal for situations requiring a rapid diagnosis.[12] Over the past several years, mass spectrometry (MS) methods such as MALDI-TOF MS (10-60 minutes turnaround time[24]) have improved conventional bacterial identification in many laboratories, including improvements in turnaround time, and such technological improvements continue to positively impact patient care.[25]

Even diagnostics that do not require culturing and that can be run directly on patient samples can be time-consuming. For instance, the turnaround time for mNGS is about five days on average, which presents a large barrier to its adoption despite its advantages in using a clinical specimen to sequence millions of DNA fragments simultaneously.[2] The exact turnaround time depends on the sequencing technology, bioinformatics program used, and the methods of the test, but in general mNGS is labor-intensive with multiple steps, including DNA or RNA extraction, library preparation, sequencing, and data analysis.[26] The sequencing step alone can take up to 48 hours, and in cases involving commercial laboratories, turnaround time is also affected by shipping time.[26] Depending on the technology, other steps in running diagnostic tests, such as data analysis and interpretation, add more time to the process. To cut down on data analysis and interpretation time, some institutions have created dedicated interdisciplinary precision medicine teams to discuss and interpret results prior to release.[26] While many novel diagnostics have already improved turnaround times via rapid bioinformatics pipelines,

bioinformatics tools require a significant degree of expertise. Making these analytic programs more user-friendly may help increase their use.[26] Advancements such as MS and bioinformatics tools have diminished turnaround times, but there are still many opportunities for further technological advancement to reduce time spent waiting for accurate diagnoses.

Delays in Clinical Guideline Development and Implementation

While clinical guidelines are beneficial and can facilitate the uptake and reimbursement of diagnostics by encouraging proper use, delays in their development and updating can hinder the adoption of novel technologies. Clinical guidelines are developed via a rigorous evidence-based process that involves the following steps: (1) Identify or refine the subject area; (2) convene guideline development groups to identify, synthesize, and interpret evidence; (3) assess the evidence about the clinical question of interest (usually via systematic review); (4) translate evidence into a recommendation; and (5) have external reviewers review the recommendation.[27] According to Susan Van Meter, the President of the American Clinical Laboratory Association (ACLA), because of this stringent process, guidelines can take a years to be developed, and in the meantime novel diagnostic technologies are constantly evolving.[2] Guideline development may not be able to keep up with evolving technology and as a result, newly-approved novel diagnostics may not be included in current guidelines.[2] Because clinicians rely on guidelines to inform their decisions, if a novel diagnostic is available but is not included in current guidelines, they may be less likely to use the novel diagnostic in their respective practices.

Additionally, although prioritization and increased support can expedite development of clinical guidelines, as was the case during the COVID-19 pandemic, there can be a lag in their implementation at healthcare settings.[2] For example, the implementation of clinical guidelines for clinical breakpoints, the criteria used to interpret AST results and determine a microbe's susceptibility or resistance to antimicrobial drugs, often lags behind the clinical guideline updates.[28] Clinical breakpoints shift over time as new AMR mechanisms and clinical data emerge, which causes previously established breakpoints to become obsolete.[29] Clinical laboratories should adopt updated breakpoints as they evolve, but U.S. regulators do not compel them to do so, which may result in the use of obsolete breakpoints.[29] According to a 2019 survey, between 38 percent and 70 percent of clinical laboratories were using obsolete breakpoints instead of the breakpoints reflected in current guidelines.[29] In this instance, a delay in clinical guideline implementation can be a patient safety issue and an impediment to progress against AMR.[2]

Clinical Practices

The uptake and use of novel diagnostics is heavily influenced by clinical practices, the day-to-day responsibilities of clinicians, including clinical decision making for patient care.[30] Several factors in addition to diagnostic test results inform clinical decisions by providers, including the patient's medical history, physical examination, and initial screening test results.[31] The extent to which providers rely on any one factor in treating patients can vary by provider, by healthcare setting, and by patient. In some settings, such as the safety net hospital studied by Burrowes et al. in 2020, clinical decisions are less influenced by diagnostic testing than in other healthcare settings.[6] For example, disadvantaged patients who seek care at safety net hospitals may experience healthcare access challenges, such as inadequate transportation, lack of insurance, or language barriers. This can mean the provider will not be able to follow up with them.[6,32] Based on the patient's individual situation, providers may decide the best course

of action is to treat the patient at the point of care (POC) without ordering diagnostics. Indeed, factors affecting clinical decisions, including the use of diagnostic testing, are influenced by the needs of the patient population in the specific healthcare setting.

Another example of a clinical practice barrier to diagnostic adoption is that certain established practices are historically recommended even though the diagnostic process could be improved with new technologies. For example, to successfully diagnose *Clostridioides difficile* infection, the current clinical practice, based on guidelines, is to run multiple diagnostic tests.[33] An initial screening test such as the glutamate dehydrogenase assay is usually employed to quickly check for presence of the microbe. If the first test is positive, a toxin test is run.[34] With such an established clinical practice in place—a practice that providers know will work—they may be hesitant to adopt novel diagnostic testing strategies even if the new diagnostics efficiently combine screening and toxin tests into one step. This implies that providers also need to be aware of currently available diagnostics to make savvy clinical decisions. While we did not identify any specific publicly available data source on available diagnostics, industry stakeholders suggest that overall industry communication about new diagnostic technologies could be improved, and physicians in particular need support to keep their knowledge of available technologies current.[2]

In their study, Burrowes et al. mentioned that healthcare settings with existing diagnostic testing workflows, like emergency departments, may find it easier to adopt novel diagnostic technologies.[6] In these healthcare settings, necessary equipment and trained personnel may already be in place and existing testing workflows can reduce the burden of novel diagnostic implementation.[35] Additionally, the adoption of new diagnostics may be more cost effective in these settings as existing infrastructure and resources can be used, including any validation and approval processes.[36] Successful uptake and use of novel diagnostic technologies into clinical practice requires not only technological advancements but also a shift in clinical culture and workflow adaptation. It is also highly important that novel diagnostics have robust evidence of their clinical utility, i.e., improved patient outcomes.[16]

Technological Limitations of Available Diagnostics

Many infectious disease diagnostics have limitations inherently associated with the specific type of technology that they use. Various limitations may deter the use and uptake of diagnostics in favor of other options that are more fit-for-purpose, depending on the use case. An example of one such limitation is a high false positive rate associated with Verigene, mNGS, sensitive PCR tests such as microarray PCR, and nucleic acid amplification testing (NAAT).[24] False positive results can lead to unnecessary isolation or quarantine,[37] unnecessary treatment,[37] misallocation of healthcare resources away from other patients who need them[38] and negative clinical outcomes for the patient, including stress and anxiety.[39] Overdiagnosis is another limitation of certain diagnostics (such as NAAT) in which an infectious disease may be detected despite the patient being asymptomatic,[40] which can lead to the same issues listed above. For instance, PCR diagnostic tests used for *Clostridioides difficile* infection cause as many as 15 percent of patients to be over-diagnosed if they are merely carrying the pathogen but are otherwise asymptomatic.[41] Another limitation of many commercially available diagnostics, such as immunoassays, MALDI-TOF MS, RAPIDEC®, BYG Carba, Microcolorimetry AST plate, NG-Test, and Droplet microfluidic platform, is that they cannot process clinical samples and instead require pure cultured pathogens,[11,8,9,24,20] which, as discussed above can lengthen the time to result. In some cases, the

diagnostic tool requires the target pathogen to be previously identified which can be limiting. For example, PCR tests cannot detect new variants of resistant genes in pathogens,[8] and MALDI-TOF MS requires a reference database to properly identify pathogens.[11,9,24] Lastly, while culture-independent diagnostics such as Xpert PCR, BioFire FilmArray, and Verigene can save time, they cannot provide antimicrobial susceptibility data,[12,20,42] which is important in determining the most appropriate therapy. While novel diagnostics offer significant advancements, their limitations can affect their use and uptake in clinical practice.

Clinician Training and Expertise Requirements

While some diagnostics require little clinical expertise, such as PCR-based rapid diagnostics,[8] others require rigorous training and expertise to conduct and read results. As a result, the training and expertise requirements required for some diagnostic technologies and their complex data act as a barrier to their widespread use.[43] For example, in the use of 'omics-based analytics, such as transcriptomics and proteomics, there is a critical need for expertise in data analytics, as even small samples can yield tens of thousands of data points that need to be compared to determine a disease's signature.[9] Additionally, specific infectious disease diagnostics require increased levels of experience and expertise to analyze their respective results. For instance, researchers in one study noted that the over- and under-diagnosis of syphilis are problematic if clinicians are not properly trained in the diagnosis process.[44] Also, certain serologic testing for syphilis requires expertise in using complex equipment and algorithms.[7] Therefore, addressing the training and expertise needed to apply these advanced diagnostic technologies is crucial for their effective implementation and widespread adoption in clinical practice.

CONCLUSIONS

The literature review reveals that a variety of information about the availability and usage of advanced bacterial infection diagnostic tests in the United States is either unavailable or inaccessible. Aside from not finding any current accessible sources of data on novel diagnostic availability and usage, our literature review provides recommendations for how data from public and proprietary sources could be used to analyze trends in diagnostic use and reveals the various barriers to uptake that different healthcare settings face regarding advanced diagnostic technologies.

Public and proprietary data sources can prove useful for evaluating diagnostic use for infection disease management. Public databases like the CDC's NHSN, NAMCS, and CMS claims data allow for analysis of testing trends by demographics, geography (e.g., rural vs. urban), and healthcare settings (e.g., hospitals, clinics). Proprietary sources, such as lab data from Quest Diagnostics and EHRs from HCCI and PCORnet, could also offer more detailed information on the types and use frequency of diagnostics. However, the fragmented nature of these data could limit the types of analyses that can be conducted as well as the populations that can be studied.

The literature review helped identify gaps in knowledge related to measuring and tracking diagnostic use and availability. Also, we have identified several barriers to the use of infectious disease diagnostics. Importantly, the cost of implementing novel diagnostic testing technology is often prohibitive for clinical practices, preventing its uptake. Beyond the substantial cost of some new diagnostic equipment, there are additional costs of running diagnostic tests for each patient. The cost of diagnostic use also causes third-party payers to generate an array of reimbursement practices that can act as a barrier to uptake.

Healthcare providers will be less likely to adopt novel diagnostic techniques if those diagnostic tests are not reimbursable. Reimbursement for diagnostic tests differs across individual patients, healthcare settings, and geographic areas, and there is little information on this issue in the literature. Hence, future research will be needed to explicate diagnostic reimbursement patterns, processes, and downstream patient impacts.

The long turnaround time for many diagnostic techniques presents another barrier to uptake. Diagnostics that require pathogen cultures or significant hands-on time will not be useful in clinical settings in which patients need immediate therapy, such as emergency departments or intensive care units. Delays in diagnosis also lead to increased AMR by promoting the empiric prescription of broad-spectrum antimicrobial therapies. Novel techniques may be preferred in these cases but entail higher costs and additional clinician training.

The time required for developing or updating clinical guidelines, as well as inconsistent implementation of guidelines across healthcare settings, may also challenge uptake of novel diagnostics. And even newly issued guidelines may not include novel diagnostics, owing to the time it takes to draft guidelines. This issue will take significant collaborative insight and innovation to solve. One industry stakeholder even suggested that declaring AMR a national emergency may spur solutions faster.[2] Clinical guidelines also influence clinical practice, which in turn affects the adoption of novel diagnostics. Established testing protocols and prioritization of other clinical factors over diagnostic tests are two clinical practices that influence diagnostic uptake and use.

Specific characteristics of individual diagnostic technologies can also stymie their use and uptake. Many tests are known to have high false positive rates, require extra steps in the testing protocol, or cannot provide antimicrobial susceptibility data and therefore may not be used. Meanwhile, novel technologies like ’omics-based analytics require specific expertise from clinicians and technicians, which could be challenging in settings with limited resources. Assessing whether individual diagnostics are fit-for-purpose and addressing the education and expertise required of staff who will apply advanced diagnostics are essential for their widespread adoption.

The findings from our literature review demonstrate the need for future research on advanced diagnostic test availability for the U.S. market. The first step should be to interview key subject matter experts, individually or as members of a panel of experts, to amass more information on availability and use. This report clearly documents that the knowledge of clinical, industry, and research stakeholders extends beyond what the literature has to offer.[2] This knowledge and experience should provide further insight into the characteristics of advanced diagnostic test availability in the United States. After engaging subject matter experts, targeted research questions should be asked about how existing data sources could be analyzed to track uptake of infectious disease diagnostics; the best strategies for measuring availability of infectious disease diagnostics in clinical settings; and what actions will mitigate the identified barriers to uptake, and to what extent can such barriers be overcome.

APPENDIX: TYPES OF BACTERIAL INFECTION DIAGNOSTICS AVAILABLE TO U.S. HEALTHCARE FACILITIES

Diagnostics available for bacterial infection management and control include diagnostics using phenotypic methods, genotypic methods, rapid POC diagnostics, and companion diagnostics across a variety of U.S. healthcare facilities (e.g., hospitals, health systems, physicians' offices, retail clinics). These diagnostic technologies often differ in their sampling methodologies, detection techniques,[45] and turnaround times.[17,25,9,24] The types of biological specimens sampled for diagnostic analysis can include blood, urine, sputum, skin swabs, or other bodily fluids, depending on the suspected site of infection as well as the pathogen involved. Detection techniques include traditional culture methods, molecular assays like PCR for DNA amplification, immunoassays for antigen or antibody detection, and advanced methods such as MS. Each of these detection techniques has its own sensitivity, specificity, and limitations, which affect its suitability for detecting different types of bacterial infections. Across the different diagnostics, turnaround times—the time elapsed from specimen collection to the delivery of diagnostic results to the clinician—can range from minutes for rapid POC tests to several days for culture-based methods that require bacterial growth and additional confirmatory tests. In addition to variations in their sampling methodologies, detection techniques, and turnaround times, these diagnostics also differ in the type and specificity of the outputs they provide. Some diagnostics simply indicate the presence or absence of a bacterial pathogen. Others provide such information as the bacterial load or concentration within the specimen, which can be critical for assessing the severity of an infection. Advanced molecular diagnostics[5] may provide detailed information on the specific bacterial species or strains, including genetic profiles that identify virulence factors or AMR genes. Culture-based methods often allow for AST, yielding data on which antimicrobials are most effective against the specific bacterium. The outputs from these diagnostics can range from basic binary results to comprehensive reports that inform clinical decision making. We summarize and provide examples of commercially available devices below.

Phenotypic Methods

Phenotypic methods use physical characteristics, such as morphology, cellular composition, and protein production, to determine bacterial species and AST. These methods can be either manual or automated. Manual phenotypic methods may include disc-diffusion assays, differentiative biochemical test panels, and immunologic assays run by trained clinical laboratory technologists, such as the ELISA. Automatic phenotypic tests are often run on bench-top machines and may characterize the resistance-profile of a microbial sample using a panel of various antimicrobial drugs simultaneously.[28] For these methods, bacteria can be sampled and grown from blood, urine, sputum, skin swabs, and other bodily fluids before testing. Some healthcare facilities have on-site capacity to perform manual and/or automatic phenotypic bacterial determination and AST methods, though clinical samples may need to be shipped to an off-site laboratory for testing if a facility's on-site laboratory lacks proper equipment or trained personnel.[46,1] As a consequence, most phenotypic methods often take between 48 to 72 hours from specimen collection to delivery of results, though some organisms and circumstances require longer. Recent technological advancements, however, have resulted in faster turnaround times for diagnostics, such as the Accelerate Pheno® system, that can return results in as little as two to seven hours.[47]

Genotypic Methods

Genotypic methods use molecular techniques to detect and identify pathogens from blood, saliva, tissue biopsies, hair follicles, and other bodily fluids. Some major genotypic technologies identified include PCR tests, mNGS, and WGS. PCR is one of the most commonly used techniques for AST and provides a comparatively fast way to test for a variety of resistance genes by rapidly amplifying copies of DNA segments.[48] PCR methods can also be classified as rapid diagnostics, as further discussed in the following section and Table 2. mNGS uses sequencing methods to either simultaneously or independently inspect nucleic acid fragments to identify bacteria, fungi, viruses, or parasites, as well as AMR genes present.[43] Recently, mNGS has seen growth in its use for the identification of multiple microbes at once.[12] Similarly, WGS uses the same targeted process to determine a microbe's genetic sequence and has the enhanced ability to identify a pathogen and its AMR using cultures.[49] According to Trotter et al., WGS is widely used in laboratory settings for AMR testing in infectious diseases; however, it is also important to note that WGS and mNGS have potential for longer turnaround times[12] and are associated with higher costs. While the cost of sequencing has decreased over time, Filkins et al. found that the cost of mNGS ranged from $2,000 to $4,000 per sample in 2020. These technologies remain expensive due to the cost of their equipment, reagents, and training required.[50]

Rapid Diagnostics

Rapid diagnostics have proven to be instrumental in the diagnosis of infectious diseases and identification of AMR to effectively treat patients as efficiently as possible. While there is no universally accepted definition of what constitutes a "rapid" diagnostic, the term generally refers to those diagnostics that provide results within a significantly shorter timeframe--typically minutes to hours--compared to traditional diagnostic methods.[17,25,9,24] Traditional diagnostic methods, such as culture-based assays, often take several days or weeks to yield results due to the time needed for bacterial growth and subsequent analysis from specimen collection. This delay can impede timely clinical decision-making and initiation of appropriate antimicrobial therapy, thereby resulting in poorer patient outcomes. In contrast, rapid diagnostics aim to expedite this process, enabling earlier detection and treatment. Most rapid diagnostics are administered at the POC, which can include inpatient, outpatient, or home settings.[51] In many cases, POC rapid diagnostics are either PCR or MS-based.

PCR-based tests are used to detect microbial presence and AMR genes in patient samples without the need for an additional, sometimes lengthy, culturing step. PCR-based POC tests are able to screen for multiple microbial species or AMR gene detections at once, reducing the cost per test while limiting the technical expertise necessary to conduct the test.[8] It is important to note that PCR-based tests are limited in their ability to test only for known targets and those specifically included on a given test panel, limiting their effectiveness for detecting non-typical pathogens, or novel resistance genes. For this reason, many PCR-based tests have not been considered comprehensive enough for pathogen and AMR detection without being complemented by cultures.[8,12]

MS-based tests use ionized samples to inspect mass to charge ratios to identify pathogens and detect microbial products that generate resistance to antimicrobials. The most mentioned of these technologies is MALDI-TOF MS. MALDI-TOF MS provides a rapid, sensitive, and economic option for identification and diagnosis of infectious diseases.[52] These tools can provide results within a few minutes but require a laboratory and technologists with advanced expertise, given their technical and mechanical complexity.

Companion Diagnostics

Companion diagnostics (CDx), historically used in oncology therapeutics, have recently seen an increase in use for infectious disease treatment. Traditional infectious disease diagnostics, while not currently designated as CDx, have been used to identify AMR in pathogens to determine treatment options.[16] CDx are a subcategory of diagnostics used to determine if a specific drug or therapy is appropriate for a given patient. With the increasing rates of AMR and the difficulty of drug development, the need for CDx for novel therapeutics in infectious diseases has increased in recent years.[45] CDx for infectious diseases often use molecular tests, including PCR, MS, and other technologies, to detect resistance to one or more drugs. These results can then be used to directly inform antimicrobial treatment decisions. Although there currently are no specific regulatory approvals for CDx in infectious disease treatment, studies have identified a need for regulatory approval and use of CDx to aid in combatting AMR.[16] While FDA published guidance on CDx in 2016, 2020, and 2023, Dailey et al. and Kalpana et al. prescribe an established market and support structure for approval and usage. In the United States, most CDx require a premarket approval (PMA) by FDA while most other infectious disease diagnostics follow the 510(k) route. The PMA regulatory pathway is costly and significantly longer than the 510(k) route, which often deters companies from pursuing CDx approvals. Enabling the 510(k) regulatory pathway for CDx would reduce CDx development costs, thereby making them more appealing investments.[16,45]

Table 2. Types of Diagnostics Used in the Management of Bacterial Infections

Diagnostic Type	Diagnostic Technology	Examples of Commercially Available Devices [a]
Phenotypic Methods	Manual	Kirby-Bauer disk manual test[53] Enzyme-linked immunosorbent assay (ELISA)[17]
	Automatic	MicroScan; BD Phoenix Automated Microbiology System; Vitek 2 System; Sensititre ARIS 2X, Accelerate Pheno® system[47,8,54]
Genotypic Methods	Polymerase chain reaction (PCR) tests	Sputum smear microscopy; Urinalysis
	Metagenomic next generation sequencing (mNGS)	Ion torrent sequencing; sequence-independent, single primer amplification (SISPA) combined with mNGS[9,24,19,55]
	Whole genome sequencing (WGS)	CRISPR/Cas9; Illuminia MiniSeq, Illumina MiSeq; Oxford Nanopore's MiniON; Nanopore's PromethION[12,11,9]
Rapid Diagnostics	PCR-based	Hyplex (Amplex); BDMax; GenerXpert; VAPChip; Xpert MTB/RIF; Xpert Carba-R; Xpert vanA; Verigene; Biofire FilmArray; Unyvero; Rapid Group A Steptococcus test; Abbott m2000; Roche SeptiFast; Anyplex vanR; Cobas liat; MeltPro TB assay; Truenat MTB; INFINITIMTB assay; Microarray PCR[12,8,20,19,24,57,17]
	MS-based	MALDI-TOF MS; Vitek MS; MBT-STAR-BL; MBT-ASTRA[8,45,20,24,9,58]
Companion Diagnostics [b]	Molecular tests; PCR-based; MS-based	CRISPR; transcriptome analyses; siRNA-aptamer combination; Western blot; RT-PCR; Fluorescence activated cell sorter; Surface plasmon resonance; Immunohistochemistry[45,16]

[a] The examples listed do not include all commercially available diagnostic devices, nor are all listed devices and/or brands commercially available in the United States.

[b] There currently are no antimicrobial drugs with an associated diagnostic test that is required or labeled as a CDx. The tests listed aid clinicians in selecting appropriate antimicrobial therapy but are not linked to specific antimicrobial drugs in a manner that would require FDA approval as a CDx.

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