

WHITE PAPER

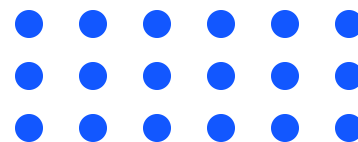
NOVEL PATHOGEN DIAGNOSTICS AND ANTIMICROBIAL RESISTANCE

WHO PAYS FOR THE WRONG ANTIBIOTIC?

David C. Danko, Ph.D.

Biotia, Long Island City, New York

OCTOBER 2026



Executive summary

Patients in the US frequently receive antibiotics that cannot kill the pathogens infecting them. Due to resource constraints, clinicians often prescribe empirically, rely on diagnostic tools that cannot reliably identify a broad gamut of pathogens, or fail to identify acquired resistance. This is often framed as a technological problem: how can new diagnostics improve on existing tools? However, the economic problems facing novel diagnostics are substantial and merit analysis. Existing diagnostics are cheap and cover most infections. Novel diagnostics can provide net savings when used appropriately, but siloed budgeting practices mean that the costs and the benefits land in different places. This mismatch stalls the deployment of novel diagnostics that would reduce healthcare costs and improve patient outcomes.

In this whitepaper, we outline the scale of discordant therapy and antibiotic resistance; the landscape of existing microbial diagnostics; how current detection technologies compare; who bears the cost when a patient's first antibiotic does not work; and where novel diagnostics, including those using AI, can create clinical impact.

KEY FINDINGS

- | | |
|---|--|
| <p>01 Antimicrobial resistance (AMR) is a common problem that costs US health care \$2.2–4.6 billion a year [1, 2]. AMR is technologically difficult to detect and can compound limitations of common microbial testing frameworks.</p> <hr/> | <p>04 Who absorbs the cost of discordant therapy depends on the setting and the insurer. Typical Medicare and Medicaid programs use fixed payments, where the hospital absorbs excess costs. Under private insurance and in outpatient care, the insurer and the patient do.</p> <hr/> |
| <p>02 Discordant therapy is a broader problem than acquired AMR alone. About one in five US patients with a bloodstream infection are initially given a drug that has no effect on their pathogen, which is associated with 46% higher odds of death [3].</p> <hr/> | <p>05 Conventional culture is cheap and ubiquitous but has blind spots. Conventional clinical culture can grow a wide variety of pathogens but often fails to detect anaerobic bacteria, fungi, and fastidious pathogens.</p> <hr/> |
| <p>03 Hospital budgets often silo the costs of tests to a clinical lab while benefits are realized by pharmacies, wards, and insurers. Realizing the net impact of more expensive diagnostic tests requires cross-departmental coordination.</p> <hr/> | <p>06 Novel diagnostics have a high sticker price but can result in net savings. An expensive test can pay for itself when it reduces patient stays and avoidable transmission. At one hospital, genomic surveillance reported a modeled 3.2x return on investment [4].</p> <hr/> |

THE WRONG ANTIBIOTIC

CONTENTS

1. Discordant therapy and acquired drug resistance	3	Reserve antibiotics put a price on a laboratory result	14
2. The clinical and economic burden of discordant therapy	5	The two programs that act on results	14
Rates of drug-resistant infection	5	What this has meant for diagnostic vendors	15
The long tail of resistant infection	6		
Impact of discordant therapy	7	4. The technological landscape	15
The cost of using the wrong drug	7	Existing detection technologies	15
What the evidence says about paying for better detection	8	Where existing technology falls short	17
3. Who pays when the first antibiotic is wrong	9	Emerging approaches	18
Medicare, Medicaid, insurance, inpatient and outpatient	10	How AI can be incorporated into clinical tools	19
Value and payment sit in different places	10	5. Implications for hospital leaders and laboratory directors	20
Three illustrative scenarios	11	About Biotia	21
What a test is paid	13	References	22

Discordant therapy and acquired drug resistance

Antibiotic treatment usually begins before the cause of an infection is known. Laboratory results take days, and for a serious infection a delay in treatment is dangerous, so clinicians prescribe empirically: they choose a drug based on the likely pathogens and revise the choice once results arrive. In most cases the empiric choice works. When it does not, the patient spends the intervening days on a drug that is not treating the infection.

Resistance rates are the standard measure of a hospital's exposure to this risk. However, they describe only part of it, because acquired resistance is one of four reasons an antibiotic can fail.

Acquired resistance is what most people mean by AMR: a pathogen from a normally susceptible species stops responding to a drug because it has gained a mutation or a resistance gene. Surveillance systems are built to count these infections.

The clinical problem is broader: whether the antibiotic prescribed to the patient is effective against their infection. Treatment that does not match the pathogen is called discordant therapy; treatment that does is concordant.

THE WRONG ANTIBIOTIC

DEFINITION

Discordant therapy

Discordant therapy is antibiotic treatment that is not active against the pathogen causing the patient's infection. It is most often the first antibiotic a patient receives, chosen before test results are available, but any mismatch between drug and pathogen at any point in treatment is discordant. Acquired resistance is one cause; another is a drug chosen empirically that ends up being wrong.

Discordant therapy has four causes:

1

Wrong class

A fungal or viral infection, or a non-infectious inflammatory condition, treated with an antibacterial

IDENTIFYING THE PATHOGEN

2

Intrinsic resistance

A species that is never susceptible to the drug chosen

IDENTIFYING THE PATHOGEN

3

Misidentified pathogen

The pathogen is mistaken for a different species, often because it does not grow in culture or is part of a mixed infection, and the drug chosen does not act on it

IDENTIFYING THE PATHOGEN

4

Acquired resistance

A pathogen from a normally susceptible species gains a mutation or resistance gene and stops responding to the drug

SUSCEPTIBILITY TESTING

Figure 1. The four causes of discordant therapy, and what resolves each. Only the fourth is what surveillance systems usually count as AMR.

3 of 4

Of note, three of the four causes of discordant therapy are resolved simply by knowing what pathogen is infecting the patient. Identifying the pathogen and testing it for resistance are components of the same diagnostic problem, and a hospital that monitors only resistance rates is measuring a fraction of the risk it carries.

The clinical and economic burden of discordant therapy

More than 2.8 million antibiotic-resistant infections occur in the US each year, causing more than 35,000 deaths [5] and adding an estimated \$2.2–4.6 billion a year to health care costs [1, 2]. Discordant therapy is broader still: about one in five patients with a bloodstream infection starts on a drug to which their pathogen is not susceptible [3]. The remainder of this section describes which infections make up these totals, what the official counts leave out, what a single case costs, and whether better detection has been shown to reduce the burden.

RATES OF DRUG-RESISTANT INFECTION

The US Centers for Disease Control and Prevention (CDC) estimates more than 2.8 million antibiotic-resistant infections and more than 35,000 deaths in the US each year, or 48,000 deaths when *Clostridioides difficile* is included [5]. These estimates rest mostly on 2017 data. CDC published a partial update in 2024 and has said it will release new estimates for at least 19 threats in 2026; until then, these remain the national figures.

Which infections matter most depends on the measure used:

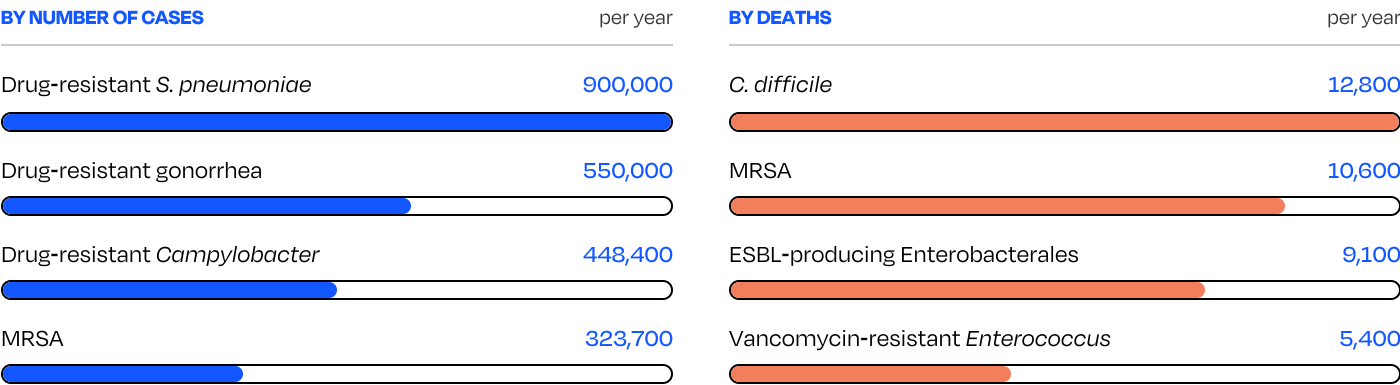


Figure 2. The four leading US resistant infections by annual case count and by annual deaths [5]. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales: Enterobacterales are the group of gut bacteria that includes *Escherichia coli* and *Klebsiella*.

Enterobacterales are the group of gut bacteria that includes *Escherichia coli* and *Klebsiella*.

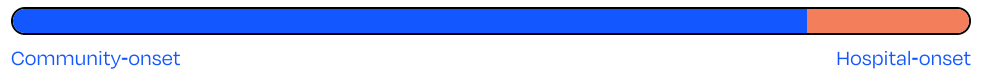
By case count, the three leading infections are acquired in the community. By deaths, the list centers on the hospital.

THE WRONG ANTIBIOTIC

83%

Most resistant infections nonetheless arrive from outside the hospital.

In a CDC analysis of 890 US hospitals, 83% of infections with multidrug-resistant pathogens in hospitalized patients were community-onset, meaning they were present at or soon after admission [6]. A testing strategy aimed only at hospital-acquired infection therefore addresses a minority of cases.



THE LONG TAIL OF RESISTANT INFECTION

CDC's counts are concentrated in a small number of pathogens: by our arithmetic on its figures, the six most common threats account for over 90% of the 2.8 million cases [5]. However, a substantial amount of resistance sits outside this head, in four places.

Resistance that is not classified as a threat. CDC's total is, by design, a count of named threat categories: combinations of pathogen and drug that it ranks as urgent, serious or concerning, generally because few treatment options remain. Resistance to a first-line drug for which effective alternatives exist is not counted, however common it is. Ordinary urinary *E. coli* is the clearest example: among 1.5 million urinary *E. coli* isolates (pathogens grown from patient samples) from US female outpatients, 25% were non-susceptible to trimethoprim-sulfamethoxazole and 21% to fluoroquinolones [7]. An alternative drug exists for each of these infections, which is why they are not ranked as threats. Nonetheless, because the first

prescription is often written without a culture, this uncounted resistance is a direct source of discordant therapy.

Pathogens that routine culture does not find. A resistance count can only include pathogens that were grown. In one study of 150 urogynecology patients, standard urine culture missed 67% of the uropathogens that an expanded culture method detected, and 50% in the women who reported urinary symptoms [8].

Resistance spread thinly across many pathogen–drug pairs. The largest global analysis modeled 88 pathogen–drug combinations across 23 pathogens. Six pathogens accounted for 73% of the deaths attributable to resistance in 2019 (929,000 of 1.27 million); the remaining quarter was distributed across the other 17 [9].

Unusual mechanisms within common pairs. Even for well-characterized pathogens, a share of resistant isolates carry rare or combined mechanisms that gene-based tests do not detect. We return to this in section 4.

THE WRONG ANTIBIOTIC

25%

of outpatient urinary *E. coli* non-susceptible to trimethoprim-sulfamethoxazole [7]

21%

non-susceptible to fluoroquinolones [7]. CDC's 2.8 million does not count resistance to first-line drugs like these on its own [5].

67%

of uropathogens missed by standard urine culture in one study [8]

IMPACT OF DISCORDANT THERAPY

In a study of 21,608 patients with bloodstream infections at 131 US hospitals, 19% received initial therapy to which their pathogen was not susceptible, and discordant therapy was associated with 1.46 times the odds of death [3]. A second study found that appropriate therapy was

delayed in 46% of resistant infections, and also in 33% of infections with susceptible pathogens [10]. Both studies are observational, so they show association rather than proof of cause. Nonetheless, taken together they suggest that the wrong first antibiotic is a routine event in hospital care, and not one confined to resistant pathogens.

19%

of 21,608 patients with bloodstream infections at 131 US hospitals received discordant initial therapy [3]

1.46x

the odds of death associated with discordant therapy [3]

Biotia's own data point in the same direction for urinary infection. In a retrospective study with SUNY Downstate, sequencing detected urogenital pathogens in 61.5% of culture-negative or mixed-culture specimens from symptomatic patients, and 85% of the antimicrobials prescribed empirically were ineffective against the pathogens detected, through off-target activity, partial coverage, or resistance [11]. These results come from a single center and have been reported as a conference abstract.

61.5%

of culture-negative or mixed-culture specimens from symptomatic patients had urogenital pathogens detected by sequencing [11]

85%

of empirically prescribed antimicrobials were ineffective (off-target, partial coverage, or resistance) [11]

THE COST OF USING THE WRONG DRUG

The two best-documented national estimates measure different things by different methods.

THE WRONG ANTIBIOTIC

\$2.2 billion a year [1]

What resistance adds to the cost of treating a bacterial infection (2014)

MEASURED FROM NATIONAL EXPENDITURE DATA

\$4.6 billion a year [2]

Inpatient care for six multidrug-resistant pathogens, compared with uninfected patients (2017 dollars)

MEASURED FROM A LARGE HOSPITAL COHORT

In our view, the first figure is the most relevant to a diagnostic decision, because it isolates what resistance adds to an infection that would have been treated anyway.

Per case, a hospital-onset invasive infection adds the following hospital cost compared with an uninfected patient, in Veterans Affairs hospital data [2]:

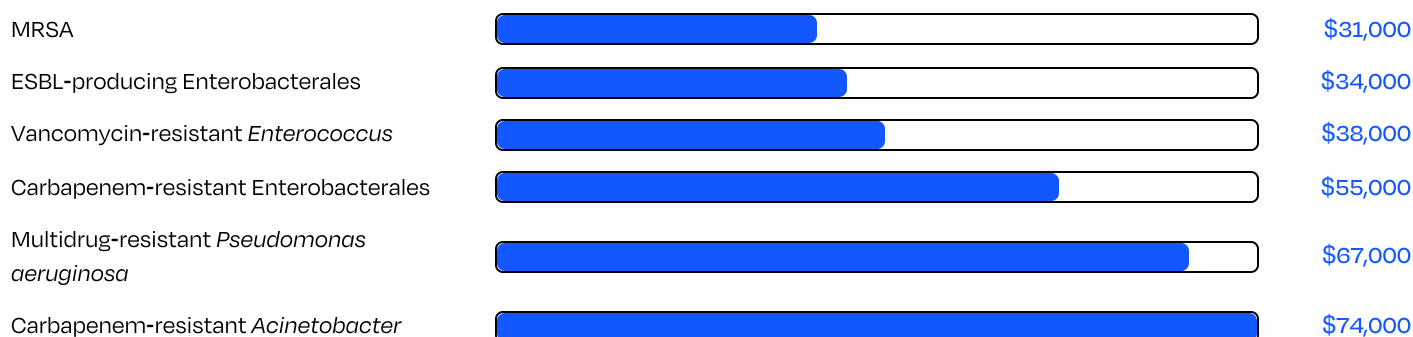


Figure 3. Added hospital cost per case of hospital-onset invasive infection, Veterans Affairs data [2].

These per-case figures, rather than the national totals, are the ones against which the cost of a diagnostic test should be weighed.

WHAT THE EVIDENCE SAYS ABOUT PAYING FOR BETTER DETECTION

If the cost of discordant therapy is real, the next question is whether better detection demonstrably reduces it. The evidence supports paying for better detection where a team acts on the result and where testing is targeted. It does not show that speed alone improves outcomes.

Speed alone has not been shown to save lives. Two US randomized trials of rapid diagnostics in bloodstream infection found that antibiotics were changed sooner, but found no difference in mortality or length of stay; neither trial was powered to detect such differences [12, 13]. A meta-analysis of 31 studies found lower mortality with rapid testing, and in its subgroup analysis the difference was statistically significant only where a stewardship program acted on results [14]. This suggests that a faster test is better understood as an investment in a workflow than as an investment in an instrument.

THE WRONG ANTIBIOTIC

Surveillance sequencing has paid for itself in at least one hospital. At UPMC Presbyterian, weekly whole-genome sequencing of healthcare-associated isolates over two years identified 172 outbreaks of 2 to 16 patients. The program estimated 62 infections and 4.8 deaths avoided,

net savings of \$695,706, and a 3.2-fold return on investment [4]. This is a single-hospital study and its savings are modeled from infections avoided. Nonetheless, it demonstrates that genomic data can function as operational infrastructure for infection control, and not only as a research tool.

3.2x

MODELED RETURN ON INVESTMENT

172

outbreaks identified over two years

62

infections and 4.8 deaths estimated avoided

\$695,706

net savings, modeled

Broad testing without targeting has had low yield.

A review of 1,000 plasma metagenomic tests (the Karius test) at one large academic center judged that results had a positive clinical impact in 16% of cases, a negative impact in 2% and none in 82%

[15]. Impact was higher for specific indications such as culture-negative endocarditis, which suggests that the value of metagenomic testing depends on where it is applied.

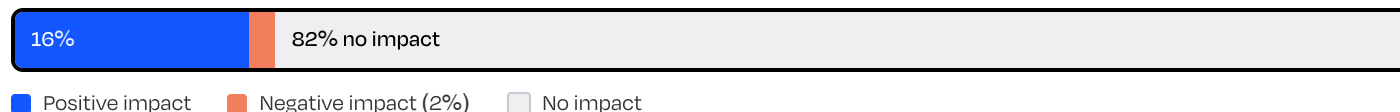


Figure 4. Clinical impact of 1,000 plasma metagenomic tests at one academic center [15].

TAKEN TOGETHER

These results indicate that the limiting factor has not been the technology itself, but the alignment between a test, the team that acts on it, and the budget that pays for it.

Who pays when the first antibiotic is wrong

The cost of discordant therapy is real, but it does not fall where the testing decision is made. Who absorbs it depends on the care setting and the insurer, and within the hospital, the department that pays for a test is usually not the one that sees its benefit.

THE WRONG ANTIBIOTIC

MEDICARE, MEDICAID, INSURANCE, INPATIENT AND OUTPATIENT

SETTING AND INSURER	HOW CARE IS PAID	IF THE FIRST DRUG IS DISCORDANT	WHO ABSORBS THE COST
Inpatient, traditional Medicare and most state Medicaid programs	One fixed payment per admission, set by diagnosis	Payment does not change unless costs pass an outlier threshold	The hospital
Inpatient, private insurance	Often per day, per case or as a percentage of charges	Payment rises with each extra day and drug	Largely the insurer
Outpatient, any insurer	Each visit, test and prescription billed separately	Each extra visit, drug or admission is billed	The insurer, and the patient's share each time

For Medicare, the outlier threshold in fiscal 2027 is about \$49,000 above the standard payment; Medicare then pays 80% of costs beyond it [16, 17]. Medicaid payment rules are set by each state. Private contracts vary, and the description above is a generalization.

VALUE AND PAYMENT SIT IN DIFFERENT PLACES

Inside the hospital, each department sees part of the picture:

DAY 0 Laboratory SEES The cost of each test and, for outpatients, the payer's reimbursement for it DOES NOT SEE What a right or wrong answer costs downstream	DAYS 1–5 Pharmacy and antimicrobial stewardship SEES The reserve antibiotic (a newer drug held back for resistant infections), at \$8,000–19,000 a course for the drug alone (7–14 days at \$1,200–1,400 a day) DOES NOT SEE The test that could have avoided or confirmed it	DAY 1 ONWARD Wards and finance SEES Extra bed-days and blocked beds DOES NOT SEE Which test result caused them	AT DISCHARGE Payer SEES A fixed payment, or the extra days DOES NOT SEE Which department spent or saved
--	--	---	--

Figure 5. What each party sees, in the order the costs of a single infection arrive.

THE WRONG ANTIBIOTIC

The laboratory's own accounts sharpen the problem. For hospitalized patients a test is pure cost, because it is bundled into the fixed payment. For outpatients the laboratory bills the payer and sees that reimbursement directly, and where a hospital expects its laboratory to break even or contribute a margin, each test is judged on whether payment covers its cost. A novel test that payers do not yet cover, or cover below cost, is therefore an uphill sell inside the laboratory even when it would save the hospital money elsewhere.

“A test is therefore usually bought on its cost, because its value appears in someone else's budget.”

This is important because it means the economic case for a better test cannot be made, or even observed, from within the laboratory alone; seeing the value requires analysis across departments.

THREE ILLUSTRATIVE SCENARIOS

The scenarios below show how the payment rules play out for individual patients. The dollar amounts and lengths of stay in the first two are illustrative, not drawn from a study.

SCENARIO 1 · ILLUSTRATIVE · INPATIENT · MEDICARE		
A Medicare patient readmitted with an MRSA infection after hip replacement		
	Concordant first drug	Discordant first drug
What happens	Stay of about 5–7 days	Stay of about 8–12 days, possibly a second operation
Payment	One fixed Medicare payment	The same payment, unless the outlier threshold is passed
Who pays the difference	—	The hospital, at up to about \$3,300 per extra day (the 2024 US average expense per inpatient day) [18]
Patient outcome	Recovery on the expected course	Longer stay, more post-acute care

THE WRONG ANTIBIOTIC

SCENARIO 2 · ILLUSTRATIVE · OUTPATIENT · PRIVATE INSURANCE		
A privately insured outpatient with a urinary infection caused by ESBL-producing <i>E. coli</i>		
	Concordant first drug	Discordant first drug
What happens	One visit, a culture, a generic oral drug	Emergency visit days later, then 3–4 days in hospital on an intravenous drug
Payment	A few hundred dollars	About \$10,000–25,000
Who pays the difference	—	The insurer, and the patient up to the out-of-pocket limit
Patient outcome	Symptoms resolve in days	Days untreated, risk of kidney or bloodstream infection

SCENARIO 3 · INPATIENT · ANY INSURER		
A hospitalized patient with a carbapenem-resistant Gram-negative bloodstream infection		
	Concordant first drug	Discordant first drug
What happens	Appropriate therapy on day 0: median infection-related stay of 8 days	Appropriate therapy after 1–4 days: 9–10 days; after 5 or more days: 13 days [19]
Payment	One fixed payment for publicly insured patients; per day or per case for privately insured ones	The same fixed payment for publicly insured patients, unless the outlier threshold is passed; rises with each extra day for privately insured ones
Who pays the difference	—	The hospital for publicly insured patients; the insurer for privately insured ones
Patient outcome	Recovery on the expected course	Longer stay, with more days on a drug that is not treating the infection

Rapid identification of the resistance mechanism may also affect survival. In a separate observational study of 137 patients with carbapenem-resistant Enterobacterales bloodstream infection at eight New York and New Jersey hospitals, 30-day mortality was 24% where the laboratory ran a rapid

test for a common carbapenemase gene (KPC) on positive blood cultures and 47% where it did not [20]. The study was not randomized, and we cannot rule out that hospitals running the test differed in other ways.

THE WRONG ANTIBIOTIC

The insurer also changes the hospital's financial result. In a 78-hospital, Merck-funded study of 1,488 patients with carbapenem-nonsusceptible Gram-negative respiratory infections, hospitals broke even on average (a mean loss of \$139 per

patient). However, the modeled result was a loss of about \$14,000 per Medicare case and \$48,000 per Medicaid case, against a gain of about \$15,000 per case for private and other payers [21].

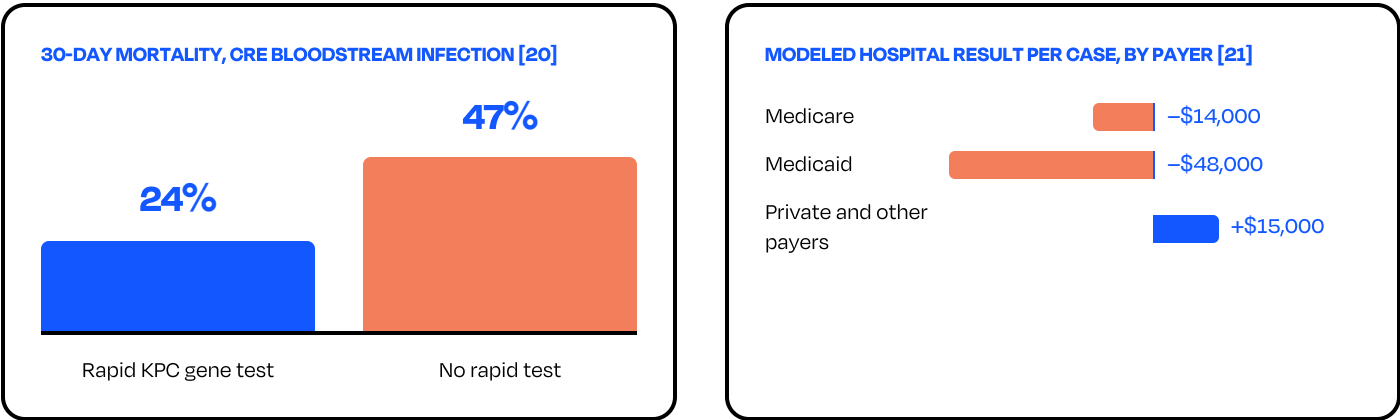


Figure 6. Left: observational, not randomized [20]. Right: modeled results from a 78-hospital, Merck-funded study [21].

WHAT A TEST IS PAID

Inpatient tests are bundled into the fixed payment and earn the laboratory nothing extra. For outpatients, Medicare pays by the test [22]:

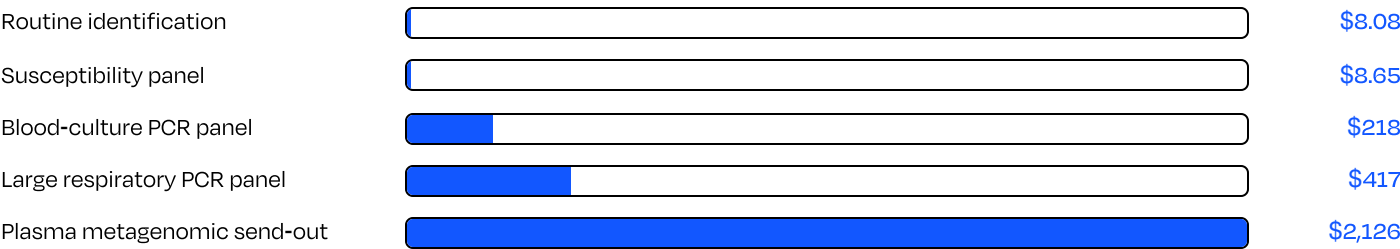


Figure 7. Medicare outpatient rates, 2026 [22]. The metagenomic send-out is paid about 260 times a routine identification.

These rates bear little relation to the value of the answer. Of note, a rate also does not guarantee coverage: some payers restrict large panels and

metagenomic tests.

THE WRONG ANTIBIOTIC

RESERVE ANTIBIOTICS PUT A PRICE ON A LABORATORY RESULT

Reserve antibiotics are last-resort drugs. The World Health Organization's classification defines its Reserve group as antibiotics that should be kept for

In US hospitals they are used mainly for infections resistant to carbapenems, a class of broad-spectrum antibiotics that are themselves kept for serious hospital infections, where standard drugs no longer work. A prescriber typically cannot order one directly; the antimicrobial stewardship team releases it, usually once laboratory results confirm that it is needed and indicate which one will work

confirmed or suspected infections caused by multidrug-resistant pathogens [23]. Hospitals restrict them for two reasons: using them sparingly slows the emergence of resistance to the few options that remain, and they are expensive.

or patients fail to improve on other drugs. The choice among them depends on the resistance mechanism the laboratory reports [24], and the mix of mechanisms is shifting: one family of carbapenemase (an enzyme that breaks down carbapenems), NDM, rose from 5% to 40% of carbapenemase-producing Enterobacterales in CDC surveillance between 2016 and 2023 [25].

5% → 40%

The mix is shifting: NDM rose from 5% to 40% of carbapenemase-producing Enterobacterales in CDC surveillance between 2016 and 2023 [25].

At one health system the newer reserve agents cost about \$1,200–1,400 a day in 2026, against about \$10 for meropenem, a standard carbapenem, so a course runs about \$8,400–9,600 for 7 days and \$17,000–19,000 for 14 days [26]. Wholesale prices in 2019 put a 14-day course at \$13,000–15,000 [26]. Under fixed payment the hospital absorbs that cost. A laboratory result that confirms or rules out the need for a reserve antibiotic is therefore one of the few with an obvious dollar value attached.

THE TWO PROGRAMS THAT ACT ON RESULTS

Two programs act on laboratory results: infection prevention and control, and antimicrobial stewardship. Both are required of hospitals that participate in Medicare; the stewardship requirement took effect in March 2020 [27].

Infection control handles surveillance, isolation and outbreak investigation, with a median of one preventionist per 121 beds [28]. Stewardship approves restricted drugs and reviews prescriptions against laboratory results. The regulations require that both programs exist but leave their design to the hospital, so their staffing, authority and day-to-day practice vary widely from one health system to another.

Neither program owns the laboratory budget, and the financial penalties attached to them are narrow: among resistant pathogens, Medicare's hospital-acquired condition penalties cover only MRSA bloodstream infection and *C. difficile* [29]. The groups best placed to act on a diagnostic result are therefore not the ones that purchase it, and most resistant pathogens carry no direct financial penalty that would prompt a purchase.

WHAT THIS HAS MEANT FOR DIAGNOSTIC VENDORS

The same mismatch has shaped the diagnostics market. Between 2023 and 2026, two of the best-known rapid-detection companies failed: Accelerate Diagnostics filed for bankruptcy in May 2025 and its assets were later sold to Bruker; T2 Biosystems announced liquidation in February 2026, having reported \$7.2 million in 2023 revenue

against a \$584 million accumulated deficit [30]. Two prominent genomic-prediction companies, Ares Genetics and Day Zero Diagnostics, ended as asset sales to bioMérieux [30]. For the two rapid-detection companies, a common thread is a product priced in the hundreds of dollars competing with an \$8.65 test inside a bundled payment.



Figure 8. Outcomes for four prominent detection and prediction companies, 2023–2026 [30].

The technological landscape

Hospital laboratories layer five kinds of detection technology. Although each newer method was introduced to overcome a limitation of culture, none has replaced it; each is added on top. This section describes the existing technologies, the gaps they leave, and the emerging approaches, many of them AI-based, that are aimed at those gaps.

EXISTING DETECTION TECHNOLOGIES

Two terms in the table need explanation. Phenotypic susceptibility testing exposes the pathogen to a drug and measures directly whether

it still grows. Metagenomic sequencing reads all the genetic material in a sample without first growing the pathogen; it is usually a send-out, meaning the sample goes to an outside reference laboratory.

Turnaround times run from sample collection and include the time the pathogen needs to grow. They are the authors' estimates (time for the culture to turn positive plus each method's run time), except for sequencing; a study of 13 US hospitals measured a median of 2.7 days from blood collection to a susceptibility result [32], and conventional susceptibility testing is commonly put at 48–96 hours after a blood culture turns positive [33].

THE WRONG ANTIBIOTIC

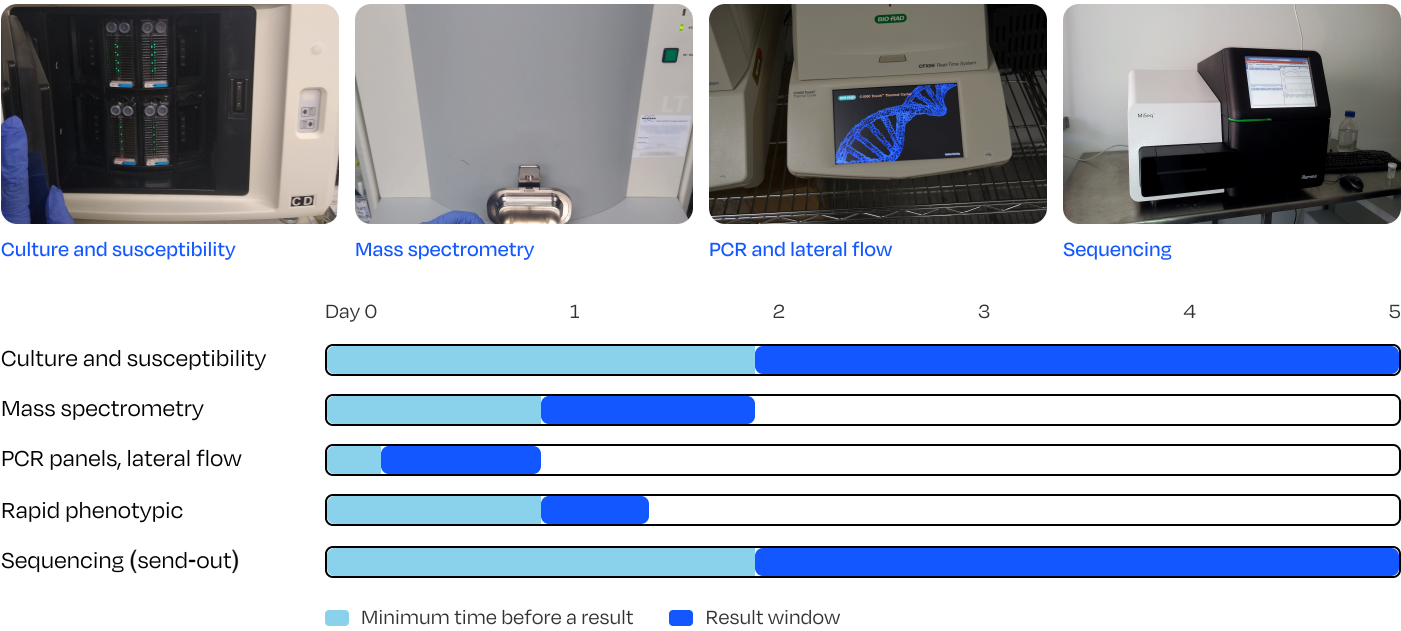


Figure 9. Approximate sample-to-result time for each technology, from Table 1. Sequencing shown as a 2–5 day send-out; isolate sequencing in one surveillance program took about 9 days [31].

Table 1. Detection technologies compared.

TECHNOLOGY	SAMPLE TO RESULT	COST	IDENTIFIES THE PATHOGEN	DETECTS RESISTANCE	REGULATORY STATUS
Culture and phenotypic susceptibility testing	2–5 days	Medicare pays \$8.65 [22]	Yes, after growth for species grown in clinical culture	Yes, measured directly	Cleared by the US Food and Drug Administration (FDA)
Mass spectrometry identification	1–2 days	Medicare pays \$8.08 [22]	Yes, minutes after growth	No	FDA cleared for identification
PCR panels and lateral-flow tests	About 1 day	Medicare pays \$218 [22]	Only pathogens on the panel	Only known genes on the panel	FDA cleared
Rapid phenotypic testing	1–1.5 days	About \$250 per test (2018 list price)	Limited panel	Yes, measured directly	Several more cleared since 2024
Sequencing	2–5 days	Typically \$200–300 for Biotia's send-out test	Any pathogen sequenced	Genes, and predicted susceptibility	LDT or RUO

THE WRONG ANTIBIOTIC

Three patterns matter for a purchasing decision:

Speed trades against breadth.

Mass spectrometry names the pathogen quickly but says nothing about resistance, whereas a PCR panel finds only the pathogens and genes it was designed to find.

Most methods still wait for growth.

For bloodstream infection, every routine method except direct-from-blood tests and metagenomic sequencing starts from a positive culture.

Sequencing sits outside FDA clearance for susceptibility.

It is offered as a laboratory-developed test, which shifts the burden of validation to the laboratory running it.

The practical consequence is that no single technology currently provides a fast, broad and inexpensive answer, and a laboratory's testing strategy is necessarily a combination of methods chosen for particular clinical situations.

WHERE EXISTING TECHNOLOGY FALLS SHORT

Existing tests handle resistance caused by a single gene well. However, they fall short when resistance has several combined causes, when nothing grows in culture, and when the pathogen is identified late or not at all.

Single-gene resistance is largely solved. MRSA, vancomycin-resistant *Enterococcus*, the common carbapenemases and rifampicin-resistant tuberculosis are each explained by one gene or a small set of mutations, and PCR detects them reliably.

Combinatorial resistance is not. Of 847 carbapenem-resistant *Pseudomonas aeruginosa* isolates tested in CDC surveillance, six carried a carbapenemase gene [34]. In the rest, resistance arises from combinations of changes, such as loss of the channel through which the drug enters the cell, and a gene panel has nothing to report.

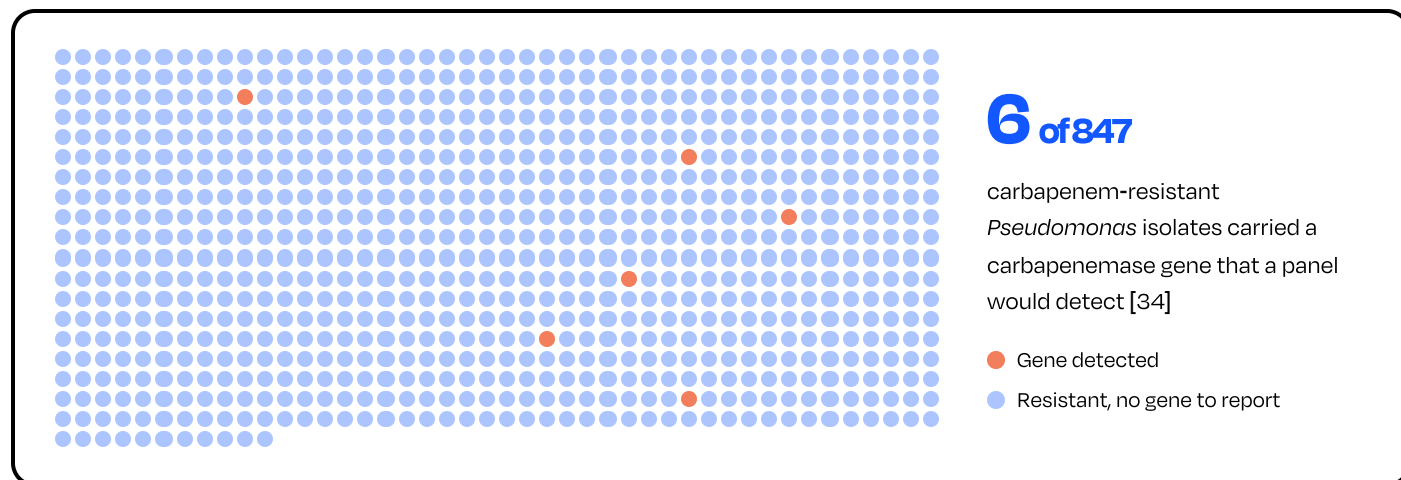


Figure 10. Each dot is one isolate. Position of the six gene-positive isolates is schematic.

THE WRONG ANTIBIOTIC

Many infections never produce a culture result.

About 47% of severe sepsis admissions are culture-negative [35], and no pathogen is identified in 62% of adults hospitalized with community-acquired pneumonia [36].

Some pathogens are not routinely sought or tested. Anaerobic bacteria, which grow only without oxygen, are the clearest case. Standard

urine culture is incubated in air, so anaerobes in urine are not looked for at all [8]. Where anaerobes are grown, they are rarely tested for susceptibility: in a 2008 survey, only 21% of hospital laboratories performed anaerobe susceptibility testing in-house [37]. We did not find a more recent US survey.

47%

of severe sepsis admissions are culture-negative [35]

62%

of adults hospitalized with community-acquired pneumonia have no pathogen identified [36]

21%

of hospital laboratories tested anaerobe susceptibility in-house (2008 survey) [37]

Identification itself arrives late or not at all. Culture needs growth, so often the first antibiotics are chosen empirically before the pathogen is known. Faster or broader alternatives exist, but they cost the laboratory far more to run: Medicare's outpatient rates, a rough proxy for cost, are 25 to 250 times the rate of a culture for tests that work directly from the sample or the blood-culture bottle [22]. For hospitalized patients, where most serious infections are treated, the laboratory receives no separate payment for any test (section 3), so that higher cost comes out of its own budget. These tests are also not available in every laboratory, and add transport time when sent out.

These gaps share a structure: in each, the information needed to choose the right drug is either not captured by current tests or arrives after the initial prescribing decision has been made.

EMERGING APPROACHES

AI is being applied to each of these gaps. The central challenge is the same in every case: converting incomplete or indirect evidence into a

prediction that can support a treatment decision.

Predicting susceptibility from the genome.

Machine-learning models take a sequenced genome and predict, drug by drug, whether the pathogen is susceptible. In principle, they are strongest where resistance is combinatorial and gene panels fail. As of October 2026, no sequencing-based susceptibility test has FDA clearance, to our knowledge, and the public data available to train such models is limited: the largest public collection holds 170,750 isolates, three species make up over half of it, and resistant isolates are over-represented [38].

Reading the patient instead of the pathogen. Host-response tests measure the patient's immune signals from a blood draw to judge whether an infection is bacterial at all and how severe it is. This addresses the first cause of discordant therapy (the wrong class of pathogen) and the culture-negative case. At least six such tests have been cleared or authorized by FDA since 2021, and one, TriVerity, also received a Medicare add-on payment for fiscal 2026 [39].

THE WRONG ANTIBIOTIC

Predicting from the health record. Models trained on a patient's history and local resistance patterns can recommend an antibiotic before any test result exists. In retrospective studies, past cultures and antibiotic purchases predicted resistance in 700,000 community urinary infections [40]; an algorithm reduced second-line antibiotic use by 67% relative to clinicians while reducing inappropriate therapy by 18% [41]; and "personalized antibiograms" (patient-specific versions of a hospital's table of local susceptibility rates) matched clinicians' coverage with narrower drugs [42]. However, we are not aware of a prospective randomized evaluation of any of them.

HOW AI CAN BE INCORPORATED INTO CLINICAL TOOLS

There are two ways an AI tool can reach clinical use and be paid for.

As a standalone product. The algorithm is itself the product: software that takes existing data, such as the health record, and returns a prediction, with its own regulatory clearance and its own payment. This route is rare and new. The first example in this field arrived in October 2026, when Medicare began a temporary add-on payment of up to \$61.84 per inpatient case for a software-only sepsis prediction tool [17].

\$61.84

Maximum temporary Medicare add-on payment per inpatient case for a software-only sepsis prediction tool, beginning October 2026 [17]. The first separate payment for an algorithm in this field.

As product-plus. The algorithm is built into something that is already bought and paid for: a test with a billing code, an instrument, or a laboratory workflow where it saves labor. Until this year, every AI tool in this field was paid for this way, and most still are. Genome-based susceptibility prediction and host-response scoring both follow this route, because the algorithm has no output without the assay that feeds it.

In either case, a hospital should evaluate AI on the same evidence as any other test or workflow.

AI-enabled results are most likely to earn their cost where they trigger a decision that someone already owns:

DECISION	OWNER	WHAT IS AT STAKE
Releasing a reserve antibiotic	Stewardship	An \$8,000–19,000 course
Lifting isolation	Infection control	Bed-days and staff time
Confirming or ruling out an outbreak	Infection control	Further transmission, and the cost of investigating

The practical importance of this framing is that it moves the question from whether an algorithm is accurate to whether its output changes a decision that already carries a cost and an accountable owner.

Implications for hospital leaders and laboratory directors

The following points are the authors' reading of the evidence above. We propose them as a framework for evaluating diagnostic investments, not as findings in themselves.

01

Measure discordant therapy, not only resistance.

The share of patients whose first antibiotic did not match their pathogen is a more complete measure of exposure than a resistance rate, and it can be computed from routine pharmacy and microbiology records [3].

02

Evaluate tests across budgets.

A test's cost falls on the laboratory and its benefit on pharmacy, the wards and, depending on the payer, the hospital's margin. A business case built inside one department will understate the value.

03

Know your payer mix.

The financial case for faster, better-targeted therapy is strongest where payment is fixed, which for most hospitals means traditional Medicare and most Medicaid inpatients.

04

Buy the workflow with the test.

In randomized trials, faster results changed antibiotics sooner but did not change mortality or length of stay, and the trials were not powered to detect such differences. In pooled studies, a significant mortality benefit was seen only where a stewardship program acted on results.

05

Target advanced testing.

Sequencing and metagenomic tests have shown value in outbreak surveillance and in specific culture-negative syndromes, and are the logical candidates where gene panels fail. Untargeted use has shown low yield.

06

Ask what decision a result changes.

For any new test, AI-enabled or not, the useful questions are which decision it informs, who owns that decision, and what that decision costs today.

More broadly, these points suggest that AMR detection should not be treated as an isolated laboratory function, but as a component of a hospital's wider infrastructure for prescribing, infection control and financial planning. When diagnostic results are coupled to the teams and budgets that depend on them, their value becomes both visible and measurable.

THE WRONG ANTIBIOTIC

About Biotia

Taking the guesswork out of infectious diseases.

Biotia is a health tech company advancing infectious disease diagnostics for challenging infections. We pair clinical metagenomics and artificial intelligence to develop diagnostic and software solutions that help patients, providers, and health systems respond to infectious disease threats, with testing in our own CLIA-certified laboratory in Long Island City.



DIAGNOSTIC TEST

BIOTIA-ID URINE

Clinical metagenomic detection of 44+ urogenital pathogens, including anaerobes and fungi that culture often misses, and 21 resistance genes from a single urine sample. 97% sensitivity and 99% specificity in an analytical validation study [43]. A New York State—approved laboratory-developed test, available in all 50 states.

FOR Patients, via a telehealth partner, and providers managing complicated or recurrent urinary infection

DIAGNOSTIC TEST

IN DEVELOPMENT

BIOTIA-ID JOINT FLUID

Metagenomic detection of pathogens and resistance markers in synovial fluid. Currently under development and not yet available for clinical ordering.

FOR Providers managing native and prosthetic joint infections

GENOMICS SOFTWARE

BIOTIA-ID ISOLATE

Identifies bacterial and fungal isolates from whole-genome sequence down to the strain level and predicts drug-resistance phenotype, with models covering more than 100 pathogen—drug pairs.

FOR Hospital and reference laboratories

GENOMICS SOFTWARE

BIOTIA-DX OUTBREAK

Compares the genomes of multiple isolates to identify clusters of related microbes, supporting outbreak detection and infection control.

FOR Infection prevention and control teams

References

1. Thorpe KE, Joski P, Johnston KJ. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding \$2 billion annually. *Health Aff (Millwood)* 2018;37(4):662–669. doi:10.1377/hlthaff.2017.1153
2. Nelson RE, Hatfield KM, Wolford H, et al. National estimates of healthcare costs associated with multidrug-resistant bacterial infections among hospitalized patients in the United States. *Clin Infect Dis* 2021;72(Suppl 1):S17–S26. doi:10.1093/cid/ciaa1581
3. Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. *Lancet Infect Dis* 2021;21(2):241–251. doi:10.1016/S1473-3099(20)30477-1
4. Sundermann AJ, Kumar P, Griffith MP, et al. Real-time genomic surveillance for enhanced healthcare outbreak detection and control: clinical and economic impact. *Clin Infect Dis* 2026;82(1):134–141. doi:10.1093/cid/ciaf216
5. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019. Atlanta: US Department of Health and Human Services, CDC; 2019. doi:10.15620/cdc:82532
6. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012–2017. *N Engl J Med* 2020;382(14):1309–1319. doi:10.1056/NEJMoa1914433
7. Kaye KS, Gupta V, Mulgirigama A, et al. Antimicrobial resistance trends in urine *Escherichia coli* isolates from adult and adolescent females in the United States from 2011 to 2019: rising ESBL strains and impact on patient management. *Clin Infect Dis* 2021;73(11):1992–1999. doi:10.1093/cid/ciab560
8. Price TK, Dune T, Hilt EE, et al. The clinical urine culture: enhanced techniques improve detection of clinically relevant microorganisms. *J Clin Microbiol* 2016;54(5):1216–1222. doi:10.1128/JCM.00044-16
9. Antimicrobial Resistance Collaborators (Murray CJL, Ikuta KS, Sharara F, et al.). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;399(10325):629–655. doi:10.1016/S0140-6736(21)02724-0
10. Bonine NG, Berger A, Altincatal A, et al. Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious Gram-negative bacterial infections. *Am J Med Sci* 2019;357(2):103–110. doi:10.1016/j.amjms.2018.11.009
11. Morfa Romero EJ, Augenbraun M, Rivera T, et al. 2835. Utilization of clinical-grade metagenomics in urinary tract infection diagnostics: improving high-risk patients' outcomes with a genomic-based assay. *Open Forum Infect Dis* 2023;10(Suppl 2):ofad500.2445. doi:10.1093/ofid/ofad500.2445
12. Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction–based blood culture identification and susceptibility testing. *Clin Infect Dis* 2015;61(7):1071–1080. doi:10.1093/cid/civ447
13. Banerjee R, Komarow L, Virk A, et al. Randomized trial evaluating clinical impact of RAPid IDentification and Susceptibility testing for Gram-negative bacteremia: RAPIDS-GN. *Clin Infect Dis* 2021;73(1):e39–e46. doi:10.1093/cid/ciaa528
14. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. *Clin Infect Dis* 2017;64(1):15–23. doi:10.1093/cid/ciw649
15. Kaur I, Shaw B, Multani A, et al. Real-world clinical impact of plasma cell-free DNA metagenomic next-generation sequencing assay. *Infect Control Hosp Epidemiol* 2025;46(5):504–511. doi:10.1017/ice.2024.242
16. Medicare Payment Advisory Commission. Hospital Acute Inpatient Services Payment System. Payment Basics, revised November 2025. <https://www.medpac.gov/document-type/payment-basics/> (accessed 9 October 2026).
17. Centers for Medicare & Medicaid Services. Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2027 Rates; final rule. 91 FR 49570, 4 August 2026 (document 2026-15833).
18. KFF State Health Facts. Hospital Adjusted Expenses per Inpatient Day (AHA Annual Survey, 1999–2024). <https://www.kff.org/health-costs/state-indicator/expenses-per-inpatient-day/> (accessed 9 October 2026).
19. Lodise TP, Kanakamedala H, Hsu WC, Cai B. Impact of incremental delays in appropriate therapy on the outcomes of hospitalized adult patients with Gram-negative bloodstream infections: "Every day matters". *Pharmacotherapy* 2020;40(9):889–901. doi:10.1002/phar.2446
20. Satlin MJ, Chen L, Gomez-Simmonds A, et al. Impact of a rapid molecular test for *Klebsiella pneumoniae* carbapenemase and ceftazidime-avibactam use on outcomes after bacteremia caused by carbapenem-resistant Enterobacterales. *Clin Infect Dis* 2022;75(12):2066–2075. doi:10.1093/cid/ciac354
21. McCann E, Sung AH, Ye G, Vankeepuram L, Tabak YP. Contributing factors to the clinical and economic burden of patients with laboratory-confirmed carbapenem-nonsusceptible Gram-negative respiratory infections. *Infect Drug Resist* 2020;13:761–771. doi:10.2147/IDR.S236026
22. Centers for Medicare & Medicaid Services. Clinical Laboratory Fee Schedule, calendar year 2026, fourth-quarter file (codes 87077, 87186, 87154, 87633, 0152U). <https://www.cms.gov/medicare/payment/fee-schedules/clinical-laboratory-fee-schedule-clfs/files> (accessed 9 October 2026).

23. World Health Organization. AWaRe classification of antibiotics for evaluation and monitoring of use, 2023. Geneva: WHO; 2023.
24. Infectious Diseases Society of America. IDSA 2026 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. Published 30 July 2026. <https://www.idsociety.org/practice-guideline/amr-guidance/> (accessed 9 October 2026).
25. Ansari UA, Campbell D, Brandenburg JM, et al. Increase in blaNDM among carbapenemase-producing, carbapenem-resistant Enterobacterales, United States, 2016–2023. *Emerg Infect Dis* 2026;32(6):1028–1030. doi:10.3201/eid3206.251404
26. (a) Allina Health Laboratories. Comparative Daily Costs for Common IV Antibiotics; costs as of February 2026. <https://labs.allinahealth.org/ima/ViewDocument?uid=1f9f2afe-9f3f-442c-b2a7-26ad1bd7748b> (accessed 9 October 2026). (b) Clancy CJ, Potoski BA, Buehrle D, Nguyen MH. Estimating the treatment of carbapenem-resistant Enterobacteriaceae infections in the United States using antibiotic prescription data. *Open Forum Infect Dis* 2019;6(8):ofz344. doi:10.1093/ofid/ofz344
27. 42 CFR 482.42(b). Medicare and Medicaid Programs; Regulatory Provisions To Promote Program Efficiency, Transparency, and Burden Reduction; final rule. 84 FR 51732, 30 September 2019 (document 2019-20736).
28. Bartles R, Reese S, Gumbar A. Closing the gap on infection prevention staffing recommendations: results from the beta version of the APIC staffing calculator. *Am J Infect Control* 2024;52(12):1345–1350. doi:10.1016/j.ajic.2024.09.004
29. Centers for Medicare & Medicaid Services. Hospital-Acquired Condition Reduction Program. <https://www.cms.gov/medicare/payment/prospective-payment-systems/acute-inpatient-pps/hospital-acquired-condition-reduction-program-hacrp> (accessed 9 October 2026).
30. Company filings and announcements: Accelerate Diagnostics, press release, 8 May 2025 (Chapter 11); Indaba Capital, press release, 24 November 2025 (sale to Bruker); T2 Biosystems, Form 10-K for fiscal year 2023 (revenue \$7.2 million; accumulated deficit \$584.3 million) and press release, 3 February 2026; OpGen, Form 10-K for fiscal year 2023, filed June 2024 (Ares Genetics insolvency, sale of assets to bioMérieux, April 2024); bioMérieux, press release, 16 June 2025 (Day Zero Diagnostics assets).
31. Waggle KD, Griffith MP, Rokes AB, et al. Methods for cost-efficient, whole genome sequencing surveillance for enhanced detection of outbreaks in a hospital setting. *PLoS One* 2026;21(9):e0355550. doi:10.1371/journal.pone.0355550
32. Tabak YP, Vankeepuram L, Ye G, Jeffers K, Gupta V, Murray PR. Blood culture turnaround time in U.S. acute care hospitals and implications for laboratory process optimization. *J Clin Microbiol* 2018;56(12):e00500-18. doi:10.1128/JCM.00500-18
33. Banerjee R, Humphries R. Rapid antimicrobial susceptibility testing methods for blood cultures and their clinical impact. *Front Med (Lausanne)* 2021;8:635831. doi:10.3389/fmed.2021.635831
34. Grass JE, Bulens SN, Bamberg WM, et al. 486. Epidemiology of carbapenem-resistant *Pseudomonas aeruginosa* identified through the Emerging Infections Program (EIP), United States, 2016–2018. *Open Forum Infect Dis* 2019;6(Suppl 2):S238 (conference abstract). doi:10.1093/ofid/ofz360.559
35. Gupta S, Sakhuja A, Kumar G, McGrath E, Nanchal RS, Kashani KB. Culture-negative severe sepsis: nationwide trends and outcomes. *Chest* 2016;150(6):1251–1259. doi:10.1016/j.chest.2016.08.1460
36. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373(5):415–427. doi:10.1056/NEJMoa1500245
37. Brook I, Wexler HM, Goldstein EJC. Antianaerobic antimicrobials: spectrum and susceptibility testing. *Clin Microbiol Rev* 2013;26(3):526–546. doi:10.1128/CMR.00086-12
38. Dickens E, Derelle R, Beardmore R, et al. A comprehensive AMR genotype-phenotype database (CABBAGE). *Nucleic Acids Res* 2026;54(16):gkag780. doi:10.1093/nar/gkag780
39. US Food and Drug Administration, 510(k) and De Novo databases: K210254, K203748, K220991, K230917, DEN230036, K241676. Centers for Medicare & Medicaid Services. Fiscal Year 2026 Hospital Inpatient Prospective Payment System final rule. 90 FR 36536, 4 August 2025 (document 2025-14681).
40. Yelin I, Snitser O, Novich G, et al. Personal clinical history predicts antibiotic resistance of urinary tract infections. *Nat Med* 2019;25(7):1143–1152. doi:10.1038/s41591-019-0503-6
41. Kanjilal S, Oberst M, Boominathan S, Zhou H, Hooper DC, Sontag D. A decision algorithm to promote outpatient antimicrobial stewardship for uncomplicated urinary tract infection. *Sci Transl Med* 2020;12(568):eaay5067. doi:10.1126/scitranslmed.aay5067
42. Corbin CK, Sung L, Chattopadhyay A, et al. Personalized antibiograms for machine learning driven antibiotic selection. *Commun Med (Lond)* 2022;2:38. doi:10.1038/s43856-022-00094-8
43. Couto-Rodriguez M, Danko DC, Wells HL, et al. Analytical validation of a highly accurate and reliable next-generation sequencing-based urine assay. *Microbiol Spectr* 2026;14(6):e0202625. doi:10.1128/spectrum.02026-25