LONGITUDE PRIZE | ON AMR

Implementing rapid diagnostic tests for UTIs in the UK healthcare system

CHALLENGE WORKS

June 2024

Challenge Works

Challenge Works is a global leader in designing and delivering challenge prizes that incentivise cutting-edge innovation for social good. As a social enterprise founded by Nesta, the UK's innovation foundation for social good, we have delivered 93 challenges to date and distributed more than £156 million to winning innovators.

About the report

Challenge Works interviewed expert clinicians, policymakers, academics and patients to understand how to best implement and use new urinary tract infection diagnostics.

We are thankful to the following people for their time: Betsy Wonderly Trainor, Alliance Director, CARB-X and Longitude Prize on AMR judge. Dr Carles Alonso-Tarrés, Head of Microbiology Laboratory, Fundacio Puigvert, Barcelona, Spain. Carla Benjumea Moreno, Microbiologist and PhD student, Fundacio Puigvert, Barcelona, Spain. Caroline Sampson, Joanna Diggle, Associate Practitioner, Public Health Wales. Kate Fordham, Antibiotic Research UK. Professor Matthew Inada-Kim, National Clinical Director for Infection, Antimicrobial Resistance and Deterioration and practising consultant. Michael Corley, British Society for Antimicrobial Chemotherapy. Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals NHS Trust. Sarah Heaton. Dr Sherry Taylor, GP Partner at NHS practice Temple Fortune Medical Group. Dr Tom Boyles, Infectious Disease Consultant at Helen Joseph Hospital, Johannesburg, South Africa and Longitude Prize on AMR Judge.

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Foreword

The Longitude Prize on AMR: Heralding a new era for diagnostic testing

Tris Dyson, Managing Director, Challenge Works

Antimicrobial Resistance (AMR) is a silent, growing and devastating pandemic. Following a century of inappropriate and untargeted use of antibiotics, bacteria have developed resistance to these lifesaving drugs at the heart of modern medicine.

In 2019, antibiotic resistant infections killed an estimated 1.3 million people around the world and contributed to the deaths of 5 million[1]. By 2050 it is predicted antibiotic-resistant infections will cause 10 million deaths annually. The World Health Organisation has declared AMR one of the top 10 global public health threats[2].

In 2014, Challenge Works launched the Longitude Prize on AMR to incentivise the creation of new point of care diagnostic tests that, in a matter of minutes, can identify whether an infection is bacterial, and if it is, the right antibiotic to prescribe.

The goal is to replace the 2-3 day lab test process that clinicians and patients must currently endure, and end "just in case" prescribing.

Following a decade of developments, and entries from more than 250 teams around the world, the £8 million prize has been awarded by Challenge Works to the PA-100 AST System from Sysmex Astrego. It is an innovative diagnostic test that has the potential to transform the treatment of urinary tract infections (UTIs) – which impact 50–60% of women[3] and are the most common bacterial infection seen in the NHS[4]. It brings the power of laboratory testing into a doctor's surgery.

By adding a patient's urine sample to a smartphone-sized cartridge containing a highly innovative nanofluidic chip, the PA-100 AST System can identify the presence of a bacterial infection in just 15 minutes and accurately identify the right antibiotic to treat it within 45 minutes.

This not only supports practitioners in their clinical decision making at the point of care but opens up the significant possibility of previously "retired" antibiotics coming back into use for

the majority of patients, since the test can demonstrate when they would be an effective treatment option.

It creates a future where patients can quickly and accurately get a diagnosis and the correct treatment, the first time they visit the doctor.

The Longitude Prize on AMR set out in 2014 to incentivise a new generation of innovators to develop urgently needed rapid, point of care diagnostic tests for AMR. In March 2023, the National Institute for Health and Care Excellence (NICE) recognised promise in four innovative tests for UTIs for use in the NHS[5], three of which were Longitude Prize competitors, including the PA-100 AST from Sysmex Astrego, Lodestar DX from Llusern Scientific[6]; and UTRiPLEX from Global Access Diagnostics[7].

Two of these tests, PA-100 and Lodestar DX are currently being evaluated for performance in UK GP surgeries as part of a study led by the University of Oxford. Once more data are available, the NICE committee will evaluate it and decide if the technologies can be recommended for early access in the NHS.

The Longitude Prize on AMR has done what it set out to, but in order for novel, game-changing medical technologies such as the PA-100 AST System to make a difference, they need to be successfully implemented and available in healthcare systems – including the NHS.

Whilst performance evaluations are under way, and we welcomed the recent Government announcement of £85 million to tackle AMR globally - including £1.8 million to support creating novel antimicrobials and diagnostics, this report sets out suggested approaches for successful roll-out of the Longitude Prize on AMR's winning test within the NHS. It also captures insights that could be relevant for implementing other new diagnostic tests in future.

The winning team's journey began in academia where it was focused on understanding the mechanics of bacteria. It first entered the prize in 2015 as Rivendell Fluidics, before the start-up Astrego was founded in 2017. The Longitude Prize on AMR shifted the team's focus to commercialisation of its research, shaping the development of the PA-100 AST System from the outset. Astrego went on to be acquired by a global healthcare leader – Sysmex Corporation – in 2022.

The conclusion of the Longitude Prize on AMR demonstrates how challenge prizes can incentivise breakthrough innovations to tackle challenges where solutions have not been forthcoming – levelling the playing field for new players and unusual suspects.

Tris Dyson
June 2024

Introduction

The scale of the problem

Uncomplicated urinary tract infections (UTIs) are an infection of the bladder. 50-60% of women will experience at least one episode during their lifetime and nearly one in three women will have had at least one episode by the time they are 24[8].

The most common treatment for UTIs is antibiotics. One fifth of antibiotics prescribed in 2019/20 (seven million prescriptions out of a total of 31.4 million) in England were for lower urinary tract infections, at a cost of £47.6 million to the NHS[9]. UTIs are the second most common cause of sepsis, a life-threatening condition which can occur if bacteria from the UTI enter the bloodstream[10].

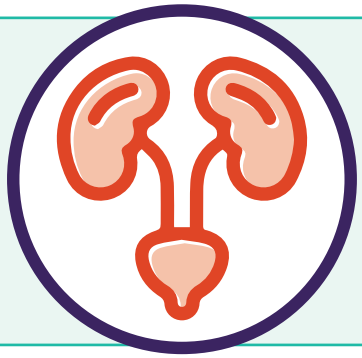
Professor Matthew Inada-Kim, Consultant Acute Physician and the National Clinical Director for Infection Management and Antimicrobial Resistance, notes urinary tract infections are one of the most common diagnoses in community settings and the most common infection that leads to emergency hospital attendance and admission[11].

He notes: "Infections are probably the most common reason for patients becoming ill and seeking help in community and hospital settings, and the NHS should prioritise optimising infection management including how they can be prevented, diagnosed, assessed and treated, minimising antimicrobial resistance through improvement strategies built on great data/evidence."

Dr Sherry Taylor, GP Partner at NHS practice Temple Fortune Medical Group in London comments: "UTI is one of the most common things we see in general practice – if you see 35 patients in one day, one or two will be for urine infections."

Impact of UTI on women

Around 60% of women will develop a UTI in their lifetime.



One in 10 women aged 18 and over report at least one presumed UTI annually.

In 20-30% of sepsis patients, the infection originates from the urinary tract.

> "UTI is one of the most common things we see in general practice – if you see 35 patients in one day, one or two will be for urine infections."
>
> Dr Sherry Taylor, GP Partner at NHS practice Temple Fortune Medical Group.

Symptoms such as burning urine and having to pass urine often, which are typical of a UTI, are not always caused by bacterial infection, in which case treatments that ease symptoms are needed, rather than antibiotics. And if there is a bacterial infection, it may not be killed by a particular antibiotic.

Currently clinicians base their diagnosis on patients' symptoms and sometimes a physical examination. They may also carry out a quick dipstick test on a urine sample. This gives a result – telling you about markers (such as white cells and nitrates) that might indicate a UTI – in a few minutes, but with low accuracy.

In order to find out which, if any, bacteria are present, and which antibiotic would be most effective, the clinician may send a urine sample off to a lab for analysis – waiting 3-5 days for the lab test result to be returned. In the meantime, if the dipstick test is positive and/or the patient showed very obvious symptoms of a UTI, the clinician may prescribe a broad-spectrum antibiotic. Broad-spectrum antibiotics can be less effective than narrower-spectrum, more targeted antibiotics.

The clinician may also have prescribed an antibiotic that is unsuitable for that particular infection, as some bacteria have developed resistance against some commonly-used antibiotics, and it takes days for GPs to get tests back about the sensitivity of bacteria to antibiotics. Using the wrong antibiotic and/or using them when they're not needed can create hard-to-treat antibiotic-resistant bacteria.

Although the practice of antibiotic prescribing with, or without, dipstick screening is widely used for UTI diagnosis, particularly in adult women under the age of 65[12,13], the resulting overuse and misuse of antibiotics is now considered to be a major contributor to the emergence of multi-drug resistant bacterial strains[14]. UTIs are the most common bacterial infection treated by the NHS – and up to half of infection-causing bacteria are resistant to at least one antibiotic.

Treating unplanned hospital admission for UTIs cost the NHS £386 million in 2017/18[15]. Drug-resistant microbes are difficult to treat, and they may be impossible to treat in vulnerable people or people with weak immune systems[16].

> "Management of UTIs is built around custom and practice and not well-evidenced, and is often based on evidence from several decades ago."
>
> Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals NHS Trust.

This is precisely why so many of the technologies that have come through the Longitude Prize on AMR have focused on UTI testing.

An accurate, rapid, easy-to-use, point of care test for UTIs can prevent clinicians prescribing precautionary and possibly ineffective antibiotics while they wait for a lab test result to come back. A quicker, more accurate test would tell clinicians there and then if the patient has a bacterial infection. This would inform their decision, potentially reducing prescription of antibiotics if the test was negative. If the test could also identify which antibiotic would be effective, it would enable a targeted antibiotic to be prescribed immediately.

Rapid tests such as the dipstick have existed for decades. Yet development of accurate rapid tests to identify the presence of urinary pathogens and inform the selection of an effective antibiotic has lagged in comparison with the advances made with testing other conditions such as cardiovascular, infectious and sexually transmitted diseases[17].

"Management of UTIs is built around custom and practice and not well-evidenced, and often based on evidence from several decades ago," remarks Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals NHS Trust.

Kate Fordham, Legacy Fundraiser, Antibiotic Research UK explains: "The dipstick test was introduced in the 50s and even then, clinicians were aware it wasn't going to be that accurate. Yet it is held up as the gold standard point of care test now in 2024.

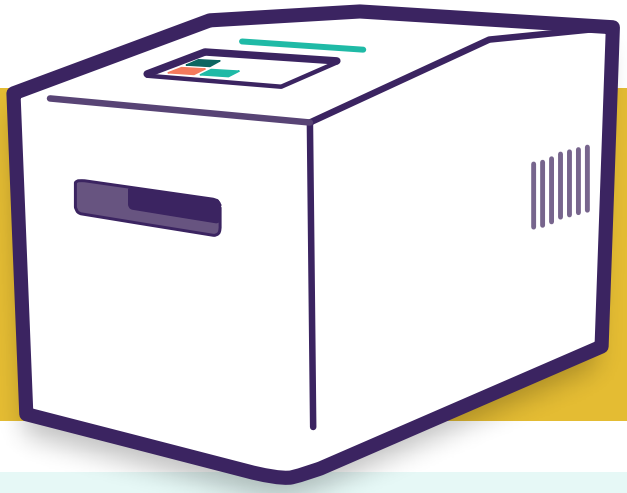
As Joanna Diggle, an Associate Practitioner at Public Health Wales who worked on a study of the Lodestar DX test, another Longitude Prize on AMR finalist, observes: "It's very easy to go to a doctor's surgery and feel like you're not being heard, especially with something like UTI which predominantly affects women. Better and more accurate testing than just a dipstick would have a profound effect on women's healthcare."

With such vast numbers of women experiencing UTIs, even small improvements in diagnosis and treatment will have a positive impact on many patients.

While lab-based tests for UTIs are accurate, they cause significant delays to diagnosis as they require the laboratory facilities and expertise of microbiologists and technicians and do not deliver the result in time to inform the prescribing practice of GPs. Considering the pattern of antibiotic prescribing in primary care is an important and modifiable driver of antimicrobial resistance[18], there is a clear need for accurate, easy-to-use and interpret, point of care tests[19].

Section 1

What value can the PA-100 AST System diagnostic test bring to the treatment of UTIs in the NHS?



"The first time I heard about this technology I was astonished...This does not exist anywhere else."

Dr Carles Alonso-Tarrés, Head of Microbiology Laboratory at Fundacio Puigvert, a university hospital in Barcelona, Spain.

"Potentially game-changing."

Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals NHS Trust.

"I describe it as an iPhone 1. It has the potential to make major strides. I'm sure the prize money will be used to upgrade it to an iPhone 10."

Dr Tom Boyles, Infectious Disease Consultant at Helen Joseph Hospital, Johannesburg, South Africa and Longitude Prize on AMR Judge.

The PA-100 analyser (Sysmex Astrego) is a revolutionary approach to testing that counts actual bacteria and observes whether they are killed by antibiotics in real-time – made possible by world-leading microfluidics and tiny tubules that filter urine and trap bacteria in single file. The test takes just 15 minutes to identify the presence of bacteria and 45 minutes to determine their sensitivity to antibiotics.

Computerised microscopy plots bacterial responses; if resistant, bacteria continue to replicate: doubling time is rapid. If resistant to an antibiotic, they swell up and die. This 'phenotypic approach' is the closest one can get to how antibiotic treatment would work in the actual patient and has many advantages to nucleic acid and biomarker-based tests such as dipstick.

It could transform UTI treatment by clinicians and nurses in GP surgeries, providing actionable information at the point of care in slightly adapted, but feasible and acceptable care pathways in primary care.

If bacteria are detected, the system assesses the susceptibility of five common urinary pathogens (*E. coli*, *P. mirabilis*, *K. pneumoniae*, *S. saprophyticus* and *E. faecalis*) for five antibiotics (amoxicillin-clavulanic acid, ciprofloxacin, fosfomycin, nitrofurantoin, trimethoprim[20]). This enables a clinician to identify the most effective treatment.

The microfluidics and light scheduling technology involved – described as a "lab on a chip"[21] – has been used in, for example, rheumatoid arthritis, multiple sclerosis and diabetes, but this is the first time it has been applied in UTI tests[22].

Enables more targeted use of antibiotics

Often antibiotics are prescribed based on the epidemiological patterns of resistance in urine samples submitted to the nearest hospital lab. This means taking into account past test results of the local population and the probability an antibiotic will be effective in that population[23,24].

However, most people do not get a lab test as usually only the most complicated cases are tested. So we don't know what the organism response will be in those with uncomplicated UTI.

Having actual results, for the individual patient, that determine sensitivity to antibiotics, available in time for the antibiotic decision, is an opportunity for a personalised approach: "It means that well-informed decision-making, previously only possible in health settings with laboratories available, is now feasible at primary care facilities including GPs," explains Betsy Wonderly Trainor, Longitude Prize on AMR judge and Alliance Director at CARB-X, a non-profit supporting the development of new antibiotics, diagnostics and preventatives to combat drug-resistant bacteria.

The introduction of a test that provides antibiotic susceptibility results within 45 minutes means we can look to a future of more accurate, targeted prescribing. This includes the use of narrow rather than broad-spectrum antibiotics, some of which may have been previously retired from use.

As Dr Tom Boyles explains: "Narrow-spectrum antibiotics have benefits for the patient in terms of limiting collateral damage to other beneficial bacteria in the body, particularly the microbiome in the bowel." In addition, older narrow-spectrum antibiotics can not only be used for longer, but their use extends the lifespan of newer antibiotics for the next generation.

Dr Carles Alonso-Tarrés, is Head of Microbiology Laboratory at Fundacio Puigvert, a university hospital in Barcelona, Spain. He led a PA-100 study to assess the performance of PA-100 against existing testing methods, using urine samples collected from patients with UTI symptoms, at the emergency department of his hospital.

Dr Alonso-Tarrés notes: "If you can give a narrow-spectrum antibiotic, the patient will benefit. It would benefit the community too as it would help reduce antimicrobial resistance - it would mean less severe infections and less expensive treatment."

> "It means that well-informed decision-making, previously only possible in health settings with laboratories available, is now feasible at primary care facilities including GPs."
>
> Betsy Wonderly Trainor, Longitude Prize on AMR judge and Alliance Director at CARB-X.

The benefit to patients

Rapid test results that can help prevent the development of chronic or severe UTI would be invaluable to patients.

Dr Brown comments: "We rarely talk about the impact of living with a drug-resistant infection. Most women who are affected are right in the middle of life, providing care for a child and possibly also for an elderly parent. They probably work as well. The burden on them is significant but mostly unspoken."

Sarah Heaton is a tutor and former English lecturer based in Leeds who has experienced chronic UTI on and off since the age of 5: "The dipstick is a stick that is unfortunately beating all patients at present. It is outdated and insufficient when it comes to the diagnosis and treatment of UTIs.

"Years of chewing down antibiotics that may or may not work has ultimately destroyed my body. It has led to my UTI becoming chronic, my gut suffering dysbiosis [imbalance], and me becoming resistant to all but two types of antibiotics. Had I had better testing, I truly believe I would not be in the position I am today."

Caroline Sampson, a tutor and proofreader based in Herefordshire, has had a chronic UTI for the past eight years. She explains: "Rapid tests are vital, without a shadow of a doubt. When you go into a GP surgery, they'll do a dipstick test which shows no infection because they aren't sensitive enough. You are then asked to come back if still unwell in two days, which you do, and then they send the sample off. So you've lost three to seven days, which risks the UTI becoming chronic and bacteria entering the blood. A friend's daughter's infection became chronic within three weeks because the testing was so inaccurate. We absolutely need on-the-spot accurate testing."

Dr Sherry Taylor further elaborates that women experiencing urinary symptoms that mimic a UTI may not necessarily have an infection but could be suffering from other non-infectious conditions such as interstitial cystitis (bladder inflammation). Therefore, the ability to quickly assess urine for bacteria would greatly assist GPs in offering appropriate treatment without resorting to unnecessary antibiotics, which can contribute to resistance and adverse effects.

"A friend's daughter's infection became chronic within three weeks because the testing was so inaccurate. We absolutely need on-the-spot accurate testing."

Caroline Sampson, tutor and proofreader.

Reduced hospitalisations

Effective UTI treatment from the outset prevents patients going on to develop complicated urinary tract infections or urosepsis (a life-threatening reaction to an infection). In addition to better clinical outcomes for the patient, prevention of more serious conditions preserves resources for the health system.

Dr Boyles explains: “People can get very sick from UTIs if you use the wrong antibiotic. They might end up in hospital with pyelonephritis, a severe and sudden kidney infection caused by bacteria ascending from the bladder to the kidneys. This test minimises that.”

Point of care tests for UTIs also provide economic advantages, saving the high costs of hospitalisation and repeat GP visits from mismanaged UTIs, and reduce laboratory workload[25].

“People can get very sick from UTIs if you use the wrong antibiotic. They might end up in hospital with pyelonephritis, a severe and sudden kidney infection caused by bacteria ascending from the bladder to the kidneys. This test minimises that.”

Dr Tom Boyles, Infectious Disease Consultant at Helen Joseph Hospital, Johannesburg, South Africa and Longitude Prize on AMR Judge.

Improving clinicians' confidence in decision-making

If successfully integrated into clinical practice the test should be a ground-breaking boost to clinicians' confidence in the diagnosis they can provide.

"The fact you can do the test at the point of care is a real benefit," says Dr Boyles.

"Firstly, the test confirms if there are any bacteria in the urine, which is useful. Then it exposes these bacteria to antibiotics and sees if they carry on growing or if they die. This is essentially what a lab does, but the PA-100 test does it using microtubes in 45 minutes."

Dr Boyles explains that previously testing a patient's sensitivity to antibiotics would need to be done by a scientist or technician who would plate the urine out onto a petri dish and look down a microscope, ahead of putting it in an incubator for 24 hours and manually interpreting the result. From here, they enter results into a computer and get it relayed back to the clinician or GP. "That whole process is condensed into this short 45-minute period of time."

Dr Brown adds: "Most GPs write a prescription with the patient in front of them while making a clinical diagnosis. It's an informed guess backed by local and national guidance. Do they have an infection or not? If so, what is the cause and what antibiotic would be appropriate?"

With the national resistance rate to commonly used antibiotics hitting 10%[26] (and in some cases higher than that), Dr Brown explains this means one in ten patients get the wrong antibiotics.

Moreover, in some cases, the patient's symptoms are not due to an infection so patients may be getting an antibiotic for an infection they don't have and not being treated for the actual cause of their infection.

"Many people are given antibiotics inappropriately and the treatment of infection is delayed by several days until the urine culture results come back. That's assuming the patient returns to get the results. A point of care test has immediate appeal because you receive the results at the point of initial consultation," comments Dr Brown.

> "Most GPs write a prescription with the patient in front of them while making a clinical diagnosis. It's an informed guess backed by local and national guidance."
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> Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals.

The PA-100 test will enable clinicians to provide informed prescriptions to tackle the actual infection present.

Dr Taylor notes that she often sends for a lab culture regardless of the dipstick result: "I send the sample off for analysis and it usually takes around 3 days to come back with results, if we get results back that differ to our prescription then we have to ring the patient back to change them to the correct antibiotic.

"Having a bedside test that would enable rapid diagnosis and look at antibiotic susceptibility would revolutionise general practice and patient care. It would be amazing – it's all about using antibiotics only when necessary and appropriate."

Dr Brown says: "Giving the right antibiotic as quickly as possible improves patient outcomes, not only in terms of the time it takes for symptoms to get better, but in terms of rare but significant complications like sepsis and hospital admissions."

It's easy to use, accurate and affordable

The test needs to be accurate[27], easy-to-use and affordable. It is the combination of these three elements, reflected in the Prize judging criteria, that make this a valuable test. Wonderly Trainor describes the developers' approach: "There are three key constraints you work to as a developer - ease of use, affordability and accuracy. This is hard to achieve in a single product. The PA-100 has done a really nice job of trying to balance delivering accurate, timely results in a clinical setting."

With a turnaround time of 45 minutes, in theory, it would be possible for patients to take the test, leave the surgery and shortly after receive a text with instructions for a targeted antibiotic prescription, if needed. There are many feasible ways in which PA-100 could fit into slightly tweaked, existing care pathways.

Conducting the test and analysing the results themselves also offers clinicians the opportunity to increase their understanding of the condition and its treatment. "Using the analyser itself will be pretty easy," says Carla Benjumea Moreno, Microbiologist and PhD student in Dr Alonso-Tarrés's team at Fundacio Puigvert: "It's so intuitive, it's not difficult. What I think may be more troublesome is interpretation of the results, because not everybody is trained to interpret."

As well as being simple to use, the PA-100 is fairly small, at 20×22×36 cm, which is helpful when it comes to accommodating it in clinical settings.

Dr Taylor says: "As it's nice and compact we'd likely store it in our nurses' room alongside our other equipment. This central location makes it convenient for all clinicians to locate and use when needed."

Dr Boyles details the potential and parameters for use in low-income settings: "The test could be used in many low-resource settings that can afford it and have a power supply, which many do. It can be used in hospital casualty departments. It's easy to use and could be carried out by lay workers which is more cost effective."

Lodestar DX – Longitude Prize Finalist

The Lodestar DX test detects six common UTI-causing bacteria (*E. coli*, *Klebsiella spp*, *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Enterococcus spp*, *Pseudomonas aeruginosa*) in around 40 minutes. The manufacturer, Llusern Scientific, says that the technology does not yet have regulatory approval, but that this is expected within 12 months.

Joanna Diggle is an Associate Practitioner at Public Health Wales. She was also part of the team to develop the Lodestar DX test. She comments: "I've come into contact with loads of different tests, with varying degrees of difficulty, and I don't think it could get any simpler.

To take a fresh urine sample and get a result within 40 minutes for the top bacterial targets is excellent. It is about speed and ease of use. But also you get to the most important end-goal without having to go through all the initial steps, which is the case with the main culture method."

Importantly, the Lodestar Dx units are small at 14×20×9 cm, meaning that space can be found for them in most clinical settings. Diggle notes: "There's no space in clinical settings to put in anything big but the Lodestar is so small you could fit between two and four of them on a tiny bench space. The bigger, more expensive, fancy machines can't fit in. This one slots in perfectly."

> "I've come into contact with loads of different tests, with varying degrees of difficulty, and I don't think it could get any simpler."
>
> Joanna Diggle.

Section 2

What needs to change in clinical pathways to ensure successful roll-out of the PA-100 AST System diagnostic test?

Support for take-up amongst clinicians

Adopting the test into clinical practice will involve financing it, training clinicians on its use and adjusting day-to-day practice to incorporate it into diagnosis and treatment decisions, tailored to each patient population.

Early engagement with clinical professionals is essential when introducing novel technologies into clinical practice, as well as clear evidence on which patient groups the test performs best for (based on the NICE evaluation). Initial support through central funding and other resources will also be required.

“The most important thing is clinical buy-in,” says Professor Inada-Kim, “It is vital that clinicians who carry the risk with managing patients with suspected infections are fully recognised and consulted in all organisations. Additionally, for these diagnostic innovations to take hold, we must support organisations in collecting the data and eventually prove some element of sustainability in terms of costs.

“Infection management is complex and there are often multiple factors affecting patients. Clinicians may not have all the information required, and diagnostic tests are imperfect, meaning clinical judgement to determine the likelihood of infection and its severity is crucial.”

A comprehensive approach

> "What we really need is a model for intervention that works and is viable economically but also in terms of professional practice."

Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals.

Professor Inada-Kim stresses the importance of finance, "We have to think about costs, and who funds this venture. Is this something you have to derive from local funding, from the national pot or from industry?"

Dr Brown says "If the investment is made by one group [GP surgeries] and the savings made by another [NHS England] then you need a top-down approach to the problem in economic terms.

"We've gone through several generations now of determining health priorities locally, with local delivery and local budgets, but there are still some national programmes for health problems which are big enough and complicated enough to require a national deal."

Dr Brown explains that the diagnostic tests that have been released have overall been more expensive than the antibiotics that they're meant to be replacing: "So this is a potentially costly alternative to just giving everybody antibiotics.

"Any benefit to the whole healthcare system might be difficult to demonstrate if the system is working to full capacity all of the time. This will be a challenge when making the case for adoption. We can measure individual patient benefit by looking at indicators such as duration of symptoms, GP re-attendance rates and repeat antibiotic prescriptions, but wider benefits are more challenging to evidence.

"With any diagnostic test, it's important to learn about the test performance and which patient group it performs best in. The ability to rule-in or rule-out an infection depends very critically on the prevalence of UTI in the population of people to be tested. If you test the wrong people, you'll get misleading results and you'll be back to square one."

The lack of success of previous point of care tests intended to counter overuse of antibiotics, such as the strep-A and C-reactive protein blood tests, highlight the need for a well-planned model for intervention.

Dr Brown says: "What we really need is a model for intervention that works and is viable economically but also in terms of professional practice.

"The rapid tests for strep-A didn't work very well because of lack of know-how about how to use them properly.

"More recently the C-reactive protein test was meant to be rolled-out to general practices as a point of care test and that hasn't been widely adopted because the funding model wasn't sufficiently persuasive – GP practices had to fund it themselves – whereas the drug bill for prescribing an antibiotic gets funded from another route outside the practice."

The C-reactive protein blood tests reduced antibiotic prescribing but only when accompanied by clinical guidance[28].

An ideal roll-out model should be drawn up in close consultation with clinicians and patient groups, and cover both the application of, and funding for, the test. This is important to ensure the test is adopted widely, consistently and sustainably.

> "We've gone through several generations now of determining health priorities locally, with local delivery and local budgets, but there are still some national programmes for health problems which are big enough and complicated enough to require a national deal."
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> Dr Nick Brown, Consultant Medical Microbiologist, Cambridge University Hospitals.

Section 3

Recommendations to support introduction of novel point of care UTI tests in the UK

There is a need for increased use of point of care tests for UTIs, respiratory tract infections, blood infections such as sepsis and infected wounds – and there are clear steps required for their effective implementation, scale-up and optimisation.

1. Effective implementation

Implementation studies need to be run with early adopters. These should be designed to yield additional real-world data and demonstrate the impact of these tests, as well as to understand how they can best be positioned within the system.

- It will be easier to carry out studies and evaluate the impact in facilities that see large volumes of UTI patients. For example, infection/ARI hubs with a catchment population of between 50,000 to 250,000. In practice this could be either a physical facility that sees that volume of patients within its building, or local networks (for example, Primary Care Networks which offer services on behalf of multiple GP practices).
- UTI patients should either be given the existing standard of care for UTI or have a consultation with access to the novel test. This should be done on a randomised basis to allow for comparison to the existing standard, to determine the benefit of the test.
- There needs to be assessment of improvements in the quality of patient care and outcomes as well as measures of patient and staff satisfaction.
- Also needed are studies to determine cost benefit, taking into consideration reduced repeat visits and wider cost savings from reduction in hospitalisation/urosepsis and chronic UTIs.

A number of interviewees recommend discreet central funding to overcome reluctance to allocating increased funding to primary care diagnostics.

Call to Action – NHS England and NHS Wales to convene a roundtable to gain input on implementation studies and estimate funding required for projects, possibly involving organisations such as National Institute for Health and Care Research (NIHR) (via the Department of Health and Social Care AMR Research Co-ordination Group) for specific site identification. This should be followed by an effort to identify study sites and provision of support to study leaders.

2. Successful scale-up

- Based on data generated from these implementation studies, and other performance studies, a 'model of intervention' could be developed so that new diagnostic tools are implemented in the most effective manner possible. This will need to include a protocol that defines the profile of patients (age, sex, and so on) among whom the test is most effective.
- Early engagement with clinicians, policymakers and the public to support uptake of new UTI tests and greater understanding of the urgent need for them, especially as a women's health equity issue.
- Additional access points to novel point of care tests such as pharmacies and diagnostic hubs need to be explored.

3. Future developments

The current target population for the PA-100 test is adult women (18 and over). However, advances could be made in the technology to support effective diagnosis of infections amongst women over 65.

Care home environments in particular are a key driver of AMR[29,30]. Overuse and misuse of antibiotics leads to AMR among care home residents.

This is an intrinsically more challenging patient population because it is more common to have bacteria present in urine when the patient is asymptomatic (due to catheterisation, urinary incontinence and urinary retention), leading to overprescription of antibiotics[31].

Dr Alonso-Tarrés notes: "Many people get frequent UTIs in long-term care settings. Normally they are given broad-spectrum antibiotics and a test isn't even done. If it is done, it will be a test strip (a dipstick). UTI is frequent in patients in this setting, and 40% of them have a multi-drug resistant strain because of antimicrobial use and frequent contact between each other from sharing equipment and space. Among these microorganisms, there are methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-producing *Klebsiella pneumoniae*, multidrug resistant Pseudomonas aeruginosa or *Acinetobacter* and others. It would be very useful in this setting."

Betsy Wonderly Trainor notes that she would like to see pathogen ID (ability to identify the specific pathogen(s) causing an infection) in a future version of the PA-100 test: "Because there are some pathogens that have intrinsic resistance which means they are naturally resistant to certain antibiotics, but give a susceptible result. So pathogen ID, at least for a few key priority pathogens in addition to the phenotypic antibiotic susceptibility testing, would make their product even stronger."

Another benefit of pathogen ID is to correctly identify polymicrobial infections (i.e. infection caused by combinations of viruses, bacteria, fungi, and parasites[32]) without triggering prescriptions for unnecessary antibiotics by failing to recognise contaminated urine specimens[33]. For this, the antibiotic susceptibility result needs to sit alongside correct organism identification. This would be of particular value for older people (including those in care home settings), people whose immune system is compromised and those with a catheter.

Sysmex Astrego is already investigating whether PA-100 test is useful for treatment of elderly populations, focussing on diagnostic sensitivity and specificity.

Conclusion

When it comes to AMR, no-one is safe until everyone is safe

Michael Corley, Deputy Chief Executive Officer at British Society for Antimicrobial Chemotherapy

> "The recognition of the PA-100 AST System as the winner of the Longitude Prize on AMR is monumental."

Getting the right drug to the right person at the right time is at the heart of the challenge when it comes to improving patient outcomes and preventing the rise of antimicrobial resistance.

To meet this challenge, we need affordable diagnostics and effective antibiotics to manage infection, alongside much more powerful prevention measures – starting with all healthcare settings having access to clean water, sanitation and hygiene facilities.

In the UK, we know at the moment we're luckier than most, but we're far from immune to the growing threat. When it comes to AMR, no-one is safe until everyone is safe.

While we are aware that many common infections contribute to the spread of resistance in the UK (respiratory tract infection, blood infections such as sepsis, and infected surgical sites), it may be that improving diagnosis and treatment of the common urinary tract infection is where we start to win the battle.

UTIs are the most common bacterial infection treated by the NHS in England – and up to half of infection-causing bacteria are resistant to at least one antibiotic.

It has taken nearly 60 years for a new generation of UTI technology to be developed. In that time, millions of women have suffered continuous pain and infection, with many going on to develop resistant infections and recurrent symptoms.

The recognition of the PA-100 AST System as the winner of the Longitude Prize on AMR is monumental. Awarding the prize to this technology marks a turning point in which clinicians can be better equipped to diagnose and treat patients. It is possible that the ground-breaking technology underlying this test for UTI could also be applied to other infections and other patient populations for even greater impact.

The Longitude Prize on AMR has been instrumental in advancing the progress of this new generation of tests. Beyond PA-100, two other contenders for the prize are being considered by NICE for conditional roll-out in the NHS, while further data on performance is being generated.

But what next? We can see from this report that implementing a new technology into an already overburdened NHS isn't easy. Where can the funding come from? Who can take on the commitment of further trials, and how soon will we start to see the results?

We hope that if this innovative, transformational diagnostic test can make it to the hands of the brilliant doctors, nurses and maybe one day even pharmacists, at the heart of our health system – it will be a first step towards containing and controlling the existential threat of antimicrobial resistance, while improving the quality of life for millions of long-suffering people.

Michael Corley
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