# Addressing Antimicrobial Resistance with Digital Approaches 3

# Innovative diagnostic technologies: navigating regulatory frameworks through advances, challenges, and future prospects

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**Diagnostic tools are key to guiding patient management and informing public health policies to control infectious diseases. However, many diseases still do not have effective diagnostics and much of the global population faces restricted access to reliable, affordable testing. This limitation underscores the urgent need for innovation to enhance diagnostic availability and effectiveness. Developing diagnostics presents distinct challenges, especially for innovators and regulators. Unlike medicines, regulatory pathways for diagnostics are often less defined and more complex due to their diverse risk profiles and wide range of products. These challenges are amplified in low-income and middle-income countries, which often do not have regulatory frameworks for this specific purpose. In the UK, initiatives aim to support innovation by providing clearer regulatory pathways and ensuring that diagnostics are safe and effective. Regulators are also collaborating internationally to expedite diagnostics for high-need regions. Harmonised standards, regulatory frameworks, and approval processes are essential to ensure consistent quality and safety across regions and facilitate faster development and global access. This Series paper explores the regulatory challenges in infectious disease and antimicrobial resistance diagnostics, focusing on the UK's response and the broader global efforts to address these issues.**

## Introduction

The global landscape of medical devices includes an estimated 2 million devices across 7000 generic device groups that are regulated by about three to four risk classifications.[1] Despite this extensive range of technologies and regulatory framework, much of the world's population lacks access to diagnostic testing and affordable, appropriate medical devices. This unavailability underlines the current key disparities in health-care infrastructure, particularly in low-income and middle-income countries (LMICs), where reliable diagnostic tools remain largely inaccessible.[2]

Innovators in the diagnostic space face substantial hurdles due to the intricate and fragmented nature of the regulatory approval processes and the lack of harmonisation between countries and regions. The absence of clarity often results in repetitive, burdensome, and costly requirements and submissions, causing delays in the adoption of innovative technologies and impacting commercialisation. This challenge is particularly pronounced for emerging technologies, such as those that incorporate software based on machine learning, where innovation outpaces regulation. During the COVID-19 pandemic, regulatory agencies responded to the urgent need for rapid evaluation and approval of novel diagnostics by using both existing and innovative approaches.[1] However, some of these processes were implemented due to exceptional circumstances and might not have long-term relevance. Despite the urgency, requirements were rarely harmonised internationally, nor authorisations recognised between jurisdictions. Nonetheless, this experience shed light on areas where changes could enhance broader challenges for diagnostic development during unexpected medical occurences, such as pandemics.

In response to these challenges, the UK has introduced the new Medicines and Healthcare products Regulatory Authority (MHRA) Innovative Devices Application Pathway (IDAP), which is aimed at streamlining and expediting diagnostic regulatory approval and health-care adoption.[2] IDAP seeks to reduce bureaucratic obstacles and accelerate access to innovative diagnostics, and reflect on knowledge gained during the pandemic.

A key barrier to progress in diagnostic innovation, particularly in antimicrobial resistance (AMR), is the absence of representative data for informed clinical decision making.[3] AMR diagnostics face difficulties in obtaining high-quality, consented, and well characterised samples for validation and testing. Data connectivity challenges are especially pronounced in LMICs, where intranational and international infrastructure deficiencies and no system harmonisation further impede innovation.[4] Many emerging tools rely on data connectivity and interoperability between health information systems, including electronic health records (EHRs), to collect and transmit data between providers and databases. Suboptimal infrastructure hinders the

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integration of these tools into existing health-care systems, underscoring the need for shared data platforms and open, interoperable EHRs. However, concerns regarding data security and privacy continue to impact the feasibility of innovative diagnostic initiatives.

Regulatory clarity is another key requirement for innovators, who often have no guidance on the clinical gaps that new products should address. Engagement with health technology assessment (HTA) organisations, such as the National Institute for Health and Care Excellence (NICE) in the UK or WHO for LMICs, is essential to ensure that diagnostic technologies are developed with clear, evidence-based use in mind. Broader collaboration between innovators, clinicians, HTA bodies, and policy makers can enhance the design of diagnostic tools and maximise their potential impact.

Funding remains a large challenge, particularly in meeting the costs associated with regulatory approvals and HTA submissions. Innovators often face difficulties securing downstream funding, and tend to focus on producing a viable test rather than covering the costs of navigating regulatory and HTA pathways. Including costs for these aspects within the original funding could prevent promising diagnostics from stalling at these crucial stages. The new EU in-vitro diagnostic regulation introduces a shift towards value-based care by requiring developers to show clinical benefit, which adds further financial and operational complexity.[5] However, this shift also allows for innovative and flexible funding models that can facilitate evidence generation and sustain products through the regulatory pathway.

For more on the **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use** see https://www.ich.org/

Clarity from regulators on specific requirements is essential. The COVID-19 pandemic highlighted how early and consistent engagement with regulators can facilitate the accelerated approval of diagnostics. The new MHRA IDAP builds on the knowledge that was gained and, alongside the MHRA Innovation Office, provides the clarity and communication channels that are necessary for new and emerging technology. Its recent launch means that it is too early to present a specific case of an innovative diagnostic that has been approved through the IDAP; however, this framework is anticipated to streamline the approval process for cutting-edge diagnostics in much the same way as the US Food and Drug Administration's (FDA) Breakthrough Devices Program and Safer Technologies Program. Through these programmes, the FDA has shown successful collaboration between innovators, regulators, and industry. Both initiatives continue to expedite the review and approval of cutting-edge medical technologies, which facilitates quicker market entry. Additionally, the FDA's pre-submission programmes foster early engagement between innovators and regulators, making the regulatory process more transparent and predictable, and thereby ensuring that innovative diagnostic technologies reach patients faster while maintaining safety standards.

Although the MHRA IDAP and the FDA's Breakthrough Devices Program each address many challenges of getting products into domestic markets, challenges persist regarding wider adoption, especially in LMICs.

## Global and equitable access to reliable diagnostics

Many LMICs do not have functional national regulatory authorities (NRAs) for medical devices,[6] which impacts access (pre-market assessment) and product quality and safety (post-market control). To address issues around the quality and availability of in-vitro diagnostic devices (IVDs) in LMICs, the WHO prequalification programme opened to IVDs in 2010. Since then, the programme has prequalified more than 100 IVDs and established itself as a symbol for safe, high-quality, and effective medical products.[6] However, only 15 types of medical device are eligible for assessment by WHO prequalification, with most being ineligible. Furthermore, general requirements for market access and procurement necessitate stringent regulatory authorisation by one of the founding competent authorities in the Global Harmonization Task Force (GHTF; the EU, the USA, Canada, Australia, and Japan), which disadvantages most regional manufacturing efforts and undermines the regulatory reform efforts of NRAs.

In 2012, GHTF activities were taken over by the International Medical Device Regulators Forum (IMDRF). Similar to the efforts of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use to harmonise and collaboratively evolve medicines regulation, as quoted from the GHTF Mission Summary, IMDRF encourages "the convergence in regulatory practices related to ensuring the safety, effectiveness/performance and quality of medical devices, promoting technological innovation and facilitating international trade, and the primary way in which this is accomplished is via the publication and dissemination of harmonised guidance documents on basic regulatory practices".[7] Although stringent assessment by a GHTF founding member will generally provide an assurance of product quality, the unmet medical needs, specific risks, and performance requirements of LMICs are not considered. The establishment of WHO Listed Authorities for medical devices and IVDs could, at some point in the future, provide a viable alternative to the present reliance on GHTF founding member authorisations. However, the scale of the regulatory challenge presented by medical devices is still likely to be too burdensome for most low-income states to tackle individually. Greater harmonisation and collaboration between states through joint regulatory frameworks, such as the EU's system where member states share regulatory responsibilities and resources, might increase the likelihood of financial and operational sustainability through

increased economies of scale and pooling of resources and expertise.

Currently, difficulties and delays in implementing the new European medical device and in-vitro diagnostic regulations (2017/745 and 2017/746) present an additional challenge to access for medical devices in LMICs.[8] Conformité Européene (CE)-marked products have historically been heavily relied upon, but several manufacturers are choosing to no longer market many of their CE-marked products, especially high-risk class D IVDs.[5] Manufacturers that do choose to continue with CE marking face uncertainty in requirements and delays of approximately 18 months while waiting for review by a notified body (an accredited organisation that provides a conformity assessment). Effective LMIC-led regulatory solutions are needed now, more urgently than before.

The *Lancet* Commission on medical diagnostics identified "[regulatory systems] to ensure diagnostic safety and quality" as essential to addressing the diagnostic gap (recommendation four of ten), and specifically highlighted that device regulation could be simplified through regional harmonisation programmes, such as the African Medical Devices Forum (AMDF).[9] The AMDF is a technical committee under the African Medicines Regulatory Harmonization programme and aims to enable access to medical devices and diagnostics of assured quality, safety, and performance across Africa through the operationalisation of IMDRF concepts. AMDF has made notable progress towards this mission in recent years and strengthened regional regulatory cooperation during the COVID-19 pandemic, showing the value and potential for AMDF-led reviews, listings, and guidance development.

After the COVID-19 pandemic, despite AMDF's harmonisation efforts, the extension of this regulatory capacity to other non-COVID-19 diagnostics has been restricted. The AMDF has worked in partnership with Africa Centres for Disease Control and Prevention towards the establishment of the continental Diagnostics Advisory Committee to provide laboratory expertise and advisory support for regulatory purposes. Most recently, the AMDF has initiated efforts to address the emerging mpox (formerly known as monkeypox) outbreak and Africa's diagnostic preparedness by inviting manufacturers and developers of in-vitro diagnostics for monkeypox virus detection to submit expressions of intent for expedited evaluation and emergency use listing status across the continent. AMDF aims to facilitate a collaborative review process among the twelve most affected African countries to ensure rapid access to diagnostics, and to evaluate the quality, safety, and performance of these diagnostics through a rolling review in partnership with the Disease Advisory Committee's network of laboratories. However, few African NRAs have adopted AMDF-led harmonisation frameworks, and the regulatory environment remains fragmented in many LMICs across Africa.[10]

Challenges such as insufficient funding, a shortage of qualified human resources, and inadequate infrastructure can decrease the effectiveness of regulatory frameworks. To strengthen and mature the regulatory capacity, LMICs can adopt WHO Global Model Regulatory Framework recommendations, which have been developed in alignment with the harmonisation efforts led by the IMDRF. These recommendations can be implemented gradually and supported by implementation resources, such as the WHO Global Benchmarking Tool.

Nonetheless, NRAs in many LMICs face staffing difficulties caused by the poor availability of training programmes, insufficient funding, and the migration of skilled professionals. As a result, the workforce capacity often does not have the necessary expertise to enforce standards or keep up with rapidly evolving technologies. To address this issue, capacity-building efforts are essential for improving the availability of skilled regulatory resources. Developing formal training programmes that are focused on regulatory affairs and collaborating with international organisations that offer mentorship programmes could enable local NRAs to enhance their workforce competencies.

Foundation for Innovative New Diagnostics (FIND) is a global non-profit organisation that works with multiple stakeholders, including regulatory bodies and local manufacturers, to drive global health security and universal health coverage. Collaboration between FIND and Unitaid to identify barriers for manufacturers and stakeholders highlighted regulatory capacity, quality management systems, and dossier preparation as areas that need targeted support, and a call for proposals intending to address these issues and strengthen regional IVD supply in LMICs has been opened.[11]

## Understanding the product journey: the UK as an exemplar

Similar to the product journey for medicines, the diagnostic product journey has several steps that involve many regulators and stakeholders.[12] Innovators should be aware of all the steps in the process from the beginning and be prepared for each stage to avoid delays or failure. Understanding of the roles and responsibilities of each stakeholder is important. In the UK, for example, market approval by the MHRA does not automatically mean NICE recommendation, or National Health Service (NHS) adoption. Successful outcomes in the later parts of the product journey depend on how well innovators have prepared for and anticipated them. We provide an overview of the diagnostic product journey in the UK and the various stakeholders involved (figure), which shows that product development should be driven by market research and engagement with the target users, with information and guidance about borderline products taken into consideration.[17] A quality management system should also be in place.[13] Any prospective clinical trial will be reviewed by the MHRA and a research ethics

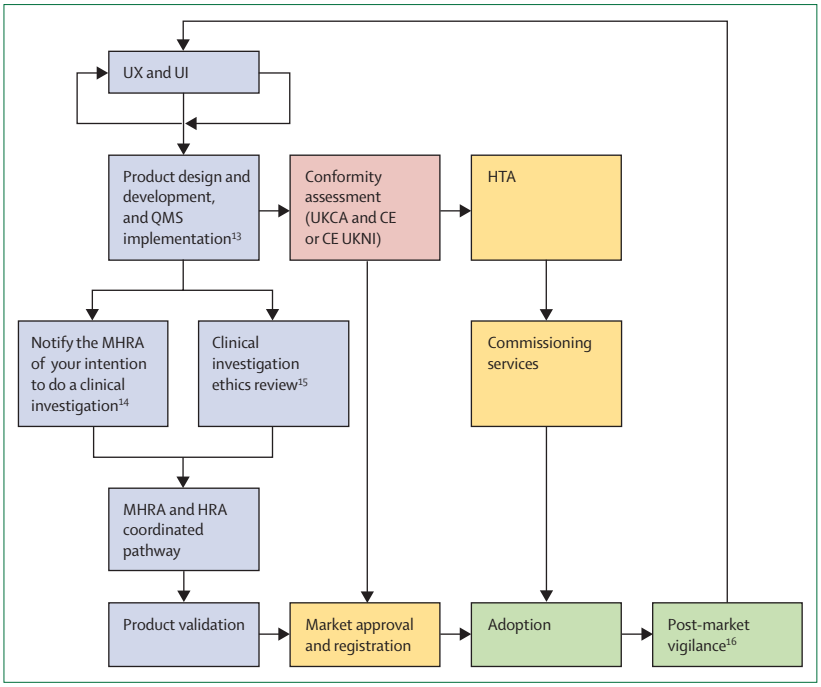


***Figure:*** **Diagnostic product journey in the UK**
UX=user experience. UI=user interface. QMS=quality management system. UKCA=UK conformity assessed. CE=Conformité Européene. UKNI=UK and Northern Ireland. HTA=health technology assessment. MHRA=Medicines and Healthcare products Regulatory Authority. HRA=Health Research Authority.

committee within the UK Health Department's Research Ethics Service. The MHRA and Health Research Authority coordinated pathway is a streamlined review process for eligible medical devices,[18] with conformity assessments being done by approved and notified bodies.[17] Once approved by a UK approved body, the product is then registered with the MHRA, who regulate the products in terms of safety and performance (post-market vigilance), and placed on the Public Access Registration Database.[16,19] The HTA bodies recommend the product, with options such as HTA by NICE being a paid for service that should be factored into development costs.[20] Selling a product to the NHS can be done through several routes with many ways to engage with the NHS; some information is provided by the Health Innovation Network and the Innovation Accelerator.[21] The UK Government Medical Technology Strategy outlines the government's plan to support a thriving UK MedTech sector and ensure that the health and care system can reliably access safe, effective, and innovative medical technologies to deliver the best outcomes for patients.[22]

For more on the **NHS Accelerator** see https://nhsaccelerator.com/

Although regulators aim to ensure that patients and the public have access to necessary health solutions, it is equally their responsibility to guarantee the safety and effectiveness of these solutions. Each regulatory body possesses a unique history and set of experiences that influence their operational procedures, risk tolerance, and criteria for approving medical products.[23] These factors contribute to the complexity of regulatory harmonisation and emphasise the importance of understanding regulatory processes within specific market territories.

Most regulators acknowledge the necessity of harmonisation and strive to achieve it whenever feasible, thereby simplifying procedures for innovators. However, achieving harmonisation could entail imposing stricter regulations from one territory onto another, potentially resulting in adverse effects. Regardless of the level of harmonisation, regulators should facilitate innovators in navigating regulatory frameworks by providing transparent and accessible information.

A fundamental principle of effective regulatory practice is transparency in safety, efficacy, quality, and performance requirements, which outline the standards and criteria that a product must meet before entering the market. The regulator's role is not to compromise quality standards to facilitate innovative products. Instead, a holistic government approach involving departments of innovation is essential to provide technical assistance. Regulators should maintain transparent requirements and establish mechanisms for the safe deployment of innovative products.

For diagnostic products, regulators could implement lower pre-market requirements for cutting-edge technologies while ensuring a safety net through stronger post-market requirements. This approach balances innovation with safety and underscores the regulator's commitment to protecting public health and fostering advancements in health-care technology.

An example of the struggle of navigating different regulatory bodies can be observed with the regulatory approval process of a molecular diagnostic platform that was released during the COVID-19 pandemic.[24] In May, 2022, this molecular diagnostic platform received CE-IVD marking, confirming compliance with the European in-vitro diagnostic directive (98/79/EC) and allowing the device to be marketed within the EU. However, it took an additional 9 months to gain approval for sale under the Coronavirus Test Device Approvals regulations. Although CE-marking was a substantial milestone, adoption by the MHRA was not automatic, as further approvals and authorisations were required, which have evolved since the UK exited the European Union.

## Approved and notified bodies, competent authorities, and health technology assessment

In various regulatory frameworks across different jurisdictions, medical devices should undergo a conformity assessment process to ensure that they meet particular safety and performance standards before they can be marketed or sold. This process often involves certification by an approved body or notified body, which is an independent organisation that is designated by regulatory authorities to assess the conformity of medical devices with relevant regulations. However, the regulatory requirements for medical devices can vary by jurisdiction,

and there might be exceptions or specific categories of devices that follow different procedures. For instance, some medical devices (particularly IVDs), could be self-certified as general IVDs if they pose a low or moderate risk to patients. These devices might not require certification by an external notified body but still need to meet particular regulatory requirements set by the relevant authorities.

The UK's competent authority is the MHRA, which works with several UK approved bodies.[25] Due to legal constraints, UK approved bodies cannot advise innovators or developers, which could lead to delays as innovators are unable to seek clarification on what they need to do. To help overcome these barriers, the MHRA has provided a mechanism as part of its new IDAP whereby the MHRA will facilitate knowledge exchange between innovators and UK approved bodies without compromising the relationship between innovators or developers and UK approved bodies. IDAP aligns processes that run through different stakeholder groups to expedite the route to approval (eg, ethics review, conformity assessment, clinical investigation review, and exceptional use authorisation). IDAP provides the ability for knowledge to be exchanged around the requirements for UK conformity assessed marking and regulatory evaluation, enables horizon scanning to prepare health technology groups for new innovations, and reduces the delays caused by lack of clarity around regulatory pathways and requirements and information flow.

All medical devices need to be registered with the MHRA before being placed on the UK market, including IVDs that are subject to new performance evaluations. The MHRA must be informed of any substantial changes to a device's registration, and these updates must be made regularly to maintain compliance. Failure to update the registration may result in suspension from the Public Access Registration Database. Following this process, post-market activities begin. "Once a medical device has been placed on the UK market, the manufacturer is required to submit vigilance reports to the MHRA when certain incidents occur in the UK that involve their device. They must also take appropriate safety action when required. The manufacturer must ensure their device meets appropriate standards of safety and performance for as long as it is in use."[26] The MHRA performs post-market surveillance on medical devices on the UK market. Signals are detected by various sources, including adverse incident reporting through the YellowCard scheme by the public and health-care professionals, manufacturer vigilance and incident reporting, and signals from other competent authorities, expert advisory groups, registries, and scientific literature. Potential signals are investigated by the MHRA and actions to mitigate risk are taken to protect patients, which can range from requiring changes to a device's information for use to recalling the device from the market. The manufacturer is responsible for submitting a field safety notice for any required field safety corrective action to the MHRA, and also to notify all affected device users. The MHRA then monitors the corrective and preventive actions taken by the manufacturer to ensure that the device is safe and effective.[27]

Well characterised reference materials provide the opportunity to evaluate the performance of assays and diagnostic devices. The MHRA South Mimms laboratories have decades of experience producing reference materials and bioassays, and they serve as a major WHO collaborating centre. The laboratories produce more than 95% of the WHO's International Standards, which represents the highest order of reference material for global assay calibration. These standards enable a wide array of harmonisation and comparability of results across various assays measuring biological activity. Reference materials are essential for the quality evaluation of medicines and can ensure the delivery of sensitive and reproducible diagnostics (eg, for Zika virus and COVID-19).[28–30] As well as supplying WHO international reference standards and other National Institute for Biological Safety and Control reference materials, the MHRA laboratories at South Mimms will work with innovators and manufacturers to produce custom reference materials to support quality and performance measurements.

For more on the **National Institute for Biological Safety and Control** see https://nibsc.org/

## Examining broader roles in regulatory oversight

Beyond regulatory agencies, various components within the health-care ecosystem play crucial roles in evaluating novel technologies and making benefit and risk assessments. In the UK, NICE assumes the responsibility of rigorously evaluating emerging technologies and providing recommendations regarding their integration into clinical practice. NICE's assessments include analyses of clinical efficacy, cost-effectiveness, and the impact of technologies on patient care. NICE recommendations heavily influence decision-making processes regarding the adoption and use of these technologies within the health-care system.

For more on the **Public Access Registration Database** see https://pard.mhra.gov.uk/

Furthermore, the NHS procurement department collaborates closely with suppliers to facilitate the procurement process and negotiate contracts for the acquisition of health-care products and services. This partnership is pivotal in ensuring that health-care facilities have access to innovative technologies that meet quality standards, while also considering cost-effectiveness and patient outcomes. Additionally, NHS procurement plays an important role in assessing health-care technologies' long-term sustainability by considering environmental impact and operational efficiency.

For more on **YellowCard** see https://yellowcard.mhra.gov.uk/

Another organisation in the UK assessment landscape is the recently established Healthcare Services Safety Investigations Body, which looks into safety concerns and events inside the NHS. The results of investigations by this body can provide valuable insights into the

real-world performance of medical devices and technologies, which can help to foster a culture of learning and development. This organisation not only monitors the safety of technologies post market, but also makes recommendations to other organisations (eg, the NHS and NICE) that could affect future regulatory changes and advice.

The recently published UK National Action Plan on AMR (2024–2029)[31] prioritises strengthening regulatory frameworks, particularly regarding medical diagnostics and devices. The plan emphasises the importance of rapid and accurate diagnostics to identify infections early, which helps prevent the misuse of antibiotics, thereby reducing AMR risks. The framework also aligns with international standards such as the IMDRF and the European Medical Device Regulation, ensuring greater consistency in regulations governing diagnostics.[31]

As previously emphasised, the landscape of regulatory oversight and technology evaluation is multifaceted and navigating these evaluation and procurement processes can be intricate and time-consuming. Therefore, the regulatory landscape and operational intricacies within their target territories must be comprehensively understood by innovators. By doing so, innovators can strategically plan and adapt their approaches to align with the requirements and timelines of regulatory and procurement frameworks, ultimately enhancing the likelihood of successful market entry and adoption of their technologies.

## Current challenges in regulations and proposed solutions

The current so-called push model for diagnostic development places the onus on innovators to identify the clinical need and respond to it. Although this approach has produced some highly effective diagnostics, as clinical pathways become more complex and regular threats such as seasonal pressures become ever more burdensome to the NHS, there is a need to rethink this and add a pull to the development model. The consumer has a key role to play in clearly signalling the clinical diagnostic need to innovators: by providing them with the necessary guidance, their prospects for crafting a successful test are enhanced.

Gaining widespread adoption of a test within the UK is not easy, although might be improved by a recommendation by NICE, despite not being mandatory for a test that is used in clinical settings. The evidence that is currently needed to show that a test works well and is fit for adoption is not always obvious to developers. The first step is to ensure test requirements are well defined. During the COVID-19 pandemic, a clear target product profile (TPP) was developed for innovators, giving them the best chance of producing tests that fulfilled the clinical diagnostic need to a high standard. Adopting this approach more widely in infection diagnostics would help innovators to produce tests that meet the needs, and guide those making decisions about which tests to implement.

However, developing a high-quality and realistic TPP is a complex process that needs active involvement and collaboration among multiple stakeholders, including clinicians, regulators, innovators, patient groups, and industry representatives. The process of reaching consensus on expectations of clinical needs, usability, and performance metrics across different settings is long and challenging, particularly for diagnostic devices due to their high diversity in applied technologies, complexity, and indications for use. Therefore, in light of evolving evidence and regulatory complexity across different jurisdictions, development of TTPs that effectively address the needs of most cases is difficult. The availability of more TPPs would probably reduce development uncertainty and motivate developers to pursue standardised product development by providing clear guidelines and expectations. However, TPPs might be less appealing if they are overly restrictive or bureaucratic, limiting developers' flexibility to innovate and adapt products to meet specific market demands and needs. Therefore, TPPs should be developed carefully, balancing transparent guidelines with the flexibility necessary to foster innovation.[32]

The development of clear TPPs is linked with a robust evaluation framework for tests coming to market and seeking adoption. Coordinated and sufficiently powered evaluations are needed to generate real-world evidence of clinical use and benefits to patients and the health-care system. Often, multiple small-scale pilots are unable to provide the high-quality evidence needed for the wider adoption of promising point-of-care infection diagnostics. Knowledge gained from the COVID-19 pandemic is key to tackling this gap. Although any test for COVID-19 must be approved by the Coronavirus Test Device Assessment panel before gaining access to the UK market, no other infection test is similarly assessed. Elements of this approach could be used to develop a national framework for evaluation alongside TPPs to ensure that the most appropriate tests can be selected for further clinical evaluations. A move towards nationally coordinated real-world evaluations would also help to ensure that funding is directed towards generating appropriately powered, high-quality data that can be used towards recommending tests for wider adoption. The implementation and adoption of point-of-care tests require more than simply proof of clinical functionality; they need comprehensive, real-world evidence that shows benefit to patient care and the health-care system to support widespread adoption. Early engagement with health economic analysis and understanding behavioural barriers to adoption are imperative to support the implementation of innovative diagnostic tools into the NHS.

All these elements rely on creating a diagnostic community of clinicians, academics, industry, policy

makers, and patients. NHS England seeks to drive this work forward with their Moving Forwards meetings, which bring together policy makers, industry, patients, academics, and clinicians.[33,34] These meetings have focused on identifying the clinical needs in key diagnostic areas while scoping TPPs for infection diagnostics and optimising evaluation, with further meetings to tackle funding, adoption, and implementation. Understanding the needs of the whole diagnostic community is the only way to achieve benefit for patients.

## Examples of challenges in diagnostics in LMICs

The diagnosis of tuberculosis can be challenging, especially in people who are at highest risk of the rapid progression of disease, such as infants or children and people living with HIV, due to the non-specific nature of symptoms and chest x-ray changes. However, a rapid diagnosis and identification of drug resistance are crucial for the timely implementation of effective treatment and reduction of associated mortality and morbidity.

Microbiological diagnosis has advanced substantially with the development of rapid molecular diagnostics that can offer improved sensitivity and semi-quantitative results of bacterial load. These diagnostics have enabled the quick and simultaneous detection of both *Mycobacterium tuberculosis* and rifampicin resistance on respiratory samples. These tests are much more sensitive than the standard sputum smear and quicker than culture methods, but use in primary care settings, where most people with tuberculosis seek care, is challenging. Further challenges include the maintenance of machines in health facilities, quality assurance, uninterrupted power supply, cost, use on different samples, transport of samples to laboratories, the inability to detect multidrug-resistant tuberculosis that can lead to underdiagnosis, and misinterpretation of results (as DNA from dead bacilli can be detected for years).[35] Furthermore, utilisation rates are lowest in rural facilities, where diagnostic needs are the greatest.[36]

## Implementing digital diagnostics for malaria in LMICs

Digital molecular diagnostics combine the high sensitivity and specificity of molecular detection with point-of-care format and mobile connectivity, representing a promising avenue for improving disease detection and management in LMICs.[37] By integrating features such as image analysis algorithms and remote data transmission capabilities, digital diagnostics offer the potential to enhance the efficiency and accessibility of existing malaria testing solutions, particularly in resource-constrained settings where standard diagnostic methods (eg, rapid diagnostic tests for screening of asymptomatic people) might not meet the appropriate standards for ensuring quality for malaria diagnosis.[38,39] Despite the potential benefits of digital diagnostics, their adoption faces several challenges, including regulatory barriers, inadequate infrastructure, and the need for robust validation in diverse clinical settings. Overcoming these hurdles requires collaborative efforts among governments, health-care providers, technology innovators, and international organisations to strengthen regulatory frameworks, invest in infrastructure development, and promote the integration of digital health solutions into existing health-care systems.[40]

These challenges hinder the timely approval and deployment of innovative solutions, thereby delaying their potential impact on malaria control efforts. The absence of clear guidelines for the validation and interoperability of digital diagnostic tools further complicates regulatory processes and undermines confidence in their reliability and effectiveness. Moreover, concerns regarding data privacy, security, and ethical considerations necessitate comprehensive regulatory frameworks that are tailored to the unique contexts and needs of each LMIC. By overcoming these barriers, LMICs can harness the full potential of digital diagnostics to strengthen malaria surveillance, improve case management, and accelerate progress towards malaria elimination goals.[41]

## The potential of microbiome diagnostics

The human microbiome (particularly the gut microbiome) influences human health, with growing evidence of links to various diseases such as chronic inflammatory conditions, obesity, and cancers.[42] Given its emerging role in disease risk, onset, progression, and treatment response, the microbiome holds potential for diagnostic testing to personalise clinical decision making.[43] Microbiome diagnostics that measure specific microbiome components could offer potential avenues to enhance disease diagnosis, quantify risk, predict progression, and tailor drug selection for each patient.

Microbiome diagnostics leverage next-generation sequencing (NGS) technologies to detect and quantify a vast array of microbes and their putative functions, using targeted or agnostic NGS methods and enabling the simultaneous detection of numerous microbes. Through use of complex statistical processes (eg, machine-learning algorithms), microbiome diagnostics could identify associations between taxonomic or functional microbial features and clinical outcomes, empowering diagnostic capabilities. However, there is additional complexity in the development of microbiome diagnostics, since the presence of a gene does not always translate to phenotypic expression. This discrepancy will be a challenge for developing and evaluating clinically useful microbiome diagnostics.

Deploying microbiome analysis for clinical diagnostic applications presents challenges that are related to laboratory and computational workflows, which are prone to errors and biases. Standardisation across microbiome analysis is crucial to ensure accurate and comparable results (eg, not all pathogens are extracted with equal success and not all are present in the same relative biomass), yet efforts in this area are nascent.

Additionally, showing analytical performance (ie, including sensitivity and limits of detection) poses complexities due to the compositional nature of NGS abundance data. In many jurisdictions, regulatory guidelines for novel NGS-based diagnostics, including microbiome diagnostics, are still evolving or are not sufficiently developed, leading to uncertainties that hinder the adoption of diagnostic technologies. Initiatives such as the IDAP aim to address these challenges by providing a streamlined regulatory and access pathway, and emphasise the importance of evidence-based guidelines tailored to microbiome diagnostics to ensure safety and reliability while fostering innovation.

## Discussion

The current state of diagnostic regulation presents a multifaceted landscape that is marked by varying degrees of clarity and complexity across different regions and income levels. In high-income countries, medicine regulation is generally well established and offers clear frameworks for the approval and oversight of pharmaceutical products at both national and international levels. However, in terms of diagnostics, the regulatory framework is less defined and more intricate. Innovators in this space often encounter challenges in understanding the comprehensive process involved in bringing diagnostics to market and ensuring compliance with regulatory standards. Furthermore, the disparity in regulatory infrastructure between high-income countries and LMICs exacerbates the complexities of diagnostic development and adoption, leaving many populations underserved regarding access to quality diagnostic testing and medical devices. Looking to the future, key stakeholders (including clinicians, researchers, innovators, regulators, and other members of the diverse health-care community) share a collective aspiration to establish a more streamlined and universally applicable regulatory framework for diagnostics: one that ensures patient safety, promotes innovation, and facilitates equitable access to essential health-care technologies worldwide.

Central to advancing diagnostics regulation is the recognition of the imperative for a patient-focused approach and fostering collaboration among innovators, regulators, and industry stakeholders. At the heart of this approach lies the commitment to address the unmet health-care needs of patients by developing diagnostics that are not only effective and accurate but also accessible and affordable. Collaborative efforts between innovators (who drive technological advancements and product innovation), regulators (who uphold safety and efficacy standards), and industry partners (who facilitate the development and distribution of diagnostic solutions) are essential for navigating the complexities of the regulatory landscape. By placing patients at the forefront of decision-making processes and fostering open dialogue and partnership among stakeholders, an environment can be cultivated to support the development of diagnostics that meet the needs of health-care systems and the individuals they serve.

The collaborative efforts between regulators and innovators underscore a pivotal moment in the evolution of diagnostics regulation, marked by a shared commitment to meaningful change and progress. Through proactive engagement and mutual understanding, regulators and innovators are working together to address the challenges that are inherent in diagnostics development and adoption, and striving to achieve a regulatory landscape that is responsive, adaptive, and inclusive. By leveraging technological advancements, embracing patient-centred principles, and fostering collaboration across sectors (including health care, technology, and policy) and regions, a future can be envisioned where diagnostics regulation promotes innovation, ensures patient safety, and enhances health-care accessibility for all. In striving to improve access to and the creation of innovative diagnostic solutions, it is essential to remain steadfast in our commitment to driving positive change, and advancing the collective vision of a healthier, more equitable world.

### Search strategy and selection criteria

We searched PubMed and the official websites of the UK government, private companies, and global and national public health organisations (such as the Medicines and Healthcare products Regulatory Agency, WHO, National Institute for Health and Care Excellence, and the Foundation for Innovative New Diagnostics) for literature including peer-reviewed articles, meta-analyses, systematic reviews, and relevant reports from Jan 1, 2010, to Aug 31, 2024. We excluded studies that did not focus on diagnostics, studies outside our date range, and studies not available in English. We used the search terms "diagnostics regulation", "evidence requirements for diagnostics", "barriers in diagnostic deployment", "target product profiles for diagnostics", "standardising diagnostic regulations", and "molecular diagnostics regulation" to ensure a comprehensive overview of the topic.

## Conclusion

Innovators often struggle with unclear regulatory pathways, complex requirements for evidence, infrastructure limitations, and high costs, all of which could hinder the swift deployment of diagnostics. These challenges are particularly pronounced in high-burden settings (eg, tuberculosis and malaria in LMICs). Regulatory bodies have made some strides in addressing these issues by developing clearer frameworks (eg, TPPs for infection diagnostics, and guidelines for digital and molecular diagnostics). However, global harmonisation and better coordination are still needed between stakeholders to foster innovation without compromising safety. To overcome these barriers, the UK and global authorities

should focus on standardising regulations, improving infrastructure, and investing in real-world evidence generation. There should also be a concerted effort to create tailored regulatory frameworks for specific diagnostic technologies, such as digital diagnostics in LMICs, to enable their rapid and effective deployment.

#### Contributors

JR-M and AHH conceived and planned this Series paper. All authors contributed to the intellectual development of the paper and provided critical feedback on the manuscript. The final version was seen and approved by all authors.

#### Declaration of interests

JR-M and KMS-L hold financial interests in ProtonDx. MR has a financial interest in AlphaBiomics. All other authors declare no competing interests.

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