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On Paper Diagnostics: A Brief History and Future Perspectives

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Abstract: For centuries, diagnostic technologies have played a key role in medicine. Effective diagnostics can help clinicians identify the presence and extent of disease in their patients, as well as their general health. Precipitated by advances in biochemistry, chemistry, and engineering, the 20th and 21st centuries have witnessed rapid advancement in diagnostic technologies. However, these improvements have brought increased complexity and a corresponding move towards more centralized and specialized laboratories. This has led to significant healthcare disparities between high- and low/middle-income regions. However, with the introduction of paper-based diagnostics this paradigm has begun to shift, with new assay formats designed for point-of-care (PoC) or at-home use. By leveraging innovations from multiple fields, these paper-based tests can translate complex assay procedures into easy-to-use, single-step tests for the end user. In this review, we summarize the interdisciplinary beginnings of paper-based diagnostics, detailing their development through market introduction and commercial successes, and discuss the current state-of-the-art. Finally, we highlight areas for improvement and propose pathways that could enable increasingly complex chemistries to be performed on simple paper-based devices.

Keywords: Diagnostics · Paper-based microfluidics · Point-of-care

1. Introduction

The past century has seen a revolution in patient care and healthcare practice, with a drastically increased standard of care. Though many innovations have fed into this increase, one that stands out as having affected every field of medicine, from oncology[1] to cardiology[2] to infectious disease,[3] is *in vitro* diagnostics (IVDs). IVD tests have been integrated into each step of the patient care process, from initial diagnosis through to prognosis, treatment monitoring, and patient observation.[4,5] IVDs have also become core parts of the therapeutic development pipeline, with Companion Diagnostics (CDx) tests becoming common tools in therapeutic trials to partition study subjects and improve the odds of regulatory success.[6,7] Such tests have also become essential in addressing other population health concerns such as antimicrobial resistance, where IVDs are used to guide treatment and thus moderate the use of antimicrobial treatments.[8,9] In extreme cases, early diagnosis can avoid the worst symptoms of diseases[10] or allow people to quarantine so as not to spread an infectious disease further.[11] In such cases, the application of IVDs directly improves clinical and societal outcomes.

Though diagnostic advances have had a widespread positive effect, the gains have not been equally distributed in society, with more developed regions disproportionally benefiting. Given the established relationship between access to diagnostic tests and overall health,[12] this issue is at the forefront of global equity initiatives.[13] The very nature of infectious diseases and our highly integrated globalized economy means that disease spread is rarely completely localized; local diagnostic testing inadequacies seldom remain a local problem, and those which affect one part of the world will inevitably affect all parts of the world.[14,15] Though many complex political, social, and economic factors affect the allocation of the most effective IVDs, the overall trend is that of inequity: wealthier and more developed areas have better access to the best tests.[16,17]

To overcome this, a significant amount of work has been put into developing IVDs specifically meant for low-resource settings and which can be widely distributed with minimal need for special handling or expensive equipment. These values have been codified in the REASSURED (real-time connectivity, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid, equipment-free, delivered) criteria.[3] Though the push to meet these criteria has spawned numerous technologies and innovations, the most popular and most commonly deployed are paper-based microfluidics, which take advantage of capillary action to induce liquid flow through the porous paper medium. In addition to removing costly manufacturing requirements, the move to paper microfluidics can drastically reduce the average per-unit cost of each diagnostic device.[18]

Though the history of paper-based assays is one of unrelated innovations in different fields being put together in a new assay format, we believe that current paper-based diagnostic device research has mostly coalesced into a small number of thematic paths, leaving a wide and diverse array of interdisciplinary applications unexplored. Especially in the commercial research and development process, this topical conservatism makes sense given the regulatory constraints and onerous process of certifying a new device *vs* one similar to an existing device.[19] However, this coalescence effectively takes off the table many potential paths and the improvements they may bring. While lab-based diagnostic assay chemistries and formats are broadly more sensitive than their paper-based point-of-care (PoC) counterparts, the path towards realizing true health equity and equality requires that the best assays are available to all who need them, regardless of resources. Moving in this direction will necessitate the translation of these more complex chemistries and formats onto paper, as well as developing assay architectures that enable complex operations beyond the ubiquitous lateral flow immuno-capture. In this review, we aim to present the history of paper-based diagnostics and

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the disparate technologies and innovations that paved the way to the first commercialized test. We further detail the innovations in paper-based diagnostic assay design and readout that could enable a future in which increasingly complex and impactful assays can be implemented within decentralized settings.

2. A Brief History of Paper Diagnostics

Though the need for low-resource PoC diagnostic tools existed far before the formalization of the field, it was only with the right tools and innovations that reliable and easy-to-use devices were manufacturable and distributable at scale. Paper substrates have been used for sensing purposes since at least the 19th century.[20] In modern use, their main utility comes from a few key properties, such as the ability to immobilize low reactant volumes and the movement of liquids *via* capillary flow.[21] Further, with the move to substituted cellulose substrates such as nitrocellulose, device developers can finely tune flow speeds by carefully selecting the pore size.[22] These features, along with shelf stability, biocompatibility, and affordability, made paper the prime substrate candidate for POC diagnostic assays.

2.1 *The Beginning: A Confluence of Fields*

Paper-based diagnostic devices are comparatively recent advances resulting from the confluence of multiple unrelated advances in the 20th century: paper chromatography, antigen-mediated bead immuno-sandwiches, and the Enzyme-Linked Immunosorbent Assay (ELISA). Paper chromatography was first proposed in 1943 as an extension of partition chromatography. The method quickly gained popularity due to the low cost of paper, the simple, equipment-free mode of operation, and its ability to separate small quantities of analyte.[23,24] Separately, in 1956, Plotz and Singer introduced a latex fixation and agglutination test for rheumatoid arthritis, which served as the groundwork for bead-based immuno-sandwiches.[25,26] Then, Yalow and Berson reported an immunoassay that used a competitive binding assay to displace radioactive beef insulin with non-radioactive human insulin.[27] To make the technique safer and more accessible, radioisotope signaling was subsequently superseded by enzymatic signal generation, leading to the introduction of the ELISA in 1971.[28] ELISA relies on colorimetric or fluorometric signaling mechanisms, where an enzyme conjugated to the antibody transforms a substrate to generate a signal proportional to the antigen present.[29] These immunoassays were rapidly adopted and by the end of the decade had been successfully implemented on paper substrates, initially using cellulose but rapidly transitioning to membranes such as nitrocellulose.[30]

2.2 *From Lab to Market*

Though paper chromatography and ELISA were developed from entirely different needs, researchers quickly realized they could be paired to make low-cost and user-friendly IVD devices. This culminated in the 1988 introduction of the first commercial Lateral Flow Assay (LFA) by Unipath Ltd, providing at-home pregnancy tests. Whereas at-home pregnancy tests had been introduced nearly a decade prior, they came in the form of a mini-lab kit that required nine steps to complete and contained multiple droppers, a test tube, and a mirror to evaluate the result from the bottom of the test tube (Fig. 1). These tests had been described by a user as '[only] easy to use for someone with lab experience'.[31] Upon its introduction, Unipath's Clearblue LFA-based diagnostic was the first single-step pregnancy test.[32] The additional convenience of this test enabled earlier recognition of pregnancies, facilitating more effective prenatal care.[33] These factors are associated with improved health outcomes.[34] By reducing the cost of the test and simplifying the user experience, the Clearblue test set both the template and benchmark for future paper-based devices.

Though pregnancy testing was the first LFA to market, additional tests for other targets were quickly developed. Within a year, Unipath introduced a single-step ovulation test measuring luteinizing hormone.[35] As with pregnancy testing, the move to at-home paper-based test formats lowered test costs and improved test access.

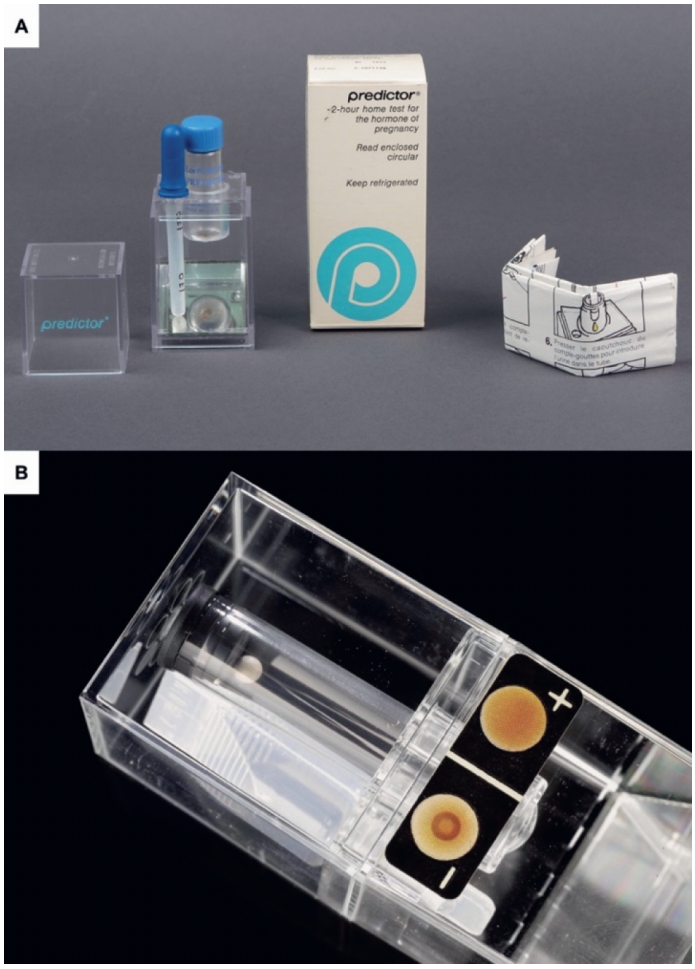

Fig. 1. **Predictor Pregnancy Test**. **A**) Image of the first at-home pregnancy test, the Organon Predictor test. This test revolutionized fertility care, allowing a woman to learn whether she was pregnant without a doctor. The test involved using a dropper to place urine in a tube, adding in a chemical solution, shaking and incubation for two hours. The result was read using an angled mirror at the bottom of the case, with **B**) a dark brown circle in a yellow background indicating a positive result (negative results generated no circle and were just yellow). Images and description adapted with permission from *Division of Medicine and Science*, National Museum of American History, Smithsonian Institution[67] and A. M. Christopher[68].

2.3 *Market Success*

Given their easy-to-use format, affordability, and transportability it is unsurprising that developing sensitive LFAs (and other paper-based diagnostic test formats) became a goal for many diagnostics developers. From at-home HIV[36] detection to RSV,[37] Flu A and B,[38] and non-infectious disease testing such as for drug and alcohol metabolites[39] or testing illicit substances for fentanyl contamination,[40,41] LFAs have become ubiquitous medical devices.

Though the immuno-LFA is the most common format, other assay chemistries and signal detection methods have been adapted for paper, most adopting the same principle of affinity-based capture. Relatively new biosensing chemistries, such as those based on CRISPR-Cas enzymes, have been adapted to a lateral flow for-

mat, enabling the detection of nucleic acid markers (*i.e.* genotypic testing).[42] Further, the scale afforded by mass market appeal has encouraged innovations that impact useability, rather than just sensitivity. For example, the introduction of a digital readout *via* a display on pregnancy tests reduced readout errors caused by untrained users, making the test more effective and accurate for widespread use.[43]

The commercial success of the LFA was cemented during the COVID-19 pandemic, as the need for distributed and accurate diagnostic testing became a globally relevant matter of individual health, public health, and national security.[44,45] Early in the pandemic it was clear that person-to-person transmission was the primary mechanism of transmission[46,47] and that asymptomatic individuals significantly contributed to the spread of the disease.[47] Consequently, many governments worldwide made developing both centralized and PoC diagnostic assays a key part of their pandemic response plans. This combination of global scale and high infectivity (even if asymptomatic) necessitated a diagnostic test that could be used at home and was inexpensive enough to remain economically viable. Within months of the first COVID case, the first lateral flow assay was approved under the FDA's Emergency Use Authorization program.[49] Like the pregnancy test nearly four decades prior, LFA testing for SARS-CoV-2 represents an exemplary case study of the benefits of paper-based diagnostics. The ability to test at home improved patient compliance, ultimately slowing the spread of the infection. This led to improvements in public health, with knock-on social and economic benefits. Much like pregnancy tests, rather than filling a niche diagnostic market, paper-based LFAs quickly became the *de facto* means of testing.

3. The Current State-of-the-Art

Though paper diagnostic devices are undoubtedly successful, with billions used each year, multiple areas for improvement remain. Significant work has focused on improving test performance across many aspects of the REASSURED criteria. Broadly, these improvements can be grouped into either assay format improvements (new signal generation or detection modalities, better assay chemistries) or practicality/user-experience (UX) improvements (such as connectivity, ease-of-use, removing requirements for specialized equipment). These highlight that developmental considerations for PoC diagnostics extend far beyond just the sensitivity and specificity of the assay itself. This is reinforced in the REASSURED criteria, where only two of the nine criteria relate to test performance, with the rest broadly focused on practicality and useability. Tests must be easy to use as there is no guarantee of trained specialists. While the exact definition of 'easy-to-use' can be debated, the REASSURED criteria emphasize many relevant aspects including no or minimal required equipment.

Scoping overall test performance to include all of the REASSRED criteria also legitimizes paths of inquiry that may depart from traditional engineering but still directly affect test use. User experience improvements such as connectivity have the potential to direct users to additional resources and care; tests without such features were shown to prompt less follow-up care, thus rendering the test results less useful in the overarching healthcare ecosystem.[50] Further, changes in device and assay format enable the implementation of new processes on paper, thus opening the possibility for more complete, easier-to-use diagnostic devices.

3.1 *Innovations in Assay Format*

Though the earlier paper-based assays were relatively simple, relying primarily on lateral flow and colorimetric or fluorometric

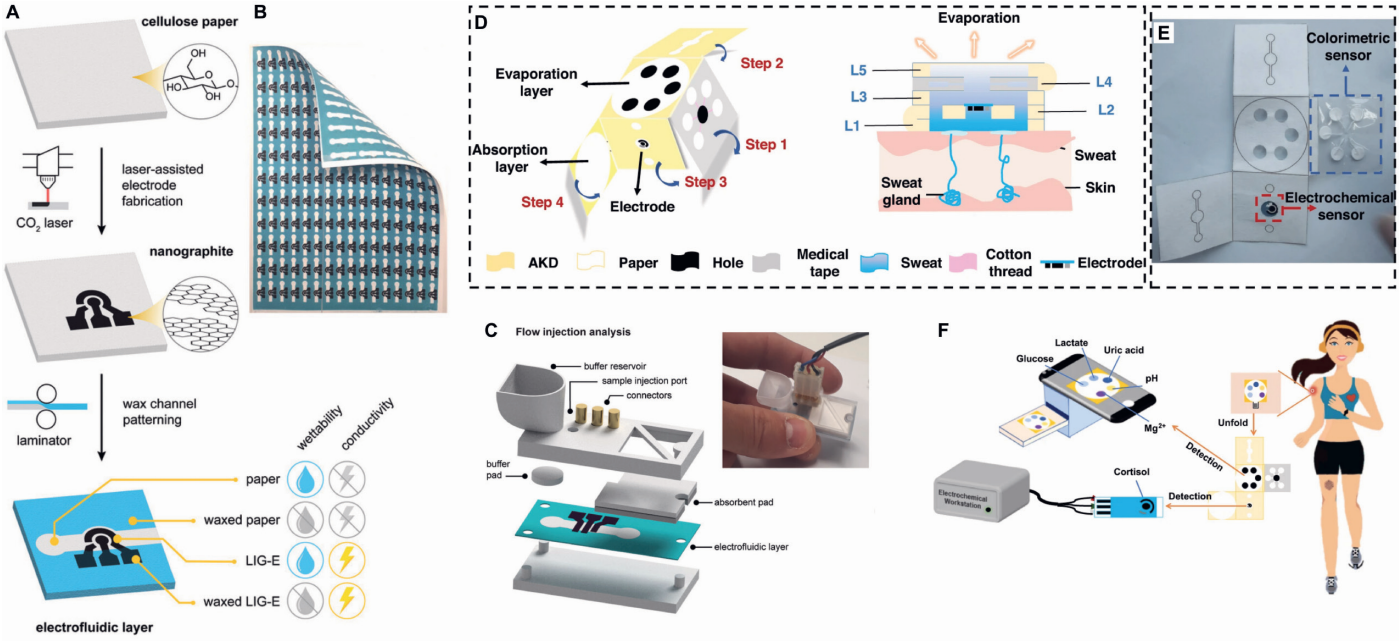

Fig. 2. **Examples of assay format innovations. A**) Fabrication of pyrolyzed cellulose paper-embedded electrodes. The paper is first pyrolyzed using a laser, and then patterned with wax lamination allowing independent control of which parts of the electrodes are wettable. **B**) A sheet of the final electrodes, patterned on A4 paper. **C**) The pyrolyzed electrode paper in a lateral flow device, with a 3D printed housing. A steady capillary flow is fed from the large buffer reservoir, as samples can be serially injected into the sample injection port for analysis over the electrodes. **D**) Structure of a wearable paper-based sensor, both unfolded (left) and folded while being worn (right). The wicking action of the nitrocellulose paper transports sweat from the surface of the skin through the colorimetric detection layers, the electrode later, and to the evaporation layer. **E**) Image of the unfolded sensor. **F**) Graphic displaying the intended sensor use. Whilst being worn, the sensor is exposed to sweat and can be colorimetrically or electrochemically read on the user's arm. Further, more quantitative readings are possible using a smartphone-based imager. **A**, **B**, and **C** and their corresponding descriptions were adapted with permission from ref. [51]. **D**, **E**, and **F** and their corresponding descriptions were adapted with permission from ref. [54].

signals, significant work has been done in the intervening decades to enhance the format and enable more complex assays. One such improvement, presented by Bezinge *et al.* is a fundamental departure from both the immune sandwich assay design as well as the lateral flow format.[51] In this work, a highly adaptable technique for manufacturing paper-based electrochemical sensors was developed. Of note is the electrode construction; this work used the cellulose assay pad as the raw material, creating the electrode through controlled laser pyrolysis. By controlling the laser power delivery *via* focus and scan speed, the paper was optimally pyrolyzed to achieve electrical conductivity while retaining substrate wettability. Further, the resulting electrodes retain their porous nature, allowing samples to flow through them. In this and follow-on works, the authors demonstrated the potential of the method across multiple electrochemical assay chemistries, including a vertical flow CRISPR–Cas-based molecular assay for *Human papillomavirus* 16 (HPV16) (Fig. 2A),[51] a lateral flow test for alkaline phosphatase in serum (Fig. 2B),[51] a flow injection analysis method for creatinine in urine,[52] and a lateral flow test for SARS-CoV-2 antibodies.[53] Significantly, the lateral flow format presented enables multiple samples to be moved sequentially over (or through) the same electrodes and paper membrane (Fig. 2C), lowering the total cost per test (individual sample) while maintaining the simplicity of a lateral flow assay.

Improving assay performance does not necessarily require a novel chemistry or detection scheme. Instead, changes to the assay format can be used to translate more complex assays onto paper. Taking advantage of the flexibility of paper and the general isotropy of capillary flow, various geometries and multidimensional flow paths can be constructed and used as part of a multiplexed or multi-step assay. One such example is presented by Cheng *et al.* where a paper substrate is used to implement multiple different assays, resulting in a multiplexed multi-modal test (Fig. 2D and 2F).[54] In this work, the authors use a relatively simple paper origami design, employing lateral flow and vertical flow elements and hydrophobic and hydrophilic modifications, to implement a test that allows for five different colorimetric readout areas and one electrochemical readout. In doing so, one paper device was able to detect glucose, lactate, uric acid, pH, Mg^{2+}, and cortisol concentration in sweat. Further, the readout methods presented were all achievable with low-cost equipment; the colorimetric readout was qualitatively readable by eye and quantitatively readable by a smartphone camera, whereas the electrochemical readout is a standard three-electrode design which could incorporate a low-cost reader (though the authors did not present such a solution). Whereas comprehensive tests that screen for multiple biomarkers have often been the purview of a more centralized facility, this work presents a viable way to bring such tests out of the lab and to the point-of-need, whilst not imposing onerous equipment burdens.

Geometries, however, are not limited to physically folding paper onto itself. Significant work has been done in developing multi-layer and multi-dimensional fluid networks on paper. Notably, Samper *et al.* reported a paper-based assay for SARS-CoV-2 antibodies, integrating blood filtration and detection on one device.[55] By harnessing multiple stacked layers of polyester membrane and hydrophobic barrier, the authors create a complex flow path that implements all ELISA assay steps on paper. Other techniques have also been presented for customizing fluid flow and directing it with delays to allow multi-step assays. For example, a dissolvable polyvinyl alcohol dam presented by Alam *et al.* shows up to a 20-fold increase in sensitivity by slowing the fluid flow over the test and control lines.[56] Similar results have also been shown with dissolvable wax barriers[57] and dried glucose barriers.[58] In each case, assay improvements were made by introducing multiple assay 'stages' to the lateral flow format.

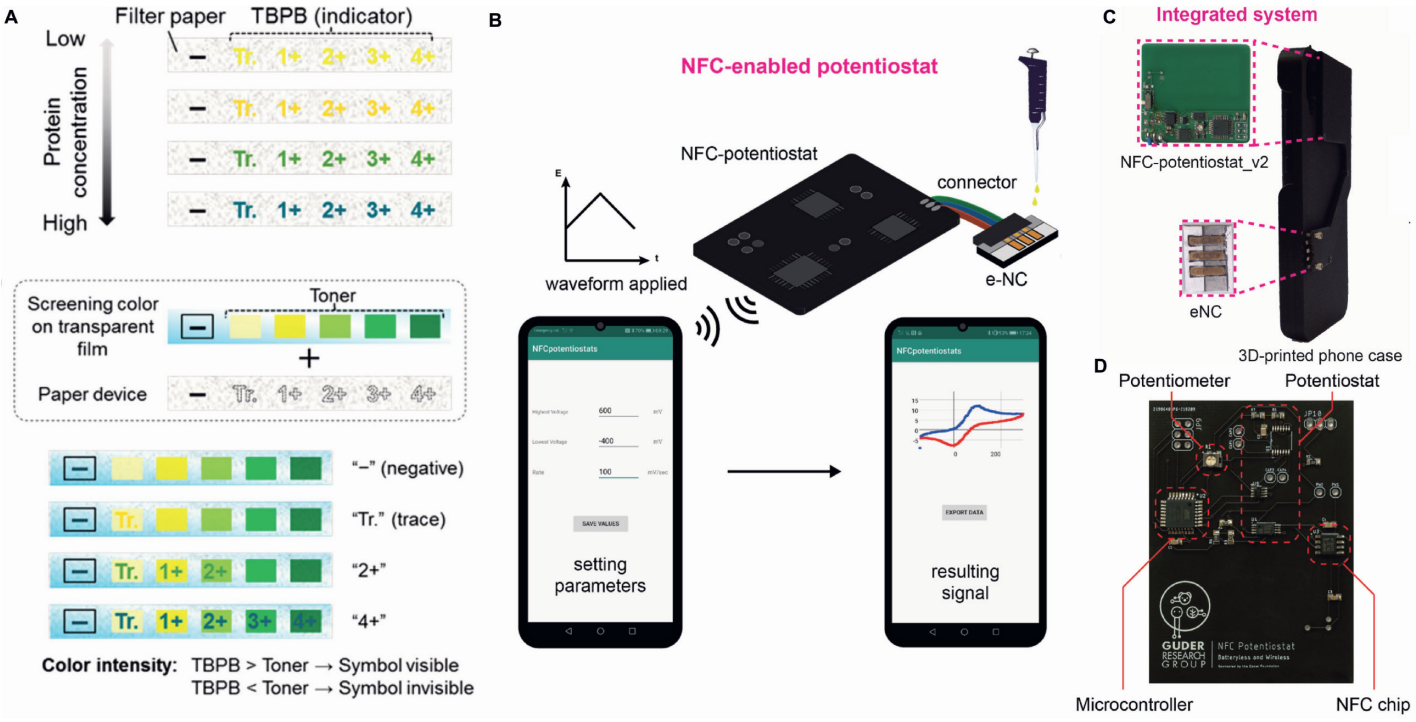

Fig. 3. **Examples of useability improvements. A**) A text-based lateral flow device showing the inkjet-deposited indicator text on paper, which changes color when exposed to higher concentrations of protein. Below, the expected readout when combined with the colored screen which selectively blocks out colors progressively. **B**) Schematic of a battery-free wireless readout process where a smartphone provides power *via* NFC to the circuitry that performs electroanalytical measurements. **C**) Image of a battery-free NFC potentiostat in a 3D printed cell phone case housing, allowing for constant contact with the NFC components inside the phone. The electrochemical detection on nitrocellulose (eNC) membranes plug into the side of the case for analysis. **D**) Image of the NFC circuit board. **A** and its description were adapted with permission from ref. [60]. **B**, **C**, and **D** and the associated descriptions were adapted with permission from ref. [63].

3.2 *Innovations in Connectivity and User-Friendliness*

As previously discussed, new test formats are far from the only way to improve a diagnostic device's overall performance. Improvements surrounding useability have been shown to reduce systemic costs, improve information available to public health authorities, and promote device adoption by the general public. A study of connected rapid diagnostic tests in remote areas of Kenya showed improvement in the facilitation of diagnosis and treatment of brucellosis in nomadic populations, with the users of the connected diagnostic test and mobile app finding it easier to access health resources and adhere to the treatment regimen.[50] In a study tracking test usage for a malaria elimination campaign, Scherr *et al.* integrated a QR code into the test control line and designed a quantitative readout of the test strip *via* an app, creating a combined solution that automatically tracks positive and negative results (Fig. 3A). This method of data collection not only ensured test integrity and made scanning the result easy for the end-user, but also allowed for the collection and aggregation of population-level spread data to inform data-driven elimination campaigns.[59] Such integrated readouts have also directly incorporated text, such as the one presented by Yamada *et al.* This work showed a model lateral flow device with a test for urinary protein. Upon using the test, the user does not just see a color intensity as with standard test lines, but rather a progressive appearance of text for semi-quantitative readout. Of note is that this text-based readout does not require an additional reader.[60] Since users often experience difficulties observing faint colorimetric signals in traditional LFAs, innovations such as these greatly enhance useability and ultimately test accuracy.[61,62]

Another part of the REASSURED ethos is '*Equipment free or simple*'. Though this is often taken to mean no equipment, or just a smartphone, it is our view that any method that does away with complex, expensive, and bulky equipment satisfies this requirement. For example, Gonzalez-Macia *et al.* developed an electrochemical assay that does not require a battery or external power supply (Fig. 3B).[63] Though the system was demonstrated on the Maize Mosaic Virus (a plant virus), the platform itself is applicable to any assay chemistry that produces an electrochemical readout. The battery-less device was enabled by resourceful design, sourcing power for the electrodes from the total power budget of a near-field communications (NFC) transmission originating from the phone (Fig. 3C and 3D). This advancement is particularly impactful as it emphasizes intentional design for resource-constrained environments. While many commercial NFC implementations may not be as parsimonious with the total specified power budget, in this work, the power usage of the electronic components was kept to 1.8 mW, which is only 20% of the nominal 10 mW NFC power budget.

4. Conclusion and Outlook

Paper-based diagnostic devices provide a perfect case study on the effect of interdisciplinary innovation on the field of diagnostics. Through a merging of fluidics, materials science, and bioassay development, paper devices have made diagnostic testing more affordable and accessible. Though this review is not exhaustive, we hope to have highlighted how this merging of fields can be leveraged to translate increasingly complex biochemical assays onto paper, and ultimately make IVDs more accessible.

Looking forward, we hope to see more research implementing complex chemistries and tests while still addressing the REASSURED criteria. Specifically, the move towards affordability and ease of use across many metrics has already shown marked improvements in diagnostic device distribution, use, and efficacy. An analysis of dengue fever diagnostic tools in Spain concluded that widespread use of inexpensive, rapid diagnostic tests (RDTs) would lead to an approximately 50% reduction in hospital admissions, around 300 € savings per febrile traveler, and about a 40% reduction in antibiotic use.[64] This effect is even more pronounced in countries with fewer resources, where cost is recognized as a main driver for diagnostic usage.[65] These studies highlight how usability improvements (notably user-friendly and equipment-free) are equally as important as technological improvements in assay design and chemistry. Integration of such tests with true connectivity, beyond a precursory use of a smartphone app for readout or similar, allows end users to not only run the test themselves but also to guide them through appropriate follow-up actions such as seeking care or reporting their result to a public health authority. Accordingly, when bringing foundational technology improvements to paper in the form of new assay formats and chemistries, researchers should do their best to ensure these are implemented in a way that maximizes useability.

We also hope to see translational work done to advance tests that have been demonstrated in the literature but have yet to make it to clinical evaluation and widespread use. For example, Nucleic-Acid Amplification Tests (NAATs) have been widely demonstrated on paper substrates, but have not yet become a mainstream test format commercially. Further, integration of the complete diagnostic process, including sample preparation and data analysis, represents a significant line of inquiry with the potential to enable new types of tests on paper substrates. Many paper-based assays still require 'off-device' sample preparation, often performed by a trained professional. This runs counter to the idea of more accessible diagnostics. The maturation of technologies that put this process on paper would move us closer to the long-term goal of true PoC 'sample in, answer out' diagnostic devices.

One notable area of paper diagnostic development not represented in this review is that which requires complex or expensive machinery to run. Examples of this include the many studies published on paper-based Surface Enhanced Raman Spectroscopy (SERS) tests.[66] While these innovations show clear and marked improvement in various aspects of the diagnostic test, many of them also represent a move away from the initial conception of point-of-need testing, *i.e.* decentralization, to one where integration of paper is just a means of lowering the cost of an expensive test. However, though not all new paper-based devices need to be focused on extremely resource-constrained applications, the fact remains that paper-based technologies are in a unique position to address almost all the requirements outlined in the REASSURED criteria. Focusing research on reducing hands-on steps and improving connectivity with little added user burden would provide the most significant impact on societal gains. For this reason, we believe that the largest innovations in the field lie in interdisciplinary applications that solve problems specific to resource-constrained diagnostics.

Author contributions

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