Assessment of Reader Technologies for Over-the-Counter Diagnostic Testing

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***Abstract*—Background: Over-the-counter (OTC) diagnostic testing is on the rise with many in vitro diagnostic tests being lateral flow assays (LFAs). A growing number of these are adopting reader technologies, which provides an alternative to visual readouts for results interpretation, allowing for improved accessibility of OTC diagnostics. As the reader technology market develops, there are many technologies entering the market, but no clear, single solution has yet been identified. The purpose of this research is to identify and discuss important parameters for the assessment of LFA reader technologies for consideration by manufacturers or researchers. Methods: As part of The National Institute of Biomedical Imaging and Bioengineering's Rapid Acceleration of Diagnostics (RADx) Tech program, reader manufacturers were interviewed to investigate the current state of reader technology development through several parameters identified as important industry standards. Readers were categorized by technology type and parameters including cost, detection method, multiplex capabilities, assay type, maturity, and use case were all assessed. Results: Fifteen reader manufacturers were identified and interviewed, and information on a total of 19 technologies was assessed. Reader technology type was found to be predictive of other attributes, whether the reader is smart technology only, a standalone reader, a reader with smart technology required, or a reader with smart technology optional. Conclusions: Pairing reader technology with OTC diagnostic tests is important for improving existing COVID-19 tests and can be utilized in other diagnostics as the OTC use case grows in popularity. Reader technology type, which is predictive of core reader attributes, should be considered when selecting a reader technology for a specific LFA test within the context of regulatory guidance. As diagnostics increase in complexity, readers provide solutions to accessibility challenges, facilitate public health reporting, and ease the transition to multiplex testing, therefore increasing market availability.**

***Index Terms*—Diagnostics, home test, lateral flow assay, OTC, readers.**

***Impact Statement*— Pairing reader technology with OTC diagnostic tests is important for improving existing COVID-19 tests and can be utilized in other diagnostics as the OTC use case grows in popularity.**

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I. Introduction

Point-of-care (POC) testing has grown in popularity over the years with a recent spike in interest due to the COVID-19 pandemic. In vitro diagnostics done at the point-of-care make results available to clinicians and patients in a timelier manner. Diagnostic methods for the detection of SARS-CoV-2 have been described as clinical, molecular, or serological with tradeoffs between sensitivity and specificity noting reverse transcription polymerase chain reaction (RT-PCR) as the gold standard for detection of SARS-CoV-2 [1]. Each of these methods carries technical advantages and disadvantages. Challenges surrounding the availability, cost, and turnaround time for molecular and serological testing along with the limitations of clinical diagnosis as the sole means of diagnosis gave rise to interest in over-the-counter (OTC) diagnostic tests [1]. The U.S. Food and Drug Administration (FDA) supported this effort to make testing more available by granting Emergency Use Authorizations (EUAs) for OTC tests in December of 2022 [2]. These efforts were further supported by The National Institute of Biomedical Imaging and Bioengineering's Rapid Acceleration of Diagnostics (RADx) Tech program which placed an emphasis on development and commercialization of at-home OTC tests.

POC testing is done with the patient present and produces a result at the point of care, whereas OTC testing may be done outside of the healthcare setting with no need for a prescription. OTC technologies may use various scientific approaches, alone or in combination, for the detection of viruses. Lateral flow assays (LFA), viral antigen tests for viral detection, are the most popular due to their low cost, short testing time, and simple operation [3], [4]. Most are embodied in a sealed cartridge with the goal of providing safety and rapidity with operational simplicity that allows them to meet regulatory requirements for low complexity [5]. LFAs have been used for diagnostic purposes such as pregnancy, kidney problems, and infectious diseases for many years, and they have comprised the vast majority of OTC test products for COVID-19. LFAs are typically interpreted visually by the naked eye. While this method has the benefit of operational simplicity, there are drawbacks. The reliance on visual interpretation of lines introduces potential for incorrect interpretation, particularly given varied signal intensity. Additionally, a test with a visual-only readout is not accessible for all users, such as those who are blind or who have significant vision impairment. A solution to these issues, and an opportunity for improvement of LFAs, is to provide an automated read-out of results [6].

For the purpose of this research, a reader is defined as a device that can determine whether or not a target analyte is detected by a diagnostic assay. Many types of readers exist and can be characterized by defined parameters. The field of reader technology expanded over the past decade, but challenges remain, and more research is needed to optimize utility. One example is previous viral assays that were coupled with smartphones. These applications were challenged to overcome connectivity issues, deliver a user-friendly data analysis, and to compensate for ambient lighting bias [7], [8].

The number of LFAs making use of reader technologies is expected to increase due to the shift to OTC testing and a more pronounced need for interpretation of test results that are below the visible threshold for some users [9]. Sensitivity and specificity challenges in viral diagnostics can be overcome with quantitative analysis through LFAs, which supports the movement of testing away from central laboratories [9].

Augmenting OTC diagnostic tests with reader technology is an important step in the evolution of COVID-19 tests. Readers are believed to be solutions for increasing healthcare outreach when used at the point of care [10]. By providing an alternative to visual readouts for results interpretation, reader technology can improve accessibility of OTC diagnostics. Other benefits to utilizing reader technology include optional reporting of test results to an institution and supporting the market shift to include multiplex capabilities, which are more complex to interpret visually.

In support of the development and commercialization of at-home OTC tests, the National Institute of Biomedical Imaging and Bioengineering's Rapid Acceleration of Diagnostics (RADx) Tech program has investigated the current state of reader technology development by interviewing reader manufacturers. We aimed to investigate the reader landscape by comparing several parameters identified as important industry standards. In this paper, we looked at readers that can be categorized in the following groups: smart technology only, physical reader with smart technology required, standalone readers, and standalone readers with smart technology optional. The purpose of this research is to identify and discuss important parameters for the assessment of LFA reader technologies for consideration by manufacturers or researchers.

II. Materials and Methods

A list of reader technologies was compiled over a three-month period in 2023. Early efforts leveraged the network of RADx consultants, who have professional backgrounds in in vitro diagnostics and reader technologies. This was supplemented by a more expansive search for reader technologies, both domestic and international. We expanded the search beyond the RADx network and consulted industry subject experts that helped to identify further technologies. Each company was contacted and interviewed through a systematic process to investigate offerings and technologies. Multiple interviews were conducted with reader companies, and a matrix of parameters was developed to guide each discussion. (Table I) At times, the interview subjects elected not to share information they considered proprietary, so these data points are omitted. Results are reported for data points that were successfully gathered with omitted points being left out.

TABLE I
READER PARAMETERS AND RANGES OF RESPONSES

PARAMETER	RANGE
Non-Recurring Engineering (NRE)	$3K - $2M (median $550K)
Maturity	Prototype - Commercial
Time to Develop	2 – 24+ Months (median 8.5 months)
Installed Base	0 – 100K
Detection Method	Camera, Sensor
Multiplex Capabilities	Yes, No
Dual Strip / Cassette	Yes, No
Assay Type	Colorimetric, Fluorescence
Current Use Case	POC, OTC
Regulatory Status	None, CE Mark, 510(k)

Non-Recurring Engineering (NRE), point of care (POC), over-the-counter (OTC)

TABLE II
READER TECHNOLOGY MATURITY SCALE

NUERICAL VALUE	DESCRIPTION
1	Technology is a concept
2	Technology is a prototype
3	Technology. Is an advanced prototype
4	Technology is commercially available
5	Technology has sizeable installed base

Specifically, this investigation sought information concerning cost, detection method, multiplex capabilities, assay type, maturity, and use case. Cost parameters, including non-recurring engineering (NRE) cost and additional fees such as monthly, per use, or other variable costs, were collected. Readers were categorized by technology type determined by embodiment and smart technology status.

Level of maturity was determined on a scale from one to five based on product development status and installed base. (Table II) Specific development times from concept to manufacturing beyond 24 months were not collected, since companies at an early stage of development acknowledged less certainty around their development timelines. Examining the installed base of a reader technology is critical in determining its maturity, as a higher installed base typically indicates greater maturity. For instance, a reader with an installed base of tens of thousands highlights successful product performance and market acceptance, whereas a reader technology with zero or minimal installed base is working to prove performance and gain market penetration.

Technologies were categorized as either colorimetric or fluorescence-based assays, and as either camera or sensor-based. Technologies were assessed for multiplex capabilities to establish if the reader could read more than one test type. Multiplex test embodiments were either multiple tests per single cassette or multiple cassettes. Use cases were determined to be either POC or OTC. Regulatory approval status was also gathered.

TABLE III
TYPES OF READERS (STANDALONE, SMART TECHNOLOGY ONLY, SMART TECHNOLOGY POSSIBLE INTEGRATION)

	TECHNOLOGY TYPE	DESCRIPTION	
(R)	Standalone reader	A reader device that does not require any smart technology connections and is used by itself to obtain a result	3
(S)	Smart technology only	A reader that is a smart technology by itself and does not require any other supporting devices or components to obtain a result	5
(RS)	Reader with smart technology required	A separate reader device that also requires smart technology to be used in order to obtain a result	1
(RSO)	Standalone reader with smart technology optional	A separate reader device that can function alone or has the option to be used in conjunction with smart technology to obtain a result	10

Standalone reader (R), Smart technology only (S), Reader with smart technology required (RS), Standalone reader with smart technology optional (RSO)

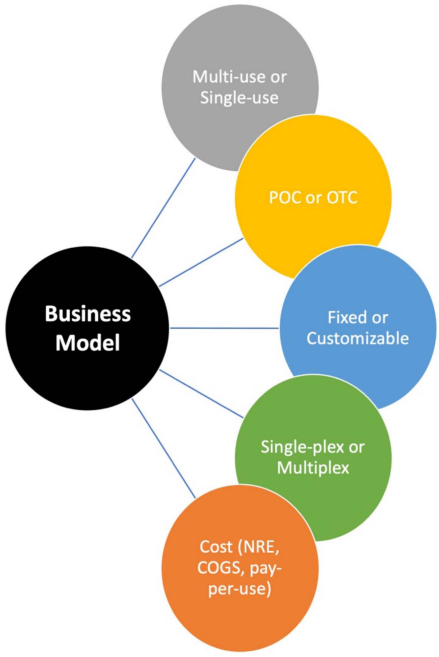

Fig. 1. Factors making an impact on the business model of a reader technology.

III. RESULTS

Fifteen reader manufacturers were identified and interviewed, and three of these manufacturers shared information about multiple technologies, resulting in a total of 19 technologies for which information was gathered: 3 standalone readers (R), 5 smart technology only (S), 1 reader with smart technology required (RS), and 10 readers with smart technology optional (RSO). A standalone reader is defined as a reader device that does not require any smart technology connections and is used by itself to obtain a result. Smart technology only is defined as a reader that is a smart technology by itself and does not require any other supporting devices or components to obtain a result. Using a smartphone or a tablet that is capable of reading the test constitutes smart technology. A reader with smart technology required is defined as a separate reader device that also requires smart technology to be used in order to obtain a result. A reader with smart technology optional is defined as a separate reader device that can function alone or has the option to be used in conjunction with smart technology to obtain a result. (Table III)

Reader technologies were found to have different cost structures that were largely influenced by their technology type. Factors such as customizability to a cassette, multiplex capability, use case designation, cost of goods sold (COGS), and whether or not the device is reusable all affect the business model of a reader. (Fig. 1) Cost structure includes non-recurring engineering (NRE) costs, and COGS. NRE refers to the one-time cost incurred at the beginning of a project associated with the research and development activities necessary to develop a commercial product. The reader technologies examined showed various NRE costs and ranged from $3 K for the smart technology only-type readers to $2 M for a standalone reader with smart technology required. COGS in this case refers to the direct costs associated with manufacturing the reader for commercial sale. Smart technology only readers did not have traditional COGS, as the readers were apps available for download; however, these readers did include NRE and other fees such as monthly, quarterly, or pay per test fees. Physical readers, regardless of associated smart technology, did have traditional COGS, which increased with product complexity as in the case of multi-use readers. However, the ability to run multiple tests with POC multi-use readers must be taken into account when considering the cost to run a single test. Some standalone readers can be customized by the manufacturer to work for an individual LFA test; however, others are fixed and require that the LFA manufacturer develop their test to fit the standalone reader. These differences impacted the overall NRE. The lowest cost structure is observed with readers using smart technology only. Cost structure increases when a physical reader is introduced.

Maturity was determined according to the range listed in Table I and the development timeline was established based on the number of months it would take to produce a reader specific to a test manufacturer's embodiment. Relationships between technology maturity and both NRE and development timeline are shown in Fig. 2. (Fig. 2) As noted previously, reader development timelines over 24 months were not included in the evaluation. From Fig. 2, more mature technologies tended to have lower NRE and development timelines with some exceptions. Overall, smart technology only readers had shorter development timelines than those using standalone readers. Ten technologies assessed were determined to have a maturity level of 4 or 5 meaning they were commercially available.

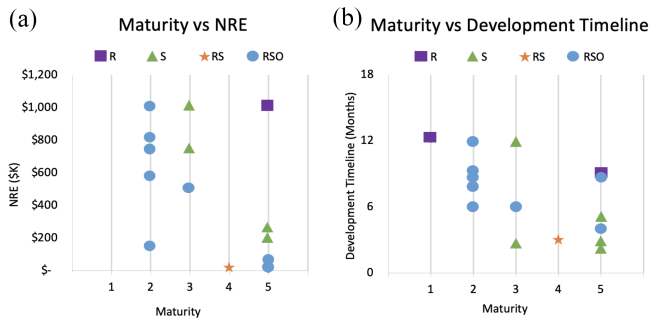

Fig. 2. (a) Maturity is shown on the X-axis with non-recurring engineering cost shown on the Y-axis with each reader technology classified by technology category. (b) Maturity is shown on the X-axis with reader technology development time shown on the Y-axis with each technology classified by technology category.

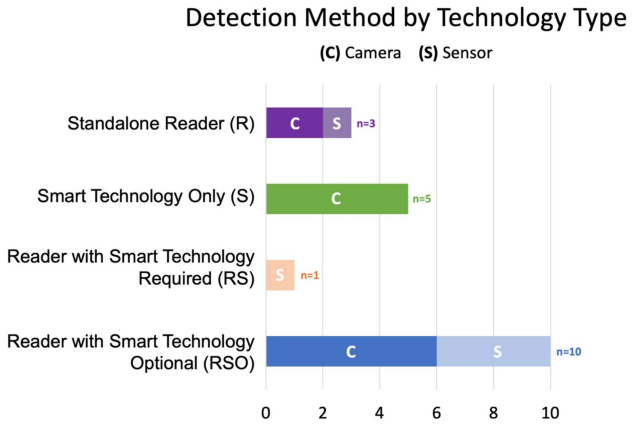

Fig. 3. Detection method (camera or sensor) by technology type – standalone reader (R) (n = 3), smart technology only (S) (n = 5), reader smart technology required (RS) (n = 1), and standalone reader with smart technology optional (RSO) (n = 10).

Lateral flow assays make use of two types of biochemical assays: colorimetric assays and fluorometric assays. Colorimetric assays use spectrophotometrics to measure color changes in the captured assay product based on light absorbance [11], [12]. Fluorometric assays measure fluorescence, which is determined through an optical mechanism that uses excitation light at one wavelength to generate an emission signal at another wavelength. They are highly sensitive and exceedingly popular in laboratory diagnostics, however ambient light exposure can cause interference in these assays [13]. Fluorescence is more sensitive than colorimetric due to detection of energy that is lower than light is absorbed [11]. Fluorescence requires an excitation light source, optical filters, and a closed container in addition to a light detector [7]. Reader technologies studied here were found to either use colorimetric technology only or to be capable of both colorimetric and fluorescence. No readers were only capable of fluorescence detection.

Readers make use of either a camera or a sensor for detection. (Fig. 3) Camera technologies are typically more expensive than sensor technologies; They are also more flexible while sensors are more prescriptive. Sensors can be implemented in two ways: (1) They can be placed where each of the LFA lines are expected to be, thereby requiring multiple sensors, or (2) A single sensor is placed where it can detect all lines' absorbance and position. Camera technology can also be utilized in two ways: (1) It can leverage smartphones with already embedded cameras or (2) A camera can be incorporated into a reader. Smart technology only readers made use of cameras exclusively. Camera-based technology was also more prevalent than sensor-based technology in standalone readers.

All interview subjects reported their reader technologies as having multiplex capabilities (100%). Nine total reader technologies (47%) indicated having the ability to read a dual strip cassette or more than one cassette at a time. Six reader technologies (32%) have regulatory approval in either Europe (CE Mark) or the United States (EUA, 510(k)). Thirteen reader technologies (68%) indicated OTC use case capabilities. Some of these had both POC and OTC use cases, however, POC use was not explored during this OTC-focused research.

IV. Discussion

Readers vary greatly with regards to cost, development, and technology. Reader technology type is predictive of other attributes, whether the reader is smart technology only, a standalone reader, a reader with smart technology required, or a reader with smart technology optional. The lowest cost structure is seen with smart technology only readers. More mature technologies with regards to state of product development have shorter development timelines and lower NRE. Most technologies investigated (80%) have current capability for either colorimetric or fluorescence while the remaining have capability for only one detection method.

Most reader technologies available for LFA use today are specific to a particular LFA strip and cannot be adapted for other tests or multiplex tests without significant design changes [14]. By contrast, 16 of the reader technologies that we investigated were adaptable, demonstrating that there is interest and ongoing research for this case. All the technologies investigated could support multiplex testing, which would involve multiple test lines within a single test cassette with each line detecting a different target like SARS-CoV-2, Flu A, Flu B, etc.

The majority of the studied readers leveraged smart technology (84%). By incorporating smart technology into a reader, the accessibility for several user populations is improved. Blind and low vision users place emphasis on assistive technology, such as a smartphone, for use in interpreting diagnostic test results [15], [16]. Additionally, colorimetric assays depend on the user's perception of color change which differs by person, and by using a reader, the user's need to interpret a color change is removed [17]. However, the requirement to use smart technology can be a disadvantage to populations that are not able to access smartphones due to economic, cognitive, or physical barriers. Aging populations may also experience barriers in using smart technology [18]. Conversely, assay technologies requiring optical-based platforms may not be found in resource limited settings and having a smartphone may make these point of care diagnostics more portable and therefore accessible in resource poor settings

[19]. We found that the lowest cost structure was for readers using smart technology only - however, this could be attributed to smart technologies already having an installed base and thus acquisition cost not being factored in. The major component in the cost structure of smart technology only readers is associated with the development or customization of an application and not a physical reader device.

The cost structure of readers depends on multiple factors that are often interconnected. Detection method, like the use of a camera, can be leveraged from a smartphone, making the overall cost of the reader less than that of one that is sensor based. Camera-based technology is often quicker to adapt to a specific LFA and consequently to implement, because only the code needs to be modified. Whereas, when working with a sensor-based reader, the physical embodiment of the reader or location of the test strip lines likely have to be changed when modifying the technology to achieve necessary alignment. However, cameras do contain challenges surrounding mechanical and optical complexity as well as further design challenges around the image quality and analysis [14]. Another factor to consider when discussing reader cost is demand. Reader manufactures will have challenges keeping costs low if the demand is low. This may be especially challenging for multi-use reader manufactures, where the multi-use nature of the reader tends to decrease the overall number of readers required, as compared to non-multi-use (single use disposable) readers. The decision between single-use vs multi-use readers is therefore an important one if the ability to drive lower costs through high volume is required.

POC readers are typically available at a higher price point when compared to OTC. A majority of the reader manufacturers entered this field with their own POC devices with the potential for OTC development and transferability. The readers that follow this trend are often more expensive than the readers that are originally developed for OTC use. Modifying an existing POC reader to be capable for OTC use case ultimately inherits the properties of a POC test which may be over specified for the target market. COGS may remain high in these scenarios. Smart technology only readers may be an exception to this since they do not require any additional physical reader manufacturing. We found that the most mature reader development companies are from outside of the United States. We suspect this is due to regulatory considerations and healthcare infrastructure.

Some commercially available readers can transmit results to a secure server and require data analytics for integration with patient clinical history [14]. In the United States, reporting capability for test results is required for all COVID-19 OTC Emergency Use Authorizations (EUAs) [20]. As a result, most of the reader manufacturers demonstrated capabilities within their technology to report test results. Within the US, hubs have been created that relay results and pertinent information to the relevant local, state, and federal public health systems. Outside the US, there are different reporting authorities that reader manufacturers partner with to satisfy any reporting requirements. Reader technologies are subject to appropriate regulatory classification and guidances and are subject to review.

Ultimately, these findings have potential to impact LFAs used for detection of many other viral pathogens such as human immunodeficiency virus, hepatitis C virus, sexually transmitted infections, and others as the need for in vitro diagnostic tests rises [5]. Multiplex technologies for detection of more than one pathogen at a time traditionally have required readers that are large and bulky desktop systems [10]. This is another large movement in the diagnostics community with a need for further reader adaptation. As over-the-counter testing grows in popularity, the need for low cost, rapidly adaptable, robust reader technologies will continue to expand.

There are limitations within the data presented. This data is limited to the companies that were interviewed, a sample size that included just 19 reader technologies. The selection process for interviewed companies and technologies was biased by the familiarity and networks of the research team. However, this was mitigated by research into the broader field that added candidate technologies outside of those known by the RADx network. There was no formal assessment done on companies themselves; only on the reader products. An early-stage company would have different costs, maturity, and overall capability than an experienced manufacturer. Some of the companies interviewed had commercialized and marketed reader technologies before and some had not. For the purpose of this paper, we were mainly searching for OTC technologies, so this is not a comprehensive POC analysis. Gathering more information on additional technologies would strengthen any conclusions made through this research. To our knowledge, this is the first paper of its kind evaluating and comparing reader technologies for over the counter diagnostics. Other considerations, such as test time, diagnostic sensitivity, design, and further accessibility features, could be investigated in future research. Further research should be done to learn more about additional reader test types beyond COVID-19 to help characterize the reader landscape as a whole. A generic reader with the ability to run multiple tests and rapidly adapt to new targets would be attractive for future pandemic preparedness.

V. Conclusion

Reader technology paired with the use of OTC diagnostic tests is important for improving existing COVID-19 tests and can be expanded further to other diagnostics as the OTC use case grows in popularity. Reader technology type, which is predictive of core reader attributes, should be considered when selecting a reader technology for a specific LFA test within the context of regulatory guidance. The reader technology market is evolving, and there are many technologies, but no clear, single solution. As diagnostics increase in complexity, readers provide solutions to accessibility challenges, facilitate public health reporting, and eases the transition to multiplex testing, therefore increasing market availability.

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