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FUTURE OF DIAGNOSTICS SERIES WHITEPAPER

Making at-home-molecular tests affordable, actionable and sustainable

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Taking diagnostic testing to patients' homes offers many advantages for global healthcare, and progress in molecular diagnostics unlocks new potential in this space. However, test devices for home use need to achieve low manufacturing costs while meeting stringent regulatory requirements. This article considers practical ways to address these constraints and discusses other considerations such as usability, sensitivity & specificity in devices for home-use.

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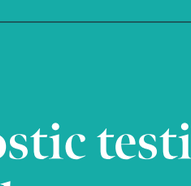

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Advances in techniques for the detection of DNA and RNA have enabled the development of simple but effective tests that take minutes to perform. This opens new avenues for diagnostic testing outside the clinical laboratory, in point of care settings or even in patients' homes.

Decentralising molecular diagnostic testing presents many benefits for global health. Better access to testing facilitates the enablement of earlier treatment as well as engagement with people who might not otherwise get tested. It lets patients avoid unnecessary trips to the physician and can reduce use of antibiotics in markets where they are available without a prescription. During the COVID-19 pandemic, at-home diagnostic testing took off in a big way, helping to reduce the spread of SARS-CoV-2 and introducing many people to the convenience of this model.

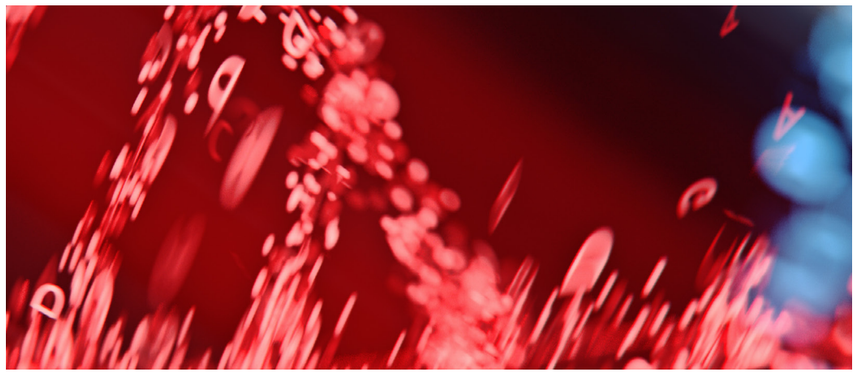
> The value of the At Home Diagnostics Market is expected to exceed USD 7 billion by the end of 2027, registering a CAGR of over 5.4% during 2020-2027. Increasing epidemics have shifted the focus of the general population towards preventive healthcare rather than curative medicines. This creates huge opportunities for manufacturers in this market.1

OTC device innovation

Scientific progress in molecular diagnostics combined with social factors such as patient acceptance creates a fertile environment for at-home diagnostic devices. In the coming months and years, we anticipate increased over the counter (OTC) device innovation for tests covering various conditions ranging from respiratory illness to STIs and cancer.

Clearly, there are many complex factors involved in the development of molecular diagnostic devices for at-home use. As well as being simple and straightforward to use, they must be cost-effective to produce. Consideration also needs to be given to the risk of false negative or false positive results, as well as the potential for undetected co-infections. The sustainability of devices and any consumable components also requires attention.

Molecular testing has historically been considered highly complex and unreliable in the hands of a layperson; only now are medical professionals and regulators' views beginning to shift. Here, we focus on manufacturing costs and the regulatory environment. OTC products are particularly price sensitive as the end user often pays directly and the cost is not shared across many patients. Furthermore, Both these issues need to be factored in at the outset of device development, alongside commercial viability, sustainability, usability and efficacy which we will also discuss.



The $10 cost per test target

Currently, OTC diagnostic devices which provide results at home range from ovulation and pregnancy tests to the nucleic acid amplification tests (NAATs) authorised for COVID testing. The latter retail in the US at around $50, indicating that this is an acceptable consumer price point for relatively infrequent but time-critical molecular tests. We suggest that the target cost of manufacture per test for any at-home diagnostic device should be less than $10 to enable a $50 price point.

Lucira and Cue – the two NAATs which received FDA Emergency Use Authorisation (EUA) for home testing for COVID in the US – are elegant devices involving isothermal assays. Their manufacturers took interesting steps to drive down costs, such as designing for capillary rather than pumped flow and opting for simple result indicators. We analysed both devices to gain insights into how they work and ascertain cost-saving features.

$50 is an acceptable consumer price point for relatively infrequent but time-critical molecular tests

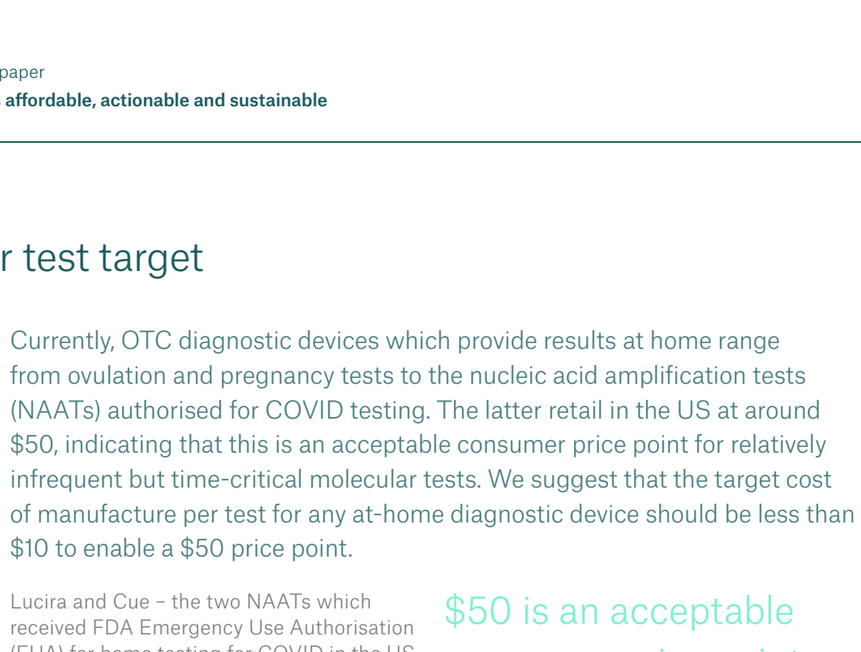


Figure 1: Retail price points for a range of at home diagnostic devices

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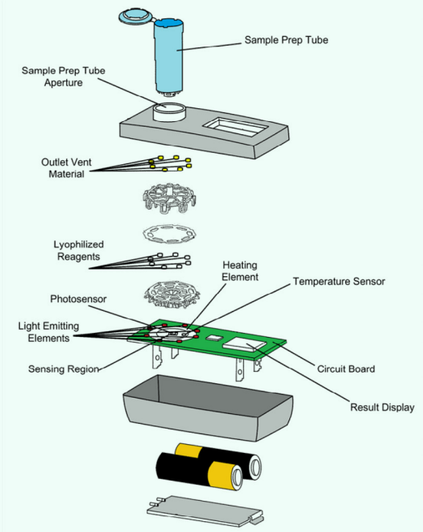

Figure 2: architecture of Lucira COVID-19

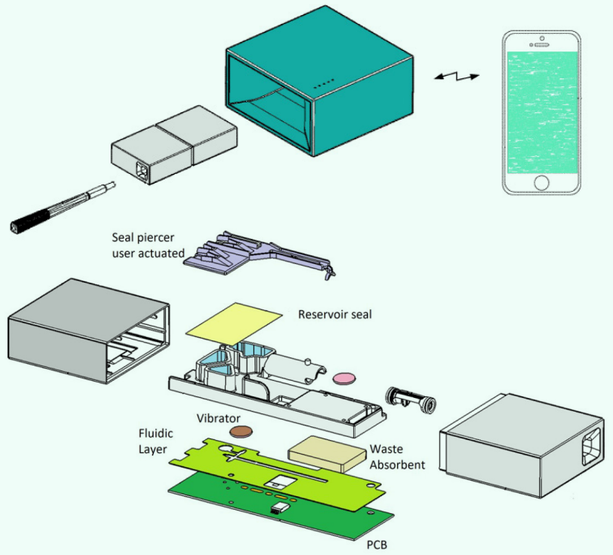

Figure 3: architecture of Cue Covid-19 test

Lucira Check It COVID-19 Test Kit

A disposable device involving a nasal swab which is inserted into the device's tube to generate a positive or negative indication. The single-use test kit can be ordered online in the US only for $75.

Cost-saving features:

- A single user-activated valve which doesn't require automation
- Capillary/gravity flow means there's no need for a pump
- Simple LED indicators for results
- Single, small PCB with heater/optics/micro
- Fluidic mouldings combine reagent storage and light pipes
- No on-board fluid storage means vapour proof seals are not required, simplifying manufacture and design

Cue COVID-19 Test

A platform technology involving a durable instrument and consumable cartridges. This involves more components than the Lucira device. It is the first molecular test authorised by the FDA for at-home use and OTC, without a prescription, in the US and Canada. In the European Union (CE Mark) and in India (CDSCO), Cue's COVID-19 Test is authorized for professional use. At time of launch (2021) the reader retails at $249 and the cost per test when you buy ten is $61 each. There is also a subscription model that reduces the cost to $48 per test. It is sensitive to all variants (including Omicron) and sends results to the users mobile phone in 20 minutes.

Cost-saving features:

- Thermally actuated valves don't require mechanical actuation
- User activated foil piercing for the reagents
- Capillary/gravity flow means there's no need for a pump
- Smartphone used for display and user engagement
- Electrochemical detection on the PCB gives lots of functionality

With both the Lucira and Cue devices, the reagents require DNA/RNA amplification which dominates costs. To further improve cost-effectiveness, a key design priority would be finding ways to reduce the volume of these enzymes without harming sensitivity. This might be achieved by adjusting the way reagents are added to the test cartridge.

A vision for cost reduction and sustainability

Taking molecular diagnostic testing to the home raises new questions surrounding waste and the sustainability of materials used. However, many cost-saving measures can dovetail with environmental considerations. Developing a low-cost architecture with paper-based and pulp-based outer packaging would reduce the need for single-use plastic in disposable devices or test components. Similarly, finding ways to reduce the materials used, make test cartridges smaller, or reuse instruments can bring sustainability as well as cost benefits. OTC use avoids the use of containers and packaging to ship samples to laboratories to perform the testing.

Cartridge cost reduction

In terms of consumable elements such as reagents and fluidic plastic parts, costs are dominated by the reagents for isotherm amplification, particularly the enzymes. We estimate that these cartridges could be manufactured in high volumes for $6 per cartridge unit. Challenges to overcome include:

1. Reducing the volume of reagents whilst maintaining sensitivity.
2. Adding the reagents to the cartridge: dry in the cartridge or dry off the cartridge with a bead added.
3. Protecting the reagents from the liquids on board.

Instrument cost reduction

If the cartridge costs $6 and the target cost per test is $10, that doesn't leave a lot of room for the single-use instrument cost. Figure 4 shows a simple embodiment of an instrument which we estimate could be made in high volumes for around $6 per instrument. Compare this with figure 5, showing a more traditional approach where (depending on the level of functionality

No motors/solenoids
Capillary flow
Simple result indicator
Single color absorbance
No external comms

Motorised valves
Pumped flow
Simple status display
Multichannel flouescence
Bluetooth to Smartphone

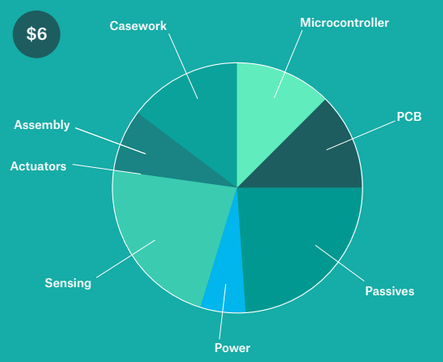

Figure 4: Simplest instrument embodiment

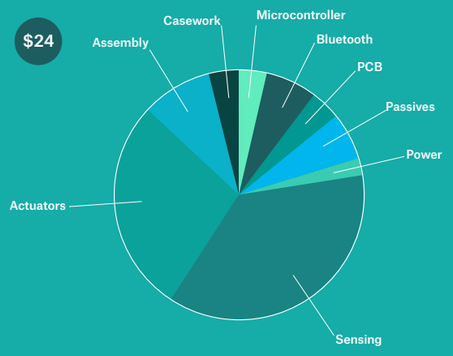

Figure 5: A more traditional approach

NRE is not included in these estimates

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Total test cost: different approaches

Several approaches can be explored in the management of total test cost, and each raises different sustainability considerations too.

If the device cost is high, the instrument could be designed for multiple-use; the more reuses, the cheaper the cost per test, as shown in Figure 7. With the single-use test approach, the test needs to be extremely simple to keep costs down.

One alternative to consider is an intermediary position involving instrument-free single-use tests. These would integrate with an existing device that the user already owns, such as a smartphone, to provide power and human readable outputs. This vision would require clever design to reduce the risk of human error, for instance using folded paper devices or heat activation to unlock consecutive stages of the test (illustrated in Figure 8).

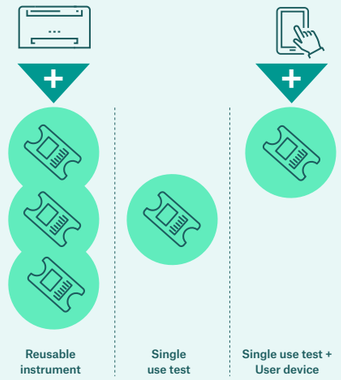


Figure 6: Durable or disposable or instrument-free

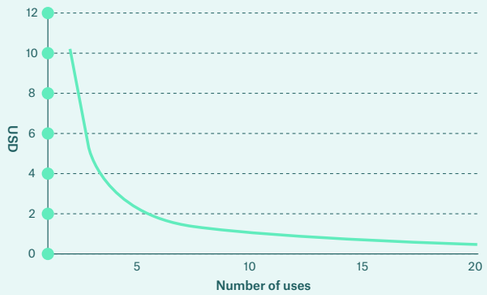


Figure 7: Contribution of instrument to cost per test

Potential technology approaches

Use of smart phones	▸ Camera ▸ User guides ▸ Online reporting ▸ Power source
Human readable output	▸ Lateral flow reporter ▸ CRISPR enhancements
User actions - step 1 unlocks step 2	▸ Folded paper devices ▸ Hydrophobic valves ▸ Heat activation
Simple heat source	▸ PTC heater ▸ Phase change ▸ Body temperature

Figure 8: Vision for an instrument-free diagnostic device

Applications for at-home testing

There's certainly breadth of opportunity in diagnostic home testing. COVID-19 home tests have been nasal-based, meaning samples are relatively easy to obtain. Other sample types, such as blood, urine, STI swabs and stools, can be more difficult to obtain for various reasons. They also bring new challenges and obstacles to overcome, including user embarrassment and perception as well as technical issues. However, exploration of this area should be on the agenda of diagnostic companies.

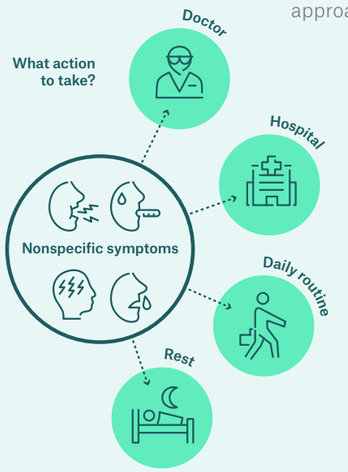
	Nasal swab	Blood	Urine	Swabs for STIs	Stool
Social embarassment	LOW	LOW	MEDIUM	HIGH	HIGH
User experience of self collection	Easy - mild discomfort	Fear of pain Hematophobia	Messy - 1st catch vs midstream	Easy	Unpleasant
Sample preparation	Lysis and dilution	Concentration + Purification	Concentration + Purification	Concentration + Purification	Suspension + Filtration + Purification

Table 1: Sample types and user perception

Another interesting avenue to consider is panel testing for more than one target for an illness or strain, with a single device. This approach is useful in the diagnosis of illnesses where symptoms are non-specific. For example, with a respiratory infection, symptoms could include sneezing, coughing, sore throat, high temperature and chest pain. These are prevalent in a number of infections from Flu and SARS-CoV-2 to RSV.

As we pull out of the pandemic, home panel testing may become a more efficient approach, informing decision making and treatment paths as an ongoing form of disease management. Many illnesses could potentially be covered, so it will be important to identify those that have the most value in the marketplace.

Gastro infections and STIs can also be panel tested, as Table 2 demonstrates. The advantages of this approach are clear; it avoids the purchase (and manufacture) of multiple tests, more informed decisions can be made, and it gives greater confidence in identifying causes of illness.



Respiratory	Gastro	STI
Flu A&B	Campylobacter	GT
SARS-CoV-2	E coli (multiple)	NC
RSV	Norovirus	
Adenovirus	Rotavirus	
HMPV	Salmonella	
HPIV		

Table 2: Syndromic panels

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Sustainability considerations for an OTC product

Traditionally, sustainability hasn't been particularly high on the agenda for diagnostic testing. However, as it moves into the home setting, we expect this to become more important due to the visibility and volume of waste. Design considerations might include:

1. Reducing use of materials: Can cartridges be made smaller? Can we change our choices of polymers?
2. Materials reuse and recycle: Could we use pulp-based casework or recyclable plastics, or hybrid materials that are designed for easy separation by the user?
3. Reconditioned and refurbished instruments: What are the options for a circular economy? How do we deal with the hygiene issue and perception of reuse of medical equipment?

The Sagentia Innovation team conceptualised a low-cost architecture that uses paper and pulp-based packaging with lateral flow reporters to give a human or camera readable output whilst keeping the consumable at a very low cost. A USB power source would be suitable to achieve temperature control and activation given its widespread adoption and accessibility. This approach would allow for a very low-cost consumable and durable, in a molecular test with a multiplexed output capable of achieving 3-6 targets.

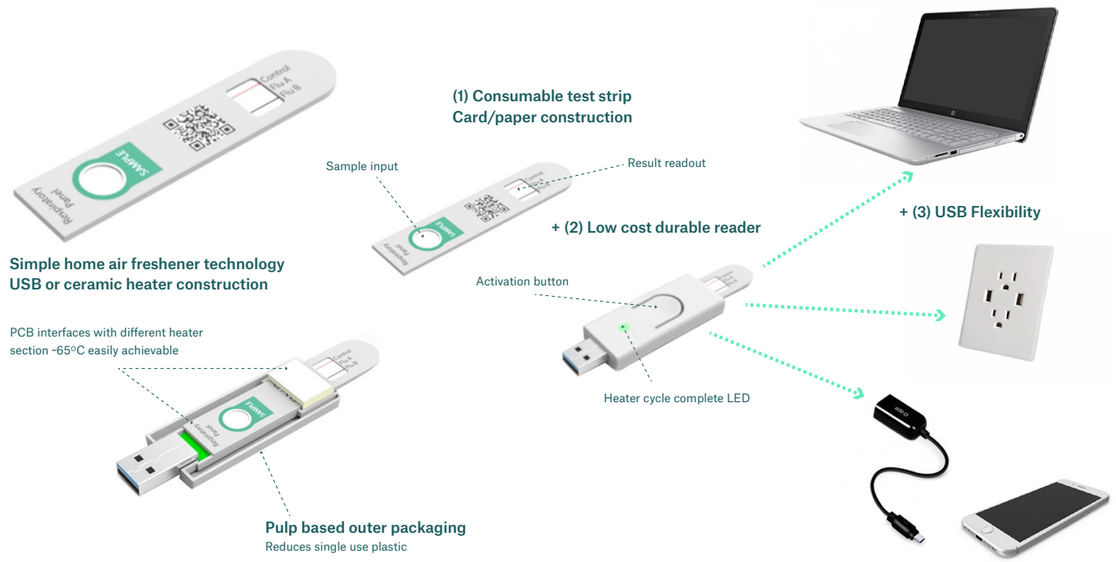

Figure 9: Example low cost architecture

Regulatory strategy

When it comes to FDA authorisation, the safety and effectiveness of OTC devices comes under intense scrutiny. In general, manufacturers would be expected to take an incremental approach whereby authorisation for use in clinical settings is sought first, often followed by point of care then at-home use. This is especially true for novel technologies such as molecular diagnostic devices where there is little historic evidence of safe and effective use.

Regulatory agencies have traditionally struggled with the concept of patients handling diagnostic testing. However, COVID-19 underlined the many benefits of bringing such testing into the home setting, whilst demonstrating the convenience and effectiveness of this approach to patients, regulators and healthcare providers alike.

Due to the public health emergency declared in response to COVID-19, rapid developments had to be made. Figure 10 summarises some of the regulatory milestones for the OTC landscape during that time.

The Lucira and Cue products (shown above the line in Figure 10) both took advantage of FDA's EUA provisioning. Nevertheless, they still adopted a stepwise regulatory strategy. Lucira's device initially obtained authorisation for prescription home use, which involves fewer regulatory hurdles, before gaining OTC authorisation five months later. Cue went straight to non-prescription authorisation, albeit in point of care settings, before obtaining clearance for at-home use nine months later.

When the COVID-19 public health emergency is rescinded, the devices' EUAs will be terminated. If Lucira and Cue are to continue marketing these products beyond that time, they will need to seek authorisation in the usual way, via the FDA's 510(k), De Novo or premarket approval routes.

So, what can manufacturers of at-home molecular diagnostic devices learn from this? A key takeaway is that regulatory strategy needs to be aligned with product development from the outset.

An incremental approach where authorisation for use in clinical settings is sought before OTC authorisation would be advisable much of the time. However, a good regulatory strategy also has the flexibility to respond to changing circumstances, whether that's a public health emergency or the emergence of a predicate that might unlock a more straightforward regulatory path.

The story behind the Lucira device underlines the benefits of an adaptive regulatory strategy. It was already on track for FDA authorisation for detection of Influenza A and B when SARS-CoV-2 hit the headlines. At this point, the organisation challenged its technical team to develop a COVID test, meaning it was ready to act fast once it became eligible for EUA. Ultimately, it was the first at-home molecular test for COVID to obtain EUA from FDA.

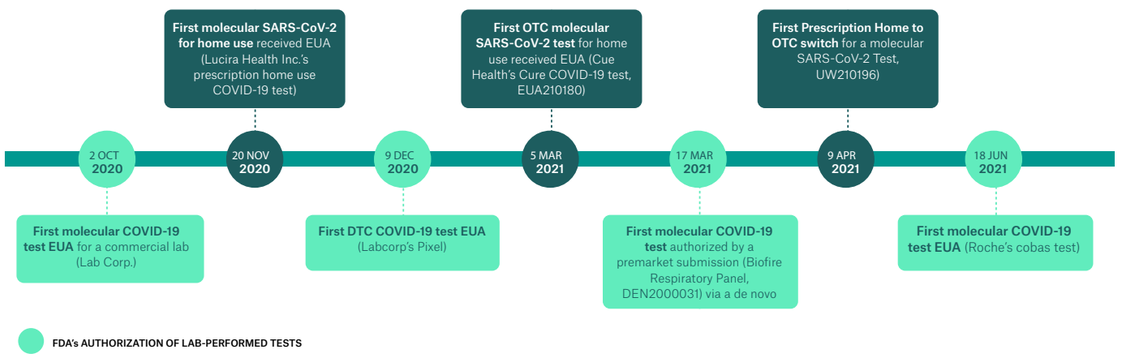

Figure 10: Select milestones for Molecular COVID-19 tests

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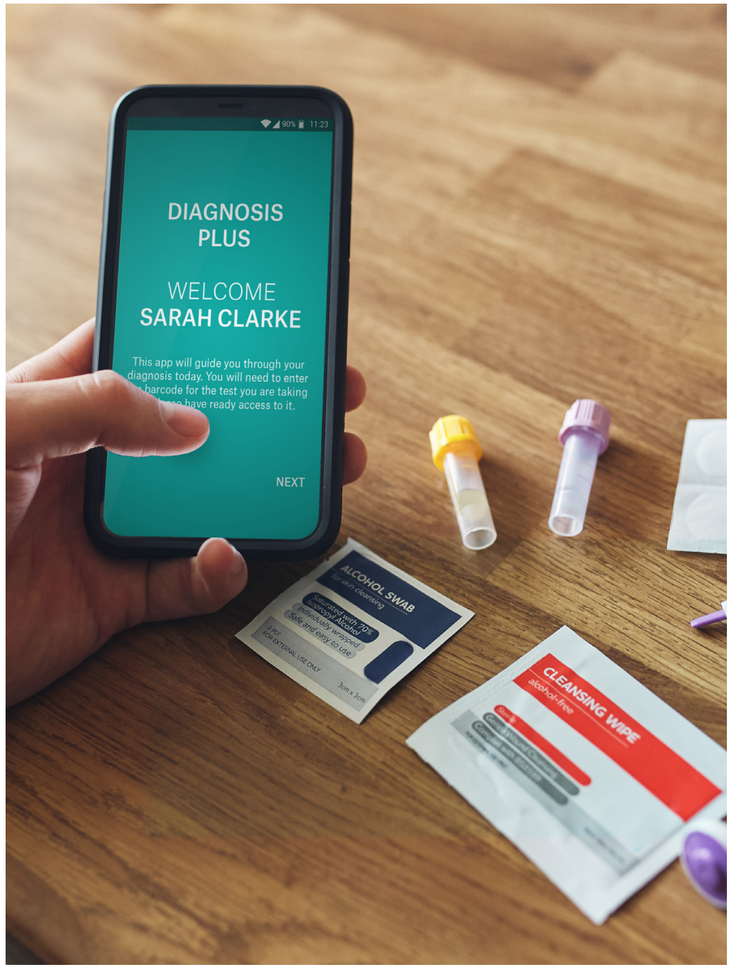
The future of molecular diagnostics is in the home

The infectious nature of COVID-19 meant at-home molecular diagnostic testing was highly advantageous in controlling the spread of the disease. Developments here could pave the way for a more lasting shift towards OTC tests being authorised and adopted for respiratory illnesses such as flu, adenovirus and human metapneumovirus.



We believe there could also be a strong market for at-home molecular diagnostics for STIs and gastro illnesses. Traditional sample collection and testing for these conditions may evoke social discomfort for some patients, preventing them from seeking treatment. If molecular diagnostics can be conducted at home at an acceptable price point, testing is likely to increase.

In time, there could be a market for platform technologies that are used for various molecular diagnostic tests in the home. This brings the scope to make devices more durable and complex, with consumable elements that are more sustainable. While the market may not yet be ready for this, simple tests designed to integrate with companion apps on smartphones could represent an effective intermediate position.

Companies that align product innovation with cost-effective manufacture and a well-informed regulatory strategy are set to gain competitive advantage in this evolving space. They could also play a valuable role enabling earlier and more widespread detection of illness, driving improved access to healthcare for populations around the world.

References
1. https://www.futurewiseresearch.com/healthcare-market-research/At-Home-Diagnostics/181

This paper was written by Sagentia Innovation and supported by sister company TSG Consulting, who are all part of Science Group.

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We serve a number of key markets and industry sectors including agricultural, industrial, consumer, food and beverage, animal health, and medical. Our teams comprise scientists and regulatory experts – many of whom have previously held positions at regulatory agencies, departments and in industry. This combination of science, regulatory expertise and knowledge of how institutions and industry operate provides our clients with superior and well-rounded guidance.

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