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WHITE PAPER

Sample collection and Point of Care testing

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Point of Care and Point of Need testing hold much potential to improve the accessibility and efficiency of medical diagnosis. Innovation is rife and extensive market growth is expected in the coming years. However, the performance of diagnostic devices is reliant on the provision of high quality samples. These are not always easy to obtain, especially outside of clinical settings. This whitepaper looks at the sample collection issue and considers how it can be resolved to improve the efficacy of decentralised diagnostic testing.

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The Point of Care (PoC) testing market is a hotbed of innovation with extensive growth forecast over the next eight years[1]. Devices in this category can enable earlier diagnosis of conditions ranging from respiratory illness to urinary tract infections (UTIs) to cancer. Increasingly, they are available over the counter (OTC) for use at 'Point of Need', and they have the potential to change the face of traditional healthcare. Affordability plays a critical role in accessibility, and Figure 1 illustrates the current costs of some common OTC diagnostic tests.

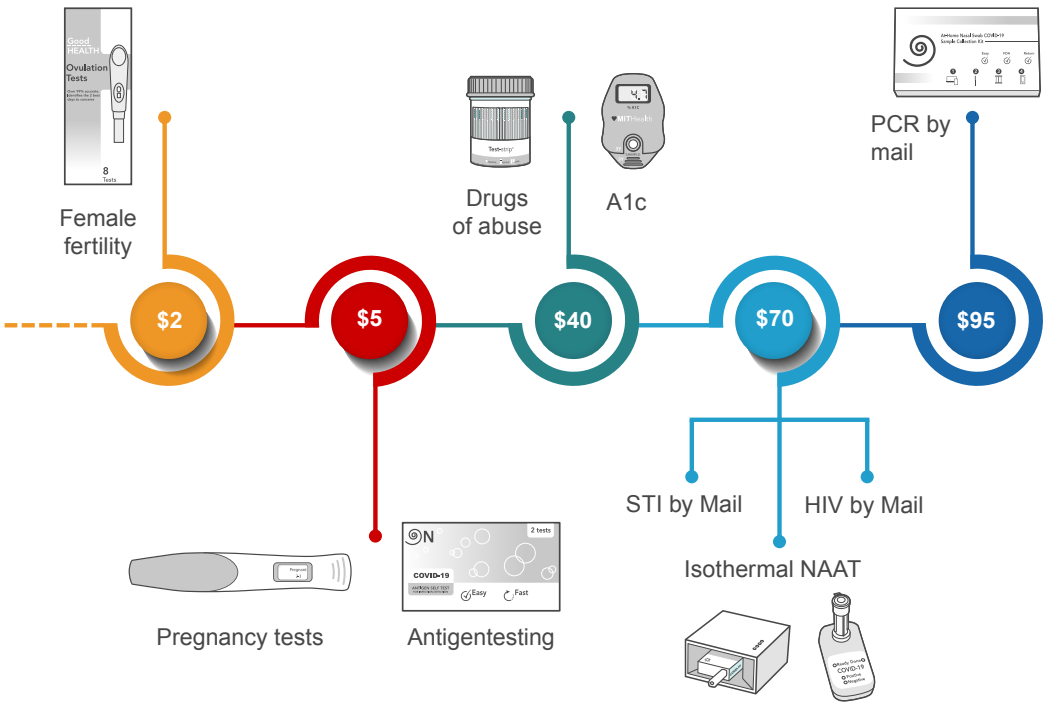

Figure 1: Current retail prices of OTC tests range from $2 to $95.

In a previous whitepaper, we looked at how advances in the detection of DNA and RNA have opened new avenues for diagnostic testing outside the clinical laboratory[2]. We considered the regulatory landscape and ways to reduce the cost of manufacture. These are critical factors, but the challenges don't end there.

Bridging the gap between sample and test

A central goal of PoC testing is to deliver actionable information that enables rapid diagnosis to improve patients' health outcomes. It's often less invasive and more convenient for patients, as well as being quicker and more cost effective than sending samples to a clinical laboratory.

PoC diagnostic tests rely on the provision of high quality samples for analysis, because low quality or contaminated samples may generate incorrect results. However, collecting samples of a sufficiently high standard in a cost-efficient way can be a challenge. Since sample collection is not the central focus of diagnostic test manufacturers' R&D teams, this may result in an efficacy gap which risks hindering product authorisation and uptake.

Improving sample collection at PoC could be game-changing. Enabling non-healthcare professionals, or patients, to consistently collect high quality samples would pave the way for increased availability of reliable PoC diagnostic tests for a wider range of conditions.

We believe that it is possible to achieve this by bridging the gap between sample collection and test using available technologies and a focus on human centred design. In this whitepaper, we consider the collection of two fluids used in the diagnosis of many conditions: blood and urine. We assess current sample collection methods and then outline theoretical concepts that could improve the patient experience and health outcomes while keeping costs under control.

Benefits of decentralised diagnostic testing

- Better access to testing facilitates earlier treatment
- Engagement of people who otherwise would not get tested
- Fewer unnecessary clinical appointments
- Reduced spread of infectious disease
- Reduced use of off-prescription antibiotics

Blood sample collection

Venepuncture is the gold standard for collecting blood samples for diagnostic testing in clinical environments. It enables large volumes to be obtained, and the risk of haemolysis – where red blood cells break down releasing their haemoglobin – is low. However, this procedure must be handled by a phlebotomist so it's not well suited to PoC testing.

Capillary blood collection is a common alternative to venepuncture when smaller volumes are sufficient. This is usually conducted using a fingerstick, so self-collection is possible, and it has become the standard for blood glucose testing. There are drawbacks to this method though, including the risk of contamination as well as haemolysis of the sample. It can also be difficult to obtain the required volume.

Existing devices for capillary blood collection

Several PoC diagnostic tests use the finger prick method and have an integral blood collection capability.

In some cases, a collection device is used to obtain the sample and transfer it into the test cartridge. These include the *Afinion 2 Analyzer* from **Abbott** and *HemoScreen* from **PixCell Medical** as well as the *Atomo* HIV Self Test which is available for at-home use in Australia.

Other devices draw the sample directly into the test cartridge from the finger prick. The *ADEXUSDx* lateral flow device from **NOWDiagnostics** is a good example, as is the *Microcuvettes* optical cell device manufactured by **HemoCue**.

While these devices perform their intended function well, the finger prick method of blood collection can be painful and messy. A new wave of minimally invasive capillary blood collection devices offers an alternative approach. Usually applied to the upper arm, they are user activated with a push-button and typically collect between 0.2 and 1ml of blood in under ten minutes. Examples include the **YourBio** *TAP II* device which uses a microneedle array to make an incision to the skin and the *Drawbridge Health* device which uses tiny lancets and vacuum technology to pull blood from capillaries onto a storage matrix within a removable cartridge. **Loop Medical** uses a similar vacuum-based technique to collect larger volumes of 1ml.

Spotlight on YourBio's TAP II

YourBio launched a COVID-19 antibody test direct to consumers, with its TAP II device used to draw the blood sample. We analysed 133 user reviews posted online and discovered that:

- 81% said it was 'easy' or 'simple' to use
- 53% said it was painless
- 20% mention being nervous using it for the first time
- 11% report a bruise or mark on the arm after use
- Only 2% said they were unable to fill the blood tube

Plasma separation at PoC

The PoC tests mentioned above accept whole blood, so plasma separation is not required. However, many quantitative assays require either plasma or serum, which is generally obtained in clinical laboratories via the centrifugation process. If this separation could be performed in a cost-effective way at PoC, a far greater range of diagnostic testing could be performed in non-clinical settings.

Figure 2 illustrates various approaches that can be used for plasma separation. To be useful in a PoC environment, they need to achieve separation in under five minutes, and ideally within two minutes. Membranes can be used to separate 60-80% of the available plasma in two to three minutes, but in tests where larger volumes are required, integrating a membrane into the chip becomes more difficult and expensive. It's often better to combine the use of membranes with additional techniques such as sedimentation or agglutination.

On market PoC tests using filtration or centrifugation include the *Triage D-Dimer* from **Quidel**. This device, which separates plasma via capillary filtration, aids the evaluation and assessment of patients with suspected disseminated intravascular coagulation and thromboembolic events including pulmonary embolism and deep vein thrombosis. The *Piccolo Xpress* from **Abaxis** delivers real-time blood chemistry information for PoC diagnoses, with plasma isolated using centrifugal separation.

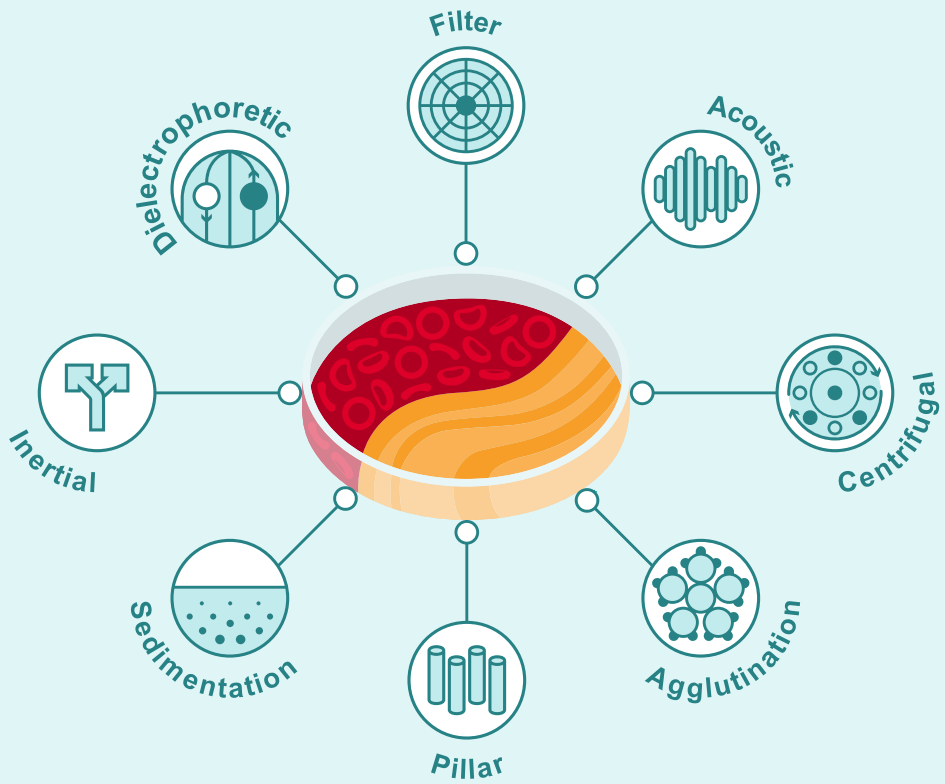

Figure 2: Combining multiple plasma separation techniques could make the process quick and effective enough for PoC testing.

A new concept for blood collection

We envisage a device which separates the plasma from blood during collection, several devices already utilise a vacuum to assist in drawing the blood from the patient. In our concept device (figure 3), we divert the vacuum through the collection vessel, enabling the vacuum to both draw the blood from the patient, and then through a filter, separating plasma from blood in one operation. When using the small volumes of blood available from the finger prick it can be difficult to achieve sufficient plasma volume through a filter, however, the larger blood volume available from the wearable devices can simplify this. In addition, as blood collection and plasma filtration are performed simultaneously, more time is available without introducing an additional waiting period for the user.

Having achieved the sample, we can simplify the transfer to the test device reducing the risk of contamination and errors. Our sample vial has a septum on the bottom, allowing insertion into a test cartridge, reducing the number of steps and single use consumables to collect and transfer usable plasma from patient to test cartridge.

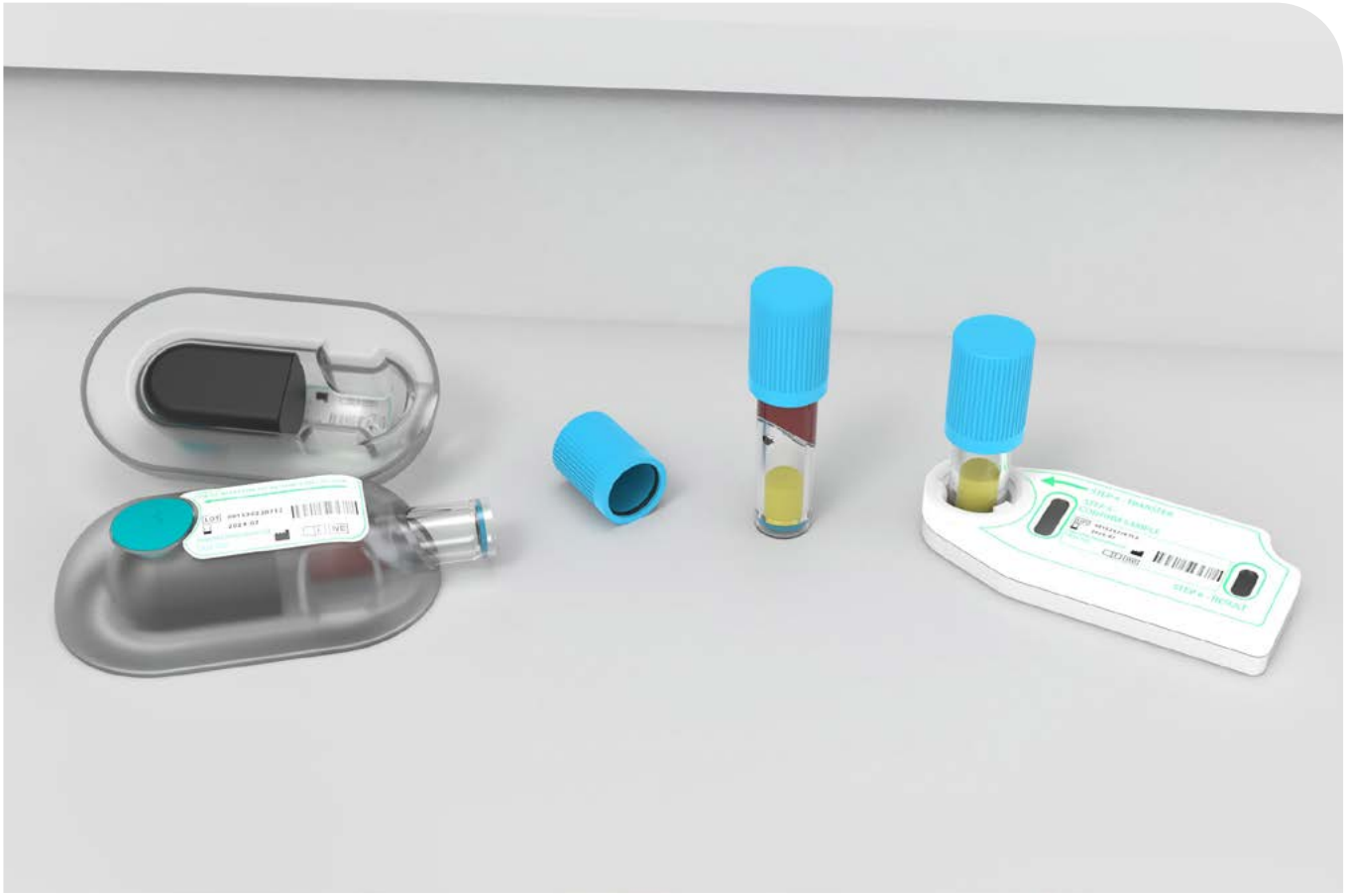

Figure 3: A new concept for blood collection.

Urine sample collection

Urine is a valuable specimen as a carrier of hormones, cells, proteins and bacteria that the body is eliminating. It's used in the diagnosis of UTIs, sexually transmitted infections (STIs), diabetes and certain cancers. Yet despite its importance and widespread use, there is no standard for device collection beyond simple cups.

Methods of urine capture range from instream sticks to funnels and/or tubes depending on the nature of the intended diagnostic test. There's a common assumption that collection is easy, but in fact, obtaining a high-quality sample is not straightforward. As urologist Professor Frank Chinegwundoh explains:

"Urine sample contamination rates in the UK range from 0.3% to over 70% according to data gathered through a Freedom of Information Act Request to 174 Trusts in 2016, a variance that belies the importance of the specimen to the diagnostic process. Haematology would be unlikely to tolerate this specimen quality variance, yet blood and urine are taken for the same diagnostic purpose."[3]

As with blood sample collection, poor sample quality is a limiting factor in the development of urine-based PoC tests that could accelerate diagnoses and improve health outcomes.

What are the challenges with urine collection?

Some tests, such as those for STIs, require 'first catch'; the first 30ml of the first morning urine. It's used when epithelial cells and debris from the urethra are needed for analysis.

Other tests, for diagnosis of conditions including UTIs or kidney infection, require a mid-stream or 'clean catch'. This is the main portion of the urine void, taken after the first 30ml has flushed any contamination from the urethra, thereby reducing the risk of cross contamination.

Controlling the flow of urine to collect the right portion for the sample is difficult for many people. Trying to capture just the first 30ml, or avoid it for a mid-stream sample, is a significant challenge for anyone with bladder control issues. This problem becomes more prevalent as we get older, or for women post pregnancy.

With capillary blood collection, it can be hard to obtain the necessary volume, but the opposite is true with urine collection and oversampling is a major issue. For instance, flooding the lateral flow strip of an instream stick risks a false negative. When it comes to samples collected in a tube, overflow is common. At best this is messy, unhygienic and potentially embarrassing for patients when handing the tube to a healthcare professional. It can also dilute first catch samples, reducing the effectiveness of testing. For diagnostic tests requiring a bacterial culture, cross contamination of the sample is a problem. This can occur if the sample runs off the patient's legs before it's caught in the tube, and it may lead to incorrect results.

The benefits of human centred design

The first step in overcoming these issues is to address the notion that it's not difficult to obtain a urine sample. A human centred mindset plays a critical role here, ensuring users' needs, experiences, and scenarios are accounted for. When you understand why things go wrong, it becomes easier to put them right. Figure 4 illustrates four drivers of human centred design.

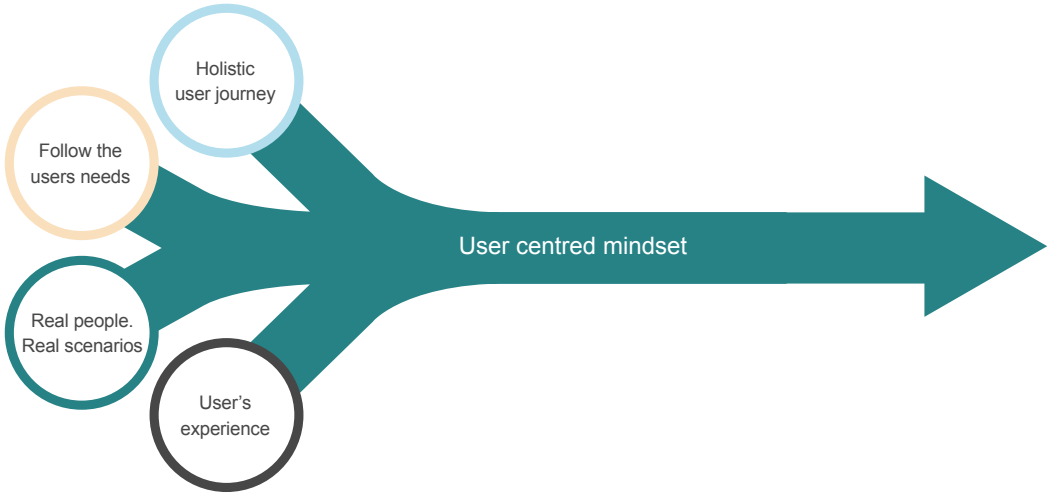

Figure 4: Understanding physical and emotional challenges associated with urine collection is key.

Some diagnostic device manufacturers are adopting a human centred approach to urine collection, as evidenced by **Clearblue** and **Forte Medical**.

Clearblue has developed an instream pregnancy test with a sample sufficiency indicator. A light flashes to let the user know when enough urine has been collected, so they can remove the device from the urine stream and avoid flooding the test strip. This improves the user experience and increases confidence in the accuracy of the result.

According to Forte Medical's website, 58,275 UK patients are misdiagnosed every day due to problems with urine specimens[3]. Its *Peezy Midstream* device (Figure 5) makes it easier for users to obtain an uncontaminated clean catch sample without the need to pause urination or hold a separate tube and funnel. When the device was trialled at the Barts Health NHS Trust, Royal London Hospital site, Professor Chinegwundoh reported that:

"Up until this point, our contamination rates were running at 17.4%...The trial is ongoing, but so far we have found contamination significantly reduced to 1.5%. The Microbiology Department are convinced that the device delivers a higher quality specimen."[4]

Figure 5: With Peezy Midstream[5], users only hold one component during urination. Patients using the device in the Barts Health NHS Trust trial reported that it was easy to use and that they appreciated the hygiene, dry hands and dry container.

A new concept for urine collection

Improvements made by the industry unlock new potential for PoC testing using urine samples. We believe it's possible to build on this, further enhancing test reliability by filtering the specimen prior to transfer to a test cartridge.

We've devised a concept that filters urine as the user passes their entire void, rather than capturing a sample which is then filtered for epithelial cells or bacteria for culture growth. It uses a wax coated pulp funnel, connected to a filter and vacuum housing (see Figure 6). The first catch fills the area above the filter, breaking down a soluble seal which allows the vacuum to pull urine through the filter. Next, the area above the filter is refilled as the user empties their bladder, with any overflow going through the device into the toilet.

Once the user has finished, the filter is removed. At this stage it is either placed into a container for transport or passed to a healthcare practitioner (HCP) for placement in a PoC test cartridge. The HCP then presses a button, releasing a set dose of elution buffer, which rinses the filter and releases the captured bacteria and cells into the cartridge for analysis.

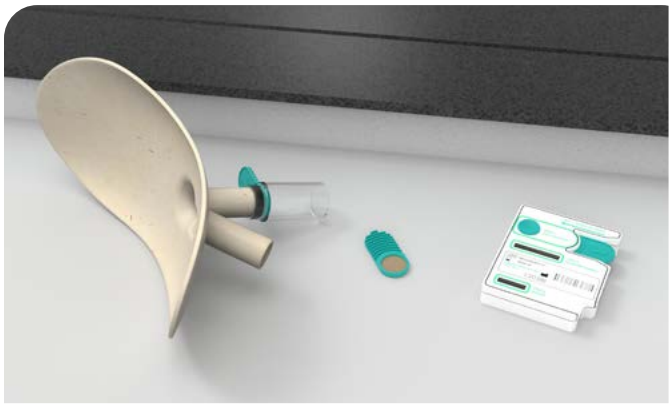

Figure 6: A new concept for urine collection and filtration.

We believe this approach to urine sample collection would resolve user experience and sample quality issues. It could be used in PoC and Point of Need (PoN) settings enabling a greater range of urine-based diagnostic tests to be performed in these environments.

The sustainability question

Sustainability is firmly on the agenda for R&D teams in all sectors. Our urine collection device uses a wax coated pulp funnel rather than plastic, but overall the concept requires more components than a simple collection pot. As such, we can't claim that it reduces single use plastic. However, we do believe that it could avoid misdiagnosis related to sample contamination thereby reducing the need for repeat tests. Improving efficiency, and avoiding wastage, play an important role in reducing the negative impacts of human behaviour on the environment.

In a follow up paper, we will explore these and other sustainability challenges within point of care diagnostics and the whole life cycle, including considerations such as manufacture, water usage, cold chain transport, and patient journeys that we are looking to improve.

Conclusion - an integrated approach

PoC and PoN testing have a vital role to play in modern healthcare. Improving the efficiency and accessibility of diagnostic testing enables resources to be used more strategically and efficiently. It also empowers individuals to manage their health more proactively.

However, it's important not to lose sight of the samples upon which these tests are based. In many cases, high quality specimens are a missing link which may stall progress. Companies that find clever ways to integrate sample collection with PoC or PoN diagnostic tests have much to gain in this evolving space.

We believe that by improving sample collection at PoC and PoN testing, by filtering the sample before sample transfer, we can improve users experience, confidence and reduce errors in sample collection and test results.

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