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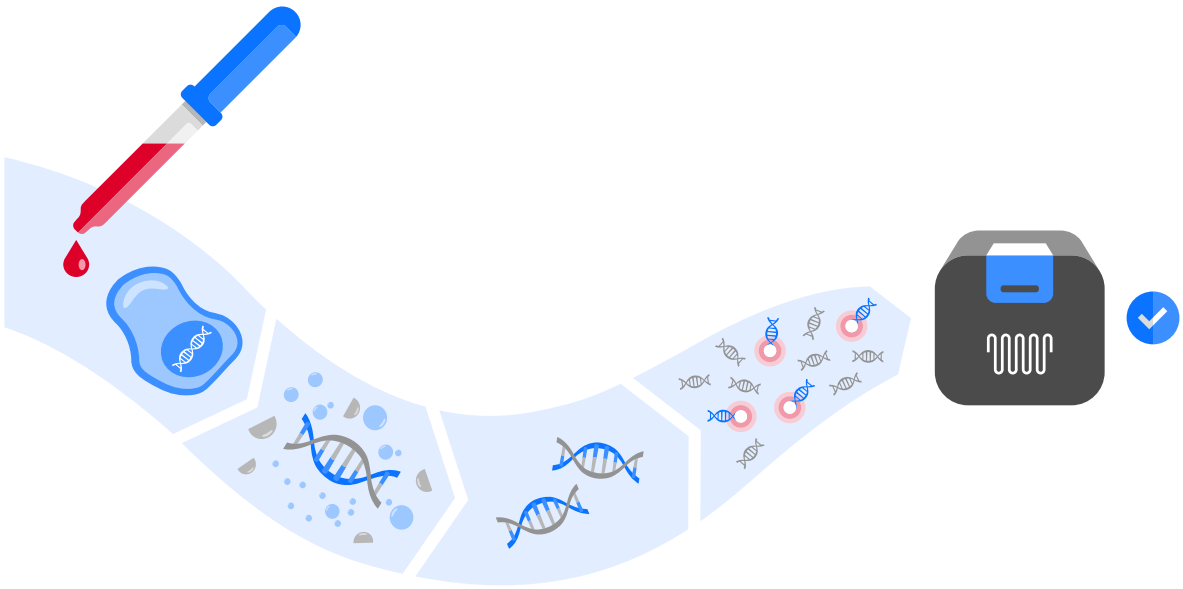
DIAGNOSTICS SERIES - POINT OF CARE FOCUS

Addressing the Point of Care sample preparation challenge

Diagnostic product development advice from Sagentia's Nick Collier and Carl Hewett



Continued innovation in Point of care (PoC) diagnostics offers many benefits, from faster patient turnaround times for improved clinical outcomes and streamlining healthcare for cost efficiency, to better "patient as customer" experiences. The COVID-19 pandemic is making the world look afresh at diagnostic assay methods where PoC testing could play a key role in providing accessible testing in workplaces and care homes to better measure and manage the spread of the virus.

Sample preparation can be a limiting factor in developing PoC diagnostic tests, especially when dealing with blood samples. This vital part of the process can introduce margin for error, expense and complication. Here, Sagentia's Chief Technology Officer and Medical Design & Innovation Specialist explain why sample preparation is an important step of the diagnostic process. They critique solutions on the market today, highlighting relevant sample preparation techniques and technologies. They discuss how to meet CLIA waiver requirements as well as how to maximize commercial opportunity. And they explain why device innovators should consider sample preparation at an earlier stage of the design cycle.

With healthcare systems facing growing pressure to achieve the dual goal of increased efficiency and improved clinical outcomes, Point of Care (PoC) diagnostics is a key enabler. The ability to fully assess a patient and make clinical decisions at PoC delivers benefits at the micro and macro level. It can stem disease progression sooner, reducing the need for critical care and facilitating high quality care outside the hospital. This is especially valuable in time-critical areas of healthcare, such as when prescribing antibiotics or antivirals, determining treatment paths for cancer or tracking progression of diseases. In each of these scenarios, earlier diagnosis and intervention is better for the patient, and the wider community.

In recent years, innovation in the field of molecular diagnostics has empowered PoC diagnostics manufacturers to develop new techniques that bypass the need for laboratory testing. However, innovation does not necessarily translate into functional devices and widespread uptake, even if the core diagnostic idea is scientifically and clinically sound.

The challenges of PoC diagnostic device development

Transitioning molecular-level diagnostics from a specialist lab with trained staff to the physician's office or hospital bedside presents various challenges. Technical innovation typically focuses on the rapid analysis of samples, but PoC diagnostic devices need to fit seamlessly into the wider healthcare ecosystem as well as delivering lab-standard analysis and results. To achieve this, device innovators and developers must consider the full end-to-end process: obtaining the sample, preparing it for analysis and delivering results, not just the analysis itself.

Much of the time, these wider considerations are neglected until later in the innovation process. So, opportunities to optimize the speed, accuracy, ease of use and cost profile of PoC diagnosis can be missed. This is a problem, because these four factors play a significant role in obtaining market approval (or a CLIA waiver) as well as improving the commercial proposition to maximize uptake.

In this paper, we look specifically at the sample preparation stage of the PoC diagnostic process. Most samples obtained from a patient need to undergo preparation before analysis can happen. The analyte may not be responsive in its in-situ form, or the result may be distorted by interfering components.

Common techniques for this critical and potentially time-consuming step include dilution, extraction, purification and concentration. They have a significant bearing on the outcome, so to ensure results are valid, the process needs to be reliable, repeatable and error-free. Achieving this cost-effectively in a busy, non-lab context with samples prepared by frontline healthcare professionals lacking specialist laboratory equipment and expertise is no mean feat.

CLIA-waived status

PoC diagnostic devices that obtain a CLIA (Clinical Laboratory Improvement Amendments) waiver can enjoy more widespread uptake as their use is not restricted to regulated laboratory environments.

To achieve CLIA-waived status, the manufacturer must demonstrate that the device is simple to use, presents insignificant risk of an erroneous result and can be used easily without training.

It's good practice to consider FDA guidance on obtaining a CLIA waiver at an early stage in product development. This encourages holistic thinking, and provides an opportunity to explore ways to integrate, automate or simplify the sample preparation step.

FDA guidance:

- Use a direct, unprocessed sample
- Conduct analysis on a fully automated or self-contained device
- Ensure only 'basic, non-technique-dependent' specimen and reagent handling is required
- Ensure no special training is necessary for troubleshooting or understanding error codes
- Avoid the need for operator intervention during sample analysis
- Avoid maintenance demands beyond changing a battery or power cord
- Deliver a result that requires no interpretation and is easy to determine

The technology landscape: manual through to automated

To optimize PoC diagnostic device development, it helps to look at the entire workflow which culminates in the detection of certain biomarkers or viral or bacterial infection. Figure 1 outlines a typical assay workflow for molecular diagnostics. For the purposes of this paper, we'll focus on the analysis of blood samples, which present a particular challenge from a sample preparation perspective.

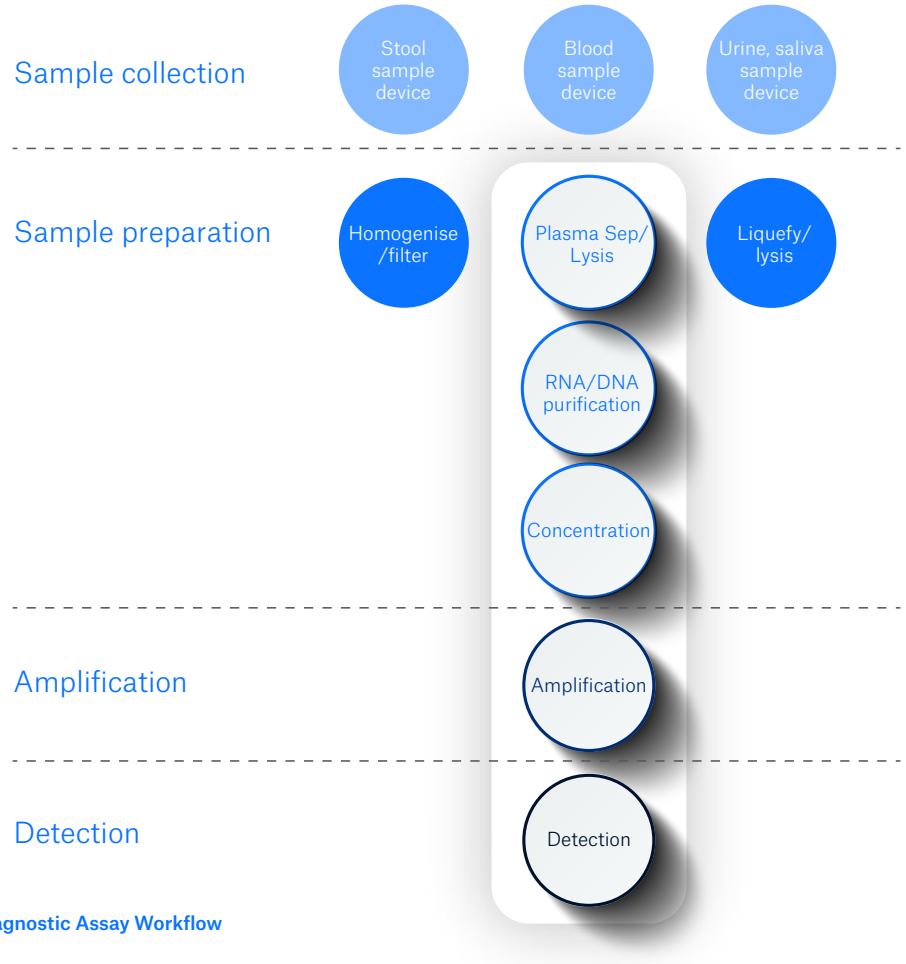


Figure 1: Molecular Diagnostic Assay Workflow

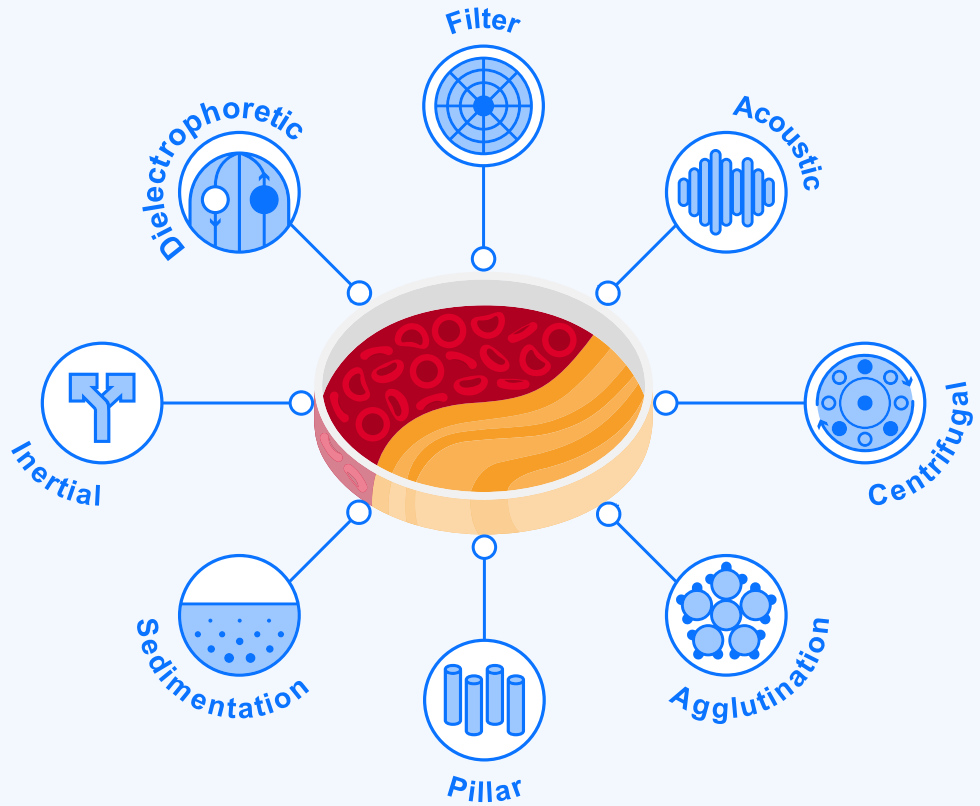
Current PoC molecular diagnostic devices on the market span from semi-automated to fully automated solutions:

- Abbott's **ID NOW™** is a semi-automatic, isothermal nucleic acid amplification technology which takes two minutes to provide molecular results at PoC.
- Roche's **cobas® Liat® System** system is fully automatic and offers on-demand Polymerase Chain Reaction testing in PoC settings, with results delivered in 20 minutes or less.
- Cephied's **GeneXpert®** system provides a wide range of fully automated molecular tests with sample preparation, analysis and results delivery achieved within one hour.

A challenge associated with many existing solutions like these is that they do not accept whole blood as a sample or they only work with small volumes of blood and hence have lower sensitivity than laboratory tests. Molecular diagnostics generally requires larger volumes of blood to facilitate diagnostic processes such as viral load counting. Furthermore, most quantitative assays require either plasma or serum, not whole blood, so the sample generally needs to be separated.

PoC separation techniques and their limitations

In a lab context, centrifugation would usually be used for blood separation, but it's not viable at PoC. And other techniques which are sufficient for smaller quantities of blood – such as filtration, sedimentation or agglutination – tend to be too slow.



PoC separation techniques

A straw poll we conducted during a webinar about sample preparation for PoC diagnostics found that 80% of delegates would like to see it integrated with the diagnostic cartridge. Integrating challenging procedures such as plasma separation so that it becomes quick, easy and cost-effective could enable PoC diagnostic devices to break new ground. We believe this area is ripe for innovation, which could be stimulated through earlier, strategic consideration of sample preparation.

Maximizing Design & Commercial Opportunity

> Just because a new idea works from a scientific or clinical perspective, it doesn't necessarily mean product development and market uptake will follow.

The importance of user centered design

As Figure 2 indicates, a typical workflow for PoC diagnostics involves sample acquisition, dosing and identification before preparation for analysis. Throughout the process, there are multiple opportunities for human and technical errors which can impact the result. Understanding where, how and why these can occur is essential, so they can be accounted for and eradicated where possible.

A detailed understanding of users and the use environment is paramount here. Voice of Customer (VoC) studies can provide valuable information, but ideally this should be coupled with direct observations in a clinical setting. Immersing product designers equipped with clinical understanding and subject matter expertise in the use environment can reveal simple but transformational insights. They can identify ways to ensure the device dovetails with existing working practices and conditions, and where misuse of equipment might pose a risk factor.

Futureproofing is another area where user-centricity can bring benefits. This is especially important with the rapid pace of change in the digital age. Understanding where future technologies are likely to improve tasks performed by frontline healthcare staff can ensure today's designs are built to accommodate them, maximizing device longevity. Likewise, trends such as single-use plastic avoidance can be used to shape decisions about consumables.

Platforming a device for scalability and ease of integration can make it more commercially attractive, as can post-sales support and serviceability. The initial development of a minimum viable product should account for the likely needs of the next-generation device.

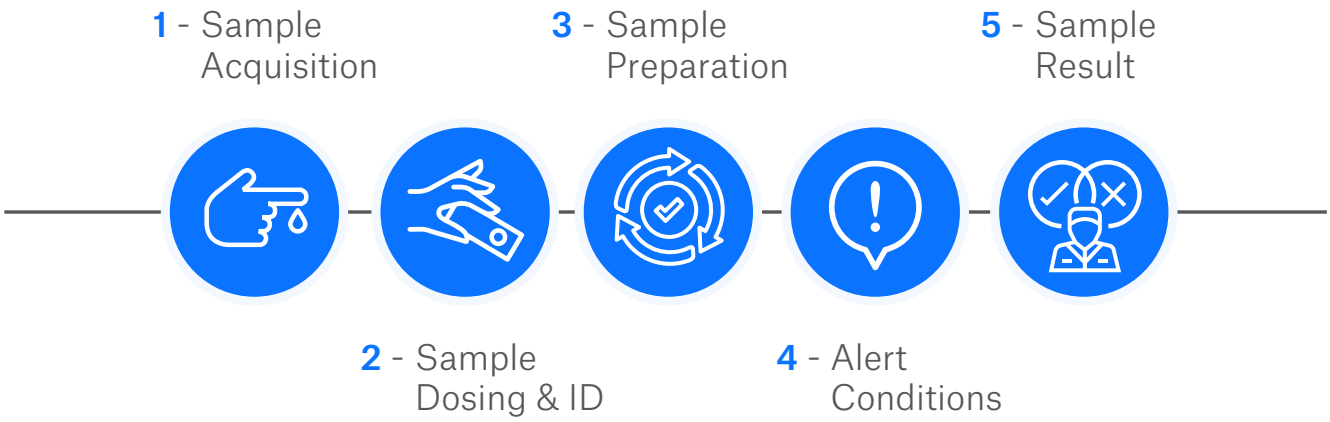


Figure 2: Use Workflow / Use Error

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How stakeholder insight can inform design

When Sagentia was briefed to support the development of a PoC diagnosis cartridge for blood samples, direct observation and VoC surveys provided valuable insights.

We identified that a vacutainer was the most efficient and effective device for sample capture and would cause least disruption to existing clinical protocols. However, in a demanding environment with many distractions, there was a risk that tubes could be inserted into the test cartridge incorrectly. To mitigate this, we introduced a go/no-go sizing interface so vacutainers wouldn't fit unless positioned the right way around. Furthermore, we incorporated automatic closure for the sample carrier, which is triggered if the user forgets to adhere to this step.

To reduce the burden on PoC healthcare professionals, we also eradicated the need to transfer a precise sample quantity. This was achieved with the introduction of considered fluidic geometry and custom pipettes for volumetric control of dosage within the cartridge.

We also considered wider external factors that may result in erroneous results. Roadmapping the manufacture and assembly pathways of the device allowed us to identify where mistakes might compromise performance. This led us to devise additional go/no-go features for the internal assay housing. Without this, there was a potential risk that the assay chemistry could be performed out of sequence, introducing processing errors.

Considering the full end-to-end process, from manufacture to PoC deployment, enabled us to optimize this device for minimal risk.

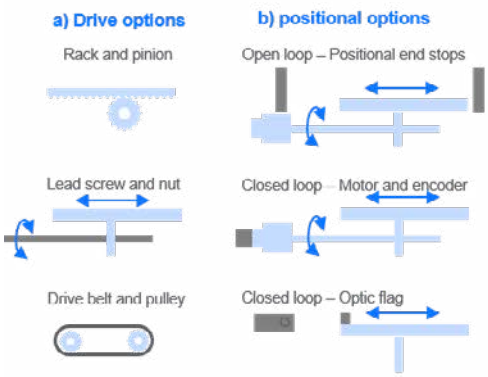
The case for morphological mapping

Morphological mapping enables design teams to explore competing functional elements of a PoC diagnostic device at its inception. This is useful when considering complex, dynamic and sometimes contradictory requirements. Putting sample preparation on the agenda at this stage can streamline the development process and unlock new creative possibilities.

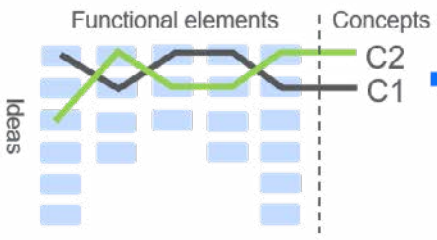
At Sagentia, we advocate a three-step process:

1. **Categorize product functions:** look at all the device objectives and challenges, segment them into functional groups.
2. **Hold an ideation session:** assemble multidisciplinary teams and leverage collective insights, skills and understanding. Record ideas and rank according to specification criteria, reliability and costs. Decisions can be informed by ethnographic research and refer back to the technical purpose.
3. **Construct concept options:** piece together the various ideas or building blocks into multiple concept options. This approach improves visibility and instills confidence that the optimum system architecture has been selected before further R&D effort is committed.

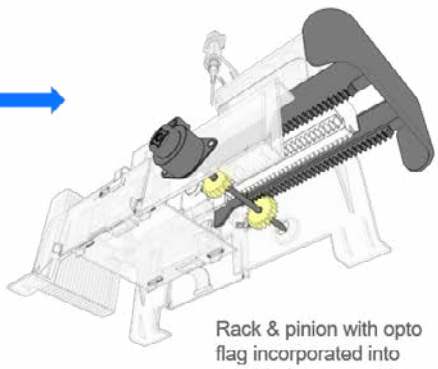
Example Ideation Output



Morphological Mapping



Collated Concept



Rack & pinion with opto flag incorporated into moulded consumable drawer.

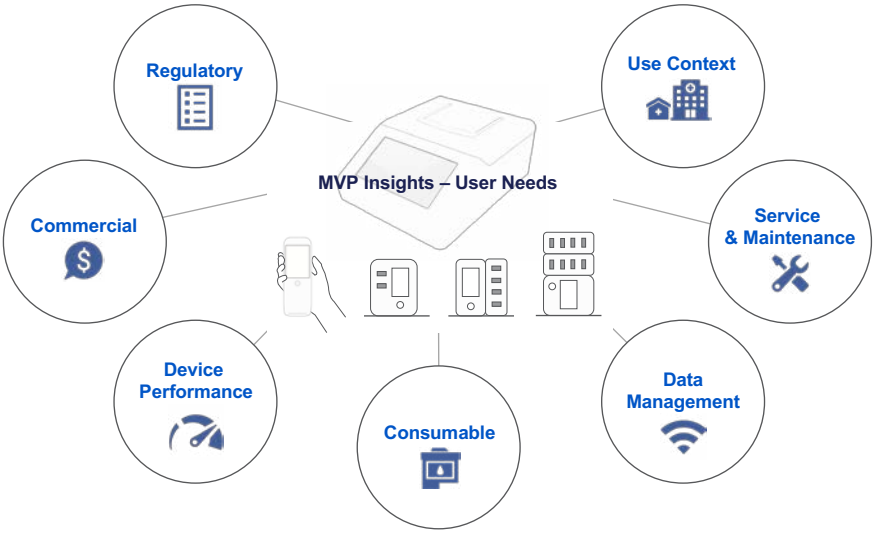
How does my device keep pace with change?

A user-centered approach coupled with a considered VoC study will arm you with an appreciation of future trends to define a platform rollout which incorporates:

Futureproofed design: Cartridge and instrument design are resource heavy endeavors, consider modular capacity for different sample acquisition techniques such as nasal swabs and urine.

Developing trends: Sample preparation cartridges are commonly disposed of as bio waste. Growing concerns and requirements of single-use plastic may force separation of wet-able and carrier cartridge components to minimize this waste.

Platforming: Designing core technology hardware in modular elements to allow quick and scalable sample prep for single or parallel processing needs (e.g. from a true handheld PoC device to a benchtop system).



Managing commercial influences

IVD and sample preparation cartridge success can hinge on development maturity into viable low "cost per test" options. Transitioning a device from laboratory concept to physical product is not a straightforward linear process. It's complex and dynamic, influenced by various social and technical factors to consider:

Cartridge-led: Don't let the instrument hardware mature ahead of the cartridge and ensure interfaces are co-developed. Modern IVD systems are underpinned by the cartridge core.

Design for X: Strive for simplicity in design by hybridizing components to reduce part counts and consider the manufacture process to reduce assembly steps and time.

Wet logistics: Lyophilization of wet chemistry can take some of the complexity out of sample acquisition processing, but ensure shipping and the filling sequence is cost optimal for the chosen diluent and reagent suppliers.

Fine margins: Precision and tight tolerances don't mean good design. Difficult to achieve tolerances can slow down quality control, increase scrap rates and narrow supplier options. Therefore identify critical functions and design out the need for precision.

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Where next with Sample Preparation?

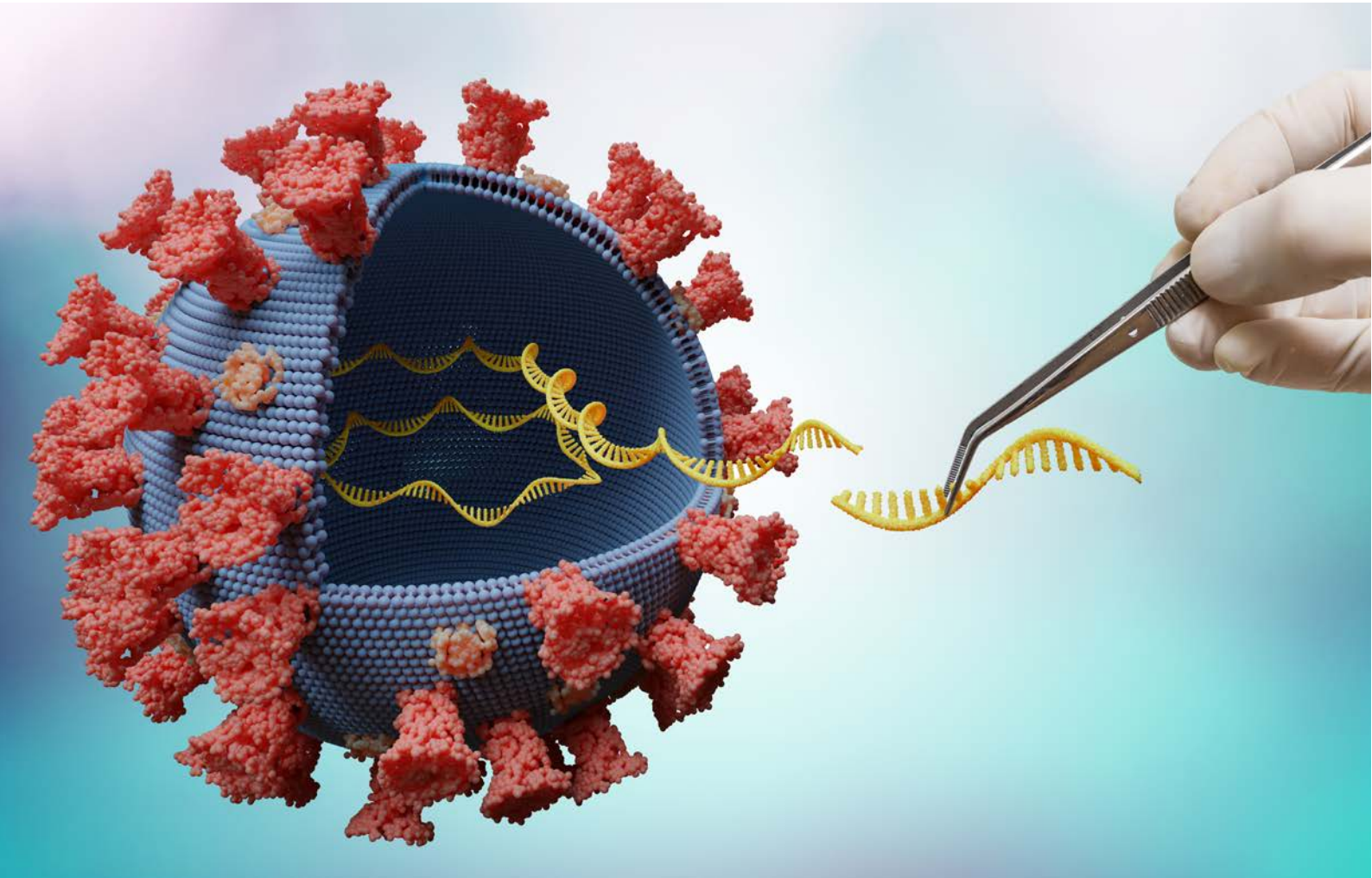
PoC diagnostics involving molecular assays have the potential to significantly improve patient outcomes and healthcare efficiency. However, while there have been impressive innovations in this area, sample preparation can be a limiting factor hindering the transition from laboratory to PoC.

We believe the following four technologies offer potential for a PoC innovation breakthrough:

- **One pot assays** – achieving end-to-end analysis in a single reactor saves time and reduces the likelihood of error.
- **Electrokinetic-like separation** – emerging use of this technique to separate blood offers exciting potential for microfluidics in PoC devices.
- **Surface acoustic waves** – research has shown that blood separation can be achieved quickly and accurately using this technique with small samples.
- **Electrowetting** – this technique has the potential to achieve high-speed transportation of microdroplets of whole blood.

Finding ways to harness these techniques could enable PoC diagnostic devices to break new ground, incorporating sample preparation and sophisticated analysis in a single, easy-to-use system.

PoC diagnostic devices must be easy to use, with simple consumable elements. Error-proofing and automation should be introduced wherever feasible. Bringing sample preparation considerations forward can help achieve this, increasing the likelihood of obtaining a CLIA waiver. It can also reveal opportunities to reduce cost per test and improve the overall clinical and commercial proposition. Ultimately, it's about focusing innovation efforts more effectively, to deliver tangible benefits for individual patients and wider healthcare systems.



Dr Nick Collier
Chief Technology Officer
Sagentia

Dr Nick Collier is CTO at global technology & product development company Sagentia and is a keen follower of innovations in science and technology. With a background in Physics and a PhD in semiconductor physics and device fabrication from Cambridge University, Nick has spent his career translating science into robust product designs. Working across the medical, FMCG and industrial sectors he has a depth of expertise in areas such as sensors, actuators and fluidics.

Carl Hewett
Medical Design & Innovation Manager
Sagentia

Carl is passionate about creating impactful user experiences by blending technology and human factors into novel devices. Working across both commercial and medical landscapes, he has in-depth experience in ethnographical needs translation, ideation and design for manufacture. Carl is an experienced project manager with a 1st class degree gained from Loughborough University in Industrial Product Design & Technology. For over 12 years Carl has partnered with international clients developing cutting edge projects to 510(k) submission in an ISO 13485 framework. Projects include molecular diagnostics cartridge consumables, restorative endodontic systems and FMCG cleansing devices.

About Sagentia

Sagentia is a global science, product and technology development company. Our mission is to help companies maximize the value of their investments in R&D. We partner with clients in the medical, consumer, industrial and food & beverage sectors to help them understand the technology and market landscape, decide their future strategy, solve the complex science and technology challenges and deliver commercially successful products.

Sagentia employs over 150 scientists, engineers and market experts and is a Science Group company. Science Group provides independent advisory and leading-edge product development services focused on science and technology initiatives. It has ten offices globally, two UK-based dedicated R&D innovation centers and more than 400 employees. Other Science Group companies include OTM Consulting, Oakland Innovation, Leatherhead Food Research, TSG Consulting and Frontier Smart Technologies.

For further information visit us at:

www.sagentia.com
or email info@sagentia.com
www.sciencegroup.com

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Sagentia Ltd
Harston Mill
Harston
Cambridge
CB22 7GG
UK

Sagentia Ltd
First Floor
17 Waterloo Place
London
SW1Y 4AR
UK

Sagentia Inc
One Beacon Street
15th floor, Suite 1500
Boston
MA 02108
USA