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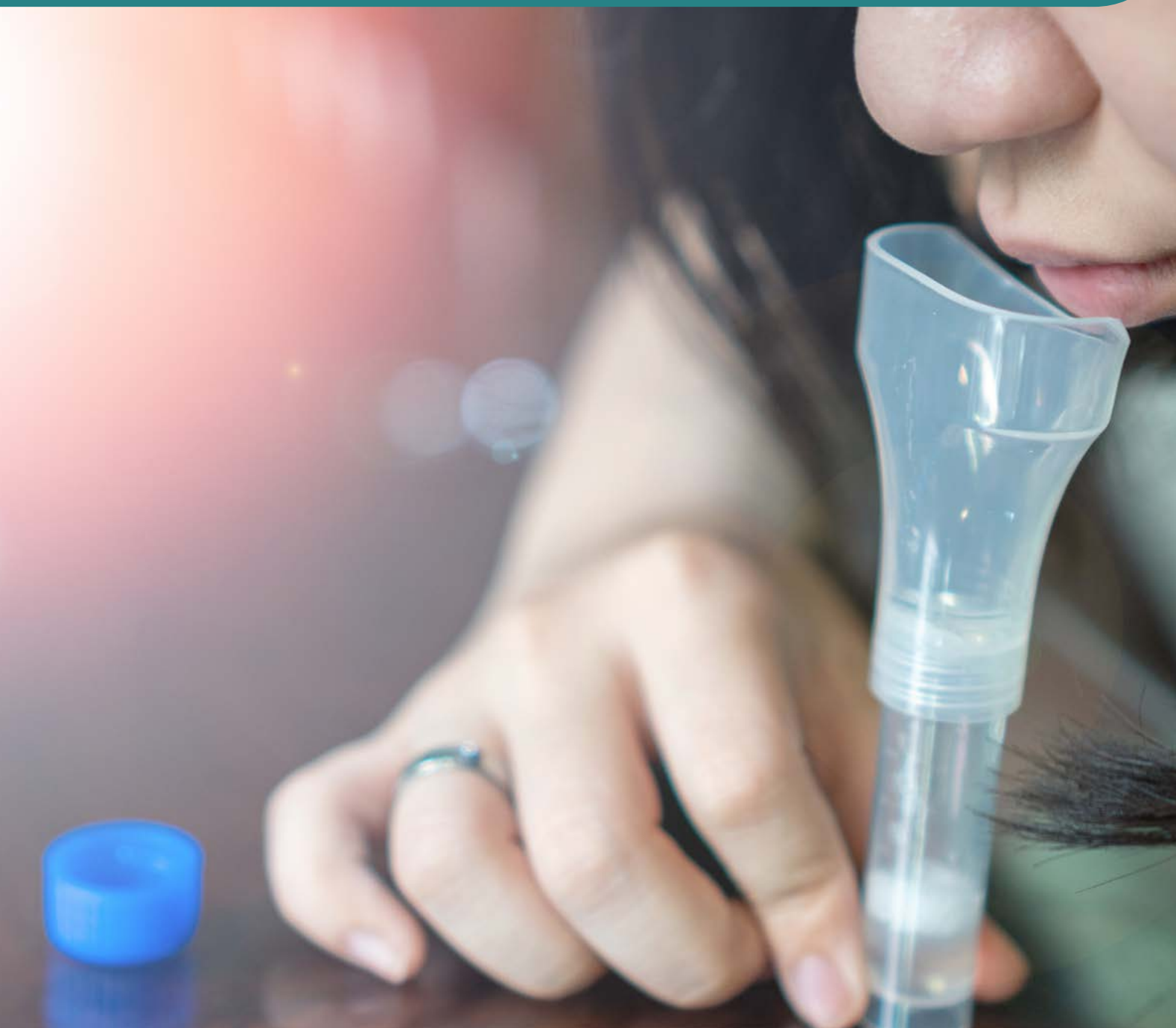
MEDICAL

WHITE PAPER

Non-invasive biomarkers: opportunities and implementation challenges for health diagnostics



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Harnessing non-invasive biomarker testing for medical and consumer health applications

Progress in the non-invasive biomarker space reveals new opportunities for their use in health diagnostics. These include risk assessment, early detection and monitoring of disease, patient stratification, and prediction of disease progression.

'Non-invasive' refers to the sampling method rather than the nature of the biomarker. The relative ease with which non-invasive samples can be obtained means more diagnostic and companion diagnostic testing could be performed in Point-of-Care (PoC) and at-home environments. This brings game-changing potential for the medical and consumer health sectors.

Reduced reliance on clinical and laboratory testing would have a positive impact:

- Accessibility and costs, specifically in the management of chronic conditions when face-to-face interactions are limited
- The ease of non-invasive testing means it can be conducted more frequently, increasing the likelihood of early detection of disease
- Healthcare interventions could be delivered more quickly, accurately, and economically
- Individuals could obtain personal health status insights more regularly, empowering them to take greater control of their own health and wellness
- Clinical studies based on frequent longitudinal sampling would be easier and more cost-effective to manage

This whitepaper summarises the current landscape of non-invasive biomarkers for health screening and diagnostics. We also identify implementation challenges, and suggest how they might be resolved with reliable, user-friendly, cost-effective solutions to help achieve commercialisation.

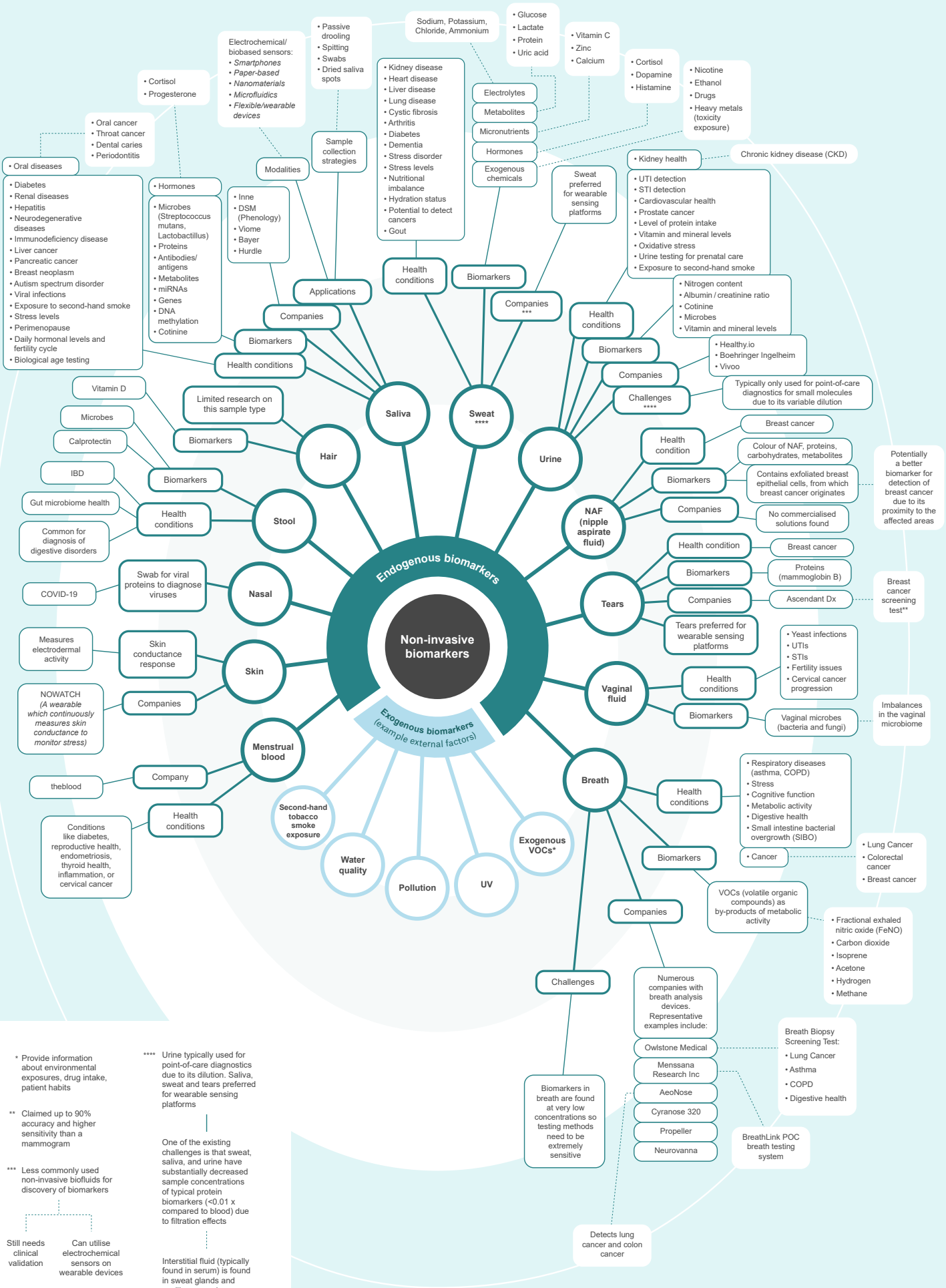
The non-invasive biomarker landscape

Biomarkers are biological substances or factors that can be measured to indicate health and wellness status. They can also be used to indicate the presence of a disease or predict its severity.

*The **World Health Organization** describes biomarkers as: "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction."*[1]

Many biomarkers can be identified in blood or tissue samples obtained via invasive means which require puncturing the skin or entering the body. Others – including chemical substances and biological components found in urine, saliva, sweat and other sample types – can be obtained non-invasively.

Figure 1 outlines a range of non-invasive biomarkers, illustrating how they can be captured and measured, as well as the diseases and conditions they can indicate.



* Provide information about environmental exposures, drug intake, patient habits

** Claimed up to 90% accuracy and higher sensitivity than a mammogram

*** Less commonly used non-invasive biofluids for discovery of biomarkers

- Still needs clinical validation
- Can utilise electrochemical sensors on wearable devices

**** Urine typically used for point-of-care diagnostics due to its dilution. Saliva, sweat and tears preferred for wearable sensing platforms

One of the existing challenges is that sweat, saliva, and urine have substantially decreased sample concentrations of typical protein biomarkers (<0.01 x compared to blood) due to filtration effects

Interstitial fluid (typically found in serum) is found in sweat glands and capillary vessels

Benefits of non-invasive biomarkers

Non-invasive biomarkers may be used to measure many aspects of health and disease status, as well as physiological and nutritional status. An obvious benefit is the reduced physical impact in scenarios where invasive biomarkers are the current standard.

Invasive biomarker sampling is expensive, often painful, and may carry the risk of complications. For certain demographics – such as young children or the elderly – the physical impact of invasive biomarker sampling is a significant consideration. Since non-invasive sample collection is more straightforward and doesn't require a clinical procedure, the diagnostic journey can also be accelerated to facilitate earlier treatment. For example, in settings such as care homes, early diagnosis of infection via analysis of biomarkers in urine could enable more timely and effective treatment interventions.

Examples that are approved, or in the late stages of development, include **Healthy.io's** at-home urine-based diagnostic test to screen for Chronic Kidney Disease (CKD)[3] and **Viome's** at-home saliva-based diagnostic test for the early detection of oral and throat cancers[4]. Meanwhile, femtech start-up **inne** has raised funding to adapt its saliva-based fertility and ovulation monitoring technology for perimenopause tracking applications[5]. See figure 2 for more details.

Who's driving progress?

Several organisations are actively involved in non-commercial developments surrounding established and novel biomarkers. The Biomarkers Consortium[6] of the Foundation for National Institutes for Health is currently exploring the development of new, non-invasive ways to assess liver health for patients at risk of Non-Alcoholic Steatohepatitis (NASH). The goal is to find an alternative to the standard surgical liver biopsy which may not present an accurate picture of disease. A five-year programme, Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE)[7] is looking to standardise and qualify non-invasive biomarkers for the diagnosis and staging of NASH, assessing them for the ability to identify individuals in need of intervention.

Traditionally, biomarker development has been driven by medical needs. However, recent advancements in this space open opportunities in consumer healthcare. For example, non-invasive test kits suitable for use at home without a prescription can be developed and used for analysis of nutritional status (e.g., vitamin and mineral levels) or detection of immunity biomarkers (e.g., salivary IgA, salivary cortisol).

This provides opportunities to develop solutions which help select the most effective Over The Counter (OTC) medicines and nutritional supplements tailored to each person (e.g., to deliver physical and mental health benefits, improve sleep, and target anxiety). It also facilitates monitoring or tracking of individual responses to the supplement and the effect of the intervention.

Figure 2 outlines representative examples of solutions for non-invasive biomarker detection. Electrochemical sensing and spectroscopy are common detection techniques employed in these solutions and, for most, it is claimed that multiple biomarkers can be detected. For electrochemical sensing, the sensors analyse either skin cells, sweat, or tears. Wireless connectivity to proprietary apps/software is another common feature among the examples.

	Company / developer	Development stage	Target use case	Year of launch / publish	Biomarker targets	Detection principle	Connectivity (mobile apps) robots	Relative cost
Vitastiq	**Vitastiq**	Commercialised	Home	2015	26 Vitamins and minerals	EAV (Electroacupuncture According to Voll)	Proprietary app and Bluetooth	Medium (218 Euro)
Vitaminyzer	**Vitaminyzer**	Test is CE approved and FDA cleared	Clinic, health and fitness centres	N/A – {Limited information available in public domain}	Vitamins, minerals, trace elements, oxidative stress and toxic metals	Spectrophotometry	Proprietary software	High (estimate)
Compact vitamin C-tracking wearable sensor	**University of California San Diego**	Academic research	Not specified	2020	Vitamin C	Electrochemical sweat sensor	N/A	Low – medium (estimate)
Wearable biosensor for monitoring metabolites and nutrients	**Caltech**	Academic research	Not specified	2022	9 Essential amino acids, vitamins (B6, C, D3 and E) and metabolites	Graphene-based electrochemical sweat sensor	Proprietary app and Bluetooth	Medium (estimate)
Eyeglasses-based tear biosensing system	**University of California San Diego, University of Sao Paulo, University of Alcala**	Academic research	Not specified	2019	Alcohol, glucose, and vitamins (B2, B6 and C)	Microfluidic electrochemical detector	Bluetooth Low energy	Medium (estimate)
Phenology platform for menopause management	**DSM** product using **inne's**	**inne** platform is CE certified for use in the EU. **FDA** certification underway in US	Home	2022	Progesterone	Saliva	-	-
Oral Heath Pro with CancerDetect	**Viome**	**FDA** breakthrough device designation granted to accelerate review	Home	2023	Biomarkers associated with oral and throat cancer	Saliva	-	-
Minuteful Kidney	**Healthy.io**	**FDA** approved	Home	-	Albumin to creatinine ratio	Urine	Proprietary app	

Figure 2: Examples of non-invasive solutions for biomarker detection.

(Development and commercialisation of the example solutions may have evolved since the time of writing)

Another area that could benefit is the assessment of food effects on the body to promote nutrient balance, energy, and effective nutrient intakes. This is traditionally based on self-reported dietary intake questionnaires which have inherent limitations. Identification of non-invasive biomarkers in urine samples (e.g. creatinine to indicate intake of meat and fish; erythronic acid to indicate sugar intake; genistein to indicate soy intake) or Hydrogen-Methane Breath Tests (HMBT) for assessing food intolerances could offer a more objective assessment of consumption[8]. Furthermore, non-invasive biomarker data points can be included in nutrient profiling models to assess the nutritional quality of single foods and food patterns to keep energy and nutrients within the healthy range.

Challenges in implementation

It is not easy to cross the gap between non-invasive biomarker health diagnostics innovation and the commercialisation of PoC and at-home test devices. Implementation challenges encompass technical, clinical, regulatory, and commercial matters, as Figure 3 illustrates.

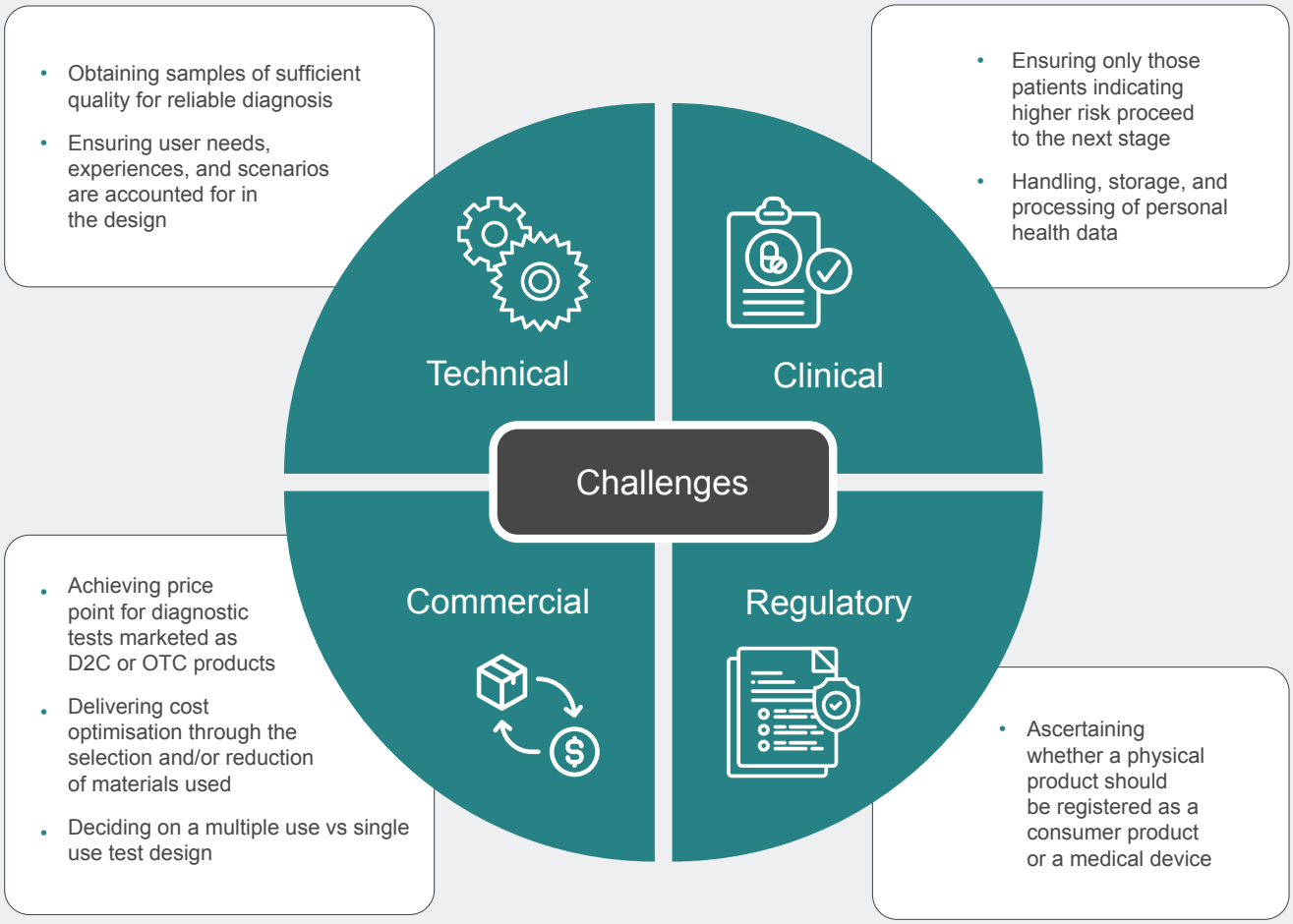


Figure 3: Implementation challenges for non-invasive biomarker health diagnostic tests.

Technical challenges: sample collection, sensitivity and specificity of testing

Sample collection and preparation should be firmly on the agenda of medical or consumer health companies looking to secure opportunities in the non-invasive biomarker diagnostic space. Obtaining samples of sufficient quality for reliable diagnosis is an enduring challenge for PoC and at-home devices. Under- and over-sampling can also prevent an accurate result from being obtained, and sample contamination is a major consideration. Some of the sample types summarised in figure 2 are easier to collect than others, but they can all present sample integrity challenges.

Urine samples are a case in point. As a carrier of hormones, cells, proteins, and bacteria that the body is eliminating, urine is a valuable specimen for non-invasive biomarker testing. However, the assumption that it is easy to collect can be a hindrance. There is no standard device for collection beyond simple cups and funnels or tubes. Yet obtaining a suitable, clean sample is not always straightforward and inconsistent quality is a limiting factor.

The prevalent gender data gap in healthcare is one factor at play here. Containers traditionally used for urine collection are more difficult for women to use than for men. Controlling the flow of urine to collect the right portion for the sample is difficult for many people. What's more, some diagnostic tests, such as those for Sexually Transmitted Infections (STIs), require 'first catch' - the first 30ml of the first-morning urine - as epithelial cells and debris from the urethra are needed for analysis.

Some challenges could be addressed using a combination of existing, readily available technologies and empathy-led design. A human-centred mindset plays a critical role, ensuring various user needs, experiences, and scenarios are accounted for. Wider adoption of products such as the **Peezy** mid-stream device could have a significant impact, making it easier for women to collect urine samples, and for all people to collect midstream samples.

The urine sample collection issue and how it can be resolved to improve the efficacy of decentralised diagnostic testing is discussed further in the Sagentia Medical white paper, Sample collection and Point of Care testing.

Non-invasive biomarkers also hold great promise for large-scale health initiatives, potentially including national cancer screening programmes. However, the complete replacement of invasive testing would require sensitivity, specificity, and reproducibility to be equal to or better than existing gold-standard diagnostic tests such as those involving tissue biopsies. In most cases, this is too ambitious a goal at present. However, an alternative is to implement non-invasive biomarker testing within the triaging models commonly used in the UK and US healthcare systems.

Clinical challenges: patient stratification and privacy

Within a triaging model for health screening, non-invasive biomarker tests aid stratification of patients at home or in PoC settings so only those indicating higher risk proceed to the next stage. This offers multiple benefits, limiting the number of patients subjected to invasive diagnostic procedures while reducing the burden on tertiary care. It could also improve the overall performance of screening, making it quicker and more straightforward to identify which individuals require further testing and possible intervention. **Healthy.io's** urine-based CKD screening solution for at-home use is an example of how this could work in practice. The start-up joined forces with **Boehringer Ingelheim** in 2023 to help drive increased uptake[9].

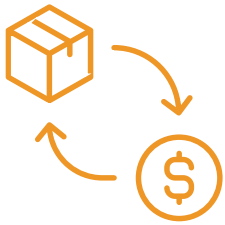
Handling, storage, and processing of personal health data around diagnostic solutions for PoC and at-home use presents challenges. Stipulations vary across markets. For instance, under the EU's General Data Protection Regulation (GDPR), personal health data is considered a 'special category' meaning many aspects of its use require explicit consent from the individual in most circumstances. Device innovation strategies need to ensure all applicable requirements surrounding data access, management, and usage are considered.

Regulatory challenges: medical device or consumer product?

Many diagnostic tests based on non-invasive biomarkers could add value in medical and/or consumer health applications. The rise of wearable devices provides additional opportunity for continuous monitoring of non-invasive biomarkers, specifically in patients and consumers with chronic diseases, reducing the need for in-person consultations.

However, when it comes to physical products, it can be difficult to ascertain whether they should be registered as a consumer product or a medical device. This is further complicated by the rise of the Direct-to-Consumer (D2C) healthcare category, which blurs the lines between consumer wellness and medical matters.

From a time and cost perspective, the consumer product route is generally preferable. The registration process is far less onerous, making it cheaper and quicker to get to market. However, it's easy for a wellness device positioned as a consumer product to stray into medical device territory. In the US, this can lead to enforcement action from the **Food and Drug Administration (FDA).**



Commercial challenges: cost optimisation

With many non-invasive biomarker health diagnostic tests marketed as D2C or OTC products, the price point is an important factor. Consumers generally pay for these tests directly, making them particularly price-sensitive. However, cost modelling for consumer tests is complex. As a rule of thumb, those intended for regular repeat testing should be lower in price than those used periodically. Results provided by the test need to be factored into the calculations too. Where a single result is provided and there is no need for additional functionality (e.g. actionable information provided via an app) cost to the user should be lower than for a test detecting several biomarkers (multiplexing). The application is another driver of costing strategy. For instance, consumers are likely to pay more for a test that enables early-stage detection of cancer than for routine screening of vitamin and mineral deficiency. There's also the question of whether price per test for PoC or at-home diagnostics should be lower for the end-user than an equivalent clinical test involving invasive biomarkers. It's important to consider this in terms of the wider context and savings that can be made through earlier diagnosis and treatment. With so many factors at play, cost modelling demands a high level of attention and cost-efficient production needs to be a primary design consideration.

A materials review process may reveal opportunities for cost optimisation through the selection and/or reduction of materials used. This applies to materials for the main diagnostic instrument, consumable elements, and packaging alike. Such cost saving measures may also present opportunities to improve environmental sustainability. For instance, it might be possible to make the main device or its consumables smaller to reduce the amount of material needed, or it may be appropriate and cheaper to use paper- or pulp-based components or packaging in some circumstances.

Designing instruments with multiple uses in mind may be beneficial for some use cases, especially for conditions which require regular testing or ongoing monitoring. A high cost for the core device can be offset against a lower cost per test over time.

With single-use tests, simplicity of design is essential to keep costs down. One option to consider is instrument-free single-use tests which integrate with commonly used devices such as smartphones to provide power and human readable outputs. This might require clever methods to reduce the risk of human error, for instance using folded paper devices or heat activation to unlock consecutive stages of the test.

Maximising market opportunities

The overall global biomarkers market is expected to reach USD 93.8 billion in 2029 with a Compound Annual Growth Rate (CAGR) of 10.2% expected from 2024[10]. Rapid adoption of liquid biopsy technologies for cancer detection is cited as one factor behind this predicted commercial growth.

Potential opportunities for non-invasive biomarker diagnostics lie in the development of technologies that identify effective treatment solutions and monitor or track individuals' responses to treatment. Moving forward, the selection of therapeutic and nutritional interventions based on non-invasive biomarker testing should be tailored to each person and re-evaluated regularly. Recent advances in the development of wearable devices for convenient testing and instant results support development in this space.

However, the commercial success of non-invasive diagnostics, specifically for medical applications, is a significant concern and will require a careful sequence of smaller steps to overcome technical, clinical, regulatory, and cost challenges. It's not easy to persuade healthcare decision makers to adopt alternatives to well-established methods of testing. Business models can also be very different to those for traditional diagnostic solutions and may pose a barrier for adoption.

Building on, or pivoting, existing platforms with a proven track record is one approach worth exploration. For instance, technologies developed for at-home diagnosis of SARS-CoV-2 during the COVID-19 pandemic could be adapted for different applications or biospecimens. Partnering with larger, well-connected organisations is another potential route for start-ups looking to boost credibility and accelerate uptake. **Healthy.io's** collaboration with **Boehringer Ingelheim** is a prime example, examining operational aspects of largescale use of the FDA-approved Minuteful Kidney solution in home environments[11].

There are additional market challenges that are yet to be overcome, including data standardisation, integration, and validation testing. However, the non-invasive detection of biomarkers, including digital biomarkers, provides opportunities for their adoption as primary end points in clinical trials, and the development of new diagnostic functionality in medical and consumer devices.

How Sagentia Medical can help

The commercialisation of non-invasive biomarker diagnostic devices requires expert planning, a pragmatic mindset, and a broad range of skills and experience. Sagentia Medical has the multidisciplinary capabilities to transform concepts into working solutions that overcome implementation challenges and ensure good user experiences. We also identify market opportunities and determine when, where, and how new solutions are likely to take off in the medtech and consumer health markets.

Contact **info@sagentiamedical.com** if you'd like to discuss R&D strategy, front end innovation, or product development activities for non-invasive biomarker diagnostic solutions.

Disclaimer:

We've done our best to ensure third party information and data contained in this report is up-to-date at the time of writing, but many of the technologies covered are under development, so change is ongoing.

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About Sagentia Medical

Sagentia Medical is a specialist independent advisory and leading-edge product development services focused on science and technology initiatives in healthcare. Working across diagnostics, surgical devices, and medical devices, Sagentia Medical works with start-up disruptors through to world leading brands in MedTech to extract maximum value from R&D and innovation investments.

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