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FUTURE OF DIAGNOSTICS SERIES WHITEPAPER

Improving accessibility of advanced molecular diagnostics in precision oncology

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Liquid biopsy genetic tests are making precision cancer diagnostics simpler and quicker than ever before. Using a blood sample instead of a tissue biopsy, they build on the specificity of genetic sequencing technologies, creating a new market of low-cost, high-speed tests. Significant opportunities exist in this early maturing market, from precise therapy recommendations to pre-symptomatic cancer detection. Recent regulatory successes have seen these technologies begin to appear in the market, with an increasingly broad range of entrepreneurial products almost ready to emerge. In this paper, we join forces with our sister company TSG Consulting to outline technical considerations and regulatory milestones that will shape the path ahead.

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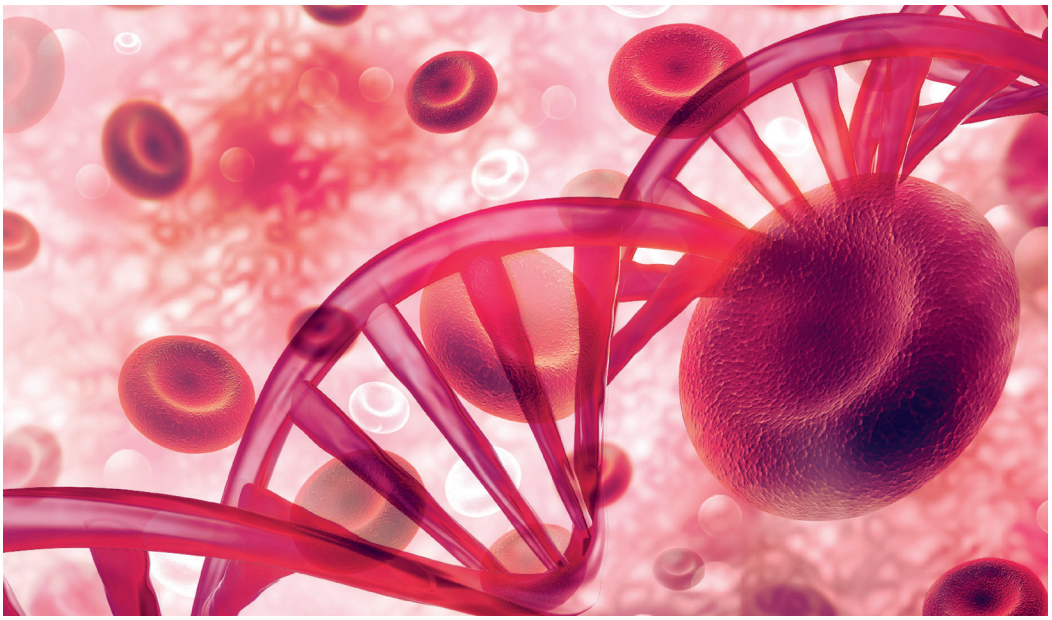
Most cancers are caused by the acquisition of genetic mutations over time, this can be accelerated for instance through smoking, or exposure to sunlight or asbestos. Key mutations act together to encourage pathological cell growth, and DNA sequencing has been used to identify these for many years.

Today, *precision oncology* is creating a new paradigm in medicine. A patient's disease is characterised based on the genetic mutations found, and they also define the applicable clinical treatments. Currently, a patient is usually referred to an oncology clinic after cancer symptoms are spotted, with genetic testing applied after imaging and surgery to remove a biopsy sample. Unfortunately, these slow and expensive processes are often applied when a patient is in the later, less survivable, stages of disease.

Circulating tumour DNA (ctDNA) tests offer great potential to improve patient diagnosis using simple blood samples rather than surgery. During cancer growth, tumour cells are replaced and die, releasing DNA into the bloodstream. This DNA can be interrogated using next-generation sequencing (NGS) technology, highlighting mutations that are causing disease.

Applying these low cost, fast tests earlier in the patient journey allows physicians to detect cancer patients at an early stage and also serve to reassure the disease-free, make treatment decisions, monitor treatment response, predict relapses and metastases, unravel tumour complexity, and detect very low levels of residual disease. Ultimately this reduces the need for clinical visits and contributes to improved patient outcome and quality of life given the disease isn't allowed to progress as far.

Making liquid biopsy genetic testing more accessible to more people creates new opportunities for precision oncology. It can reduce the average cost and impact of cancer across population healthcare as well as for individuals. The core scientific and technological capabilities for this diagnostic capability already exist, and an exciting range of entrepreneurial activity is exploring its deployment potential. Recent successful FDA approvals and clearances indicate that the regulatory environment is warming up too. Next steps focus on ways to improve the sensitivity, speed and price of the tests, aiming to detect disease quicker and earlier to reduce its impact on individual patients and healthcare providers.

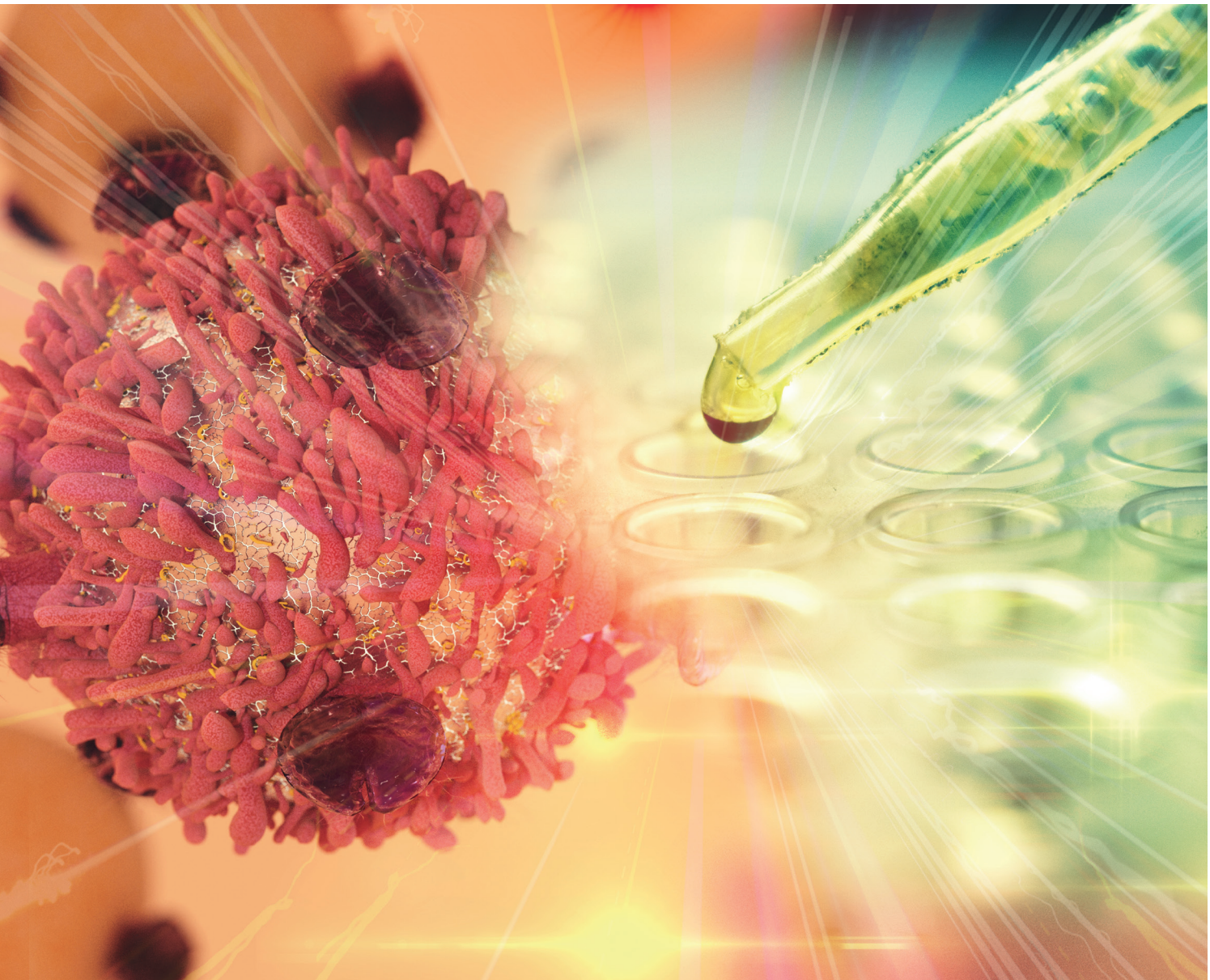


How ctDNA aids precision oncology

Precision oncology involves the use of genetic mutations found in tumours to direct therapy. For instance, EGFR mutations found in lung cancer require treatment with tyrosine kinase inhibitors whereas BRCA mutations in breast and ovarian cancer are best treated with PARP inhibitors.

For years, traditional gene sequencing has required surgical biopsies from the tumour itself. However, ctDNA is a much simpler sampling source. These tumour DNA fragments are collected easily via quick non-invasive blood draw, then assayed to identify mutations which indicate the presence of disease and determine therapy options.

This approach has the potential to make precision oncology much more accessible than was previously possible. It could enable earlier diagnosis and more effective treatment across much larger patient numbers. And it offers ways to unlock individualised patient care where the right treatment is delivered at the right time based on the nature of the tumour.



Liquid biopsy regulations

Specific mutations in blood-circulating free DNA fragments (cfDNA) were first detected in 1994, but it wasn't until June 2016 that the FDA first approved a liquid biopsy test. This approval was for the detection of exon 19 deletions or exon 21 (p.L858R) substitution mutations in the epidermal growth factor receptor (EGFR) gene to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with Tarceva® (erlotinib).[1]

Following on from this, further FDA regulatory milestones were reached for liquid biopsy tests, diagnostics and companion diagnostics in 2020:

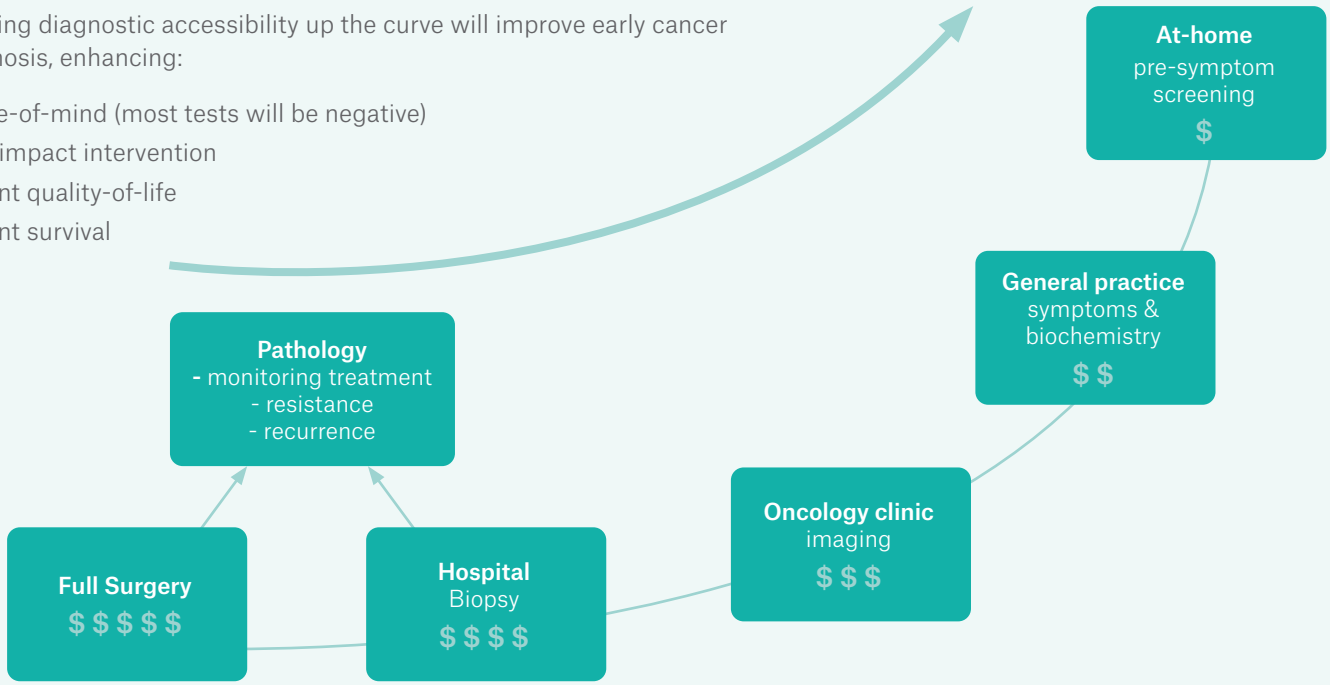
- **First liquid biopsy for minimum residual disease (MRD) detection approved**
  Adaptive Biotechnologies' ColonoSEQ Assay for chronic lymphocytic leukemia[2]
- **First next-generation gene sequencing (NGS) liquid biopsy test approved**
  Guardant360 lab test as a companion diagnostic for NSCLC[3]
- **First liquid biopsy companion diagnostic for two cancers approved**
  FoundationOne Liquid CDx for NSCLC and prostate cancer[4]. *Subsequently, the FoundationOne device also gained Premarket Approval as a companion diagnostic for ovarian and breast cancers. This was followed by Premarket Approval as a companion diagnostic for additional therapies and/or additional gene mutations*[5].

Together, these developments mark 2020 as a watershed moment for liquid biopsy diagnostic device regulations. The products outlined here may be useful predicates for future product applications. So, where does the technology go from here?

Figure 1: Easy accessibility is the key to reducing cancer's impact and cost

Pushing diagnostic accessibility up the curve will improve early cancer diagnosis, enhancing:

Peace-of-mind (most tests will be negative)
Low-impact intervention
Patient quality-of-life
Patient survival



Getting from insight to action faster

There are two key goals of cancer liquid biopsy genetic tests: to detect the presence of disease as early as possible when the patient has the best chance for survival, and to provide clinically actionable information based on a tumour's individual genomic profile.

The genetics of lung cancer (predominantly NSCLC) illustrate this very well. For a gene panel to highlight actionable treatment opportunities, only a handful of genes need to be screened, as approved by the American Society of Clinical Oncology (ASCO). Focusing on EGFR mutations, tumours with common exon 19 deletions respond well to first-generation inhibitor drugs such as Gefitinib and Erlotinib. The most common substitution (p.L858R mutation) also responds to these drugs, but to a lesser degree. However, if a KRAS p.G12 mutation is found in the same tumour, this overrides any EGFR therapies, negating their effect. New drugs targeting specific KRAS mutations (e.g. Sotorasib) hope to use this precise information to improve the outcomes for these particular patients.

Further complicating the patient journey, the tumour continues to evolve during cancer treatment and new mutations arise. During EGFR therapy involving Gefitinib/Erlotinib, the sudden appearance of mutation p.T790M immediately causes resistance to these drugs, negating their effectiveness. New precision drugs, designed exactly to this mutation are required to continue successful patient therapy, and Osimertinib has been very successful in p.T790M tumours. Of course, a range of novel mutations have subsequently been found which cause resistance to this new drug, creating an 'arms race' between precision pharmaceuticals and the growing tumour.

Beyond looking for immediately druggable mutations, there is substantial value in screening a larger gene panel to simply discover the presence of disease. In this case, early detection is the goal and uncovering any cancer-causing mutation (whether treatable or not) highlights disease for clinical follow-up while the disease is easier to treat, since late-stage detection usually has poorer prognosis.

With this in mind, we believe three critical factors need to be satisfied by liquid biopsy genetic test procedures to advance precision oncology.

1. Establish a clinically actionable or early-detection gene panel

Gene panels for molecular diagnosis must strike a balance between the need for efficiency and access to the greatest spread of mutated genes. To fully characterise a tumour, all mutations associated with it need to be considered. However, this can be unwieldy and won't necessarily aid actionability. Instead, it can be preferrable to focus on the sequencing of carefully curated target gene mutations with druggable or prognostic consequences.

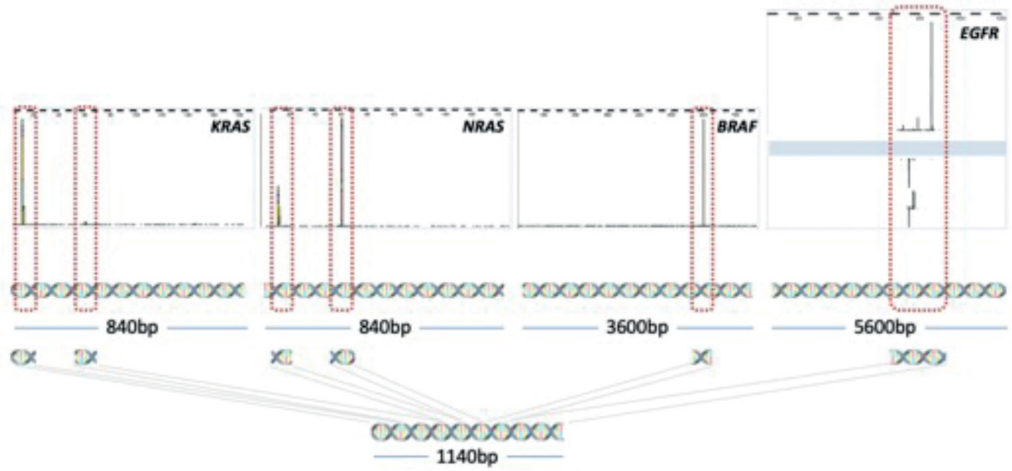
For instance, a gene panel for lung cancer might prioritise the genes defined by ASCO guidelines on actionable targets. A skeleton lung cancer panel might include very few actionable genes (EGFR, BRAF, KRAS and NRAS) to minimise costs (using DNAseq only and minimising coverage) while still offering disease detection for roughly half of cases. For early detection rather than actionable reporting, covering a broader range of genes, such as TP53, ALK, PIK3CA, RBM10, substantially raises sensitivity. Raising this sensitivity is desirable but it comes with additional cost and complexity and is the balance that must be achieved differently across customer groups (by age, lifestyle, etc).

The core genes for Lung cancer detection using simple DNA sequencing are EGFR, KRAS, BRAF, NRAS. Focusing the assay on highly mutated positions reduces the DNA sequencing coverage by 90% with these efficiency gains positively impacting price and speed. To increase sensitivity, additional genes and assay types can be combined, but with increases in price.

2. Understand target genes

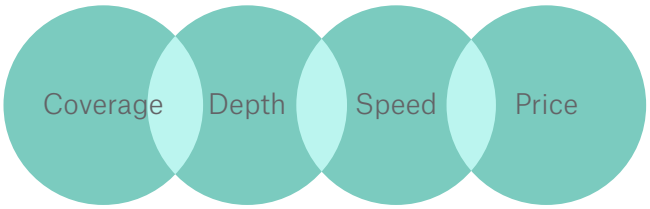
The four actionable genes mentioned above encompass the most frequent mutations in lung cancer, and they also provide the greatest levels of actionability. Each has different patterns of mutation, so to maximise the efficiency and sensitivity of tests it's best to focus on exons that include frequent mutations. Looking at the entire gene would result in cost and complexity, vastly increasing the amount of data to be handled with little extra value. By selecting small portions of target genes for sequencing, the number of base pairs is reduced, enabling greater depth of analysis (and hence sensitivity) while lowering the interpretation complexity. It's about prioritising genetic regions that have the greatest diagnostic potential.

Figure 2: Highly efficient panels improve sensitivity, speed and price



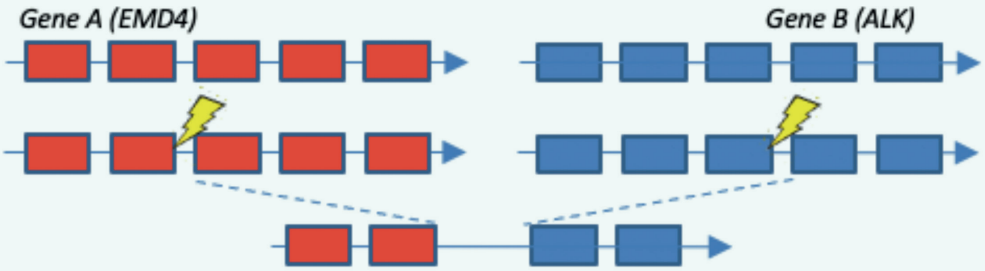
3. Balance key aspects of accessible design

Managing complexity is a top priority in the development of accessible molecular diagnosis technologies. Controlling coverage (the amount of DNA to be sequenced) is just one part of this. Test sensitivity also needs to be considered. This is especially important when it comes to the improvement of early diagnosis as small, or encapsulated tumours, shed less DNA and therefore require greater depth of analysis. It may be necessary to assess the same DNA sequence many times looking for rare mutations. The price and speed of tests also need to be factored in, and ultimately may dictate what can be achieved in terms of depth and coverage of analysis.



Complicating factors

Standard sequencing of genomic DNA doesn't always go far enough to deliver the clinically actionable insights needed for precision oncology.



For instance, gene fusions caused by chromosomal breaks and rearrangement complicate matters, and they have been identified as common drivers in a number of cancers. It can be useful to detect these genomic translocations (and they are included in ASCO's actionable lung panel list), but this inevitably introduces further complexity and cost. Adding gene fusion testing capability to a liquid biopsy genetic test requires the sequencing of RNA as well as DNA, increasing sensitivity by more than 10%, but also increasing the cost. Similarly, DNA methylation can be an important biomarker for disease at specific genes, but requires yet another assay, MethylSeq.

At this exciting time in the wider deployment of genetic technologies, it is possible to design a repertoire of tests, aimed at a range of different patient groups, potentially before any symptoms. For instance, greater sensitivity tests for people with early-stage symptoms or predisposing lifestyles, will include broad genetic coverage and multiple technologies to reveal individuals in need of further care or treatment, providing details of therapy requirements. However, for lowest-price regular assessment of 'worried well', we can design a small-scale minimum coverage DNAseq test that can be regularly used to highlight the emergence of common mutations, with potentially massive savings in long-term healthcare costs and quality of life improvements.

A growing opportunity

We're at an exciting juncture for liquid biopsy genetic testing, where the science, technology, and regulatory environments are broadly aligned. It's still early days however, and particularly the technology requires further development and refinement.

Costs need to decrease significantly to drive the levels of engagement needed for better rates of early cancer diagnosis. The pan-cancer solutions from FoundationOne and Guardant 360 have broken new ground from a technology and regulatory perspective but currently cost $5,000+ per test. Since the cost of DNA sequencing is continually reducing, with clinical-grade full-genome coverage available to consumers for as little as $300, there is huge scope for price reductions to make DNA testing accessible and entice a broad audience to include DNA tests in regular health check-ups. For example, BUPA is already offering a wide gene panel for general health & fitness in the UK for £149 ($182) including follow-up consultation. For comparison a cervical HPV test regularly used for screening costs less than $50, excluding physician and collection costs.

There are also many opportunities to improve the coverage, sensitivity, and speed of liquid biopsy genetic test devices. This is an area where we expect to see a lot of activity over the coming months and years. It will be important to take a pragmatic and strategic approach, since not all cancer types release enough ctDNA for the NGS analysis to be effective at standard sequencing depth.

Grabbing these opportunities is key to maintaining a leading position in the precision medicine market. To do this requires a substantial knowledge of how genetic variants and mutations impact human health, how they interact with each other to modify their effects, and which are directly actionable. Of course, it's important to understand the growing competition to seek novel targets and market niches but also a clear understanding of how to use morbidity statistics and population variant frequencies is essential to ensure a sustainable product is developed with clear revenue expectations. Beyond initial product design, a growth plan is important to ensure your product isn't overtaken by a rapidly moving market, either by growing its genetic range, or by applying similar techniques to a growing range of medical and lifestyle situations.

While there are many challenges to overcome, the regulatory situation is encouraging. Companies that pay mind to the recent FDA approvals and develop regulatory strategies in tandem with product development strategies that empower customers and patients will be best placed to accelerate time to market. Those that make it could play a lead role at the forefront of molecular diagnostics for precision oncology and beyond, enabling many people to live longer and have better lives after cancer.

Our specialist team have decades of experience in the genomics of cancer, precision medicine, and genetic product personalisation, and can help develop the strongest products in your personalisation range.

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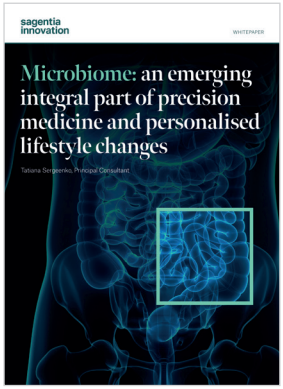

Microbiome: an emerging integral part of precision medicine and personalised lifestyle changes

When should you contact the FDA about a new medical device?

References

1 FDA, Approved Drugs, cobas EGFR Mutation Test v2
2 FDA Report, Adaptive Biotechnologies ClonoSEQ Assay
3 FDA, Recently Approved Devices, Guardant360 CDx – P200010
4 FDA, Recently Approved Devices, *FoundationOne Liquid CDx* – P190032
5 FDA, Approved Drugs, *FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers*

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Sagentia Innovation 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 Innovation employs over 180 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 centres and more than 400 employees. Other Science Group companies include Leatherhead Food Research, TSG Consulting and Frontier Smart Technologies.

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