WHITEPAPER

Complex Therapies, Complex Diagnostics

Creating companion diagnostics for innovative drug classes such as Antibody-Drug Conjugates (ADCs), bi- and tri-specific antibody therapies and immuno-oncology combination therapies.

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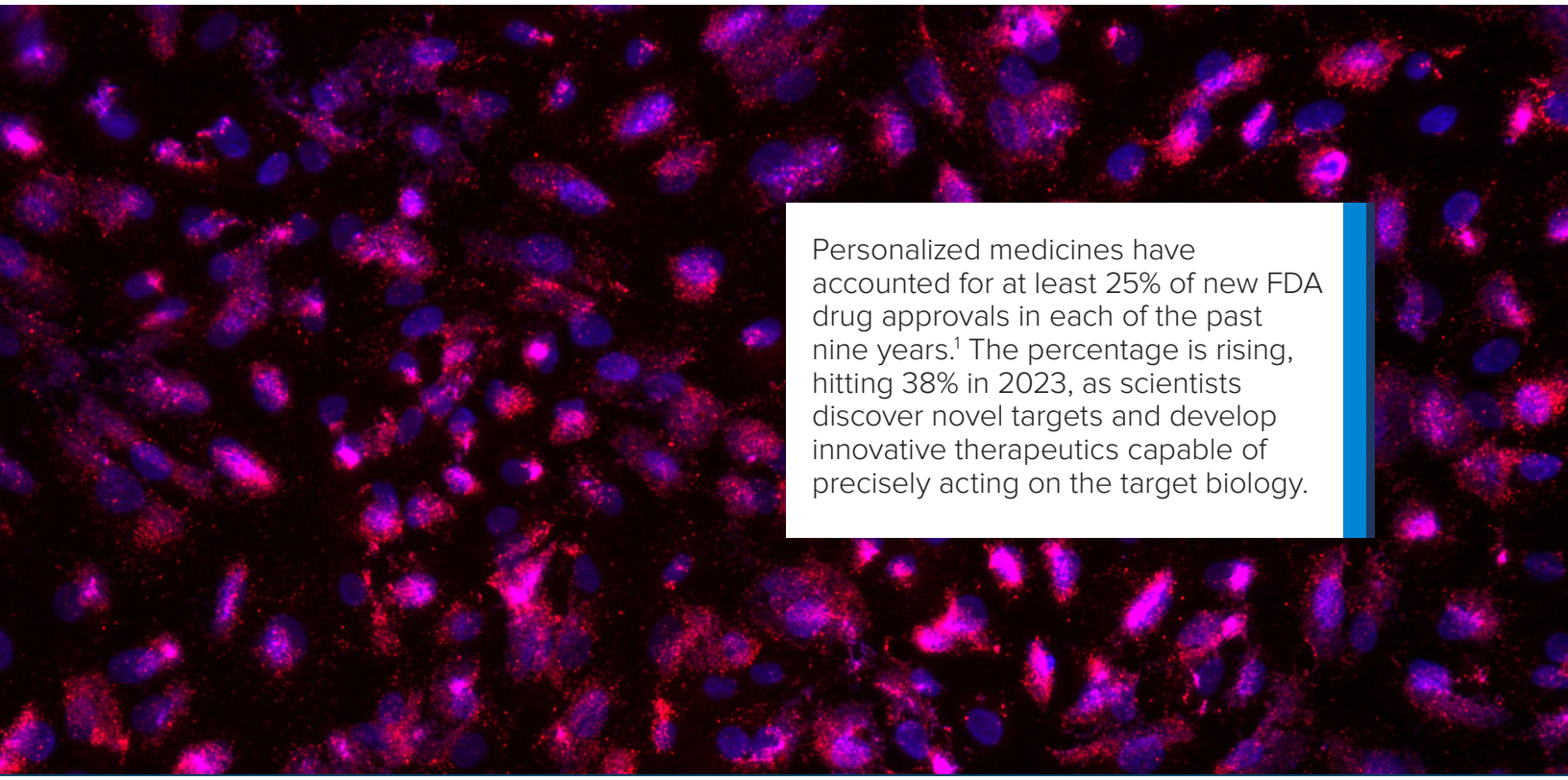
Executive Summary

The age of precision medicine is well underway. Personalized medicines have accounted for at least 25% of new FDA drug approvals in each of the past nine years.[1] The percentage is rising, hitting 38% in 2023, as scientists discover novel targets and develop innovative therapeutics capable of precisely acting on the target biology. Yet, the emergence of new drug categories is creating new challenges. As companies expand the frontiers of drug development, many new therapeutics necessitate more advanced diagnostics.

The demands on diagnostics are changing quickly as the drug development pipeline expands beyond small molecules and monoclonal antibodies. Today, those modalities are just part of a mix that includes Antibody-Drug Conjugates (ADCs), bi- and tri-specific monoclonal antibodies, immuno-oncology combination therapies, cell and gene therapies, RNA drugs and more. New modalities treat major unmet medical needs, but their effectiveness will depend on new diagnostics.

This white paper addresses the shift to novel modalities and its implications, covering topics such as:

- The rapid rise of new categories of targeted therapies
- Dependence of novel therapeutic modalities on new types of diagnostics
- Role of multiplexing and digital pathology in shaping the next generation of companion diagnostics (CDx)
- Mitigating risks and controlling costs when exploring novel, complex tests
- Drug developers' needs, beyond technology, from CDx partners



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The rapid rise of novel therapeutic modalities

By multiple metrics, drug development has undergone a rapid transformation in recent years. ADCs have been at the forefront of the change. The number of ADCs in clinical development jumped by more than 30% between 2018 and 2023, according to PhRMA, as the next generation of ADCs began to fulfill its potential.[2,3]

The FDA approved the first ADC, Wyeth-Ayerst's Mylotarg, in 2000 but that drug was an outlier.[4] By 2018, the agency had only authorized four more ADCs.[5] Only one of the drugs became a blockbuster. Having approved five ADCs in 18 years, the FDA authorized three molecules in 2019 alone. The surge in activity came as developers fixed problems such as weak antibody-payload linkers that hindered older ADCs.

In 2020, pharma interest in ADCs took off, with AstraZeneca, Gilead Sciences and Merck & Co. all paying more than $1 billion upfront to expand in the space over a three-month period.[6–8] In 2022, the number of ADCs entering the clinic rose 90% and by 2023, the drug class accounted for 6% of all drugs in development.[9,10] ADCs continued to dominate deal activity in oncology 2023 and 2024.[11]

While the ADC sector blossomed after decades of struggles, bi-specific and multi-specific molecules have undergone a faster rise. The FDA granted accelerated approval to the first bi-specific antibody, Amgen's Blincyto, at the end of 2014.[12] In 2018, PhRMA said 40 bi-specific molecules, mostly antibodies, were in the clinic. The figure had more than doubled by 2023, climbing to 109, after the number of drugs entering the clinic jumped in the preceding years.[13] Tri-specifics are now in human testing too.

The increased R&D focus and investment in targeted therapies led to improvements in therapeutic efficacy and is translating into regulatory approvals. In 2023, four of the 13 novel cancer drugs approved by the FDA were bi-specifics.[14,15] The FDA singled out bi-specific T-cell engagers—drugs that direct the immune system against cancer cells—as a highlight of oncology approvals in 2023.[16]

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Small molecules and monoclonal antibodies remain a core part of the pipeline but are increasingly being used in combination with immuno-oncology drugs, rather than as single agents. Monotherapies accounted for 70% of cancer clinical trials in 2007.[17] By 2018, the figure had fallen to approximately 20%.

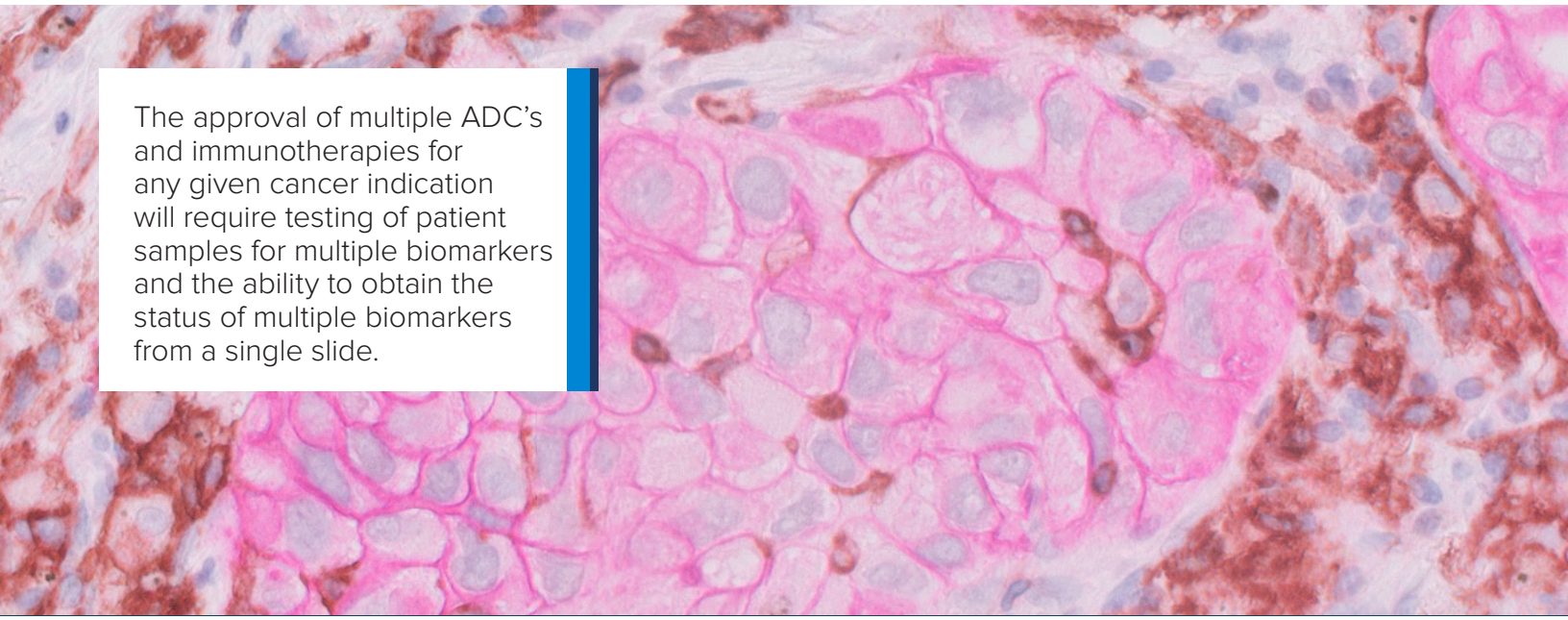
Interest in cell and gene therapy is rising too. In June 2023, the Alliance for Regenerative Medicine (ARM) found there were 693 phase 1 cell and gene therapy trials.[18] By December 2023, the figure had increased to 807. ARM tracked increases in all other phases of development over the period. At the same time, the number of companies developing the drugs increased, rising to more than 1,200 in North America alone.

ARM's data reflect the continuing rise of cell-based immuno-oncology therapies and the expansion of cell and gene therapies into diseases beyond cancer. Investigators started around 30 clinical trials of CAR-T cell therapy candidates in lupus in the 18 months after a research group shared promising human data, and interest in applying the modality to other autoimmune diseases is growing.[19,20]

How the novel therapeutic modality boom is reshaping diagnostics

The novel therapeutic modalities reflect increased understanding of the molecular and biological basis of disease, facilitating development of drugs that precisely target the specific processes that drive disease. As they pursue those R&D opportunities, biopharma companies need diagnostics that deliver new information such as in-depth spatial biology measurements to identify patients who are most likely to respond to a treatment.

In response, the diagnostic industry has improved the identification of factors including DNA mutations, changes in RNA expression and changes in protein level. Significant investments have been made to expand development of CDx solutions across a variety of technologies including next-generation sequencing (NGS), immunohistochemistry (IHC), flow cytometry, ELISA assays, mass spectrometry and gene expression profiling.



The approval of multiple ADC's and immunotherapies for any given cancer indication will require testing of patient samples for multiple biomarkers and the ability to obtain the status of multiple biomarkers from a single slide.

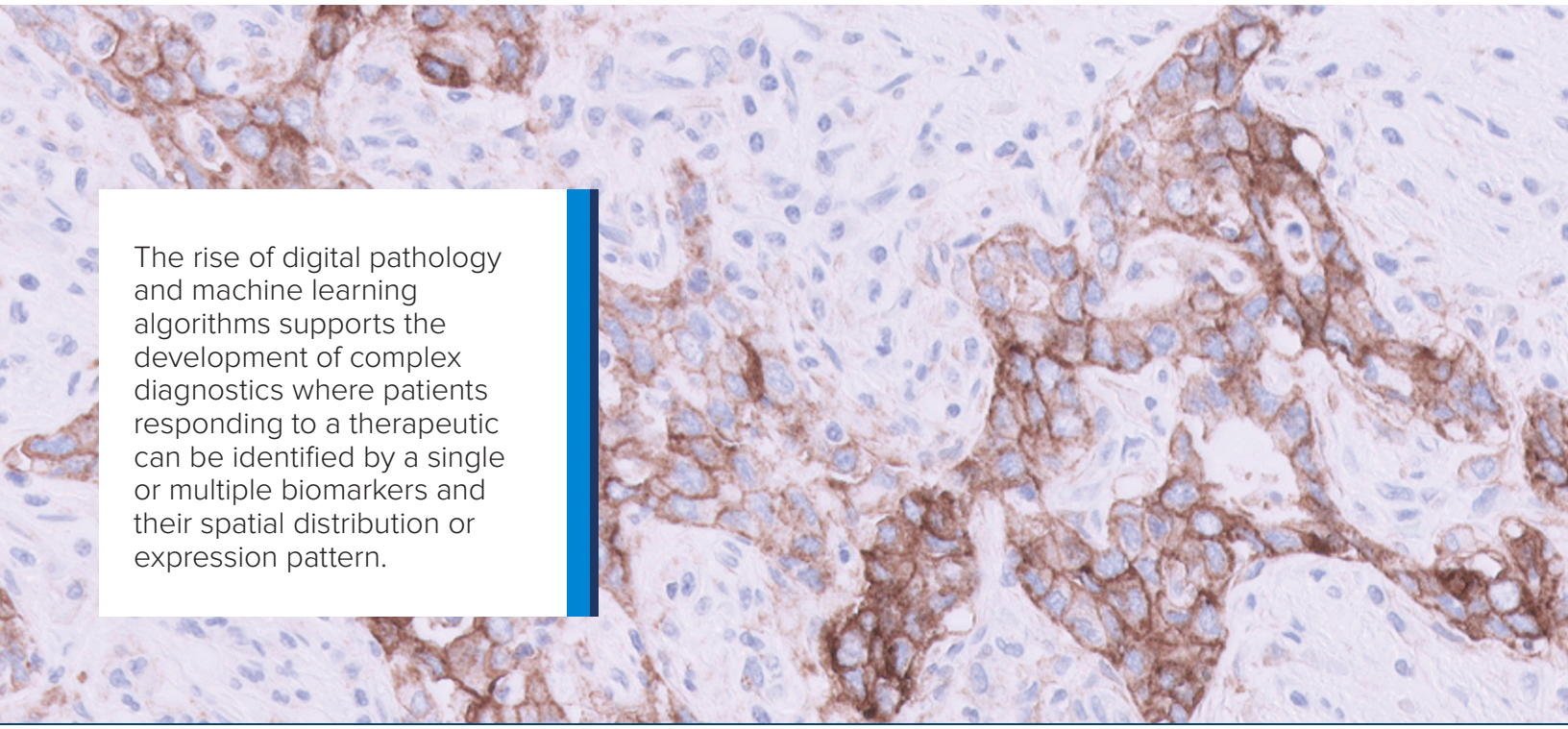
The investment is advancing new technologies and expanding the capabilities of well-established diagnostic tools. Researchers published the first IHC study in 1942 but their successors continue to improve detection chemistries, labeled antibodies, automation and digitization in detection of target antigens.[21] These IHC improvements are critical enablers of ADCs that continue to push the boundaries of diagnostic technologies, for example by detecting very low levels of biomarkers such as HER2.[22]

Furthermore, the approval of multiple ADC's and immunotherapies for any given cancer indication will require testing of patient samples for multiple biomarkers and the ability to obtain the status of multiple biomarkers from a single slide. While highly efficacious, ADC's utilize toxic payloads and bear high toxicity potential from use in patients who do not express the biomarkers. Those attributes increase the need for determination of biomarker status with greater sensitivity.

Scientists working with computational experts continue to innovate IHC with digital imaging and analysis, transforming it from a qualitative to a more quantitative technology. The rise of digital pathology and machine learning algorithms supports the development of complex diagnostics where patients responding to a therapeutic can be identified by a single or multiple biomarkers and their spatial distribution or expression pattern.

The FDA has already authorized machine learning based software as a medical device (SAMD) for identifying areas of prostate biopsy images with the highest likelihood of harboring cancer, creating a precedent for AI-assisted or AI-augmented pathology slide read and interpretation.[23]

Newer technologies and approaches such as antibody multiplexing or more in-depth spatial biology measurements supported by machine learning algorithms can visualize the relationship between biomarkers and the landscape of biomarkers across a tissue. Further, digital pathology and evolving reagents have the potential to extend the dynamic range of the assay beyond current cutoffs or limits of detection and visualize low abundant biomarkers.



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Finding the right diagnostic partner

Biopharma companies understand the need for innovative diagnostic solutions such as antibody multiplexing and digital pathology to identify patients that will benefit from novel therapeutics. However, the industry's appetite for innovation is tempered by regulatory acceptability of the diagnostics and their availability and ease of implementation in the market. The success of the therapeutics requiring a CDx is intricately tied to the diagnostic partners' ability to create the appropriate diagnostic, provide regulatory and technical expertise, collaborate effectively with the biopharma and make the test available on a global scale.

The diagnostic and the diagnostic partner are important factors for the success of the drug program. Here, we consider the attributes drug companies should look for when evaluating potential partners.

Infrastructure

To support biopharma companies from development through commercialization, diagnostic developers need strong technical and regulatory capability, an understanding of end-user requirements, experience in market access and reimbursement, and scalable infrastructure that will ensure unimpeded access to quality testing and enable commercial success of the therapeutic.

The requirements differ from the need for low-cost solutions during early development, to timely availability of testing to support registrational clinical trials, to ultimately unimpeded global access to testing during commercialization. Assay development needs to be one contiguous path.

The required infrastructure varies greatly by the technology and sample type used in the diagnostic solution. IHC, being well-established globally, has the required instrumentation and capability generally available worldwide but considerations must be made when employing innovations and digital tools to ensure global access.

Leading diagnostic companies such as Agilent are mitigating risks through considered implementation of technologies. Agilent has invested in a laboratory and implemented an assay development model to

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The lab will also support the use of novel diagnostic technologies and modalities early in development. The IHC assays in this facility utilize digital pathology from the start supported by whole slide imaging, an image management system and digital algorithm development as needed. The lab will ensure not only availability of the infrastructure to support novel diagnostic methods, but also provide a seamless transition to full CDx development and commercialization.

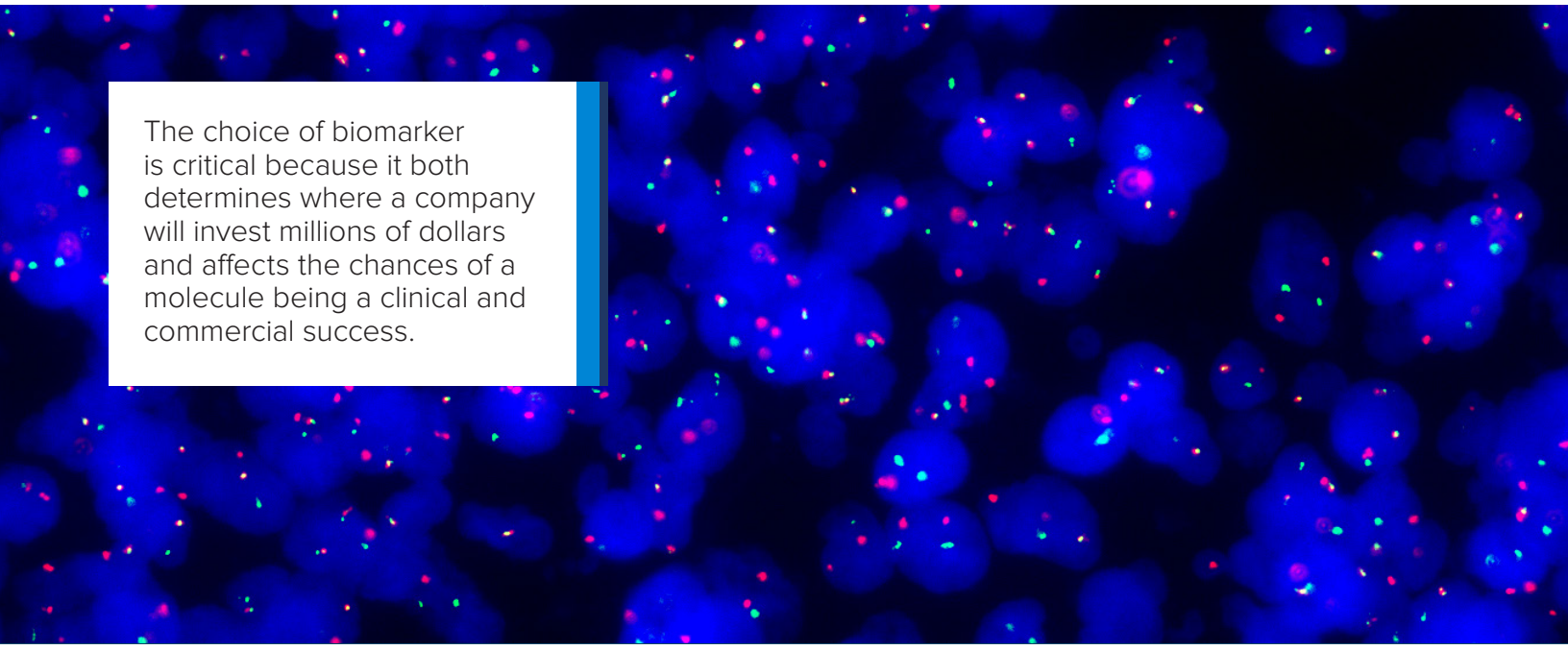
Flexibility

Drug development often requires the adjustment of clinical development plans to optimize for success based on new data and competitive activities. These changes require the diagnostic partner to pivot quickly to modify diagnostic development to meet the new requirements of drug development.

Acceleration of development plans, for regulatory or competitive needs, often requires the diagnostic developer to adopt innovative development approaches to ensure simultaneous approval of the assay. While a program may initially focus on identifying a subpopulation for a clinical trial, drug developers need the option to expand into a broader population and scale up as a therapeutic advance through clinical development on to the market.

Successful models must be flexible to accommodate the unpredictable path of early clinical studies but must also conform to the rigid and growing number of regulatory constraints on IVD development and use in clinical studies.

Biopharma companies may consider multiple biomarkers early in development before needing a CDx. The choice of biomarker is critical because it both determines where a company will invest millions of dollars and affects the chances of a molecule being a clinical and commercial success. Drug developers want data on the assays to make informed decisions but also need to control costs, particularly at a time when access to capital is constrained. Flexible partners can help manage the challenges.



Regulatory expertise

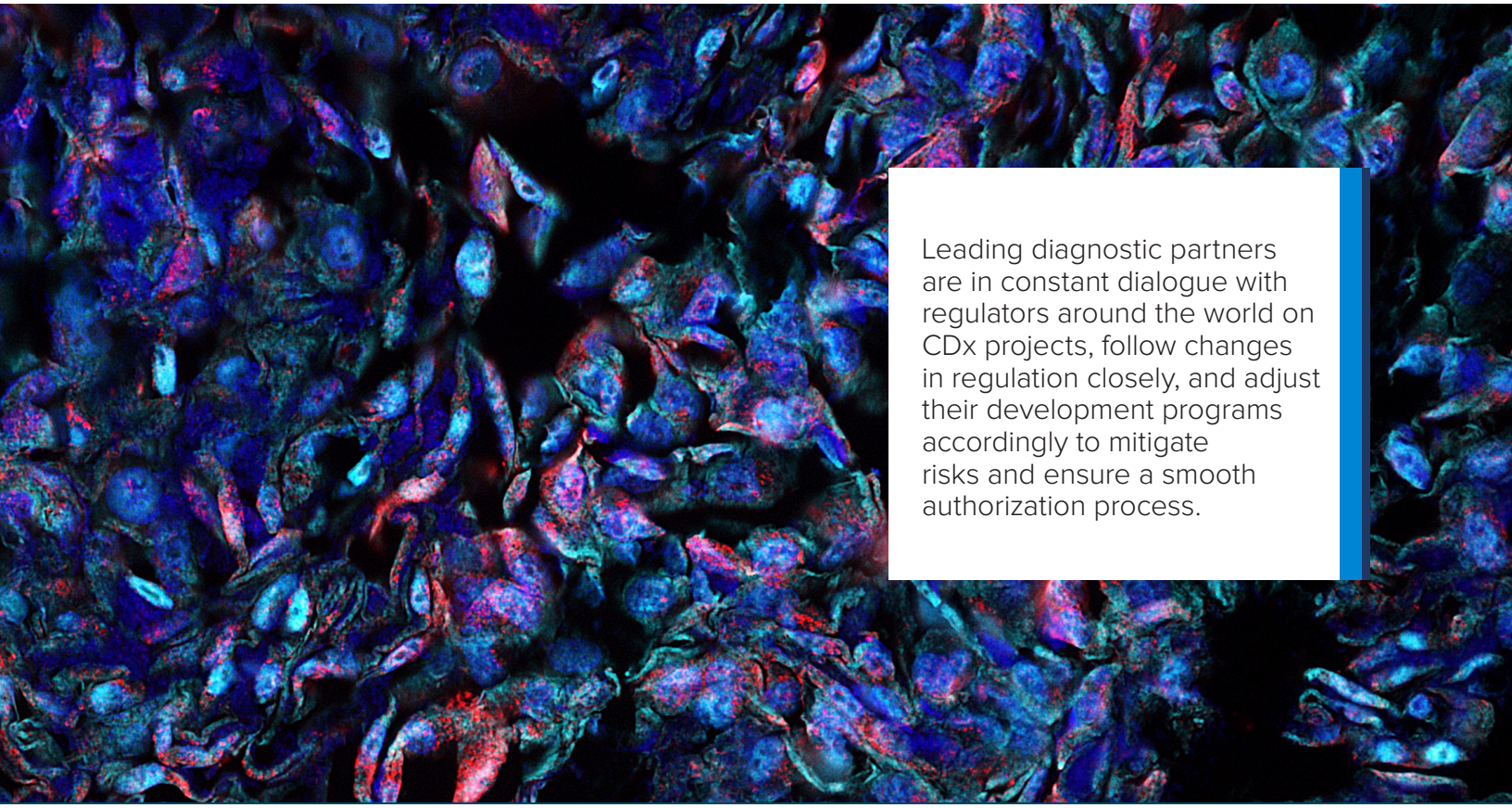
The regulatory environment for diagnostics has been undergoing changes in geographies including the U.S., EU and China. A diagnostic partner's regulatory expertise provides critical contributions in creating a successful diagnostic development plan that is optimized for the therapeutic development strategy.

Leading diagnostic partners are in constant dialogue with regulators around the world on CDx projects, follow changes in regulation closely, and adjust their development programs accordingly to mitigate risks and ensure a smooth authorization process.

Innovation

Biopharma companies value partners that can innovate to address needs across their portfolios and implement the innovations in a compliant manner to create successful diagnostic solutions. Such innovation can create new models of asset development that allow for multiple biomarkers, such as multiplexing, and result in AI-assisted SAMD that address industry-wide resource constraints. The current needs of the biopharma R&D pipeline make innovation in spatial biology and the detection of low abundant biomarkers particularly valuable.

As a life science tools company, Agilent can support biopharma companies as the industry moves toward multi-omics with NGS and other technologies. Agilent plans to incorporate the technologies into its new laboratory to provide a test bed for assessing the feasibility and clinical utility of innovations.



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Conclusion

Drug development is increasingly relying on precision medicine approaches facilitated by ever-more detailed models of human biology and the use of diverse drug modalities to precisely modulate the pathways that drive disease. As has happened in many cancers in recent years, all-comer therapies will be replaced by a new generation of targeted treatments that maximize efficacy in the biomarker-selected patient population and exclude patients unlikely to respond to the therapeutic.

The vision of precision medicine requires drug and diagnostic developers to work in close collaboration to innovate diagnostic approaches to meet new diagnostic challenges created by novel therapeutics. The success of novel targeted therapies requires more complex and more sensitive CDx assays that are highly selective to identify the right patient population. In addition, diagnostic developers must make available low burden solutions for early development, timely robust solutions for full development and commercialization models to support the diverse requirements of precision therapeutics. Innovation in drug development must be matched by innovation in the diagnostic sector.

Agilent foresaw the fast-emerging need for innovative diagnostics, leading it to invest in creation of novel models to support early development, digital pathology, spatial biology and innovative commercial models to support the existing and future needs of its biopharma partners. The investments are enabling Agilent to match the pace of innovation in drug development and facilitate the blossoming of novel modalities that address major unmet medical needs.

About Agilent Technologies

Agilent supports scientists in 110 countries in cutting-edge life science research; patient diagnostics; and testing required to ensure the safety of water, food and pharmaceuticals. Agilent's full range of solutions includes instruments, software, services, and expertise that provide trusted answers to customers' most challenging questions.

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