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LIST OF ABBREVIATIONS

AI	Artificial intelligence
CDx	Companion diagnostics
CMS	Centers for Medicare & Medicaid Services
EHR	Electronic health records
EMA	European Medicines Agency
FDA	Food & Drug Administration
HTA	Health technology assessment
IVD	In vitro diagnostic product/medical device
LDT	Laboratory-developed test
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
P4P	Pay for performance
RWD	Real-world data

In the race to transform customer value through technology, the healthcare sector has traditionally been an also-ran. Precision medicine may be changing the game. Its visionaries hope that it will bring us ever closer to a world where you can take one pill for all your customized medications, and control it with your smartphone; where an app that integrates everything from your molecular makeup to your sleep patterns to your postcode can show you exactly what diseases you face, when they will occur and how you can avert them; and where gene editing is making serious diseases with no known cures a thing of the past.

Precision medicine has the potential to upend our very conception of healthcare. It's changing the focus from treating disease to maintaining health, and from episodic care to continuous vigilance. It's turning passive patients into proactive participants in their own healthcare. And it's replacing trial-and-error approaches based on population averages with more accurate diagnoses and targeted therapies.

But such transformative outcomes require profound changes. We often hear about the impact that precision medicine will have on healthcare systems and how we personally manage our health. But what about those tasked with bringing precision medicine tests and treatments to the market? What are they doing, what challenges do they face, and how are they working with stakeholders within the wider healthcare ecosystem?

In order to find out more about industry approaches, Bristol-Myers Squibb, Medidata Solutions and Thermo Fisher Scientific sponsored research by Newsweek Vantage to survey diagnostics developers and biotechnology and pharmaceutical (biopharma) organizations involved in drug discovery and development, in the US, UK, Germany and France. We supplemented survey insights with in-depth interviews offering different perspectives on the role of precision medicine in healthcare.

The road ahead

Back in 2003, the human genome was sequenced after 13 years, at a cost of nearly \$3 billion; today, that can be done in about a day, for a mere \$1,000.¹ There are over 70,000 genetic tests now available in the US, and 42% of all novel drugs approved by the US Food & Drug Administration (FDA) in 2018 had information on their labels about biomarkers—identified using diagnostic tests—that determine drug response.²

But some question why more precision medicine tests and treatments aren't available or accessible, and how effective they really are. It's a good time to take stock of what is and isn't working, and what's needed to drive future growth.

Our survey points to four overarching and deeply intertwined themes that define how industry is rising to the challenge:

Putting patients first. Precision medicine is putting fresh impetus behind industry efforts to focus on patient needs. Indeed, its very success depends on understanding as much as possible about patients, in order to deliver the tests and treatments that are most suitable. Moreover, this approach has the potential to deliver a much-needed boost to industries in turmoil. But it requires a transformation in business models that's being felt in every part of the value chain.

Embracing data. The focus on patient data is taking the need for data governance, management and analytics to whole new levels. Health data siloes are giving way to unified data strategies that converge sources like electronic health records (EHRs), patient-reported outcomes, sensor feeds and population statistics to transform drug and diagnostics development. Analytics capabilities are being enhanced to make sense of the vast amount of data being amassed, leveraging the power of artificial intelligence (AI).

What is precision medicine?

Precision medicine is an emerging approach that factors in an individual's molecular profile, environment and lifestyle in order to prevent, diagnose and treat diseases more effectively.

It's not about developing new treatments for each and every individual; it's about considering individual differences in the course of prevention, diagnosis and treatment. For example, by identifying specific biomarkers—indicators such as an individual's molecular makeup or the molecular profile of their disease characteristics—patients can be classified into subgroups based on how susceptible they are to certain diseases, how those diseases will develop, or how they'll respond to particular treatments. This information can then be used to predict what the most effective course of action will be for those individuals.

Although genomics has grabbed the spotlight, other "omics" technologies are allowing us to study all the molecules in fluid or tissue samples, including RNA (transcriptomics), proteins (proteomics), metabolic by-products (metabolomics), fatty acids and other lipids (lipidomics), and microbes (microbiomics).

But precision medicine is aimed at capturing much more than molecular information, including socioeconomic, cultural, environmental and behavioral factors, drawn from a diverse range of sources. The nascent field of exposomics, for example, looks to measure how the sum total of all the exposures from an individual's environment, occupation, diet, lifestyle and other sources impact on health.³ The new study of behavioromics, meanwhile, aims to reveal how changes in behavior, monitored throughout a range of activities, could relate to health.⁴ Together, all this information has the potential to provide a better understanding of the many complex mechanisms underlying a person's health, disease or condition.

Redefining value. Despite these efforts to further the pursuit of precision medicine, there are many barriers to its widespread adoption. A value-based approach to pricing and reimbursement—focusing on patient health outcomes to deliver clinical and economic benefits to stakeholders—is seen as a key enabler of growth. Precision medicine's patient-centered, evidence-based ethos encapsulates this, but tough challenges include aligning stakeholder views on what value means, and demonstrating the effectiveness of tests and treatments.

Working together. The sheer ambition of precision medicine, in aiming to understand patient needs and patient data as never before, and in seeking to redefine the very value of healthcare, means that no one can do it alone. Enablers of growth—including companion diagnostics (CDx), next-generation sequencing (NGS), advanced data analytics, regulatory innovation and clinical adoption—come from all corners of the healthcare ecosystem. With new levels of national and international collaboration, driven by societal trust, we have the potential to truly accelerate the growth of precision medicine and create value for everyone.

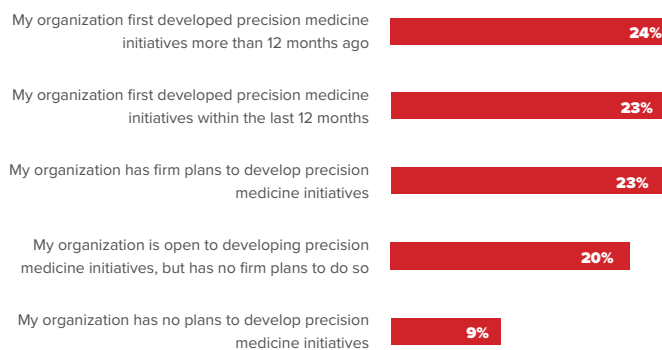
PUTTING PATIENTS FIRST

With 70% of the executives we surveyed saying that their organization has precision medicine plans or initiatives in place, the drug and diagnostics industries appear to be poised on the brink of significant change (see Figure 1).

These efforts, to be sure, are defined in broad terms, and include exploratory measures. They're also still very new. But only 9% of executives said their organization had no plans at all for precision medicine.

Figure 1: 70% of executives say their organizations have precision medicine plans or initiatives in place

Q: Has your organization developed precision medicine initiatives (including e.g. product development or marketing efforts) or have plans to do so?



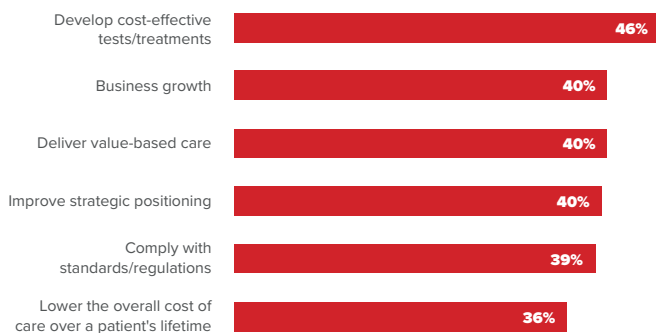
Better patient outcomes, better business outcomes

It's not the first time these industries have faced sweeping changes. But what's different now is that precision medicine is stepping up the focus on patients. This involves capturing and analyzing data at the level of the individual patient, and it's starting to extend to engaging patients in how this information is used, and in decision-making more generally.

Forty percent of executives say that value-based care is a top-three driver of their organization's precision medicine goals, and 46% say the same of the need to develop cost-effective tests and treatments (see Figure 2). But this hasn't knocked more traditional business drivers from their perch, with both business growth and strategic positioning cited by 40% of executives. This indicates that organizations see patient outcomes as aligned with business outcomes.

Figure 2: Executives say value and growth drive their organization's precision medicine initiatives

Q: Which three of the following are the main drivers for your organization's current/planned precision medicine initiatives?



The general aim of value-based healthcare is to achieve better health outcomes in more cost-effective ways (see discussion in *Redefining value* on p.14). Aligning precision medicine with this approach can deliver greater value to patients, healthcare providers and payers by improving health outcomes through more targeted interventions, and lowering costs through preventive measures and reduction in unnecessary or ineffective tests and treatments. This, in turn, can help achieve business goals for drug and diagnostics developers in a number of different ways.

The limited efficacy of one-size-fits-all drugs—affecting the willingness of payers and patients to pay for them, and for regulators to approve them—has made it imperative for the biopharma industry to change its strategic focus. More precise clinical trial designs can also reduce R&D timescales and costs, which are not insignificant: drug development can take 10-15 years, with a price tag of up to \$4 billion.⁵ Improving the cost-effectiveness of drugs will also increase the potential for reimbursement, boosting market penetration.

For the diagnostics industry, the focus on patient outcomes offers the opportunity to address serious challenges around value. Diagnostic tests drive the majority of medical decisions, yet account for just a tiny proportion of healthcare spend, due to misperceptions about the value they create, and ineffective reimbursement policies. The development of ever-better molecular tests offers the opportunity to drive a change in thinking. The role of CDx's, for example, which are deemed essential for the safe and effective use of their companion drugs, is helping to put the spotlight on the role of tests in improving outcomes and limiting unnecessary costs.

Revamping the business model

A value-based, patient-focused approach has profound implications for industry business models. It requires an entirely different view about how value is created and delivered, from the outset; a transformation in strategies and processes along the entire value chain; and greater collaboration across business functions in order to achieve a holistic and consistent view of patient needs. Organizations are bracing for change—in particular the largest companies, with revenues of \$1 billion or more. The large investments they stand to lose, combined with greater resources to fix ailing business models, help to explain why.

Twenty-eight percent of executives—and 40% of those in large organizations—say changes are being made in the R&D or manufacturing process (see Figures 3 and 4). And 31% of executives—rising to 45% at large organizations—say commercialization strategies are changing, too. But executives also recognize the many challenges that lie ahead in all of these areas.

Figure 3: Precision medicine initiatives are impacting every part of the value chain

Q: Which of the following activities have been undertaken/planned by your organization to implement precision medicine initiatives?

Q: Which three of the following do you consider to be the biggest barriers to the development of your organization's precision medicine plans/initiatives?

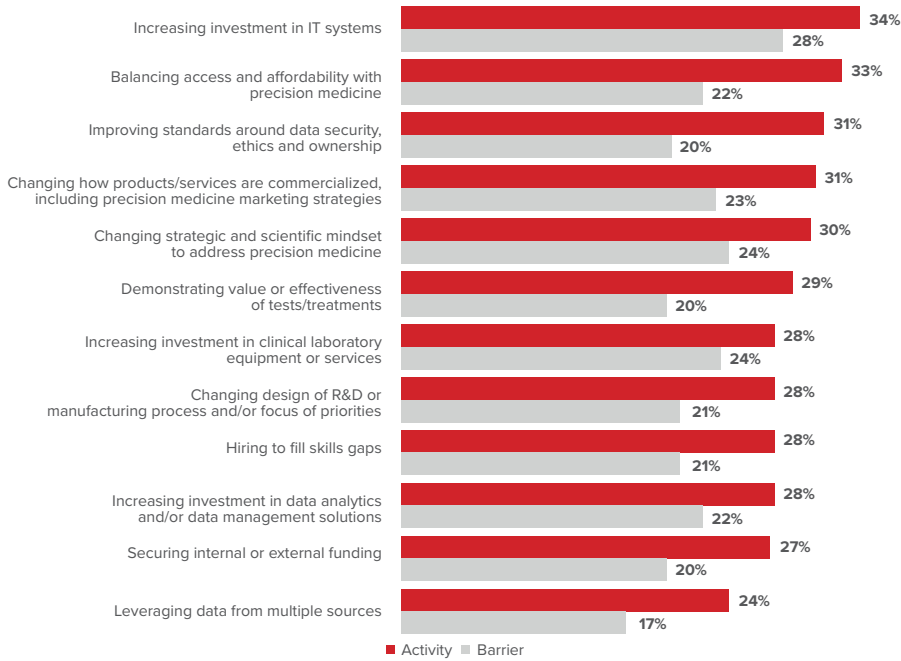
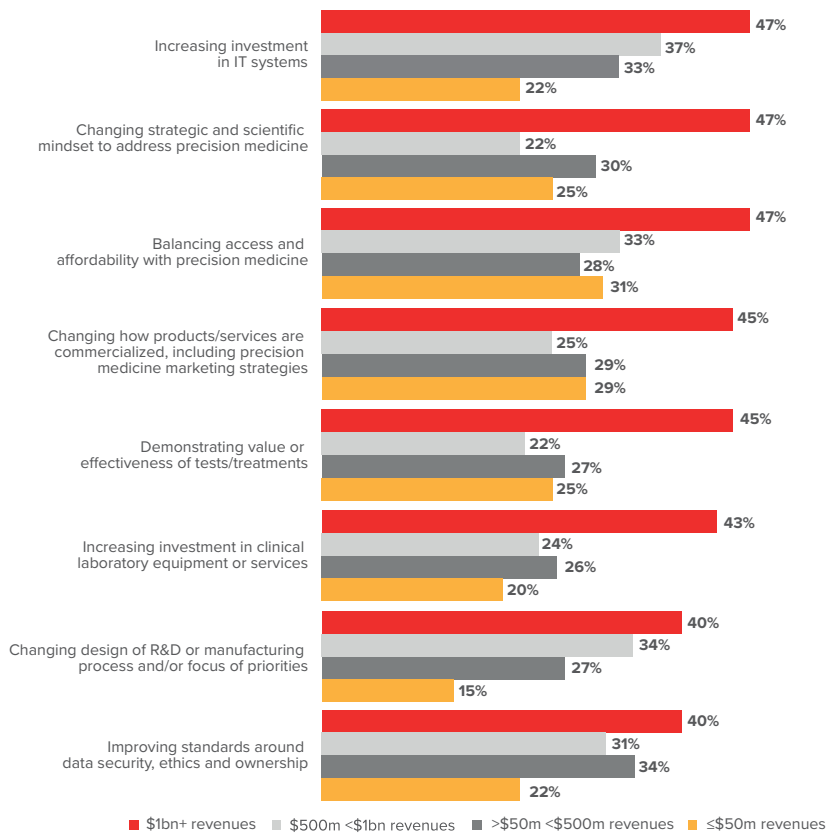


Figure 4: Executives in large organizations see precision medicine initiatives transforming multiple business areas

Q: Which of the following activities have been undertaken/planned by your organization to implement precision medicine initiatives?



Base: executives at organizations with revenues of \$1bn+ (53), \$500m up to \$1bn (67), >\$50m and <\$500m (116), and ≤\$50m (55). The answer options shown are those where significant differences in responses were found between organizations with revenues of \$1bn+ and smaller organizations.

A new era in drug development

Clinical trials are one area seeing significant innovation. Eighty-four percent of executives agree that precision medicine represents nothing less than a new era in drug development (see Figure 5). And many executives cite the importance of flexible trial designs and a much wider range of data and data sources than traditionally used (see Figure 6).

Figure 5: 84% of executives think precision medicine represents a new era in drug development

Q: To what extent do you agree that precision medicine represents a new era in drug development (e.g. clinical trials, manufacturing, companion diagnostics)?

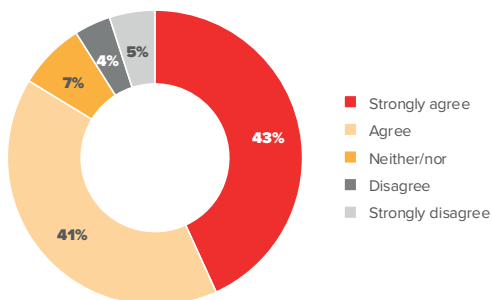
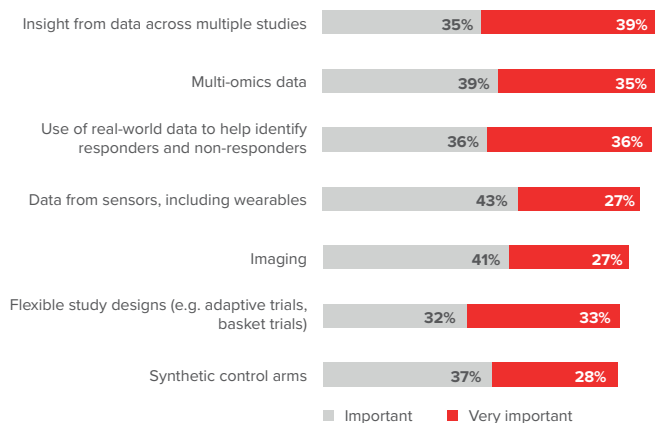


Figure 6: Executives see great value in innovating the design of clinical trials

Q: How important are each of these to your organization in designing clinical trials and achieving precision medicine goals?

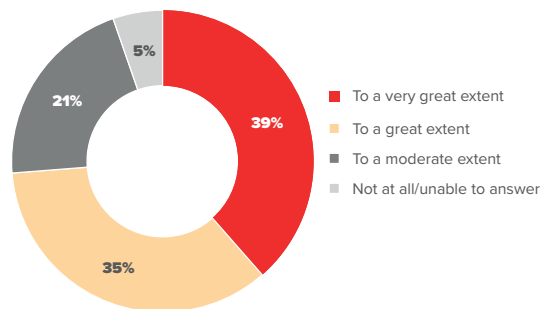


Yet, fully 74% of executives say their organization’s current trial models already greatly support precision medicine goals (see Figure 7), although the proportion is far less at small organizations, with revenues of \$50 million or less (51%).

One answer to this seeming discrepancy is how precision medicine approaches are currently being applied to research. Much of it focuses on retrospective analyses of patients’ molecular makeup or disease characteristics, in order to form hypotheses as to how patient groups will likely respond to given therapies. The next step—validating those hypotheses in a prospective manner through targeted trials—is still at an early stage.

Figure 7: 74% of executives think current clinical trial models support precision medicine goals

Q: To what extent do you think your current clinical trial models, if any, support precision medicine plans/initiatives?



And precision medicine doesn’t change the fundamentals of scientific research; rather, it’s about refining classic trial design. “There are things that are not going to change from the current clinical trial model,” explains Glen de Vries, co-founder and president of US-based life science technology firm Medidata Solutions. “A novel therapy is still going to be developed in a structured, scientific way, where data is gathered prospectively, using a predetermined protocol, in a way that can demonstrate how and why a therapy is safe, effective and valuable.

“Another important element in traditional trial design that’s not going to change is that we will always evaluate outcomes by comparing control groups and treatment groups. But as therapies become more precise—designed to benefit fewer people—the harder it will be to find enough patients, so the more important it is to generate as much evidence as possible for each patient. So what *is* going to change is that evidence models will evolve significantly.”

A case in point is the increasing spectrum of ways to reduce the number of control participants needed for a trial. This has additional benefits of reducing time and cost, and exposing fewer patients to placebos or existing standard-of-care treatments that might not be effective for them. One model involves multiple treatment arms, or groups, that share a single control arm. Another method to reduce (or even eliminate) the need for control patients is the use of synthetic control arms. This is done by collecting data on real patients from outside the trial in question, and in effect, “synthesizing” them into a single comparator group. The data can come from historical control data from other clinical trials and from real-world sources outside a trial environment.

Such designs, however, supplement rather than supplant randomized controlled trials, whereby patients are randomly assigned to either a treatment or control arm, typically in a one-to-one ratio. While these trials do have important limitations, they remain the “gold standard” for clinical research.

Multi-arm trials have other evidence-generating (and efficiency) benefits. They’re a type of so-called adaptive trial, which can be modified in many different ways depending on interim outcomes, using rigorous pre-established protocols. The ability to test multiple treatments in the same trial means enrolling fewer patients. And the ability to use evolving outcomes from certain treatment arms to inform the course of other arms generates yet more evidence using the same number of patients.

Oncology trials in particular are evolving toward more innovative designs. There are so many cancer subtypes, based on different types of mutations, that it's increasingly hard to run ever-smaller trials for each one. Multiple sub-studies can, however, be run at the same time, under a master protocol. One example is basket trials, which test a drug on a specific mutation found across different cancer types.

As large trial populations gradually give way to highly targeted enrollment requirements, recruitment strategies will need to change too. They will require searching much more widely for participants—leading to increasing use of methods such as social media and collaborations with healthcare organizations—as well as collecting much more data on each patient.

Growing interest in co-developing CDx's—in order to launch the diagnostic and drug at the same time, maximizing benefits for patients—is also bringing diagnostics developers into drug trials (see discussion in *Raising the game for CDx* on p.17). Patients, too, are having a greater voice in trial design, which is helping to identify unmet needs and uncover what matters most to patients, such as risk–benefit considerations, tolerability of medications, and quality-of-life measures.⁶ This can lead to improved uptake and outcomes, by developing treatments that people want and will adhere to.

As beneficial as all these developments are, they add new dimensions of complexity and raise a number of regulatory concerns. They also run counter to a model that has traditionally addressed issues of broader patient satisfaction and recoupment of development costs in the post-launch stage.⁷

Dx: all change ahead

Diagnostics R&D is also starting to see significant change, especially in levels of cross-sector collaboration, and a drive to generate value through novel solutions that address unmet needs.⁸ A case in point is the OncoPrint Childhood Cancer Research Assay developed by US-based life sciences company Thermo Fisher Scientific. It's an NGS-based genomic-profiling tool developed in collaboration with Children's Hospital Los Angeles (CHLA), and is the first test designed for the sensitive detection of mutations associated with multiple forms of childhood cancer, simultaneously profiling DNA and RNA across more than 200 genes and thousands of translocation-derived “fusion” genes.⁹

One success story leveraging this novel comprehensive profiling assay, or test, concerned the enrollment of a two-year old individual with a severely compromised airway due to a soft-tissue tumor in her neck. CHLA was able to run a complete genomic analysis in an unprecedented 48 hours, from a tiny amount of tissue, allowing the subject to be immediately admitted into a clinical trial deemed to be relevant based on the genomic findings—leading to a rapid and durable reversal of the cancer.¹⁰

CHLA provides the test as a service across the country, and can help laboratories interpret results. The program's collaborative nature extends to the establishment of the International Childhood Cancer Network (ICON), which facilitates the sharing of data, best practices and experiment protocols in the global research community, to promote an increased understanding of the genomic underpinnings of pediatric cancers and improved outcomes in the pediatric, adolescent and young-adult patient population.¹¹

Less is more

Precision medicine also heralds wide-ranging implications for manufacturing. The mass production of small numbers of drugs for large markets will yield to smaller-scale production of larger numbers of drugs for smaller markets. For example, 3D-printed pills are being developed which can be adapted in size and shape, and designed to release multiple medications at customized rates.¹² Researchers have also developed a wirelessly controlled, 3D-printed capsule which can deliver at least a month's worth of medications, detect infections and other conditions, and interact with wearables and implants.¹³

Mass marketing will increasingly be replaced by more targeted strategies. There are, for example, over 260 drugs in the US with genetic information on their labels.¹⁴ Pricing and market access are also key considerations, with 33% of executives—and 47% at large organizations—saying that making precision medicine more accessible and affordable is a priority (see Figure 3). Clinician training is another area that organizations recognize is creating barriers to adoption (see discussion in *Working together* and p.18). And, aided by digital technologies such as smartphone apps and implanted wearables, drug manufacturers are engaging more with patients to monitor treatment efficacy, improve adherence and encourage greater self-care.¹⁵

Movements to increase patient participation in medicine aren't new, but industry efforts to involve patients in R&D and commercialization have developed slowly, whether due to regulatory concerns, entrenched practices or funding constraints. Consequently, few organizations have the capabilities to design end-to-end customer experiences.¹⁶ The shift in focus from product to customer is a substantial one; it's little wonder that 30% of executives—rising to 47% in large organizations—cite changes to strategic and scientific mindsets as part of precision medicine goals (see Figure 4). As patient participation grows, the level of customization and collaboration will only increase, and extend beyond patient needs to encompass attitudes, preferences, goals and values.

“The consideration of the needs and values of individual patients is becoming an economic imperative, not just a moral imperative.”

—Barbara Prainsack, Professor for Comparative Policy Analysis,
University of Vienna

Unsung heroes

None of these transformational efforts would be possible without the people, equipment and technology required to make them happen.

Twenty-eight percent of executives said their organizations were hiring to fill skills gaps (see Figure 3). But it hasn't been easy, with 21% citing this as a top-three barrier to the development of precision medicine initiatives. Part of the challenge is how diverse skill sets need to be, with key gaps spanning the core biological and chemical sciences to a breadth of computational disciplines.¹⁷

The large network of healthcare service and supply organizations is also critical to industry efforts. They include providers of clinical laboratory equipment and services, which 28% of executives—rising to 43% at large organizations—cited as a focus for increased investment (see Figure 3). But 24% also identified this as a top-three barrier to precision medicine initiatives.

A key issue is that much of the current equipment measures only one or two substances—something which has to be weighed against capital, servicing and other support costs. With finite resources, organizations need more efficient tools that increase productivity and lower costs, while also being easy to use and maintain. Large manufacturers are actively looking to plug the gap, including consolidating different assays into fewer platforms, and developing instruments that can run multiple assays on a single sample, alongside solutions to optimize workflow and reduce complexity.

In the context of genomic testing, the improved NGS technologies developed by such organizations has enabled greater efficiency, and can now sequence numerous samples simultaneously, as well as undertake deep sequencing of target regions through hundreds or even thousands of reads. Though many challenges remain, NGS-based diagnostics are improving the ability to test many genes at once for specific biomarkers, and to test single samples for multiple biomarkers, as well as bringing whole-genome testing into the clinical setting.

Last but not least, the central role of data and information in precision medicine has made data and technology solutions key enablers of organizations' initiatives. A top priority is increasing investment in IT systems, cited by 34% of executives—and 47% of those in large organizations—with a further 28% saying their organizations are increasing investments in data analytics and management solutions (see Figure 3). The next section explores how organizations are using these solutions to further precision medicine goals.

EMBRACING DATA

The patient-centered approach, which has a long history in medicine, focuses on patients' unique needs as individuals who have a condition or disease, rather than putting the focus squarely on the latter. It's traditionally been a high-touch, low-tech exercise, but precision medicine is putting a new spin on it, with a "patient data-centred approach".

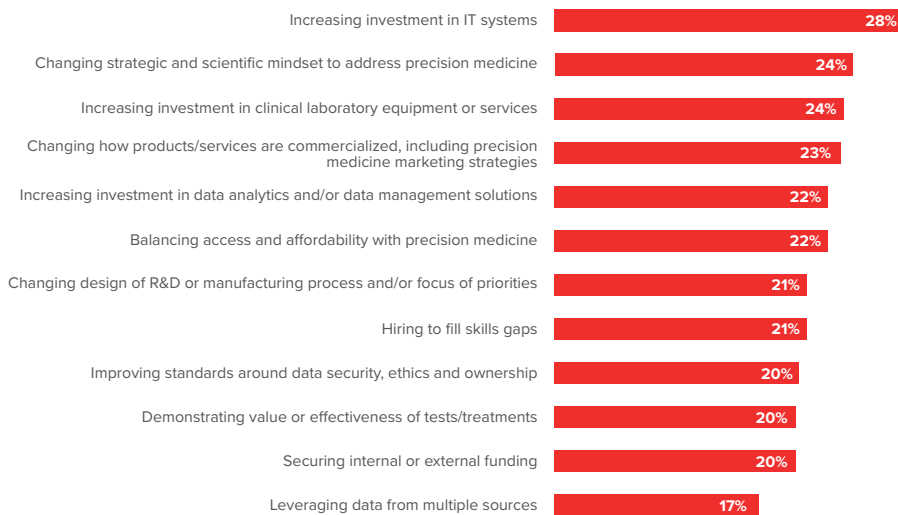
It's leading to a desire to access more data, from a greater variety of data sources—and putting greater emphasis on data integration, preparation and analysis, in order to make sense of it. And it's not only about collecting ever-larger amounts of data; it's also about the challenge of interpreting it.

All this has led to increased investments in data and technology solutions—but executives also cited these as top-three barriers to the development of precision medicine goals (see Figure 8).

One obstacle for organizations is how to use the data they have at scale, in terms of generating new hypotheses, developing new products, and leveraging existing portfolios in new ways—which legacy systems may not be able to do. A broader challenge concerns organizational siloes that act as a barrier to thinking in terms of the full product life cycle and future state of the business, and the digital environment needed to support those goals.

Figure 8: IT investment heads executives' list of top-three barriers to developing precision medicine initiatives

Q: Which three of the following do you consider to be the biggest barriers to the development of your organization's precision medicine plans/initiatives?



“The big opportunity is using digital platforms to connect people in new ways and enable greater efficiency and better evidence generation. That requires investing in bigger, more sophisticated systems, which is not an easy thing for a company making decisions in siloes. It’s not just the cost of the IT; it’s the organizational change management involved.”

—Glen de Vries, co-founder and president, Medidata Solutions

Putting the “big” in big data

Many executives point to a wide range of data and data sources that their organizations use, or plan to use, to a great extent (see Figure 9). The variety and volume of data used, and the speed at which it’s received and acted upon, will only increase as greater amounts of molecular information become available, and as individuals increasingly generate their own health data.¹⁸

At the same time, however, just 24% of executives said that their organizations have actually leveraged multiple data sources, or have plans to do so, in order to advance their initiatives (see Figure 3).

This seeming discrepancy may be in part down to the fields of research that these organizations are focusing on, given that much of the current usage of new data sources is in oncology. And, while organizations have been steadily collecting an ever-wider range of data, not all of it is being used today. There are likely to also be challenges in deciding what data to prioritize and invest in: it’s not any and all data that’s needed, but relevant, quality data.

Data strategies, unite!

Organizations most prize data solutions that improve access to a range of quality data sources, and which allow that data to be integrated and managed in one place (see Figure 10). These are, moreover, areas that over a third of executives think their organization needs to improve on.

The need for data integration solutions is particularly great at large organizations, with 62% of their executives citing its importance (see Figure 11)—and 55% saying improvement was needed (see Figure 12).

Clinical trials are one area where data unification will play an especially large role, as a greater variety of data and data sources promises to transform how evidence is generated. Medidata’s trial platform, for example, brings together data from multiple clinical trials sponsored by multiple drug companies, for use in synthetic control arms.

Figure 9: Executives say their organizations are looking at many data types and sources in precision medicine initiatives

Q: To what extent, if any, does your organization use, or plan to use, the following data sources or technologies for precision medicine initiatives?

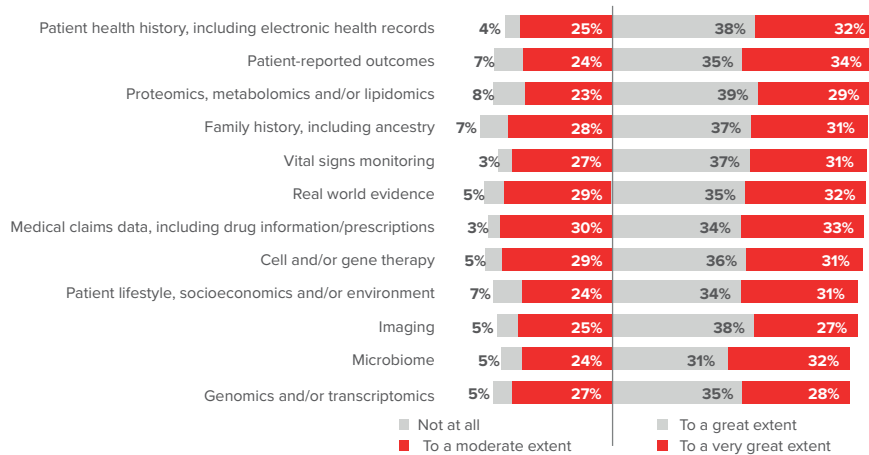


Figure 10: Executives see unified data strategies as key to precision medicine initiatives

Q: Which of the following data analytics solutions are important to your organization’s precision medicine plans/initiatives?

Q: Which of these capabilities do you believe that your organization needs to improve on?

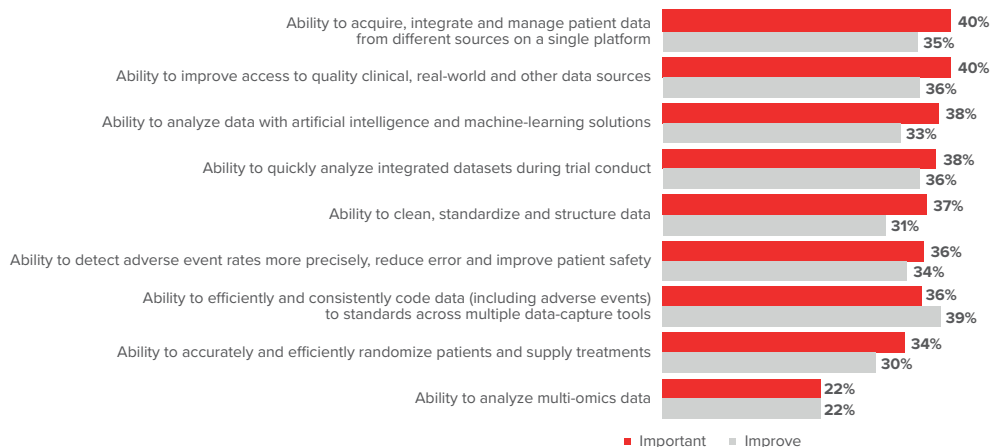
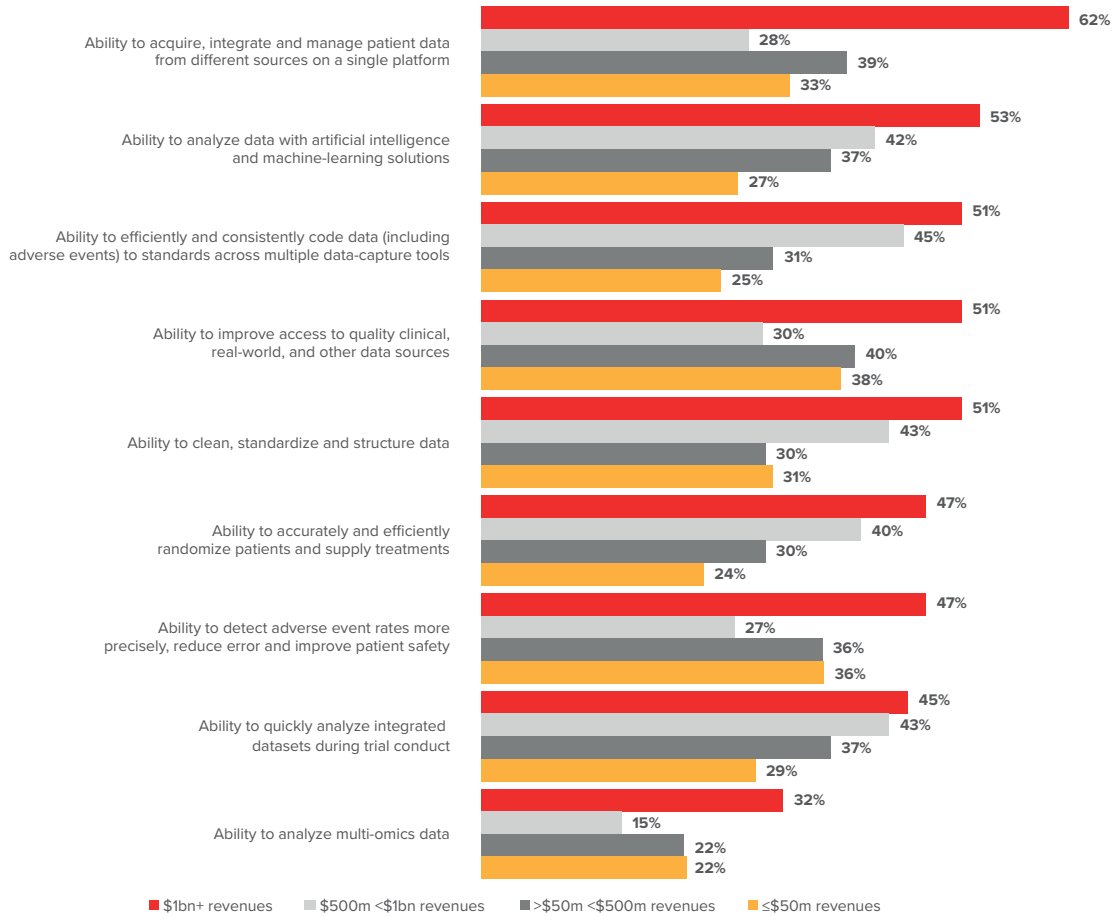


Figure 11: Executives in large organizations see data integration as particularly important for precision medicine initiatives

Q: Which of the following data analytics solutions are important to your organization's precision medicine plans/initiatives?



Base: executives at organizations with revenues of \$1bn+ (53), \$500m up to \$1bn (67), >\$50m and <\$500m (116), and ≤\$50m (55).

Crunching the numbers

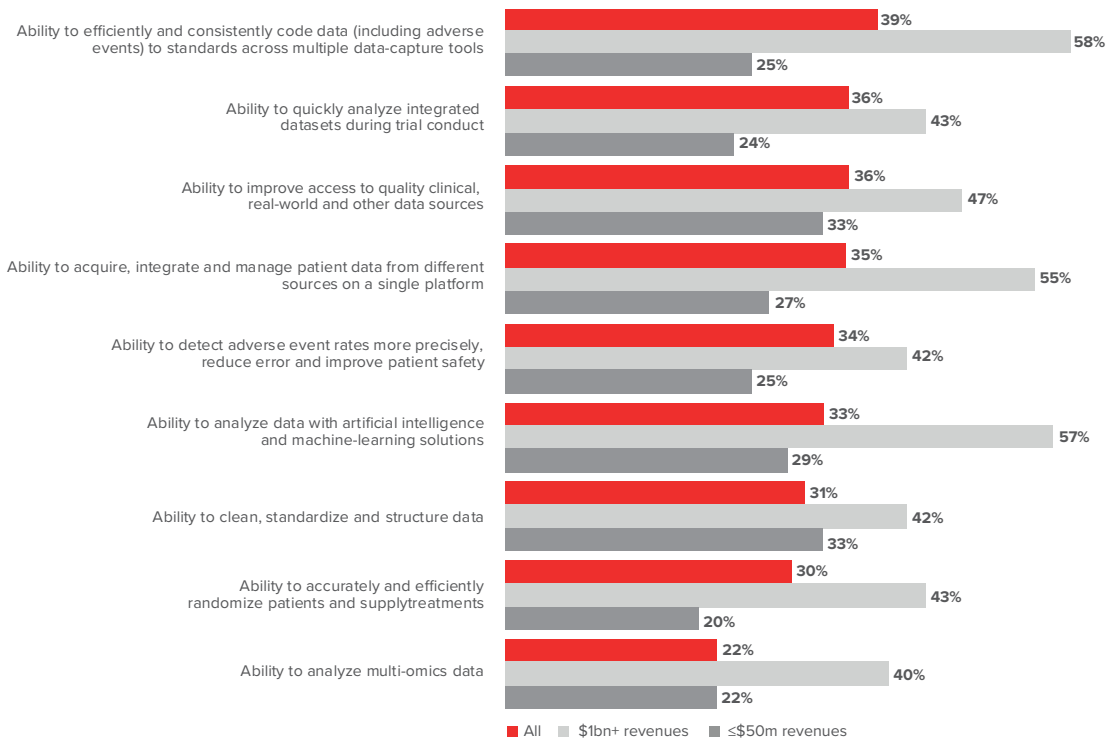
Without preparation and analysis, of course, big data is meaningless—a vast pool of unstructured data riddled with corrupt, inaccurate or irrelevant records of varying quality. That’s why 37% of executives—and 51% at large organizations—said the ability to clean, standardize and structure data is important to their organization’s precision medicine goals (see Figures 10 and 11). And 36%—rising to 51% at large organizations—said the same for the ability to efficiently and consistently code, or categorize, data from multiple sources.

The latter is particularly challenging, with the highest percentage of respondents citing it as a capability that needed to be improved (see Figure 12). This could in part be due to challenges presented by data interoperability requirements, as organizational siloes start to break down, and as more data is shared between organizations.

Data analytics also has the potential to transform the efficiency and effectiveness of clinical trials. Well over a third of executives cited the importance of improved abilities to randomize patients and supply treatments; detect adverse events; and quickly analyze integrated datasets during trials—rising to 45% or more across these areas for large organizations (see Figures 10 and 11).

Figure 12: Executives see improvements needed across the data value chain in order to pursue precision medicine goals

Q: Which of these capabilities do you believe that your organization needs to improve on? (Executives were first asked which of these data solutions was important to their organization’s precision medicine plans/initiatives.)



Base: all respondents (301); executives at organizations with revenues of \$1bn+ (53); executives at organizations with revenues of ≤\$50m (55).

Finding the needle in the haystack

Thirty-eight percent of respondents said that AI and machine-learning solutions were important to their organization’s precision initiatives, with 33% saying that capabilities needed improvement (see Figure 10). But AI is especially prized by large organisations, with 53% of executives there citing its importance—and 57% saying capabilities had to be improved (see Figures 11 and 12).

One reason AI is becoming increasingly indispensable is the need to make sense of the sheer quantity of data involved in precision medicine research. Finding highly specific characteristics that can help to distinguish between subsets of patients would be like looking for a needle in a haystack were it not for the use of machine-learning algorithms.

US-based biopharmaceutical company Bristol-Myers Squibb, for example, is using digital pathology to get a much more detailed view of the complex tumor microenvironment. This includes quantifying biomarkers, visualizing how cancer cells interact with the immune system and the stroma (connective tissue cells), and identifying whether tumors are “hot” (full of immune cells) or “cold”. This degree of specificity will be key to selecting the right treatment for each patient.¹⁹

AI is also proving instrumental in getting the right amount of quality data needed for machine learning to work well—something which would otherwise require millions of patients. As Saurabh Saha, M.D., Ph.D., SVP and global head of translational medicine at Bristol-Myers Squibb says, “We can analyze a patient’s pathology samples using digital images combined with deep learning in ways that are not possible with a human’s visual assessment using a microscope. For example, we use AI to find patterns in millions of data points on a single slide. If we integrate that across hundreds of patients, we can predict who will respond to therapy and what their prognosis might be. That’s just the tip of the iceberg: we can intersect the pathology data with the patients’ genomic data—and now you’re getting to a point where you need incredible computational power to make sense of it.”

Clinical trials are another area that will be transformed by AI, including the challenging task of finding the right participants, and collecting and analyzing the huge amounts of data coming from a growing number of sources. Leveraging AI to extract information from fragmented medical records, including EHRs and imaging, is particularly in demand, and would be one key way to match patients with trials.²⁰

AI additionally has the potential to optimize usage of multi-omics data. Many executives say their organizations plan to use these datasets to a great extent (see Figure 9) and many identify them as important for clinical trial design (see Figure 6). Yet just 22% say the ability to analyze multi-omics data is important for precision initiatives (see Figure 10). The seeming discrepancy may be due to the considerable challenge in integrating and analyzing what are quite different subsets of information, requiring innovative algorithms to make sense of their complex and dynamic inter-relationships.²¹

Medidata's Rave Omics solution is a case in point. Its usage led to the discovery of new proteomic biomarkers for Idiopathic Multicentric Castleman Disease, a rare disorder. This revealed six new patient subgroups—and, in one of these groups, the response rate to an existing treatment improved from the mid-teens to 65%.²² It's also illustrative of the ability to gather more evidence from a relatively small number of patients—a key issue with rare diseases. This was achieved by supplementing existing clinical trial data with proteomic data from patient samples from around the world. The new data, moreover, provided new insights into a poorly understood disease, and is being used to generate new hypotheses to test treatments for the patients who weren't helped by the existing drug.

AI can also help with data interpretation—a key bottleneck in bridging the gap between research and clinical use, as ever-more molecular variants are discovered. Diseases may be caused by rare mutations and the interplay of multiple variants—the combinations of which vary from person to person.²³ There are also numerous variants that don't cause disease, as well as those of unknown clinical significance.²⁴ And consensus about what mutations mean changes over time, with new information.²⁵ Moreover, there is only so much that a person's genetic sequence alone can tell us; environmental factors can cause disease through so-called epigenetic changes, which turn some genes “on” or “off” without changing their DNA sequence. One way data interpretation can be improved is through the ability to compare much more data, from a wide range of sources. Prediction algorithms are currently being used to address some of the challenges, though there are limitations.²⁶

The use of AI in precision medicine is still in its early stages and remains one of many tools—which may be why it isn't cited by more executives as being important to precision initiatives. Moreover, AI brings its own set of challenges. There is a need to address the skills gap in this field, and to work with data solutions providers to better access and analyze the vast amounts of data required to develop robust algorithms. And, in the highly regulated and controlled world of clinical trials, there needs to be a clear understanding of when and how AI can be used, as well as to ensure that data is of sufficiently high quality and can be analyzed in a meaningful way.²⁷ There will also be the need to balance the enormous power of AI and algorithms with measures to ensure transparency and accountability.

“There are three key ingredients for AI to be successful in the clinical setting. Firstly, you have to ask the right questions. Secondly, you have to have huge amounts of well-curated, quality, labelled datasets. Thirdly, you have to have the right inter-disciplinary expertise in order to fully understand the data and generate the right algorithms.”

—Saurabh Saha, M.D., Ph.D., senior vice president, global head of translational medicine, and site head for Cambridge, MA, Bristol-Myers Squibb

REDEFINING VALUE

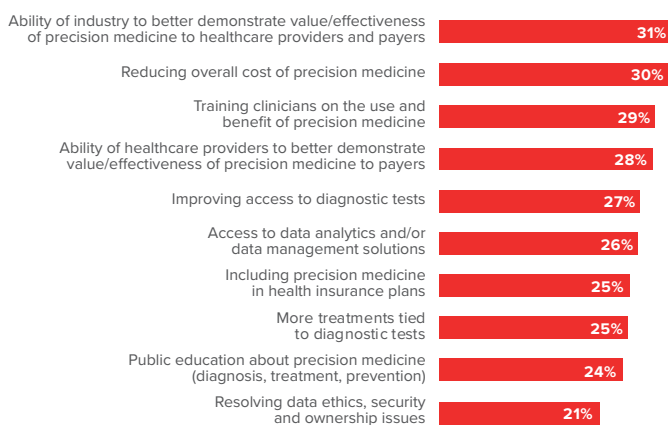
We've looked at how organizations are furthering precision medicine goals through a greater focus on patients and on their data. But despite these efforts, there have been some questions about the effectiveness and availability of, and access to, precision medicine. For example, only a minority of advanced cancer patients in the US can be matched with one of the 30-odd targeted cancer therapies approved by the FDA.

So what's needed to drive progress? A complex set of factors is at play, including the pace of research, the regulatory environment, challenges to implementation, barriers to funding/reimbursement and societal concerns. But a common theme underlying these issues is lack of understanding or agreement about the value that precision medicine creates, and should create.

When asked which three factors would be most important in advancing the widespread adoption of precision medicine, executives homed in on the ability to demonstrate value: to patients, payers, healthcare service organizations, clinicians and the wider public (see Figure 13). And when asked about their own organization's activities, 29% of executives—rising to 45% at large organizations—said that demonstrating the value of tests or treatments was a focus, and 33%—47% at large organizations—said the same of balancing access and affordability with precision solutions (see Figures 3 and 4).

Figure 13: Executives see value-based approaches as key to driving widespread adoption of precision medicine

Q: Which three of the following do you think would be most important in promoting the widespread adoption of precision medicine?



Misaligned incentives

Healthcare stakeholders share a common value-based goal: high-quality, cost-effective patient care. Precision medicine aims are aligned with this: patients should benefit from more targeted tests and treatments, while healthcare providers can minimize low-value interventions, and payers can see fewer claims.

But without well-defined criteria for value, which are agreed upon by all stakeholders, cost considerations tend to overshadow patient needs, with mismatched incentives obscuring the quest for value. Indeed they can lead to an increase in unnecessary costs, along with lower-quality care.

The situation in the US is illustrative. Payers, motivated to minimize claims, are cautious about the expense and uncertainty of precision medicine—and some consider it to be experimental, as it's not yet part of the generally accepted clinical practice guidelines set by professional bodies. As a result, reimbursement is limited and variable, and can be subject to long delays.

Pharmacy benefit managers (PBMs)—hired by payers to administer prescription drug programs—want to minimize costs, so they negotiate with manufacturers to secure rebates and discounts. The extent of these determines whether products get on the formulary—the list of drugs which will be reimbursed—and how incentivized patients will be to use them. The “per pill” cost, therefore, becomes more important than the relative effectiveness or longer-term cost of drugs within a therapeutic class. Yet this hasn't stopped an outcry over high drug prices, amid much finger-pointing.

Patients, traditionally shielded from the full cost of medical care because of health insurance, want to pay as little as possible, so are reluctant to increase cost-sharing or pay out of pocket for precision medicine, especially when they don't know much about it. Instead, patients are incentivized to accept as much of the preferred insurer and formulary choices as might help their condition, even if of lower value or more costly in the long run.

Physicians are incentivized to treat what they get paid for, not necessarily what might be best for the patient in all respects. Indeed, existing models can lead to over-utilization and higher costs (like the fee-for-service model which predominates in the US) or under-utilization in order to save costs (as can be the case with bundled payments). The choice of treatment is also steered by drug formularies and clinical practice guidelines. Moreover, physicians might not see the value that precision medicine creates, nor have sufficient expertise to use it, even if available.

Drug and diagnostics developers, meanwhile, are looking to recoup high upfront costs and get the necessary funding to address the very criticisms levelled against precision medicine—for example, developing better tests or a broader range of treatments, or to make them more affordable.

Caught in this catch-22 are patients— and it's leading to growing inequalities in terms of access and affordability. Changes are, however, afoot. In 2018, the US Centers for Medicare & Medicaid Services (CMS) extended coverage to include NGS testing for advanced cancer patients.²⁸ The decision, however, caused controversy when it led to the revision of coverage for tests performed on early-stage cancer patients, and evidence is being reconsidered for using such tests for patients with hereditary cancer.²⁹

The UK's National Health Service (NHS), meanwhile, will offer genomic tests to all new cancer patients from October 2019, as part of their standard treatment.³⁰ France also has plans to incorporate precision medicine into the care pathway, as one of the aims of its Genomic Medicine 2025 program.

However, these overburdened healthcare systems, like others, are battling stagnating budgets and/or rising spend, and won't be able to support more widespread adoption of precision medicine under current models. In fact, the National Institute for Health and Care Excellence (NICE), which decides which tests and treatments are available on the NHS, recently came under fire for not approving a precision drug for cystic fibrosis, due to cost reasons.³¹ And, the decentralized procurement, funding and reimbursement structures typical of European healthcare systems can also lead to long, cumbersome and unclear decision-making processes.

To gap-fill or complement state coverage in these markets, patients must have private schemes in place—facing the same issues of mismatched incentives between insurers, healthcare providers and industry. In fact, twice the proportion of executives in France (42%) as in the US (21%) think that including precision medicine in health insurance plans would be a top-three factor in promoting its widespread adoption.

The value journey

Finding ways to achieve better health outcomes in more cost-effective ways has been a topic of discussion for years in both the US and Europe, with different types of financial models being explored.

There are many types of value-based reimbursement schemes, but they generally reward or penalize healthcare providers for adhering to defined metrics such as those for outcomes, cost, clinical best practices and patient satisfaction. Value-based pricing—which has mainly focused on drugs—also takes many forms, but the aim is to link specific criteria relating the effectiveness of the drugs to their payment, which can be through the prices set, and/or the rebates and discounts paid to manufacturers.

There has been a growing trend toward value-based healthcare in the US and Europe, using different pricing and reimbursement models. It has, however, been challenging, with debate about how well current approaches work.

As of 2016, 29% of healthcare payments in the US were associated with non-fee-for-service models—including, but not exclusively, value-based models.³² However, CMS has an ambitious program that includes several value-based pricing and reimbursement schemes under various stages of development.³³ And some of the country's largest health insurers now make about half or more of all their reimbursements under value-based models, and have also introduced value-based pricing on certain pharmaceuticals.³⁴

In the UK, a number of pay-for-performance (P4P) initiatives have been introduced in various parts of the NHS over the years, though evidence about their impact on outcomes is scarce.³⁵ De facto value-based pricing for pharmaceuticals, however, is virtually non-existent.³⁶ In Germany, some progress is being made, though efforts have mainly focused on cost savings, and have also led to controversy, especially the cap imposed in 2011 on reimbursements for drugs.³⁷ In France, where the focus has traditionally been more on outcomes than cost, value-based drug pricing has gained some traction, and P4P incentives have also been introduced, though the latter is based more on efficiency or process than outcomes.³⁸

The value challenge

The mixed experience so far underscores the many challenges, both conceptual and practical, that face value-based models—particularly when precision medicine is added to the mix.

Ultimately, whatever dimensions of value are considered must be evidenced. A key obstacle, therefore, is the lack of information about precision medicine that's available to, or gathered by, payers, when they undertake health technology assessments (HTAs) to evaluate medical products and services. Published studies are limited in number and scope, especially for new products, and can be conflicting. HTAs also don't typically consider other valuable sources of information, like patient and physician demand, patient-reported outcomes or real-world studies.³⁹ The latter highlight how tests and treatments are used in care settings, including unexpected barriers to adoption, or "off-label" prescriptions, which are used for conditions that aren't in line with what the drugs are approved for, but which are known to be effective.⁴⁰

Lack of longitudinal accounting is another issue for precision medicine, as its cost-effectiveness can't be adequately assessed without looking at the entire cycle of care. This can determine whether it avoids unnecessary investigations or ineffective treatments as a result of earlier, more accurate interventions—or indeed whether it contributes to wastage through over-diagnosis and over-medication. The time horizon is extended even further for risk assessment tests—particularly as people live longer—which is a further disincentive for payers, due to high customer turnover. Yet 36% of executives say that lowering the cost of care over a patient's lifetime is a main driver of their organization's precision medicine initiatives (see Figure 2).

There will, moreover, always be uncertainties about costs. The additional costs of new precision therapies may, indeed, be unknowable, such as those for data management or tailoring of treatments. The degree of cost savings can be also highly uncertain. CDx's, for example, could result in huge cost savings—or reveal that only a small percentage of people can avoid expensive treatment, or that pricier alternative therapies should be used. Even the relatively low cost of tests, when administered to scores of patients, may not be offset by the benefits.

In Europe, centralized agencies which perform HTAs, like NICE, have advantages in terms of the ability to gather information and achieve consistency in processes and evaluation techniques. But constraints remain, particularly around diagnostics, where methodologies are often unsuitable, such as evidence requirements akin to those for medicines. The process can be very lengthy, with no clear connection to uptake, and there are substantial differences across the EU. While harmonization efforts have accelerated, questions have been raised about how proposed initiatives define clinical effectiveness, and about evidence requirements.⁴¹

Diagnostics' value problem

Precision diagnostics face an especially tough challenge, with much lower and more variable rates of reimbursement than for drugs, and an HTA process that can take years in France and Germany, for example.⁴²

Far fewer studies have been conducted on the cost-effectiveness of diagnostics, or their impact on outcomes. In some cases it's due to the nature of the diagnostic. Screening tests, for example, don't indicate if the patient will actually develop the condition, or when—and there may be no course of action available to address it. But other types of tests, whether used to detect the presence/absence or course of a disease, or how a patient will respond to treatment, are still difficult to assess, and that can be due to the nature of the disease.

Take cancer for example. It affects some organs and not others, can affect different parts of the same organ in different ways, and evolves over time. Tumor heterogeneity presents major obstacles for diagnostics. As Alan Sachs, chief scientific officer at Thermo Fisher Scientific, says, "Scientists come up with these incredible biomarker discoveries that they know are causing disease, and build tests around them, but the payer looks at it and says, 'Prove it to me.' In order to do that, you have to run a pretty big study, and what you might find is, some very tumor-specific or person-specific factors are preventing that mutation from actually having an effect. So, having the statistics to prove that your test measures what it says it's going to measure isn't enough; it's a lot more complicated to make a test that's predictive, and then make it reimbursable."

Gathering that evidence that payers need, however, is challenging, in no small part due to the variability in regulatory requirements. In the US, the FDA regulates tests developed by diagnostics companies for commercial use (*in vitro* diagnostics or IVDs)—but has generally chosen not to regulate “home-brew” tests used only by the laboratories that produce them (a subset of IVDs known as laboratory-developed tests or LDTs). The certification program that LDTs are subject to requires only that they demonstrate analytical validity—that they measure what they’re intended to.⁴³ IVDs must, however, show both analytical and clinical validity—how accurately they indicate the presence, absence or risk of disease.⁴⁴ But only FDA-approved CDx’s must generally also demonstrate clinical utility—how likely they are to lead to improved outcomes or provide useful information about the course of action.

In the EU, most tests have been self-certified, with no clinical evidence required.⁴⁵ New IVD regulations, however, came into force in 2017 and will be fully implemented by 2022. Crucially, they demand evidence to support claims of analytical validity, clinical validity *and* clinical utility—on an ongoing basis.⁴⁶ LDTs will also be regulated, and can only be developed if there’s a gap in the market. And only LDTs developed by health institutions will be exempt from many of the requirements governing IVDs.

Evidentiary challenges also derive from how tests are used in practice. This is the case even for CDx’s, which often come out after therapies have long been in the market, due to differences in development and authorization, making it harder to establish a link to outcomes. One study also shows that payers don’t necessarily require CDx’s to be used in conjunction with treatments, or may not cover them.⁴⁷ And, even if they’re used, it’s hard to ensure that physicians will interpret or use results correctly. Moreover, where diagnostics aren’t specified, different testing strategies can lead to different outcomes. And, an insurer might cover a test but not the treatment recommended as a result, which will impact the associated outcome.

Reimbursement methods and processes also make it difficult to link tests to outcomes, or include value creation in pricing. In the US, for example, molecular tests were traditionally reimbursed via “code stacking”: adding up the cost of each step involved in testing. This was replaced in 2013 with new codes based on what the tests measure, but they still present challenges. With no clear system for repricing, most reimbursement rates are still based on cost—and, if anything, are even lower.⁴⁸ Additionally, with less than 200 billing codes for over 70,000 genetic tests, it’s still hard for payers to know what test was performed for what reason.⁴⁹ Manufacturers may apply for new codes, with the opportunity to set new rates, but it’s a lengthy and involved process, with requirements including evidence of clinical utility and widespread use.

The commoditization of diagnostics, together with uncertainties around coverage and delays in reimbursement, are a disincentive to invest in innovation and in demonstrating clinical utility, perpetuating a vicious cycle. It’s particularly the case for IVDs, which have far higher development costs than the LDTs which dominate the market.

Toward greater value

Despite the many challenges in evaluating the effectiveness and costs of precision medicine, and the uncertainties over the pros and cons of value-based schemes, it’s clear that current systems must change, and that a better understanding of value is needed.

Industry leaders will be those which engage in discussions about different dimensions of value—such as unmet medical needs, quality of life or life expectancy, or broader considerations such as benefits for caregivers or even the scientific community—alongside supporting frameworks, metrics and analytical methods. The broad range of stakeholders needed to inform such dialogues include physicians, who will be tasked with implementing quality measures, and patient advocacy groups, which can help to develop patient-centered measures.

Leading organizations will also be proactive in undertaking earlier and more comprehensive, collaborative and iterative efforts to address the many challenges of assessing value. This includes generating additional evidence during R&D—and working with regulators to determine what can be shared beyond approved product label claims, and what standards are appropriate to produce, assess and use the data.⁵⁰

It also includes RWD, collected pre- and post-launch, such as medical and claims records, patient-generated data, and product and disease registries. There are opportunities to work with government agencies and other organizations that are moving to plug the data gap. For example, the European Medicines Agency (EMA)—the EU regulator—facilitates consultations between industry, regulators, HTAs/payers, healthcare providers and patient representatives regarding the collection of RWD, with the aim of enabling defined patient groups to get earlier access to novel treatments.⁵¹

The development of registries and other databases to gather, measure, evaluate and share such information will be a vital part of any discussions about value, and will entail the development of robust data infrastructures, data governance policies, and data management and analytical tools.

Best-in-class diagnostics developers will be particularly focused on demonstrating value, well before product conception. The few examples where value has successfully been incorporated into diagnostics pricing reveal the importance of both design, such as speed and ease of use, and clinical benefit, including strong levels of evidence, high degree of accuracy, and independent verification.⁵² Service-focused solutions, such as making it easier for physicians to interpret data, or helping healthcare providers meet goals like streamlining patient care or increasing patient satisfaction, are also being pursued.⁵³ And the potential of drug-diagnostic combinations to enhance value will drive better approaches to co-development. Choosing partners with aligned interests will also be beneficial; for example, insurers with low turnover rates will be more incentivized to reimburse the costs of prevention or early diagnosis of long-term diseases.

WORKING TOGETHER

The challenges facing industry organizations as they seek to understand many facets of value—what patients value, the value that can be derived from patient data, and the value that precision medicine creates—make it clear that they can't go it alone. No single organization, industry or stakeholder group has the multi-disciplinary capabilities nor scale required to truly accelerate progress in precision medicine. Industry executives agree: when asked which stakeholders

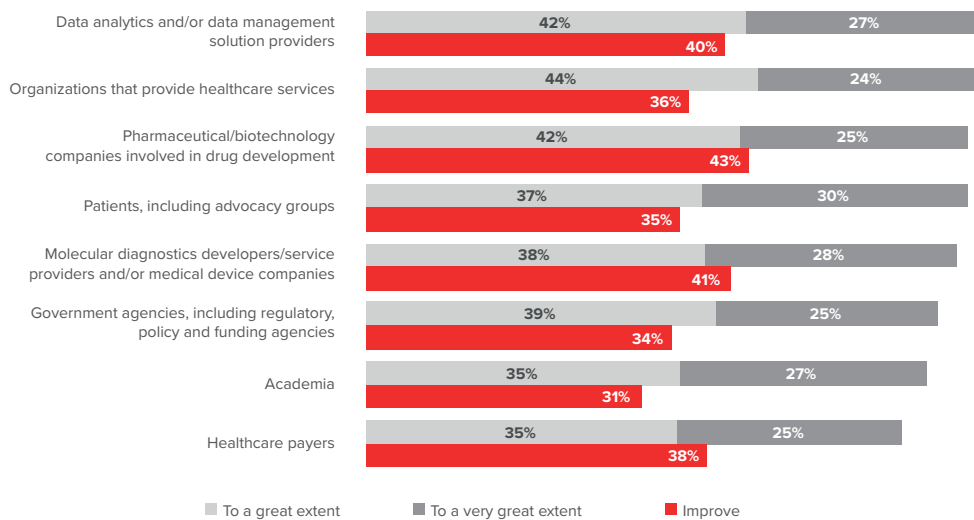
their organizations collaborate with—and need to better engage with—the even spread of responses across diverse groups points to an ecosystem-wide approach (see Figure 14).

This section looks at three areas where collaboration is vital: the co-development of CDx's; the uptake of precision medicine in clinical practice; and the regulatory framework for precision medicine.

Figure 14: Executives see an ecosystem-wide approach to collaboration in precision medicine

Q: To what extent does your organization collaborate with the following stakeholders in order to pursue precision medicine plans/initiatives?

Q: Which of the following stakeholders do you believe your organization needs to improve collaboration with, in order to pursue precision medicine plans/initiatives?



Raising the game for CDx

Improving collaboration with industry peers was the highest priority for executives (see Figure 15). This included a desire to improve biopharma–diagnostics collaboration, with 39% of biopharma respondents and 36% of diagnostics respondents holding this view.

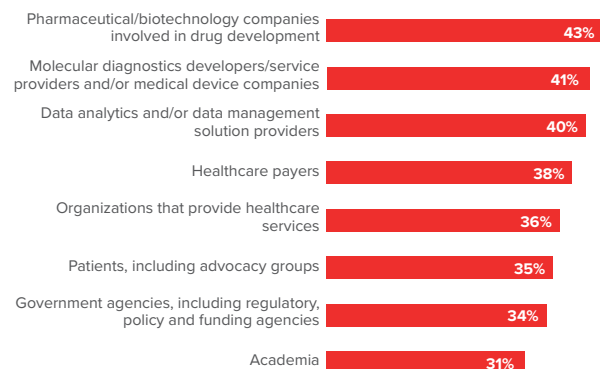
This is perhaps not surprising, given that 25% of executives also identified CDx-enabled therapies as a top-three driver of the widespread adoption of precision medicine (see Figure 13). CDx could streamline R&D costs by as much as 60%, improve outcomes significantly, increase the likelihood of drug approvals and increase physician uptake.⁵⁴ For the diagnostics industry, CDx can help address some of the many hurdles around coverage and reimbursement, through better demonstration of value.

“If you see on a drug label that patients with this mutation should use this drug, you can believe it.”

—Alan Sachs, chief scientific officer, Thermo Fisher Scientific

Figure 15: Executives see opportunity for greater collaboration between biopharma and diagnostics

Q: Which of the following stakeholders do you believe your organization needs to improve collaboration with, in order to pursue precision medicine plans/initiatives?



Yet, even though there's been rapid growth in drug-diagnostic combinations, they still represent a small proportion of tests. Less than 5% of IVDs approved by the FDA, for example, are CDx's.⁵⁵ They're more expensive and time-consuming to develop, due to more stringent regulatory requirements. This also applies to CDx's wholly developed by single laboratories, which become subject to FDA regulation, albeit with less onerous filing requirements.⁵⁶

Co-developed CDx's are even rarer, and present a challenging prospect for two industries with very different business and revenue models, development timescales and technologies, and regulatory processes and requirements.

For biopharma, it represents a departure from the traditional one-size-fits-all model and focus on maximizing revenue after launch. As useful as biomarker indications are, they're also restrictive: some drugs, for example, may benefit all patients with a certain condition, even if a specific subset of these patients will benefit more. There are also additional costs and complexities of introducing CDx's in clinical trials, at the end of which a suitable test might not be approved nor indeed even found.

For diagnostics developers, it means even more economic challenges. Early development poses big investment risks, given that many drugs don't get approved. Even if a CDx launches successfully, lack of patent protection for diagnostics means immediate risk of competition.⁵⁷ And while CDx's may benefit from improved coverage, rates are far lower than for companion drugs.⁵⁸ Moreover, the timescales are extremely challenging, requiring biomarker identification, hypothesis generation, and incorporation into early-stage trials, all before large-scale phase III testing, by the end of which commercialization strategies need to be underway.

An increasingly popular route is for a single laboratory to initially develop the assay, which can then be bridged to an IVD in later phases of clinical trials. This minimizes upfront investment, though it can lead to higher risks and delays.

Despite the challenges, there's a recognition that the benefits of CDx's can only be fully realized through co-development. Bristol-Myers Squibb, for example, starts developing biomarker strategies, where warranted, at the start of the drug discovery process.

Biopharma companies are collaborating extensively with IVD manufacturers and laboratories through partnerships or contracting arrangements, though some have acquired or developed in-house expertise. The most successful collaborations will be those that engage stakeholders as early as possible, set joint R&D and commercialization strategies, clearly define the intended uses of the CDx, and clearly define patient needs, from both a clinical and marketing perspective.

They will also put a strong focus on demonstrating the value that the CDx creates, including multiple sources of evidence, discussions with payers, and early engagement with healthcare providers and commercial laboratories.⁵⁹ Not least of all, mutually beneficial financial arrangements need to be agreed. Collaborations have, for example, included funding of diagnostics by drug manufacturers pending coverage and reimbursement decisions.⁶⁰

Regulatory developments are also smoothing the way. The FDA recently issued draft guidance facilitating the broader labeling of CDx's for oncology treatments, to include an entire class of therapeutic products as opposed to specific products, where appropriate.⁶¹

Into the community

One of the most pressing topics in precision medicine is how to bring it into the community setting, making it accessible not just in cities but in rural areas, and not just to the privileged few but across society.

Coverage and reimbursement is certainly a big part of this, but equally important is the ability of healthcare providers to implement initiatives on the ground. Education and awareness are key components of this, as executives recognize: 24% cited public education and 29% cited clinician training as top-three drivers that would promote the widespread adoption of precision medicine (see Figure 13). With 68% of executives also saying that their organization collaborates to a great extent with healthcare service providers, there's clearly a role for industry to work with healthcare systems to meet the challenge (see Figure 14).

One of the biggest bottlenecks is the uptake of precision medicine among clinicians, particularly when it comes to diagnostics. One barrier is not knowing which tests to order, due to insufficient information about the value they offer, or having too many products and providers to choose from, or lack of best practice guidelines and other decision support resources. The process of ordering tests, moreover, and accessing or comparing lab results, isn't easy.⁶²

Once they have the results, it may be unclear how clinicians should interpret them, or effectively communicate what they mean, or use them to guide patient care. For example, there may be uncertainty about discussing disease risk or preventive measures—or dealing with situations where a test reveals something other than what it was ordered for, or if no treatment is available. Clinicians might also not be aware of the availability of treatments or trials in their area, or the effectiveness of targeted therapies or how to incorporate them into an overall care plan.

The quality of clinician interactions is an area of growing importance for industry. It's starting to expand from a narrower focus on demonstrating clinical utility toward enhancing the entire customer journey for physicians, including understanding their needs and customizing how knowledge is acquired.⁶³ But it's a very expensive endeavor, and particularly challenging for diagnostics developers to fund investment in sales capacity. Things have started to change with higher-priced molecular diagnostics, and larger developers are increasingly focusing on clinician support.⁶⁴

Growing collaboration on CDx's will also be important: if a drug developer can explain to a clinician how the CDx works, it will drive understanding of why the drug works. Test design will also be a key facilitator of uptake. Those that clearly relate to a drug's mechanism of action, or which measure something that clinicians know to be important for a disease, will be more readily understood, and more easily conveyed to patients.

IT and data capabilities are also key barriers to clinical adoption. Interoperable and user-friendly EHR systems are currently lacking, for example, as are adequate clinical decision support systems for precision medicine, or performance tracking tools. There are also substantial challenges around the security, privacy and usage of patient data, which will only increase as digital medicine increasingly takes hold. Dealing with such issues is a tall order for the many healthcare providers lacking adequate IT and data capabilities.

Industry can play a role in many different capacities. Switzerland-based healthcare company Roche, for example, is funding initiatives to support healthcare service providers in implementing precision oncology solutions at scale, including access to real-world evidence to support care decisions; development of electronic patient-reported outcomes; provision of tools to match patients to clinical trials at point of care; and research into value-based health economics.⁶⁵

Moving with the times

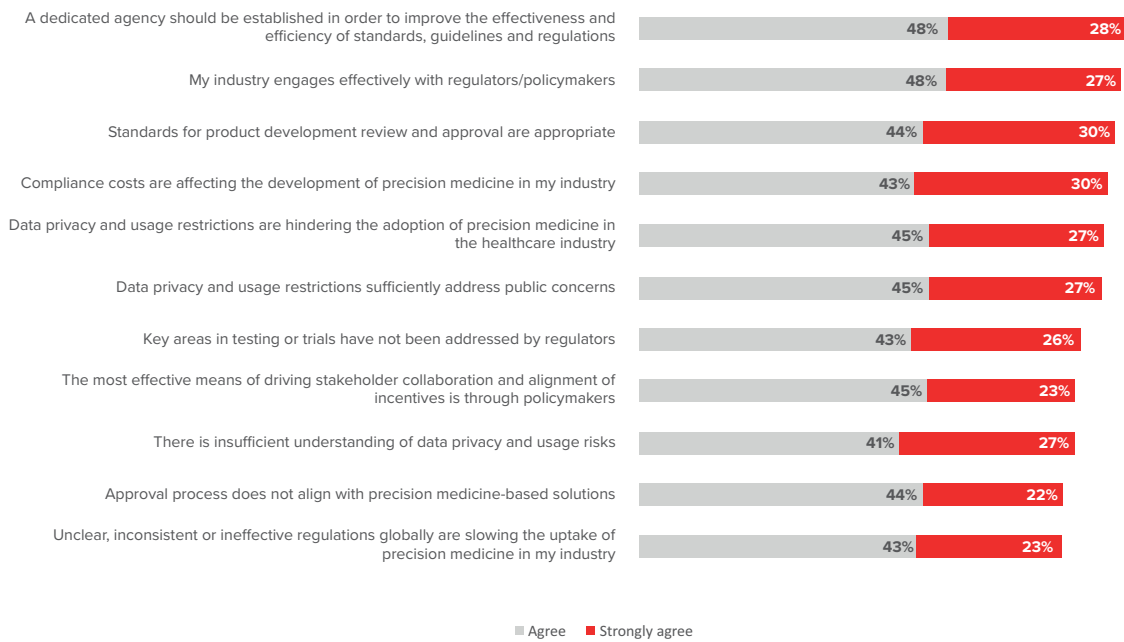
Widespread adoption of precision medicine also clearly depends on the policy and regulatory environment. Here, issues identified by executives fall into three broad categories: product review and approval; data security and privacy; and harmonization of regulations (see Figure 16).

Most executives agreed that standards for product development review and approval were appropriate. But more US executives (83%) held this view than those in the UK (68%), France (66%) or Germany (57%). The FDA has, in recent years, approved novel trial designs for certain drugs, and put in place a framework for using real-world evidence in making decisions.⁶⁶ The EMA has also explored new approaches, including accelerated approvals and greater reliance on real-world evidence to supplement randomized controlled trials, but has met resistance from some national HTA agencies, including those in Germany and France.⁶⁷ Moreover, the EU's Clinical Trials Directive has drawn criticism for being too cumbersome—though it's due to be repealed by new regulations that come into application in 2020.⁶⁸

Executives in both the US and Europe are, however, in broad agreement that key areas in precision medicine testing or trials haven't been addressed by regulators, with 69% holding this view (see Figure 16). Regulatory uncertainty likely plays a big role. The FDA, for example, is accelerating efforts to start regulating LDTs and NGS-based tests.⁶⁹ And there are uncertainties over the interpretation of the EU's new IVD regulations.⁷⁰ The drug approval process also faces uncertainties, for example around novel trial designs. Even if regulators have shown flexibility in the past, clear guidance is being sought by industry.⁷¹ Another gap is the disparity between how diagnostics, as devices, and drugs, as medicines, are regulated. There have been multi-stakeholder efforts to address the issue, though progress remains slow.⁷²

Figure 16: Regulation: executives zero in on product licensing, data laws and harmonization

Q: To what extent do you agree or disagree with the following statements regarding the role of policymaking and regulation in precision medicine?



The privacy gap

Seventy-two percent of executives agreed that data privacy and usage restrictions are hindering the adoption of precision medicine in the healthcare industry (see Figure 16). This is likely due in part to new regulations imposing new conditions on how organizations handle personal data.

The EU General Data Protection Regulation, for example, which came into force in May 2018, represents sweeping changes in data protection regulations, and will affect all entities that process personal data relating to individuals in the EU.⁷³ Another example is the tough new consumer privacy act in California, which goes into effect in 2020.⁷⁴

Meeting data privacy requirements likely plays a big role in the compliance costs that 73% of executives agree are affecting the development of precision medicine in their industry (see Figure 16). And it's also likely to factor into why 66% of respondents agree that the regulatory approvals process doesn't align with precision solutions, relying so heavily as they on patient data (see Figure 16).

Getting the balance right

The global impact of such regulations is reflected in the fact that 66% of executives agreed that unclear, inconsistent or ineffective regulations globally were slowing the uptake of precision medicine in their industry (see Figure 16).

There have been efforts to harmonize international regulations for diagnostics, as well as develop globally accepted practice standards for clinical drug trials. Regional regulators like EMA have been in a position to make some progress, as have international bodies. Progress has, however, been slow, in large part due to the lack of clear standards within national borders for regulatory approvals, reimbursement or best practices.

One answer to regulatory challenges, many executives believe, is to establish a dedicated agency to improve the effectiveness and efficiency of precision medicine standards, guidelines and regulations. Seventy-six percent of respondents agreed this was the way forward (see Figure 16), though many more in the US (84%) were in favor compared to the UK (67%) or Germany (65%).

Executives also point to the need for better collaboration. Although 75% say their industry already engages effectively with regulators/policymakers (see Figure 16), and 63% say their own organization engages to a great extent with government agencies (see Figure 14), 34% of executives say more needs to be done—rising to 49% at large organizations.

There are major points of agreement between industry and regulators; it's getting the balance right that dialogues will need to focus on. Most executives agree that standards for product approvals work, but less traditional approaches around trial designs and CDx development will require early discussions, as well as consultation in the development of better guidance.⁷⁵

Many executives also agree that existing data laws sufficiently address public concerns—but believe regulators have gone too far. With just 21% of executives believing that data concerns will hold back public adoption of precision medicine (see Figure 13), and 68% agreeing that regulators lack sufficient understanding of data privacy and usage risks (see Figure 16), there's clearly a very large gap in perception about where the right balance lies. There's a need to come together on issues such as who owns personal data generated in clinical trials; the extent to which companies can put existing data to new uses; and how risks such as genetic discrimination can be mitigated.

The future, together

One thing is for sure: without much better collaboration, underpinned by societal trust, progress in precision medicine will stall. Consider cancer therapies: only a small percentage of people will respond to the small number of treatments currently available, and even for those successfully matched to therapies, chances are their cancer will mutate or become resistant to treatment. Addressing such challenges can only be done by pooling resources on a scale never before seen.

A key enabler in developing a better and broader range of treatments is the ability to obtain and analyze a vastly larger amount of data than has been possible thus far, at the population level. This requires the participation of many actors.

There are numerous biobanks worldwide, ranging from small operations to national research programs. The latter include *All of Us* in the US, which aims to collect health data from at least a million volunteers; the UK's 100,000 Genomes Project, which is the foundation for the NHS's new genomic medicine service; and France's Genomic Medicine 2025 program, which aims to sequence 235,000 genomes a year by 2020.⁷⁶ It isn't just molecular data that's needed, however, but a wide range of information from EHRs and a multitude of other sources.

There are, of course, large data security, privacy and ethical ramifications, with much work needed to ensure that effective safeguards are in place. One potential solution that's attracting interest is the use of blockchain technology to give individuals ownership and control of their own data, rather than having it stored centrally.⁷⁷

Better, faster and more cost-effective NGS techniques are required to sequence the increasingly vast repositories of data, and overcome current limitations in the ability to discover clinically useful biomarkers. It's necessitating better regulatory guidance on the development of NGS tests. It's also necessitating the development of much more extensive computational tools and power to store, integrate, analyze and interpret these extremely large and complex datasets, and the advanced interoperability and data-sharing infrastructures required.

Further development of partnerships will be needed between the private sector and the government and academic institutions that have traditionally used such resources. These include large-scale research-based collaborations like Europe's Innovative Medicines Initiative, and precisionFDA, the FDA's cloud-based portal aimed at NGS research.⁷⁸ It also includes collaborations to improve data interoperability, such as EU-STANDS4PM, which aims to establish a European standardization framework for precision medicine initiatives.⁷⁹

The scientific and technical expertise needed also go far beyond what either data experts or molecular biologists can provide on their own, requiring more people with the skills to engage in a multi-disciplinary approach, including bioinformatics, computational biology and mathematics.

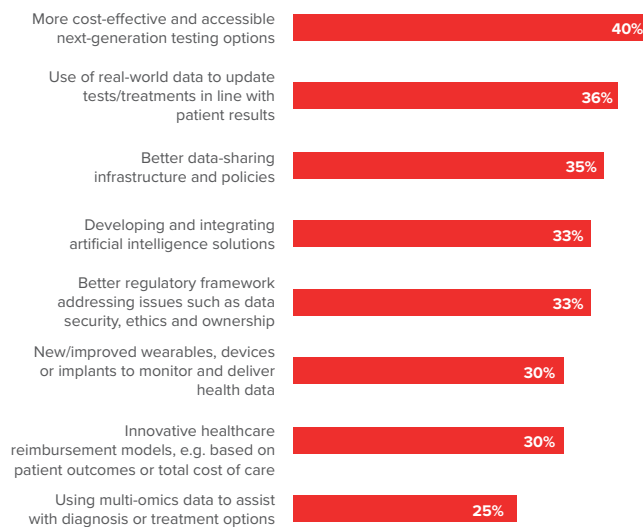
But all the research in the world won't be any use unless the breakthroughs that result can be implemented at a clinical level, and in patients' day-to-day lives. Nor will it be any use unless someone pays for it—unless there are effective payment and reimbursement policies in place that are based on value for all stakeholders.

It's a vision of the future that executives share, with many of these developments cited as advances that would most advance progress in precision medicine (see Figure 17). Executives also recognize that it will require collaboration on a national and international scale, with more than two-thirds (68%) agreeing that the best means of driving stakeholder collaboration and alignment of incentives is through policymakers (see Figure 16).

By any measure, the scale of the challenge ahead is enormous. But so, too, was the idea of sequencing a whole genome fifteen years ago. That required a degree of collaboration that was at the time unprecedented. Today, there is the opportunity to bring it to a whole new level, to accelerate the growth of precision medicine and create value for everyone.

Figure 17: Executives' vision of precision medicine's future involves efforts on many fronts

Q: Which three of the following advances do you believe would most accelerate progress in precision medicine?



ABOUT THE SURVEY

The analysis in this report is based on an online survey fielded in April 2019 by Newsweek Vantage, on behalf of Bristol-Myers Squibb, Medidata Solutions and Thermo Fisher Scientific.

A total of 301 executives were surveyed, representing organizations involved in diagnostics development and drug discovery and development. We selected respondents from a market research panel, who were based in the US, UK, Germany and France, with a level of seniority ranging from the C-Suite to two levels below the C-Suite, and with roles spanning a range of activities and disciplines relevant to precision medicine.

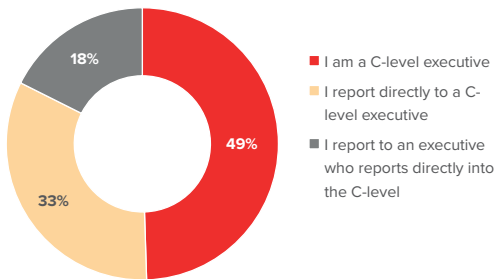
Eighty-seven percent of respondents worked at organizations which had precision medicine initiatives in place or firm plans in this regard. The purpose of the survey was not revealed during the screening process and respondents were also asked if their organizations did not have any plans in place.

All interviews were conducted on a confidential basis.

The base for all figures in this report is 301 (all respondents) unless otherwise stated. Not all figures that should add up to 100% may do so, due to rounding and/or exclusion of “neither/nor”, “don’t know” and “unable to answer” options.

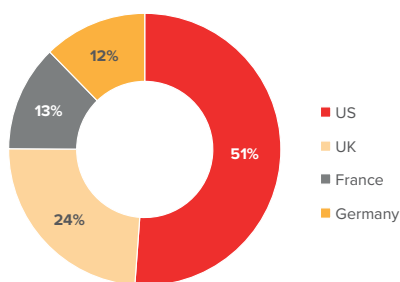
Seniority

Q: Which of the following best describes your reporting relationship within your organization?



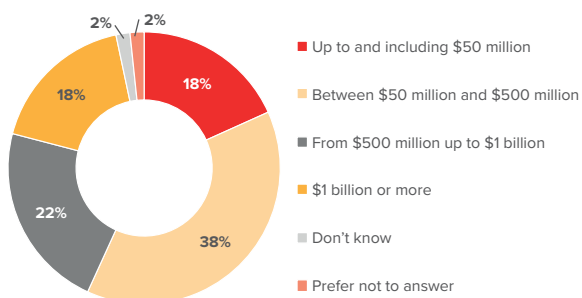
Geography

Q: In which of the following countries are you based?



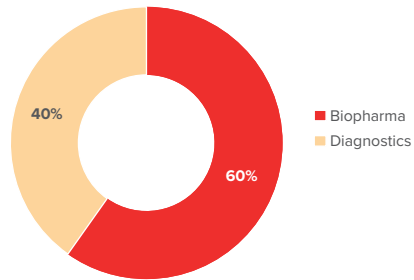
Organization size (revenues)

Q: What was your organization's global gross revenue, in USD, in the last fiscal year?



Industry

Q: Which of the following best describes the industry you work in?



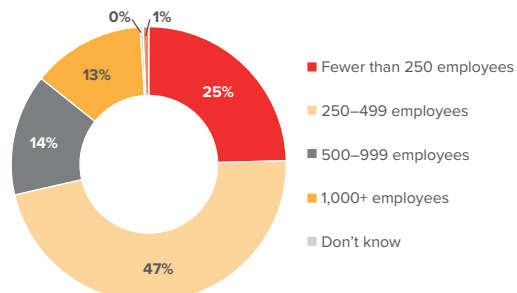
Precision medicine plans/initiatives

Q: Has your organization developed precision medicine initiatives or have plans to do so?



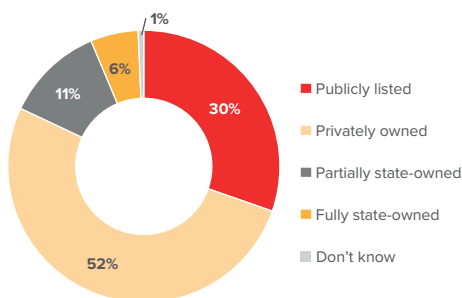
Organization size (employees)

Q: How many employees does your organization have?



Organization ownership

Q: Is your organization publicly listed, privately owned or have any form of government backing?



References

- 1 "Human Genome Project FAQ," National Human Genome Research Institute, accessed May 18, 2019, <https://www.genome.gov/human-genome-project/Completion-FAQ>.
- 2 Personalized Medicine Coalition, *Personalized Medicine at FDA: A Progress & Outlook Report* (Washington: Personalized Medicine Coalition, 2019), 5, http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf; Personalized Medicine Coalition, *The Personalized Medicine Report 2017: Opportunities, Challenges, and the Future* (Washington: Personalized Medicine Coalition, 2017), 29, <http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The-Personalized-Medicine-Report1.pdf>.
- 3 "Exposome and Exposomics", Centers for Disease Control and Prevention, accessed May 15, 2017, <https://www.cdc.gov/niosh/topics/exposome/default.html>.
- 4 "For Big Data to Help Patients, Sharing Health Information is Key, Experts Say," Stanford Medicine, May 26, 2015, <https://med.stanford.edu/news/all-news/2015/05/for-big-data-to-help-patients-sharing-health-information-is-key.html>.
- 5 John D. Loike and Jennifer Miller, "Infographic: The Cost of Drug Development," *The Scientist*, February 1, 2017, <https://www.the-scientist.com/infographics/infographic-the-cost-of-drug-development-32088>.
- 6 Sarah Karlin, "Adding the Patient Voice to Drug Development," Politico, January 11, 2016, <https://www.politico.com/story/2016/01/adding-the-patient-voice-to-drug-development-217561>.
- 7 Jan Ascher et. al., "From Product to Customer Experience: The New Way to Launch in Pharma," McKinsey & Company, August 2018, <https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/from-product-to-customer-experience-the-new-way-to-launch-in-pharma>; Karen Palmer and Joshua Tepper, "Patient Engagement: A New Frontier for Drug Makers," *Healthy Debate*, April 27, 2017, <https://healthydebate.ca/2017/04/topic/pharma-patient-engagement>.
- 8 Luis Hakim and Sonal Shah, "The Next Wave of Innovation: Technology and Value-Based Care are Transforming Medtech R&D," *Deloitte Insights*, November 30, 2018, <https://www2.deloitte.com/insights/us/en/industry/life-sciences/medtech-research-and-development-innovation.html>.
- 9 "Oncomine Childhood Cancer Research Assay," Thermo Fisher Scientific, accessed May 18, 2019, <https://assets.thermofisher.com/TFS-Assets/CSD/Flyers/oncomine-childhood-cancer-assay-flyer.pdf>.
- 10 "Oncologists Identify Cancer Patient's NTRK Gene Fusion in Unprecedented 48 Hours," Thermo Fisher Scientific, accessed May 18, 2019, <https://www.oncomine.com/outcomes>.
- 11 "Thermo Fisher Unveils International Childhood Oncology Network," *Clinical Omics*, April 16, 2018, <https://www.clinicalomics.com/topics/precision-medicine-topic/cancer/thermo-fisher-unveils-international-childhood-oncology-network/>.
- 12 Sriram Renganathan, "3D Printing Drugs—The Latest Advancements Around the World," *All3DP*, February 23, 2019, <https://all3dp.com/2/3d-printing-drugs-the-latest-advancements-around-the-world/>.
- 13 Anne Trafton, "Ingestible Capsule can be Controlled Wirelessly," *MIT News*, December 13, 2018, <http://news.mit.edu/2018/ingestible-pill-controlled-wirelessly-bluetooth-1213>.
- 14 Jill Sederstrom, "Pharmacogenomics and the Future of Pharmacy," *Drug Topics*, July 19, 2018, <https://www.drugtopics.com/article/pharmacogenomics-and-future-pharmacy>.
- 15 Karen Taylor, Dr. Mark Steedman and Amen Sanghera, *Pharma and the Connected Patient: How Digital Technology is Enabling Patient Centricity*, (London: Deloitte Centre for Health Solutions, 2017), 2–3, <https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-pharma-and-connected-patient.pdf>.
- 16 Jan Ascher et. al., "From Product to Customer"; Karen Palmer and Joshua Tepper, "Patient Engagement."
- 17 The Association of the British Pharmaceutical Industry (ABPI), *Bridging the Skills Gap in the Biopharmaceutical Industry: Maintaining the UK's Leading Position in Life Sciences* (London: ABPI, January 2019), 15, https://www.abpi.org.uk/media/6657/190124-final-abpi-bridging-the-gap-in-the-biopharmaceutical-industry_v3.pdf.
- 18 Eric Topol, "Letter to the Secretary of State for Health and Social Care," in *The Topol Review: Preparing the Healthcare Workforce to Deliver the Digital Future*, by National Health Service (Health Education England, February 2019), 7, <https://topol.hee.nhs.uk/wp-content/uploads/HEE-Topol-Review-2019.pdf>.
- 19 "Hacking R&D: The Role of Artificial Intelligence," Bristol-Myers Squibb, January 7, 2019, <https://www.bms.com/life-and-science/science/the-role-of-artificial-intelligence.html>.
- 20 "The Future Of Clinical Trials: How AI & Big Tech Could Make Drug Development Cheaper, Faster, & More Effective," *CBI Insights*, August 7, 2018, <https://www.cbinsights.com/research/clinical-trials-ai-tech-disruption/>.
- 21 Sijia Huang, Kumardeep Chaudhary and Lana X. Garmire, "More Is Better: Recent Progress in Multi-Omics Data Integration Methods," *Frontiers in Genetics*, June 16, 2017, <https://doi.org/10.3389/fgene.2017.00084>.
- 22 "Medidata Rave Omics Collaboration Uncovers Novel Insights for Rare Disease Research," Medidata, December 4, 2018, <https://www.medidata.com/en/press-releases/medidata-rave-omics-collaboration-uncovers-novel-insights-rare-disease>.
- 23 Chiara Di Resta et. al., "Next-Generation Sequencing Approach for the Diagnosis of Human Diseases: Open Challenges and New Opportunities," *The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine* 29, no. 1 (April 30, 2018): 4–14, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5949614/>.
- 24 Chiara Di Resta et. al., "Next-Generation Sequencing," 4–14.
- 25 Chiara Di Resta et. al., "Next-Generation Sequencing," 4–14; Megan Molteni, "Now You Can Sequence Your Whole Genome for Just \$200," *Wired*, November 19, 2018, <https://www.wired.com/story/whole-genome-sequencing-cost-200-dollars/>.
- 26 Chiara Di Resta et. al., "Next-Generation Sequencing Approach," 4–14.
- 27 Filshitsky, "AI in Clinical Trials?"
- 28 "CMS Finalizes Coverage of Next Generation Sequencing Tests, Ensuring Enhanced Access for Cancer Patients," Centers for Medicare & Medicaid Services, March 16, 2018, <https://www.cms.gov/newsroom/press-releases/cms-finalizes-coverage-next-generation-sequencing-tests-ensuring-enhanced-access-cancer-patients>.
- 29 "CMS Reopens National Coverage Determination for NGS Testing in Advanced Cancer," *genomeweb*, May 1, 2019, <https://www.genomeweb.com/reimbursement/cms-reopens-national-coverage-determination-ngs-testing-advanced-cancer#XNp7xS2ZnQI>.
- 30 Ian Sample, "Routine DNA Tests Will Put NHS at the 'Forefront of Medicine'," *The Guardian*, July 3, 2018, <https://www.theguardian.com/science/2018/jul/03/nhs-routine-dna-tests-precision-cancer-tumour-screening>.
- 31 Ross Davies, "Is the UK's Drug Evaluation System in Need of an Overhaul?," *Pharma Technology Focus*, accessed April 29, 2019, https://pharma.nridigital.com/pharma_jun18/is_the_uk_s_drug_evaluation_system_in_need_of_an_overhaul.
- 32 Cision PR Newswire, "U.S. Health Care System Ties 29% of Payments to Alternative Payment Models," Health Care Payment Learning & Action Network (LAN), October 30, 2017, <https://www.prnewswire.com/news-releases/us-health-care-system-ties-29-of-payments-to-alternative-payment-models-300545354.html>.
- 33 "What are the Value-Based Programs?" Centers for Medicare & Medicaid Services, accessed April 15, 2019, <https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/value-based-programs/value-based-programs.html>; A. Towse, A. Cole and B. Zamora, *The Debate on Indication-Based Pricing in the U.S. and Five Major European Countries*, OHE Consulting Report (London: Office of Health Economics, 2018), <https://www.ohe.org/publications/debate-indication-based-pricing-us-and-five-major-european-countries>.
- 34 Bruce Japsen, "UnitedHealth, Aetna, Anthem Near 50% Value-Based Care Spending," *Forbes*, February 2, 2017, <https://www.forbes.com/sites/brucejapsen/2017/02/02/unitedhealth-aetna-anthem-near-50-value-based-care-spending/#7965cd321d4e>; Bruce Japsen, "Anthem Blue Cross Nears 60% Value-Based Care Spend," *Forbes*, April 27, 2017, <https://www.forbes.com/sites/brucejapsen/2017/04/27/anthem-blue-cross-nears-60-value-based-care-spend/#4c74a0ad6fe7>.
- 35 Economist Intelligence Unit (EIU), "Value-Based Healthcare in the UK: a System of Trial and Error," (London: Economist Intelligence Unit, 2016), 8, <https://eiperspectives.economist.com/sites/default/files/ValuebasedhealthcareUK.pdf>.
- 36 EIU, "Value-Based Healthcare in the UK," 7, 9; A. Towse, A. Cole and B. Zamora, *The Debate on Indication-Based Pricing*.
- 37 Economist Intelligence Unit (EIU), "Value-Based healthcare in Germany: from Free Price-Setting to a Regulated Market," (London: Economist Intelligence Unit, 2016), 3, 5, https://eiperspectives.economist.com/sites/default/files/Value-based%20Healthcare%20in%20Germany_0.pdf
- 38 Economist Intelligence Unit (EIU), "Value-Based Healthcare in France: A Slow Adoption of Cost-Effectiveness Criteria," (London: Economist Intelligence Unit, 2016), 3, <https://eiperspectives.economist.com/sites/default/files/ValuebasedhealthcareFrance.pdf>.
- 39 Jason T. Hurwitz, Mary Brown, Jennifer S. Graff, Loretta Peters and Daniel C. Malone, "Is Real-World Evidence Used in P&T Monographs and Therapeutic Class Reviews?," *Journal of Managed Care & Specialty Pharmacy* 23, no. 6 (2017): 613–620, <https://doi.org/10.18553/jmcp.2017.16368>.
- 40 Jason T. Hurwitz et. al., "Is Real-World Evidence Used?"
- 41 P. Kanavos, A. Angelis and M. Drummond, "An EU-wide approach to HTA: An irrelevant development or an opportunity not to be missed?," *The European Journal of Health Economics* 20, no. 3 (2019): 329–332, <https://doi.org/10.1007/s10198-019-01037-2>. Creative Commons licence: <http://creativecommons.org/licenses/by/4.0/>.
- 42 Joshua P. Cohen and Abigail E. Felix, "Personalized Medicine's Bottleneck: Diagnostic Test Evidence and Reimbursement," *Journal of Personalized Medicine* 4, no. 2 (April 4, 2014): 163–175, <https://doi.org/10.3390/jpm4020163>; Nicole St. Jean, Carla Pinto, Ines Tenente and Grace Murray, "Collaboration is Key to Accelerating Diagnostics Access to Optimize Benefits of Precision Medicines," *Personalized Medicine* 15, no. 3 (2018), <https://doi.org/10.2217/pme-2018-0018>.
- 43 "What Are In Vitro Diagnostic Tests, and How Are They Regulated?," The PEW Charitable Trusts, May 14, 2019, <https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated>.
- 44 "What Are In Vitro Diagnostic Tests?," The PEW Charitable Trusts.
- 45 GeneWatch UK, *The EU's In Vitro Diagnostics (IVD) Regulation: A Summary of the Regulatory Requirements for Software and Genetic Tests* (Berkshire: GeneWatch UK, 2017), Page, 1, http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/IVDReg_GWbrief_fin.pdf; "How Ready Are You for the In Vitro Diagnostic Regulation?," BSI, accessed May 10, 2019, <https://www.bsigroup.com/en-GB/medical-devices/our-services/IVDR-Revision/>.
- 46 "EU Regulation on In Vitro Diagnostic Medical Devices - What is behind it?," Central BioHub, accessed May 11, 2019, <https://www.centralbiohub.com/help/34/20/eu-regulation-on-in-vitro-diagnostic-medical-devices-what-is-behind-it/>.
- 47 Cohen and Felix, "Personalized Medicine's Bottleneck," 163–175.

- 48 Joshua P. Cohen, "Precision Medicine Success Hinges On Diagnostics' Clinical Utility," *Forbes*, July 23, 2018, <https://www.forbes.com/sites/joshuacohen/2018/07/23/precision-medicine-success-hinges-on-diagnostics-clinical-utility/#7b1f92ce2dd9>; Personalized Medicine Coalition, *The Personalized Medicine Report 2017: Opportunities, Challenges, and the Future* (Washington: Personalized Medicine Coalition, 2017), 37, <http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The-Personalized-Medicine-Report1.pdf>.
- 49 "Coverage and Reimbursement," National Human Genome Research Institute.
- 50 Greg Reh et al., *Delivering Medical Innovation in a Value-Based World* (Washington, DC: Deloitte Center for Health Solutions, 2016), 11, <https://www2.deloitte.com/content/dam/Deloitte/lu/Documents/life-sciences-health-care/lu-delivering-medical-innovation-value-based-world-092017.pdf>.
- 51 "Adaptive Pathways," European Medicines Agency, accessed May 12, 2019, <https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways>; "Parallel Consultation with Regulators and Health Technology Assessment Bodies," European Medicines Agency, accessed May 12, 2019, <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies>.
- 52 "Value Based Pricing," Executive Insight.
- 53 Greg Reh et al., *Delivering Medical Innovation*, 17; Luis Hakim and Sonal Shah, "The Next Wave."
- 54 Manisha Samy, "Companion Diagnostics (CDx): More Drugs At a Fraction of the Cost," ARK Invest, August 25, 2016, <https://ark-invest.com/research/companion-diagnostics-cdx>.
- 55 Joshua P. Cohen, "Precision Medicine Success."
- 56 Friends of Cancer Research, "A Risk-based Approach for In Vitro Companion Diagnostics Designation," (conference draft, Alexandria Center for Life Science, New York City), 3, <https://www.focr.org/sites/default/files/Breakthrough%20cDx%20Summary%20Report%20-Final%20Conference%20Draft%209%203%2013.pdf>.
- 57 Joshua P. Cohen, "Precision Medicine Success."
- 58 Joshua P. Cohen, "Precision Medicine Success."
- 59 Nicole St Jean et al., "Collaboration is Key to Accelerating Diagnostics."
- 60 Nicole St Jean et al., "Collaboration is Key to Accelerating Diagnostics."
- 61 U.S. Food & Drug Administration, FDA-2018-D-3380, Developing and Labeling In Vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products: Guidance for Industry (December 2018), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-or-class-oncology>.
- 62 John Kuelper, "Community Providers Will Help Drive the Future of Precision Medicine," STAT, February 23, 2018, <https://www.statnews.com/2018/02/23/precision-medicine-community-providers/>.
- 63 Jan Ascher et al., "From Product to Customer."
- 64 "An Inside Look at Diagnostics," Diaceutics, accessed May 12, 2019, <https://www.diaceutics.com/?case-study=an-inside-look-at-diagnostics>.
- 65 Cision PR Newswire, "Synapse Enters Strategic Collaboration with Roche to Advance Precision Medicine in Oncology," Synapse, January 9, 2018, <https://www.prnewswire.com/news-releases/synapse-enters-strategic-collaboration-with-roche-to-advance-precision-medicine-in-oncology-300578395.html>.
- 66 Frank Vinluan, "Woodcock: New Approvals Show FDA Is Adapting to Precision Medicine," *Xconomy*, May 30, 2017, <https://xconomy.com/national/2017/05/30/woodcock-new-approvals-show-fda-is-adapting-to-precision-medicine/>; U.S. Food & Drug Administration, *Frameworks for FDA's Real-World Evidence Program* (Silver Spring, MD: U.S. Food & Drug Administration, December 2018), 3, <https://www.fda.gov/media/120060/download>.
- 67 Ludwig Burger, "EU Rapid Drug Approval Plan Worries Some National Agencies," *Reuters*, March 29, 2017, <https://www.reuters.com/article/us-pharmaceuticals-europe-regulators-ana-idUSKBN1701E3>.
- 68 Natalie Richards and Ian Hudson, "UK Medicines Regulation: Responding to Current Challenges," *British Journal of Clinical Pharmacology* 82 (2016): 1471–1476, <https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.13077>; "Clinical trials - Regulation EU No 536/2014," European Commission, accessed May 17, 2019, https://ec.europa.eu/health/human-use/clinical-trials/regulation_en.
- 69 "Laboratory Developed Tests", U.S. Food & Drug Administration, September 27, 2018, <https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests>; Frank Luh and Yun Yen, "FDA Guidance for Next Generation Sequencing-Based Testing: Balancing Regulation and Innovation in Precision Medicine," *npj Genomic Medicine* 3, no. 28 (2018): 1, <https://doi.org/10.1038/s41525-018-0067-2>.
- 70 Dave Smart, "What Does the EU IVD Regulation Mean for Companion Diagnostics and LDTs?," *Diaceutics*, January 19, 2018, <https://www.diaceutics.com/?expert-insight=eu-ivd-regulation-mean-companion-diagnostics-ldts>.
- 71 Lori Knowles, Westerly Luth and Tania Bubela, "Paving the Road to Personalized Medicine: Recommendations on Regulatory, Intellectual Property and Reimbursement Challenges," *The Journal of Law and the Biosciences* 4, no. 3 (December 2017): 453–506, <https://doi.org/10.1093/jlb/lx030>.
- 72 Amanda Craig, "Personalised Medicine with Companion Diagnostics: The Intercept of Medicines and Medical Devices in the Regulatory Landscape," *European Medical Journal* 1, no. 1 (January 2017): 47–53, <https://www.emjreviews.com/innovations/article/personalised-medicine-with-companion-diagnostics-the-intercept-of-medicines-and-medical-devices-in-the-regulatory-landscape/>.
- 73 "2018 reform of EU data protection rules," European Commission, accessed May 28, 2019.
- 74 California Legislative Information, Assembly Bill No. 375, Chapter 55, An act to add Title 1.815 (commencing with Section 1798.100) to Part 4 of Division 3 of the Civil Code, relating to privacy (June 29, 2018), https://leginfo.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB375.
- 75 Kate Yandell, "Clinical Matchmaker," *The Scientist*, June 1, 2015, <https://www.the-scientist.com/bio-business/clinical-matchmaker-35380>.
- 76 Jane Williams, "Exploring The World's Largest Biobanks," Global Engage, October 5, 2018, <http://www.global-engage.com/life-science/exploring-the-worlds-largest-biobanks/>.
- 77 Kurt Yaeger, Michael Martini, Jonathan Rasouli and Anthony Costa, "Emerging Blockchain Technology Solutions for Modern Healthcare Infrastructure," *Journal of Scientific Innovation in Medicine* 2, no. 1 (2019): 1, DOI: <http://doi.org/10.29024/jsim.7>.
- 78 "IMI Mission and Objectives," Innovative Medicines Initiative, accessed May 9, 2019, <https://www.imi.europa.eu/about-imi/mission-objectives>; About precisionFDA, precisionFDA, accessed May 9, 2019, <https://precision.fda.gov/about>.
- 79 "About," EU-STANDS4PM, accessed May 9, 2019, <https://www.eu-stands4pm.eu/about>.