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Precision Medicine

Opening the aperture

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Precision medicine: Opening the aperture

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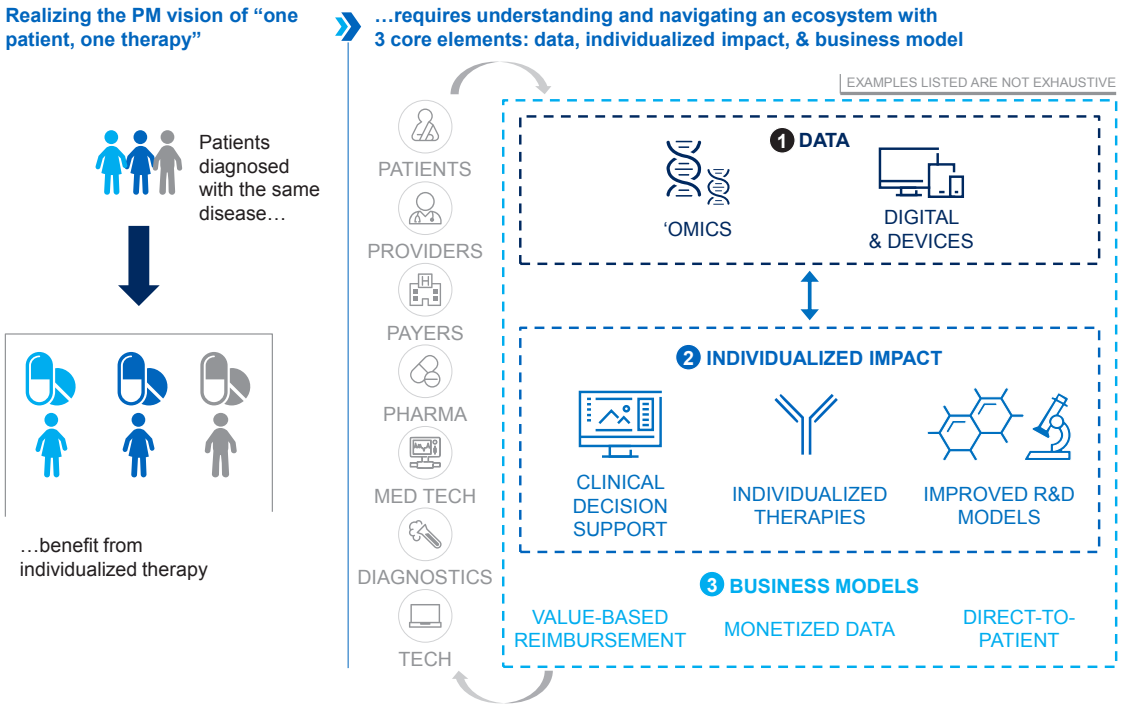
As originally conceived, personalized medicine referred to the tailoring of medical treatment to the individual characteristics of each patient,[1] ultimately leading to a shift in the clinical treatment paradigm from a trial-and-error approach to "the right drug, for the right patient, at the right time." Today, a combination of public investment, biotechnology development, and digitization of health profiles has evolved personalization beyond therapy selection and into the realm of drug discovery, how care is planned for and delivered, and increasingly, to how we as consumers engage with companies seeking to improve health. Driving this transformation are advances in diagnostics, digital devices, and imaging, alongside an arsenal of analytics tools working across a multitude of institutions and stakeholders. Encompassing this entire ecosystem, medicine will be driven by three key components: 1) Data collection through diagnostics and behavioral devices that capture us in various states of health and disease; 2) Individualized solutions through advanced analytic engines and personalized therapies; and 3) Business models necessary to sustain value and incentivize continued growth. In this compendium, we discuss the recent advances in each of these three areas, the challenges the industry faces going into the next five years, and the implications for key stakeholders.

Acceleration of data generation, advances in developing insights, and personalization of the healthcare ecosystem have added dimensionality to precision medicine



1 As defined by President Obama's Council of Advisors on Science and Technology

Data

Previously, we thought about precision medicine as data from targeted genomic panels informing therapy selection. Today, with the explosion of data collection at the population level with multiple data points, it's common to say that data has become the "oil" for our time. The sheer scale of data proliferation is breathtaking. According to a 2017 white paper from Stanford University School of Medicine, 153 exabytes[2] of healthcare data were produced in 2013, and an estimated 2,314 exabytes will be produced by 2020, a 48 percent growth rate annually.[3] This growth rate is so extreme that we can say that 99 percent of the world's data has been created in the past 18 months—a staggering statistic. Analyst reports estimate the market size for big data in healthcare at between $53 billion and $69 billion by 2025, with CAGR of up to 27 percent.[4]

Beyond generating such vast quantities of data, health systems are getting better at integrating datasets to more easily aggregate them and gain better access. In the United States, the Department of Health and Human Services (HHS) has invested $35 billion in healthcare IT[5]; this has rapidly advanced medical data storage through the proliferation of electronic health records (EHRs). Such integration and aggregation of data is allowing us to close the loop to fully understand patients from their symptoms, to treatment, to outcomes. Roche is an interesting example of starting to "own the patient" from end to end. With the organization's recent acquisition of Flatiron Health ($1.9 billion) and the remaining stake in Foundation Medicine ($2.4 billion), it is now has access to genomic data from thousands of oncology patients.[6, 7] Combining this data with innovative, targeted therapies, such as those coming from their acquisition of Ignyta ($1.7 billion), could provide Roche with a continuous data loop from identifying a patient, confirming genomic signature, treatment selection, and on to monitoring outcomes.[8]

While genomic data in oncology is still a critical part of healthcare today, we have "widened the aperture" to understand all of the ways in which we can personalize healthcare: continued growth of genomics beyond oncology, additional modalities to understand our molecular phenotype, and collection of behavioral data through devices. In the not-too-distant future, we envision that every patient will have his or her own data ecosystem, a closed loop of continuous learning based on ubiquitous data, enabling each patient to benefit from insights generated by the collective experience of the entire medical community. Challenges of siloed data collection, interoperability,

2 One exabyte = one billion gigabytes.

3 *Harnessing the Power of Data in Health, Stanford Medicine 2017 Health Trends Report*, June 2017, https://med.stanford.edu/school/leadership/dean/healthtrends.html.

4 MarketsandMarkets data extrapolated to 2025 using 27.3 percent CAGR, see https://www.marketsandmarkets.com/PressReleases/healthcare-data-analytics.asp; *Healthcare analytics market size worth $53.65 billion by 2025,* Grand View Research, March 2018, https://www.grandviewresearch.com/press-release/global-healthcare-analytics-market; *Global Big Data in Healthcare Market: Analysis and Forecast, 2017-2025 (Focus on Components and Services, Applications, Competitive Landscape and Country Analysis)*, BIS Research, 2018, https://bisresearch.com/industry-report/global-big-data-in-healthcare-market-2025.html.

5 *HHS should assess the effectiveness of its efforts to enhance patient access to and use of electronic health information*, Publication No. GAO-17-305, U.S. Government Accountability Office, March 15, 2017, https://www.gao.gov/products/GAO-17-305.

6 "Roche and Foundation Medicine reach definitive merger agreement to accelerate broad availability of comprehensive genomic profiling in oncology," Roche media release, June 19, 2018, https://www.roche.com/media/releases/med-cor-2018-06-19.htm.

7 "Roche completes acquisition of Flatiron Health," Roche media release, April 6, 2018, https://www.roche.com/media/releases/med-cor-2018-04-06.htm.

8 "Roche and Ignyta reach definitive merger agreement," Roche media release, December 22, 2017, https://www.roche.com/media/releases/med-cor-2017-12-22.htm.

and policies for data sharing have slowed the realization of this vision, but these are slowly being overcome. We discuss the implications for pharma, providers and diagnostic players in terms of how they can compete in this digital, data-driven world.

Individualized impact

In the original concept of precision medicine, insight generation centered around univariate analysis: that is, understand what mutation leads to what disease through retrospective research, and use that algorithm to prospectively identify mutations in a new population. This has become increasingly powerful in oncology, through integration of genomics, EHRs, and advanced analytics. However, across therapeutic areas, we are seeing an explosion in the availability of data over multiple dimensions, which in turn leads us to a much broader set of questions to solve.

The advent of new technologies and mobile medical apps has allowed us to actively track a patient's physiology in real time. Whereas previously we collected descriptive statistics of discrete populations, we can now take this multidimensional data and create predictive algorithms, which use the collective learnings to predict outcomes for an individual. This approach implies a cyclical, dynamic feedback loop whereby processes and underlying capabilities are constantly modified based on the inputs from patients. To continue to push the potential of precision medicine, healthcare stakeholders are actively trying to build capabilities along three dimensions: data acquisition, data analysis, and analytics-based decision-making. As the number of data inputs increases and the level of analysis becomes more and more sophisticated, we are seeing both start-ups and established technology players with core competencies in advanced analytics also trying to enter the healthcare space.

One recent example is Tempus, which describes itself as a "technology company that has built the world's largest library of clinical and molecular data and an operating system to make that data accessible and useful, starting with cancer."[9] Recently valued at $2 billion, the company has established data partnerships with large cancer centers across the United States, including Vanderbilt-Ingram Cancer Center and ASCO. It provides a proprietary platform to ingest unstructured data (clinical notes, pathology images) and structured data (next-generation sequencing) to deliver actionable, personalized insights. More established players in this space include IBM and Google. Google's DeepMind recently published impressive results analyzing 3D optical images, outperforming experts in making referral recommendations for a range of retinal diseases, while IBM's Watson has continued to improve its ability to tailor treatment options to a patient's genomic profile. While still a work-in-progress, both the level of commitment and investment by major technology companies to advance AI in medicine is a harbinger of things to come.[10, 11]

In 2017 and 2018 we also saw approvals of two truly individualized therapies, Yescarta and Kymriah, for leukemia and lymphoma. These CAR-T therapies are a type of immunotherapy where a patient's own immune cells are genetically modified to fight cancer cells. Other gene therapy techniques, most notably CRISPR, are in active development, and we expect more and more individual therapies to be approved in the next 5-10 years.

9 See https://www.tempus.com/.
10 De Fauw J et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med 2018;24(9):1342-50.
11 Faye Flam, "IBM's Watson Hasn't Beaten Cancer, But A.I. Still Has Promise," *Bloomberg Opinion*, 24 August 2018, https://www.bloomberg.com/view/articles/2018-08-24/ibm-s-watson-failed-against-cancer-but-a-i-still-has-promise.

Business models

While we can all appreciate the importance of data and insights, it's much less clear how to derive value from those insights, and who will pay for it. Each stakeholder grapples with this differently in the precision medicine ecosystem. Diagnostic players need to understand the market for future tests, whether the value will lie in the test itself or the insight generated, and the best commercial model to support that. In addition to providing quality, personalized care, providers are considering how best to aggregate and mine patient data, and what insights could be commercialized from that data. Pharma companies are partnering with payers and providers to be part of the data ecosystem, and are also trying to determine the best commercial model when considering smaller and smaller patient populations. There is no gold-standard business model to pave the way for how to unlock value. Some are giving away genomic sequencing in order to own the data (for example, Nebula Genomics, Tempus), while others are solving tangential problems for health systems (such as billing, tumor board management, data aggregation) in an effort to access and own the data; however, most pharma and med device players are tapping into the precision medicine ecosystem to bolster conventional business models (for instance, selling more tests or therapies through conventional channels). Given all of the changing healthcare dynamics, the time is ripe for disruption through business model innovation. In this compendium, we consider the five aspects of business model innovation (value proposition, economic model, delivery model, production model, operating model) through the lens of key stakeholders, and also explore the potential for new entrants to unlock further value in the precision medicine ecosystem.

Learning from the past as we look ahead

Given the rapid pace of change in this field, we expect the fundamental ways in which we deliver healthcare to transform. Within that process are a number of unknowns as the technology evolves with different stakeholders taking multiple approaches to the importance and value of data, how its worked with and analyzed, and how that's applied to patient care. With this in mind, there are three key questions we should be asking ourselves as all players in the industry consider and shape the future of this space.

1. Who will own the future value?

In an information economy, the ability to gather data, generate insights, and then transform those insights into impact in the real world form the backbone of value creation. Such capabilities exist natively in the tech ecosystem because, in large part, digital companies are the ones that have taught us how to build wildly successful businesses around data. Accordingly, tech players—Apple, Amazon, Google, Facebook—possess a tremendous advantage as they enter biomedicine, being the incumbent experts in the components of the operating model that we expect to drive value in precision healthcare: data stewardship, excellence in analytics, agile product design, and superior analytics talent.

Yet, to this point, the biomedical incumbents have remained unthreatened in the delivery of healthcare and the development of therapies; while there have been interesting partnerships, acquisitions, and enabling technology development, there have been no at-scale examples of healthcare disruption by a major tech player to date. An important open question is whether one set of players will ultimately win the day, or whether the coming years will see greater collaboration and joint product development that will ultimately transform how most patients interact with the healthcare system.

2. How will most patients experience precision healthcare?

The ability to collect more and more information about our health comes at a cost: molecular diagnostics can be hundreds to thousands of dollars and are not always reimbursed, while

devices for collecting behavioral data are a costly personal expense (for example, Apple Watch, Fitbit). Health systems are continuing to evolve, and we could see stakeholders that would benefit from lower costs of care (providers, payers) helping to defray costs in order to allow more patients access to such tools. Additionally, the cost of targeted therapies resulting from personalization can run from tens to hundreds of thousands of dollars a year. As we discover the importance of all of these data inputs to drive clinical insights and inform new treatments, and find tremendous clinical benefit in novel personalized therapies, how broad do we expect access to be, and how quickly will it scale?

3. Which geography will lead the advancement of precision medicine?

Macro factors will invariably determine the trajectory of innovation in precision healthcare: from the way that information is regulated (for example, GDPR) and how payment for medical services is rendered to how new therapies are tested and approved. These factors will have an impact at least at the regional level but, in most cases, at a national level or beyond. Traditionally the United States has seen the most funding, innovative technology and therapy development; however, China is investing heavily and has a much less stringent regulatory environment. Interestingly, many European countries have healthcare models that are most aligned with the value proposition of precision medicine, and have been quite aggressive in developing initiatives around individual patient data collection, especially for large, de-identified patient data sets (for example, UK Biobank). However, data privacy issues and regulations could dampen this momentum. Given the diversity of possible approaches, where will precision healthcare accelerate the quickest?

■ ■ ■

Over the past five years, healthcare's collective description and understanding of what constitutes precision medicine has evolved for the simple mandate of "one patient, one drug" to a more complex data, analytics, and business model ecosystem. We look to the next five years to see how far this data revolution in precision medicine will go, and what transformative new therapies it will usher in.

Articles in this compendium

Data:

Data ecosystem: Here we consider the vision for the future PM ecosystem, the critical enablers for this vision, and implications for pharma, provider, and diagnostic players.

Genetics in R&D: The investment to produce innovative therapies is long, costly, and extremely risky, with only 11% of novel drugs entering clinical trials making it to market. In the article we discuss how human genetics can impact R&D productivity.

Beyond genomics: While genomics will continue to gain traction in clinical care, the advent of recent technologies will allow "multi-omic" analyses—we discuss the implications for industry stakeholders.

Individualized impact:

Oncology and EHR analytics: Advances in oncology care continue—we predict further progress as systems begin to use advanced analytics to combine biomarker and EHR data.

Beyond oncology: We explore the drivers of PM growth in other therapeutic areas, offering perspectives on how and where we will see PM growth beyond oncology.

Mobile medical applications: In this chapter, we look at the role of digital and mobile medical apps in healthcare, and how they are leading us to predictive algorithms for disease at the level of the individual.

Business model:

While there is no silver bullet for how to "win" in PM, we discuss examples of successful disruption by players in this evolving market.

A new vision for precision medicine in a data-driven world

George Xu, Meredith Reichert, Kevin Webster, Edd Fleming

Advances in data collection, aggregation, and impact generation promise a new paradigm of continuous learning fed by ubiquitous data and real-time analysis.

Introduction

In the past five years, rapid technology progress in collecting, storing, analyzing, and connecting complex medical data has reshaped our world. Instead of the traditional model of clinical development based on discrete, methodical trials with relatively small populations, these advances promise a new paradigm—whereby continuous learning is fed by ubiquitous data and real-time analysis. Although some hurdles still remain before this goal can be achieved, the growth of data has enabled a new, bolder vision of precision medicine (PM).

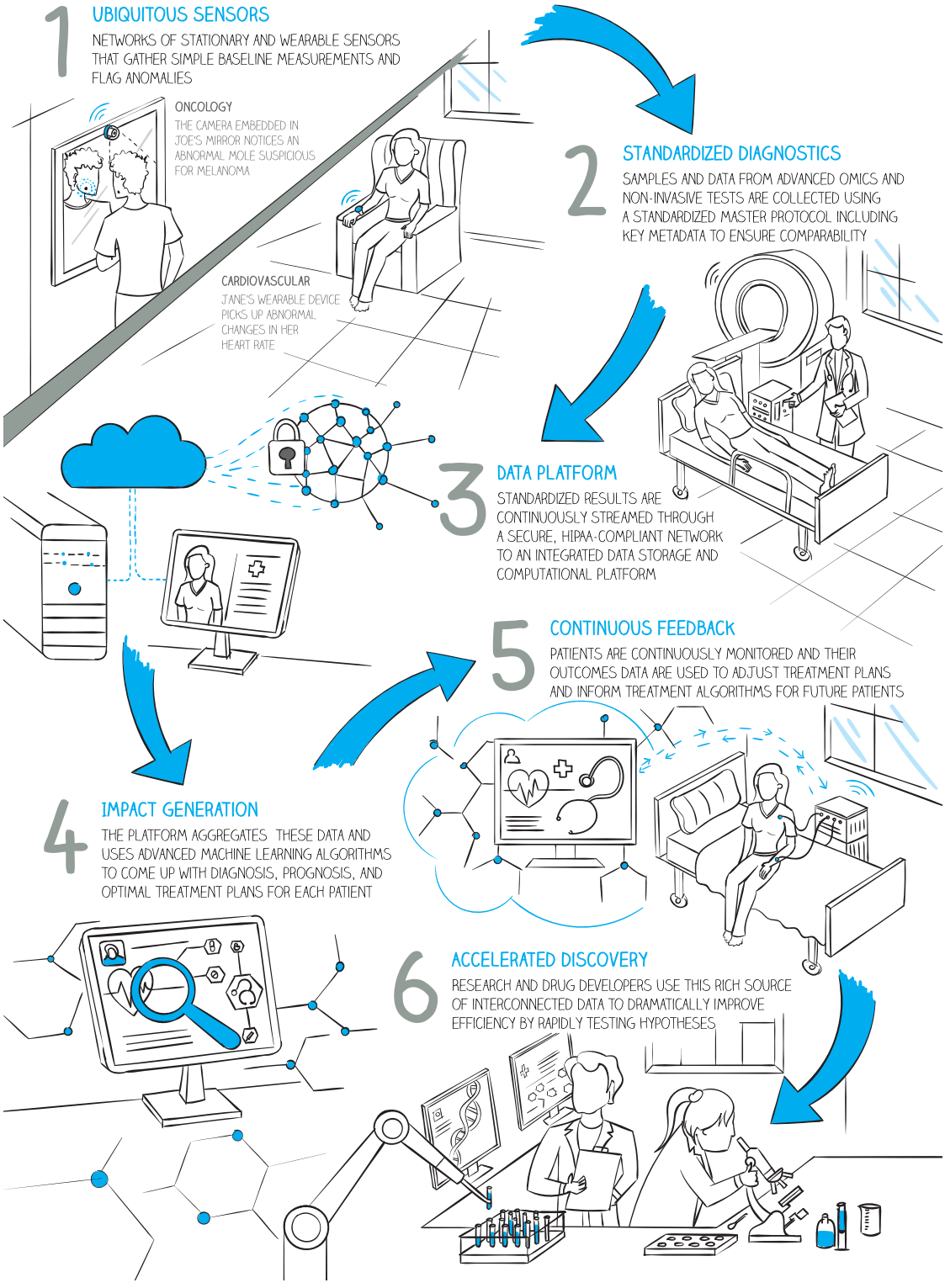
In this new vision (illustrated in Exhibit 1), a closed loop of continuous learning based on ubiquitous data enables each patient to benefit from insights generated by the collective experience of the entire medical community. At the center is a data platform with integrated computational and data storage capabilities that are connected to the external world through a secure, HIPAA-compliant network.[1] The platform aggregates data from multiple sources and uses advanced machine learning algorithms to inform diagnosis, prognosis, therapy selection, and drug development.

There are several continuous learning cycles that emanate from this central vision. Networks of stationary and wearable sensors feed simple baseline measurements from individuals to the platform, which then flags anomalies with high confidence through the combination of multiple data sources. Follow-up diagnostics use advanced, non-invasive technology and “omics” to comprehensively assess multiple factors of individuals’ health status. Samples and data for these tests are collected using a standardized master protocol, including the necessary metadata to ensure comparability across the platform. While on treatment, patients are continuously monitored and their outcomes data are used to adjust treatment plans and inform treatment algorithms for future patients. In

1 The US Health Insurance Portability and Accountability Act of 1996.

addition, these data are made available to researchers and drug developers through data agreements that enable them to dramatically improve drug development by enabling rapid discovery of molecules and targets, new indications for existing drugs, new combinations, and responsive patient subpopulations.

Exhibit 1



Recent progress and implications

Evolution towards this vision will have profound implications for the biopharma industry. The power of this rich data ecosystem and the distinctive capabilities it enables could dramatically shift industry dynamics. These changes will not only impact multiple players within the industry, from biopharma to diagnostics companies, but also multiple functions within these players, from research & development to commercial organizations.

Effective use of data represents a new front in the battleground between competing pharmaceutical companies. Indeed, we have already witnessed significant movement in this space, from Roche's $1.9 billion acquisition of Flatiron to Novartis's recent commitments to digital technologies.[2] Keeping up in the emerging world of continuous data will require timely access to datasets, analytics infrastructure, and a whole host of new capabilities that haven't traditionally existed in biopharma companies. In fact, distinctive analytical capabilities to integrate and interpret disparate datasets may become a source of competitive advantage, just like salesforce targeting or patient services functions today. Current industry players will need to grow and adapt to the new environment or be outpaced by competitors who are able to tap into the rapid learning cycles enabled by the data revolution.

> Over the next five years, just under 90 percent of both payers and provider organizations will adopt "big data analytics capabilities"

Beyond pharmaceutical companies, payers and providers have also begun using the same types of data and analytics in their operations. Over the next five years, just under 90 percent of both payers and provider organizations will adopt "big data analytics capabilities".[3] Given their longitudinal management of patients, payers have historically enjoyed better access to medical datasets and maintained a privileged knowledge differential. However, this balance is increasingly shifting as pharmaceutical companies have started to view these capabilities as a source of competitive advantage. Now that payers and providers are increasingly relying on data to inform ongoing reimbursement, it is even more critical for pharmaceutical companies to be equipped to participate and shape the narrative on healthcare value—50 percent of drug submissions to health technology assessment authorities already use real-world evidence.[4]

2 Vas Narasimhan, "Reimagining Novartis as a 'medicines and data science' company," LinkedIn, January 12, 2018, https://www.linkedin.com/pulse/reimagining-novartis-medicines-data-science-company-vas-narasimhan/.
3 Jennifer Bresnick, "93% of Payers, Providers Say Predictive Analytics are the Future" *Health IT Analytics*, June 9, 2017, https://healthitanalytics.com/news/93-of-payers-providers-say-predictive-analytics-is-the-future
4 Based on a sample of submissions to European health technology assessments (HTAs), not oncology-specific, Quintiles 2015.

As the number of viable single and combination therapies for each disease continues to grow, comprehensive and integrated diagnostics will play an increasingly important role in ensuring patients receive the right treatment at the right time. The most effective diagnostic technologies will require large datasets to deliver the best predictability. Diagnostic companies will likely draw on multiple "omics" technologies whose value is compounded with additional data—unlike traditional single assays, "omics" technologies comprehensively assess multiple biomolecules, and large datasets are required to translate the complex outputs into actionable insights. A positive feedback loop, where companies with flexible platforms and large datasets will be most in demand, will allow companies to generate even more data, and ultimately build up a broad "moat".[5] This will likely lead to a "winner-take-all" paradigm, where the market leader will ultimately enjoy preferential partnering with drugs in late-stage trials so that the drugs won't have to wait for real-world data to accumulate post-launch. The increasing important of these partnerships could fundamentally shift how drugs compete and alter the balance of power among pharmaceutical companies, diagnostic companies, payers, and providers.

50 percent of drug submissions to health technology assessment authorities already use real-world evidence

Moreover, pharmaceutical marketing could fundamentally change. Although physicians will still make the ultimate decision, they will rely heavily on algorithms for support as the number of treatment options expands and the complexity of diagnostic technology grows.[6] For many new drugs, pharmaceutical companies will likely need to gain usage quickly in order build up the necessary data for these algorithms to recommend them with confidence. This may require testing on larger populations or high discounts upfront to drive volume. In either case, standard promotional tactics will likely become less effective as healthcare decisions become more and more data-driven.

Finally, strong partnerships with patient advocacy and policy groups will be vital to advancing towards this future state. There are already a variety of initiatives to enable components of the vision, such as ORIEN, Project DataSphere, CancerlinQ, and Project Genie. Moreover, the Food and Drug Administration (FDA) has taken some steps to encourage development of emerging assays and algorithm-based diagnostics by clarifying their regulatory approach to these products. It is in the interest of these groups to enable a world of PM, but it will still be a challenge to overcome interests in the healthcare system, such as health systems who want to own their patients' medical data or electronic health records companies who prefer proprietary data formats that keep customers in their system.

5 A data moat is the competitive advantage a business derives from its proprietary dataset.

6 Siddhartha Mukherjee, "A.I. Versus M.D. What happens when diagnosis is automated?" *New Yorker*, April 3, 2017, https://www.newyorker.com/magazine/2017/04/03/ai-versus-md.

Critical enablers

Although there has been considerable progress to date, achieving this vision of PM still needs to make significant progress in the way data is able to flow along the path from collection, through aggregation, and then onwards to generate impact (Exhibit 2). Moreover, it should be noted that, while this process on the face of it seems straightforward, overcoming the various hurdles is a relatively complex task in practice.

Exhibit 2

Progress toward the future vision of precision medicine.

	Data collection *Defining & validating standards*	**Aggregation and interoperability** *Enabling integration and analysis across multiple datasets*	**Impact generation** *Demonstrating proof of concept and making an economic case*
Recent progress	▪ Rapid growth in data availability ▪ Emergence of new "omics" technologies	▪ Large investments in healthcare IT ▪ Proliferation of EHRs	▪ Advanced algorithms in specific medical applications (e.g., radiology) ▪ Small proof-of-concept studies
Remaining challenges	▪ Variable measurement procedures ▪ Outcomes, context, metadata not captured ▪ Fragmented data standards	▪ Datasets are often siloed ▪ Few integrated datasets across health systems	▪ Additional evidence needed to support expanding precision medicine beyond genomics
Critical enablers	▪ Certified standards for measurements devices ▪ Broad adoption of foundational data standards	▪ Incentives for stakeholders ▪ Robust digital infrastructure to support sharing	▪ Small prospective trials ▪ Clinical decision support tools to disseminate new evidence

Data collection—defining and validating standards. The amount of data available is growing rapidly with the emergence of new "omics" technologies for biomolecules beyond nucleic acids, as well as ubiquitous sensors that track environmental exposures. The next-generation sequencing market is expected to grow 21 percent annually over 2017–22.[7] However, the procedures for measuring such data are highly varied, the context/metadata

The next-generation sequencing market is expected to grow 21 percent annually over 2017–22

7 Mr. Rohan, "Next Generation Sequencing (NGS) Market worth 12.45 Billion USD by 2022," https://www.marketsandmarkets.com/PressReleases/ngs-technologies.asp

are not always captured, and outcomes are often not linked to diagnostic results (at least for the test manufacturers). In addition, although there are some standards for data storage and representation, they are fragmented and not interoperable. Achieving the vision of PM will require certified standards for measurement devices—such as in vitro diagnostics (IVDs), radiology equipment, and so on—and broad adoption of foundational data standards supplemented by adaptable extensions. For example, recording the result of a PD-(L)1 expression assay requires much more information than just whether it was positive/high expression; there are multiple assays with different reagents and thresholds for measurement, all of which are important information for a diagnostic algorithm. To demonstrate feasibility and catalyze adoption, it may be necessary to first define and validate a minimum set of core variables before expanding to broader data collection.

Aggregation and interoperability—enabling integration and analysis across multiple datasets. Since 2009, the Department of Health and Human Services (HHS) has invested $35 billion in healthcare IT.[8] This investment has rapidly advanced medical data storage through the proliferation of electronic health records (EHRs). There are now over 13 million electronic medical records for cancer patients in the United States.[9] However, these data are kept siloed in each healthcare system. Other medical datasets (such as genome sequences) are also stored in various fragmented silos that are difficult for outsiders to access. Numerous companies are entering the space (for example, CancerIQ, Syapse, Foundation Medicine, Flatiron Health, and DNAnexus), but few, if any, players are able to offer integrated datasets. Achieving the future vision will require clear incentives and tools for stakeholders to share data openly, promptly, and securely. In addition, it will require robust digital infrastructure to support transfer, integration, and interrogation of heterogeneous and large datasets.

...the Department of Health and Human Services (HHS) has invested $35 billion in healthcare IT.

Impact generation—demonstrating proof of concept and making an economic case. Impact generation based on big data is still in its nascent stages, because the earlier data collection and aggregation steps have yet to be fully developed. There have been major advances in machine learning algorithms, which are now being applied to specific medical applications (for instance, radiology). A critical step to achieving the future state vision is making an economic case for payers to cover PM practices. Intermountain's seminal study showed that patients treated with targeted therapies based on molecular profiling had greater progression-free survival than those treated with historical standard of care, at the

8 U.S. Government Accountability Office, "HHS should assess the effectiveness of its efforts to enhance patient access to and use of electronic health information," Publication No. GAO-17-305, March 15, 2017, https://www.gao.gov/products/GAO-17-305.

9 National Cancer Institute, US, 2017.

...over 13 million electronic medical records for cancer patients in the United States

same cost.[10] As the definition of PM expands beyond genomics, further proof-of-concept analyses will need to be performed. Subsequently, new evidence could be generated cost-effectively using a combination of retrospective analysis and small prospective trials comparing outcomes from treatment decisions made with and without support from PM. These findings would then need to be disseminated, likely through clinical decision-support tools. Traditional guidelines may recommend which software tools to use, but are too limited to capture the full complexity of big-data driven decision making.

Conclusions

Though data collection, aggregation, and impact generation will occur sequentially, all three must be developed in parallel to ensure adoption and successful integration of a PM data ecosystem. However, healthcare stakeholders may need to further embrace help from innovative technology companies to grow, structure, and aggregate their data. At the same time, initiatives to set quality standards will ensure data are comparable across different inputs. While many of the seeds of this new ecosystems already exist in today's consortiums and companies, over the coming years, we should see dramatic steps toward the future vision as technologies advance exponentially, companies grow as data aggregators, and consortiums continue to align stakeholders on the value of this new vision.

10 Derrick S. Haslem et al. "A retrospective analysis of precision medicine outcomes in patients with advanced cancer reveals improved progression-free survival without increased health care costs," *Journal of Oncology Practice*, 2016, 13.2: e108-e119, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5455156/.

Human genetics: The next phase of biopharma R&D

Devin Scannell, Katarzyna Smietana, Edd Fleming, Martin Møller

The goal of biopharma research and development (R&D) is to discover and develop innovative new drugs that improve the lives of patients. Typically, biological targets—molecules or structures in the organism that can affect disease pathology—are discovered through basic research. Drugs are designed to modulate these targets and are ultimately tested in human clinical trials. After an average of 9.6 years, 11 percent of novel drugs entering clinical trials will successfully reach the market[1]—the entire R&D process is even longer and riskier, as it can take years for a drug candidate to enter human trials. While the past few years have seen improvements in R&D productivity,[i] more fundamental change needs to happen for the R&D model to remain sustainable.

In this article, which is divided into two parts, we address six questions:

Part I: Challenge and solution

1. Why are clinical trial success rates so low?
2. How can programs be re-risked early in R&D to significantly increase clinical success?
3. How much impact can human genetics have on R&D productivity?

Part II: Implementation and implications

4. Where can biopharma access advanced human genetics capabilities?
5. Who will benefit most from human genetics?
6. What can pharmaceutical R&D executives do to successfully lead human genetics-enabled R&D organizations?

1 Time to market and probability of success based on historical phase transitions data (2007–16) for novel products across all therapeutic areas (source: Pharmaprojects 2017, based on methodology described by Smietana et al.[i]).

We believe that clinical trial success rates can be improved by using large-scale human genetic analyses to validate biological targets and inform early termination or acceleration of clinical trial programs. Target validation is only one of the aspects of verifying "druggability" of a molecular target; nevertheless, we estimate that it can enable biopharma R&D costs to be almost halved in certain therapeutic areas, with a corresponding transformative impact on biopharma R&D productivity. Given the potential, biopharma companies that fail to embrace this technology may be at a structural competitive disadvantage. Larger biopharma—not smaller players—may be best placed to harness this innovative tool due to the need for significant investments. There are three big questions – discussed in the following chapter – that biopharma companies must answer to fully capture the potential of human genetics and transform their innovation engines.

...the *drug* may have performed well...but the *biological target* was ineffective in altering the disease enough to improve the patient's condition

Part I: Challenge and solution

1. Why are clinical trial success rates so low?

A retrospective pipeline analysis by Cook et al., (2014) showed that lack of efficacy was the overwhelming cause of late-stage program terminations[ii]: approximately 60 percent of phase 2A and some 90 percent of phase 2B terminations were due to failure of the drug to impact disease.[2] However, the most commonly cited reason for lack of efficacy (40 percent of all efficacy-based failures) was not the drug *per se* but failure to link the biological target to the disease. To put this more starkly: the *drug* may have performed well—bioavailable, good target binding, target impacted as expected, few side-effects—but the *biological target* was ineffective in altering the disease enough to improve the patient's condition. This is striking because it means a misinformed decision early in discovery (target selection) or in the translational phase was carried through to the end of the phase 2 clinical trial stage, and the interim investments of time and money were effectively wasted.

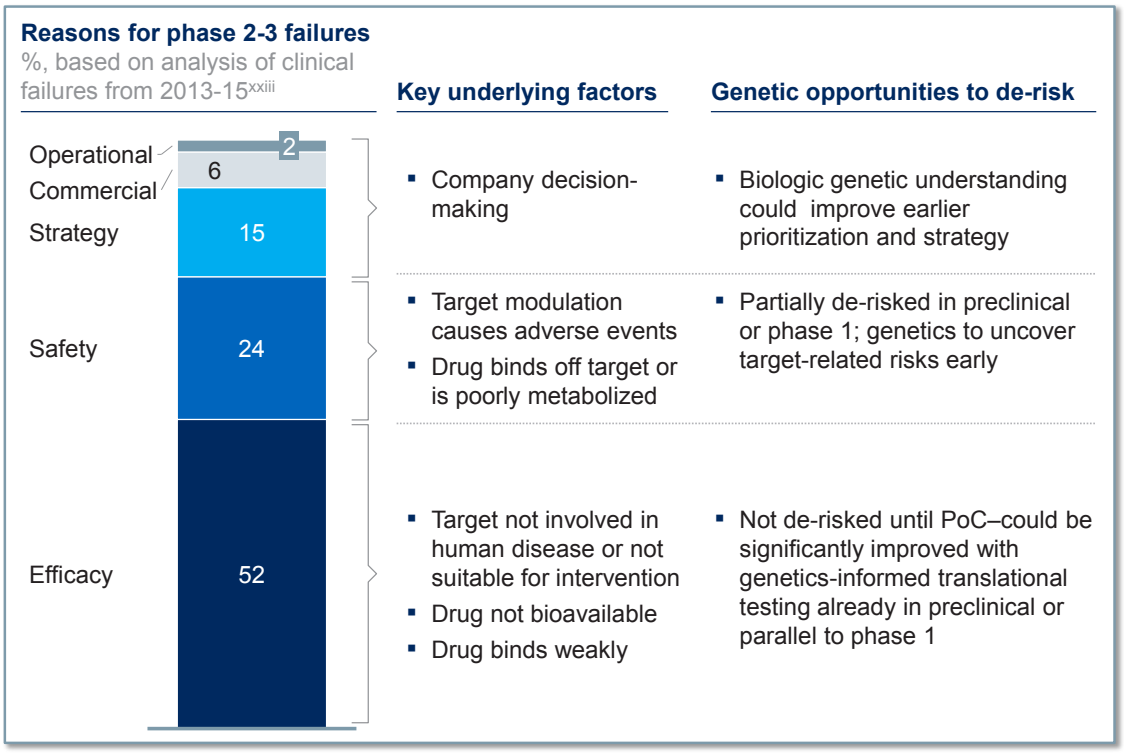
Why is target-related efficacy risk among the most important causes of late-stage clinical trial failure? The answer is two-fold. First, target identification relies to a large extent on non-human model organisms; some of the putative targets are introduced into the pipeline but are not relevant for human disease. It is well established that, for many potential biological targets, the underlying biology has evolved "between mouse and man"[iii] and even subtle changes in a target's function have potential to undermine a therapeutic hypothesis.

2 A recent industry-wide analysis of late-stage failures between 2013 and 2015 attributes 52 percent of phase 2 and 3 discontinuations to efficacy.[xxiii] Moreover, a significant number of failures (15 percent) is attributed to strategic reasons, and lack of clear efficacy advantage could be a factor contributing to those decisions. The analysis was performed in an outside-in manner hence it does not allow us to uncover the specific failure root causes.

Also, while biopharma companies have developed approaches to efficiently address other R&D risks (for instance, safety), *target-related efficacy risk* is not addressed until late-stage clinical development (Exhibit 1). A significant portion of safety risk is discharged during pre-clinical and phase 1 testing. Similarly, drug-related efficacy risk is significantly discharged during phase 1 when *in vivo* pharmacokinetics and target engagement are validated. By contrast, target-related efficacy risk is often not robustly tested until phase 2 when the target is modulated *in vivo* with a seemingly effective molecule. This is where genetic validation can play a critical role in de-risking earlier.

Exhibit 1

Opportunities to de-risk clinical development



SOURCE: Reasons for clinical failures analysis from Harrison (2016) Nat Rev Drugs Discov.[xxiii]

2. What options exist to de-risk programs early and significantly increase clinical success?

It is clear that establishing the human disease relevance of a putative biological target as early as possible is a powerful lever to manage target-related efficacy risk. The advances in genomic sequencing technology enable rapid genetic profiling of people with and without a disease of interest, as well as identification of distinct subtypes of that disease with different clinical manifestations and molecular root causes. These advances combined with the increasing availability of large-scale genomic datasets, and ongoing efforts to link genomic data to phenotype and/or drug response data, allow human genetics analysis to inform more effective biological target risk assessment.

Human genetic analysis relies on the link between an individual's clinical profile ("phenotype") and their personal genetic makeup ("genotype"). Specifically, gene

variants—naturally occurring genetic differences between individuals that increase or decrease individual disease risk[3]—may positively identify genes as human disease relevant. Human genetic analysis relies solely on the relationship between clinical history and genetic makeup (for example, from a blood sample) and can be conducted without individuals entering the clinic and even before (or in parallel with) drug development. The critical success factor is data quality—access to well-defined clinical materials linked to accurate medical records to increase accuracy of genetic correlations.

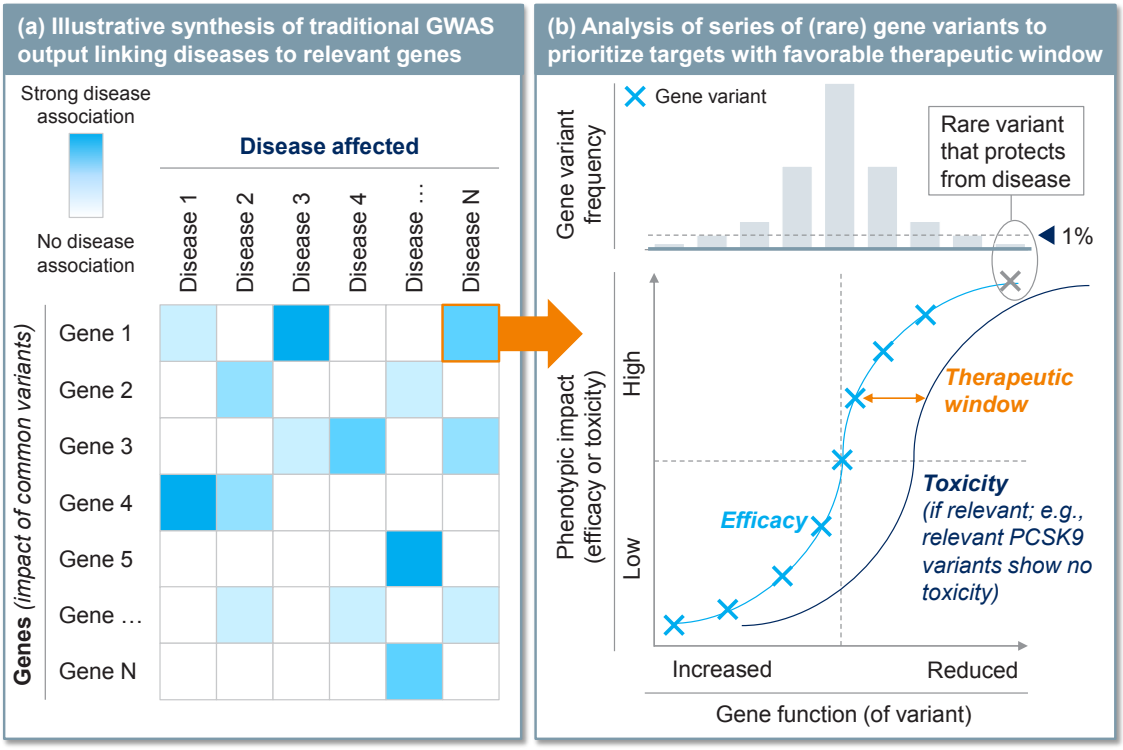
The application of human genetic analysis to drug discovery has been envisioned for many decades[iv] and has progressed through the Human Genome Project[v] and International HapMap Project[vi] to the current boom in genome-wide association studies (GWAS).[vii] GWAS studies (Exhibit 2a) commonly involve tens—or hundreds—of thousands of patients and survey "common" genetic variants (found in 5 percent of the population or more). Nearly 3,000 GWAS have been published[viii] and hundreds of thousands of gene-to-disease associations identified.

While GWAS studies have been successful at linking—and as importantly, decoupling—genes and diseases, much of the opportunity in human genetic analysis stems not from the study of "common" variation but from "rare" variations that may be found in only a tiny fraction of people. This is of interest for two reasons. First, common variants tend to have small effects on disease pathology compared to rare variants, which often have much larger clinical impact. Rare variants are thus more informative about the disease and can be very instructive about the molecular roots of the disease, bringing in deeper insight into molecular pathways at play and their focal points, potential drug targets, and opportunities to identify new molecular biomarkers and disease sub-types. Second, going beyond individual variations, it has been recognized that it is possible to build a "genetic dose response curve"[ix] (Exhibit 2b) that is logically equivalent to a drug dose response curve. Genetic dose response curves predict efficacy potential and give insight into the safety of target modulation (target-related safety risk), which together define a therapeutic window. Thus, human genetics offers a set of powerful and specific tools to guide target selection and drug discovery. However, the identification of rare variants as well as building a detailed perspective of phenotypic impact both require genomic data collection on a very large scale—otherwise certain gene variants might be missing in the investigated population, and small sample observations might lead to false conclusions (both false positives and false negatives). False positives are especially difficult to tackle because negative findings (disproving falsely reported connections) are rarely published, and increasing prevalence of large uncontrolled studies and data sets make rejection of the null hypothesis (that there is no correlation) more uncertain.

3 Most commonly, single nucleotide polymorphisms (SNPs) or copy number variations (CNVs).

Exhibit 2

Using human genetic analysis to prioritize drug targets



(a) Simplified summary representation of genome-wide association study (GWAS) output for multiple diseases of interest. Scenarios shown are intended to be typical for GWAS leveraging common gene variants (many associations between genes and disease, the majority of which are weak).

(b) Illustration of how functional analysis of multiple genetic variants for a single gene of interest can be used to generate a "genetic dose response curve" that predicts how a disease or phenotype of interest (for example, blood lipid levels; y-axis) is affected by level of gene function (x-axis). Different mutations/variants (blue and grey Xs) can be more or less disabling to gene function. As level of gene function is analogous to target modulation with a drug, insights from analysis of a series of genetic variants can be predictive of how doses of a hypothetical drug would impact the clinical phenotype of interest (light-blue curve). This approach works best in diseases with clear modes of action and high impact phenotypes, and may require more multifactorial assessment in diseases with multiple genetic and epigenetic mechanisms at play.

Several examples support this approach including sclerostin,[x] SCN9A,[xi] ANGPTL4,[xii],[xiii] and, most famously, PCSK9. Interest in PCSK9 as a biological target began with the discovery of rare gene variants that either increased LDL cholesterol and heart disease risk[xiv] or reduced both.[xv] Importantly, an individual who carried two completely disabled copies of the PCSK9 gene (equivalent to complete inhibition of the PCSK9 enzyme molecule by a drug) had no other related health issues indicating that the benefits of low LDL cholesterol levels did not incur other health problems. Thus, a "clean" inhibitor of PCSK9 could be both efficacious and safe, as was later demonstrated.

What does this mean for drug discovery? In the last few years, several large, retrospective analyses have examined whether, overall, biological targets with human genetic support have higher clinical success rates and decisively validated the hypothesis:

*"Overall, we estimate that drug mechanisms with [human] genetic support would **succeed twice as often** as those without it (from phase I to approval)." – Nelson et al., Nature Genetics*[xvi]

*"A post hoc assessment of phase 3 successes and failures (initiated 2000–2008) … **all targets** with clear [human] genetic evidence … produce the clinical effect predicted." – Kamb et al., Nature Biotech*[xvii]

"***73% of projects with … genetic linkage** of the target to the disease were active or successful in Phase II compared with **43% of projects without** such data." – Cook et al., Nature Reviews Drug Discovery*[xviii]

The emerging tools of human genetic analysis provide a robust framework for biological target validation and can have a meaningful impact on clinical success rates through the reduction of target-related efficacy risk. Biopharma companies that most effectively adopt these tools and draw on them to translate their discovery model and *in silico* prediction into the human validation early in development can have increased R&D productivity and a potential competitive advantage.

3. How much impact can human genetics have on R&D productivity?

To understand the implications of human genetics on R&D productivity, we modeled the impact of only pursuing targets with human genetic support and compared this to historical industry performance. Our base model builds on the work of DiMasi et al., (2016) from the Tufts Center for the Study of Drug Development[xix] and the work of Paul et al., (2010)[xx] as well as others. Similar to those, our output metric is the cost of R&D for a single approved drug from the start of drug development (after target validation) to regulatory approval.

We used industry attrition rates to estimate the historical number of programs required at each stage of development (discovery through submission) to deliver one approval. We then used benchmark costs for each stage of development to estimate the total cost at each stage and summed over all stages to obtain the cumulative cost of one new approved drug. Our estimate of $1,289 million (Exhibit 3b) for the out-of-pocket cost is close to that developed by DiMasi et al., $1,395 million (in 2013 dollars). To model the impact of human genetic support on clinical trial success, we used data from three studies,[v-vii] which together comprise several thousand clinical trials with differing levels of human genetic support. We averaged the effect on attrition seen in these studies at each development stage and used this to recalculate the number of programs required at each stage to deliver one new molecular entity (NME) approval (Exhibit 3).[4] We assumed costs per program at each stage did not change.

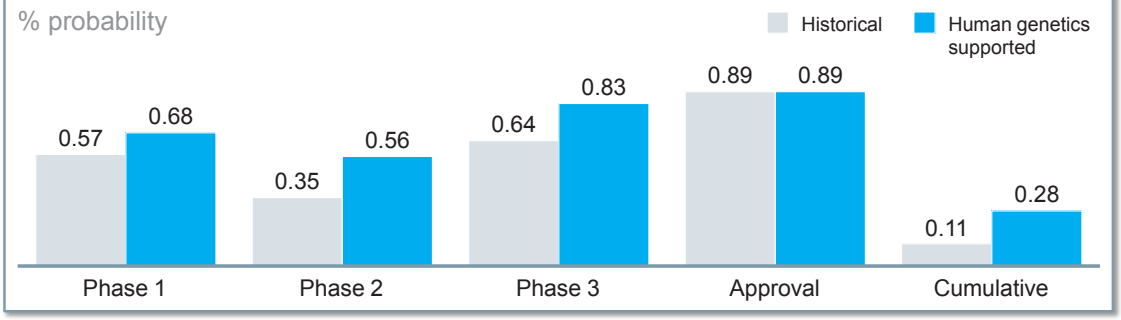
Exhibit 3 shows that human genetic support (estimated using DisGeNET score[xxiv] for the given gene-disease linkage) could raise the cumulative probability of success from phase 1 to regulatory approval from 11 percent to 28 percent and reduce the out-of-pocket

4 Even though the effect would be most visible for first-in-class assets, we would argue that industry's increasing competitive pace (leading to parallel development of multiple assets in the same class, and the time between first-in-class and subsequent launches shortening to under two years across competitive areas) and limited sharing of data—particularly on failure root causes—makes the observation applicable to a large, and growing, portion of the NME pipeline. It does not apply to reformulations or combinations of already established molecules nor biosimilars; hence we are not accounting for this part of R&D in our assumptions.

Exhibit 3

Impact of human genetics on biopharma R&D productivity

(a) Probability of NME advancement by stage of clinical development



(b) Estimated number of programs and costs by stage to secure one approved NME

#, $M	Discovery	Pre-clin.	Phase 1	Phase 2	Phase 3	Submit	Approval
Programs	38.7	13.5	8.8	5.0	1.8	1.1	1.0
Cost	387	68	176	251	351	56	**$1,289**
Programs	15.5	5.4	3.5	2.4	1.4	1.1	1.0
Cost	155	27	71	121	270	56	**$699**

(a) Historical rates of advancement for NMEs in their primary indication (grey; henceforth "projects") and estimated rates of advancement for projects where the link between the NME target and the primary indication is supported by human genetic evidence (blue). Advancement probabilities are based on phase transitions occurring between 2007 and 2016 for all novel products in development globally (excluding reformulated molecules and biosimilars) as tracked by Pharmaprojects. To estimate advancement rates for projects with human genetic support we first tabulated the relative increase in advancement rate for projects addressing target-indication pairs either with or without human genetic support based on multiple retrospective analyses. We then estimated the advancement rate for projects addressing target-indication pairs with human genetic support as the product of the rates for all historical projects and the relative increase observed for projects with human genetic support. We did not correct for the fact that some historical projects have human genetic support as this has been estimated at just 2–8 percent of projects (Nelson et al., 2015[xvi]).

(b) Estimated number of programs and costs by stage to secure one approved NME based on advancement probabilities in (a) and costs per stage

cost to develop a new drug by approximately 46 percent (from $1,289 million to $699 million). The fully capitalized cost would be similarly reduced, implying a striking reduction in the cost of new drug R&D and the financial barrier to biopharma innovation.

Our results are broadly consistent with a similar analysis conducted by Hurle et al., (2016)[xxi] but we nevertheless wished to exclude possible alternative explanations for the increased success of programs with human genetic support. Specifically, it is known that large molecules tend to have higher success rates than small molecules and that molecules brought to market as part of a licensing partnership perform better than non-partnered.[i] To rule out these

potential biases, we analyzed the progress of new drugs over the past ten years, having determined which programs were supported by human genetic evidence. We explicitly modeled these potentially confounding factors. When we compare the effect different product characteristics have on overall probability from phase 1 to launch, very strong gene-disease linkage (DisGeNET score >0.42) outclasses all other parameters resulting in a 49.3 percent overall success rate (based on phase transitions between 2006 and 2015 for non-reformulated, non-biosimilar products across all therapeutic areas except infectious diseases where human genetics is not as relevant). Such strong level of genetic evidence is not frequently found; hence the sample size and availability of molecular targets in that group are limited. However, assessing all products with moderate-to-high genetic evidence (DisGeNET score greater than 0.2) results in overall success rate of 23.4 percent, which is also significantly higher than the industry average of 9.8 percent.[5] In comparison, an analogous analysis for biologics results in an overall success rate of 15.8 percent, while products partnered through in-licensing achieved 15.7 percent. Our analyses confirmed a large contribution from human genetic support similar in magnitude to previous work to meaningfully improve R&D productivity.

Despite the opportunity, we see three challenges to capturing the full value outlined in Exhibit 3. First, as discussed below, the opportunity and benefit differ by therapeutic area. Second, we have not included the cost of implementing a human genetics capability, which is not trivial. Finally, and most importantly, the opportunity depends on the starting point and some companies may already have captured some of the benefits associated with human genetics.

There are also some plausible incremental sources of value from genetic insight that we have not considered in our calculations:

1. Cost impact of accelerated development. Multiple sources suggest that, due to increased confidence, the total time to market could be streamlined for well-supported targets. We estimate a 2-year reduction on a total timeline of 14 years (supported by existing sources[xxii]) could reduce capitalized costs by 10 percent or more. This reduction has already been achieved for already-known and validated targets, but could be extended onto emerging targets as well.

2. Revenue impact of accelerated development. Faster time to market has potential to extend active patent life and confer first-to-market benefits.

3. Patient stratification. Our calculations do not explicitly account for improved patient stratification or biomarker development which may yield further benefits—see a recent study pointing to probability of success improvement across all clinical development stages, most notably in phase 1 and 2.[xxv]

5 Industry value mentioned here is lower than 11 percent referenced earlier in this article, as this calculation excluded anti-infectives (where the contributions of seasonal vaccines and antivirals lead to higher than average likelihood of success).

Part II: Implementation and implications

4. Where can biopharma companies access advanced human genetics capabilities?

A human genetics capability consists of three key components:

1. Access to consented DNA samples ("samples") linked to accurate clinical data such as longitudinal electronic health records (EHR) in a well-controlled way

2. Genomics technology to “read” the DNA samples (for example, genome or exome sequencing and array technology) and convert it to digital format

3. Analytics capabilities (such as statistical genetics and bioinformatics) to analyze the genomic and clinical data to identify which genomic variants are relevant to a disease and derive additional insights

For maximum value, clinical records should be “deep” (as many years as possible), detailed, accurate with known genealogical relationships,[6] and ideally prospectively collected in well-defined trials. Consents ideally include the right to re-contact participants for follow-up research.

Access to samples is the first step in the process and in many ways the key challenge to building a human genetics capability. Due to the number of samples required (for example, 50,000–200,000 for a single study) accessing high-quality consented samples can be extremely onerous. Robust longitudinal EHR are not yet the norm and are often hard to compare/combine across institutions.

Analytics talent is also important—and scarce—but can generally be attracted if the other elements are in place. By contrast, genomic sequencing is largely commoditized though specific design choices and can affect costs to the point of impacting strategic goals.

Access to samples on the scale needed for advanced human genetic analysis can come from four main sources:

Independent health systems. Some US-based health systems have created databanks of patient samples linked to electronic health records. Most notable is Geisinger Health System, which was selected as a partner by Regeneron due to its high-quality EHR system (20 years of records and many multigeneration families). Following an initial $100 million investment in 2014, Regeneron has reportedly raised its interest and is now aiming to sequence and analyze 250,000 samples. Vanderbilt University Medical Center has also invested heavily in EHRs (approximately 2.5 million records) and has spun out Nashville Biosciences to allow biopharma partners to access the resource. As many health systems have incomplete EHRs, it remains to be seen how many will be robust enough for biopharma R&D.

National health systems. Some single-payer systems are also enabling access to biobanked samples and their "cradle to grave" health records through authorized parties. Examples include Swedish National Patient Summary (rolled out across the country’s hospitals, with 300,000 samples collected in its first year of operation, and expanded vastly since then); Danish National Patient Registry (with detailed patient history data available since 2000); deCODE Health (Iceland, 140,000 samples); the UK Biobank (500,000 samples);

6 Favorable genetic population structure is also highly desirable but is beyond the scope of this discussion.

and The Institute for Molecular Medicine Finland. As an example of a biopharma company placing bets in the area, deCODE's (whose samples are linked to highly curated electronic health records and genealogical information) was acquired by Amgen in 2012 for $415 million. The Institute for Molecular Medicine Finland has joined a partnership with AstraZeneca, while the UK Biobank initiative as well as several other national systems are accessible to researchers by request. There are a variety of questions related to whether national health systems can be nimble enough partners for biopharma companies, can address the data privacy concerns of their populations, and maintain public support.

Many companies are pursuing partnerships to access large datasets but the path for distinctive bioinformatic and statistical expertise is more varied

Research consortia. Academics and medical societies frequently maintain sample banks and partner with biopharma companies. In general, these are smaller scale and historically have not prioritized linked health records. Consortia are now emerging, however, which attempt to aggregate sample banks and provide a common data infrastructure. For instance, the Accelerating Medicines Partnership brings together ten biopharma companies with medical societies to study four diseases. They have a combined 100,000–150,000 type 2 diabetes samples. The US and Chinese Precision Medicine Initiatives may offer similar opportunities with each planning over one million samples. Consortia can be cost effective and an efficient way to achieve scale. We expect that the industry will be experimenting with pre-competitive formats for collaboration to reap scale benefits.

Genomics companies. To date, consumer genomics companies have created the largest human genetic resources available for biopharma R&D. 23andMe has collected over three million samples from consumers. Although these are not linked to EHRs, consumers provide medically relevant information through online surveys. 23andMe reports more than 200 ongoing research studies, including partnerships with Roche, Pfizer, and GlaxoSmithKline. Perhaps most telling, it has started internal drug development programs. AncestryDNA, which also plays in this space with a database of over four million samples, has teamed up with Google-backed biopharma Calico to study the genetics of human longevity.

Each of these options has been pursued by biopharma companies (Exhibit 4), and the optimal choice can be influenced by many factors (such as scale, therapeutic area focus). Many companies are pursuing partnerships to access large datasets but the path for distinctive bioinformatic and statistical expertise is more varied. Some represent significant commitments to own proprietary capabilities like Amgen through the deCODE deal. Others are prioritizing the advancement of computational methods. The Open Targets Validation Platform established by GSK and the European Bioinformatics Institute is a tool to inform biopharmaceutical decision making by visualizing the gene-disease associations identified by mining the wealth of published scientific evidence. Finally, some are moving toward extensive partnerships for both data and expertise as with GSK's recent 23andMe collaboration.

Exhibit 4

Examples of investments by major biopharma to access samples for human genetic analysis

	Biopharma	Partner	Date	Samples K	Disclosed Investment $M	Comments
Health systems	REGENERON science to medicine®	Geisinger	Jan, 2014	100 (initial) – 250 (revised)	100 (initial)	▪ Interest raised to 250K+ samples after initial investment of $100M for 100K samples
National health systems	AMGEN	deCODE genetics	Dec, 2012	140	415	
	AstraZeneca	FIMM	Apr, 2016	2,000 (planned)	"Hundreds of millions"	▪ Includes Human Longevity Inc., Sanger Institute & trial samples
Consortia	REGENERON science to medicine®, abbvie, AstraZeneca, Alnylam, Biogen, Pfizer		Jan, 2018	500 (planned)	50 (total biopharma funding)	▪ The entire project is expected to cost ~$100 million
Genomics companies	Pfizer	23andMe	Jan, 2015	800	n/a	▪ 23andMe database now exceeds 3M samples as of February 2018
	gsk	23andMe	Jul, 2018	5,000	300	
	Pfizer	FOUNDATION MEDICINE	Jan, 2018	> 120	n/a	▪ Foundation Medicine also offers proprietary data analytics platform for biomarker discovery and clinical trials
	Roche	FOUNDATION MEDICINE	Jun, 2018	> 120	2,400	

SOURCE: Press releases, as of November 2018

From a competitive perspective, this has important implications. As noted above, the number of independent US health systems with high-quality EHRs is potentially limited. Similarly, the number of national health systems with high-quality EHRs that are competent partners for biopharma may also be limited. We therefore foresee a scenario where biopharma slow movers are relegated to lower-quality human genetics resources, and access to the largest and most robust data repositories constitutes the competitive edge. Alternatively, we can imagine the emergence of a consortium that enables multiple biopharma companies to tap into the same sample banks and share costs—in such a world, the ability to successfully mine genomic data and quickly draw insights into their implications for human health becomes the key source of competitive advantage. In both cases, the winning capability can either be built in-house or secured through partnerships.

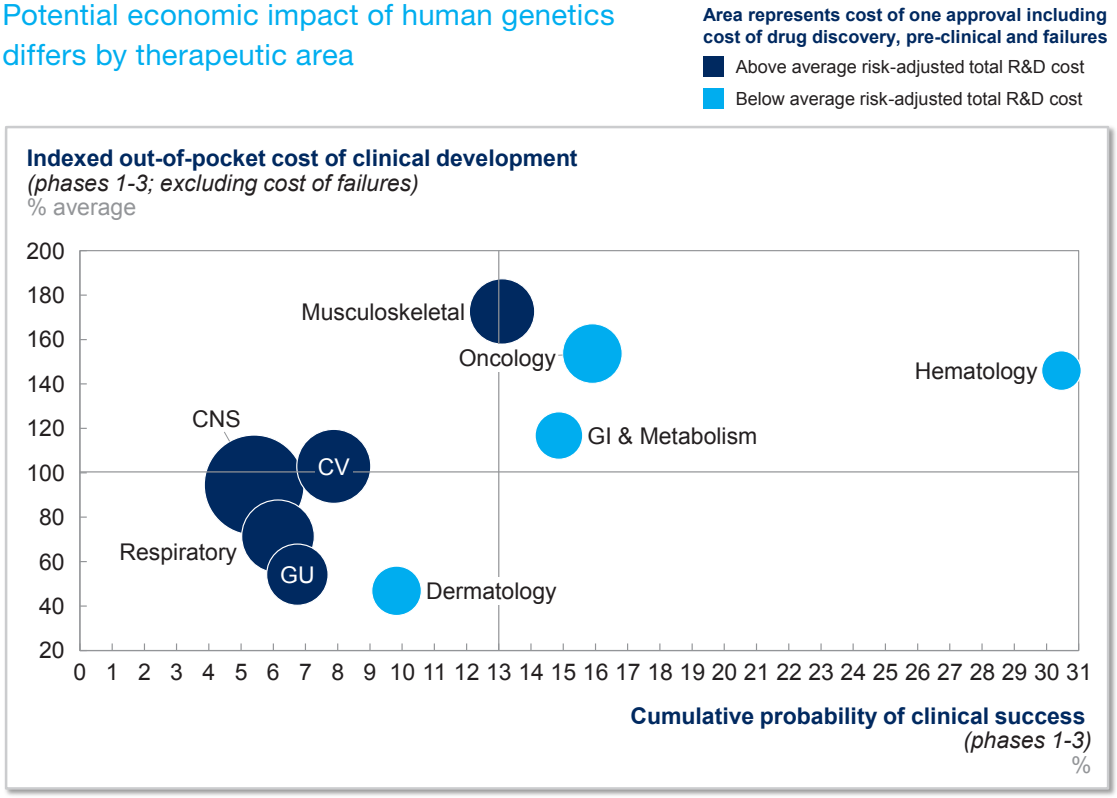
5. Who will benefit most from human genetics?

We anticipate three factors will correlate with human genetics impact beyond the "early adopter" advantage described in the previous section. Specifically, therapeutic area focus, scale, and alignment with broader innovation strategy will all drive significant variation in the impact of human genetics on successful drug discovery and development.

Therapeutic Area (TA) Focus. Not all TAs stand to benefit equally from advanced human genetics capabilities. TAs where target-related efficacy risk is highest and where the cost of these failures is greatest will benefit disproportionately from improved decision making. For instance, central nervous system (CNS) and cardiology (CV) are two TAs with both low clinical success rates and high clinical trial costs (Exhibit 5). Consistent with this, CNS is an

Exhibit 5

Potential economic impact of human genetics differs by therapeutic area



Relationship between cumulative probability of clinical success (x-axis; source: Pharmaprojects, based on methodology described by Smietana et al., [2016][1]) and relative clinical development cost assuming no failure (y-axis) for various therapeutic areas. Clinical cost calculated based on EvaluatePharma®, based on average trial cost per TA (based on product's ATC class) and number of pre-approval phase 1–3 trials per product. The area of circles represents the total cost of development (including drug discovery and pre-clinical but excluding target discovery and validation) *including* cost of failures. Larger areas may represent greater opportunities for human genetics-based target validation to mitigate costs. Anti-infectives are not included while oncology is shown for reference only as the human genetics considerations for these two therapeutic areas are different than in other areas.

area that many biopharma companies have deemphasized due to challenging ROI, while cardiology is a focus area for all companies that have invested substantially in human genetics capabilities to date (that is, Amgen, Regeneron, and AstraZeneca).

We also note that there are TAs that will benefit less from the type of human genetics strategies and capabilities described here. Diseases with simple Mendelian genetics can generally be addressed with small family-based studies and do not require large population genetics analyses. Most notably perhaps, we expect oncology will benefit to a much smaller extent from the approaches described, as cancer is driven predominantly by somatic mutations rather than inherited variation. This means that disease-agnostic genomic data collection efforts have lower chance to enable biological target identification and validation for oncologic disorders—albeit a targeted genomic investigation of cancer patients cannot be underestimated for oncology molecular target and biomarker studies. Similarly, infectious diseases may depend more on the genetics of the pathogen than

the hosts; hence the relevance of genomic investigation of human genome alone (without accounting for the microbiome) might not be sufficient.

Scale. Barring the emergence of a readily accessible shared resource, we believe that scale will also dramatically influence who benefits from human genetics. Because the investment needed to build a proprietary capability is in the order of hundreds of millions of dollars (see Exhibit 4), smaller players will be less able to participate directly or forced to focus on narrow therapeutic niches. To access leading capabilities, they will need either to partner with larger companies or access consortium resources. Larger biopharma companies could create an innovation advantage over smaller players.

...the value of human genetics depends on the overall innovation strategy

Innovation strategy. Finally, the value of human genetics depends on the overall innovation strategy. A company focused on exploiting a novel drug modality (such as CAR-T) may be successful pursuing established targets. For others, however, improved target validation may be a critical strategic element. As our modeling (Exhibit 3) shows, a head start of a few years on a target can translate into significant commercial value. With multiple drugs that could be used in combination, such an advantage may also enable advanced contracting strategies that would further secure market position against late arrivals.

In summary, we predict an industry dynamic where human genetics pioneers—predominantly large, diversified biopharma companies or specialized genomics players with a solid network of partnerships—could derive significant value from a combination of novel targets, improved external innovation sourcing decisions, speed to market and meaningfully improved clinical success rates. Fast followers who invest in inferior assets may be challenged to compete, while industry laggards may find few insights left to mine from their investments. Finally, due to the broad potential of human genetics, TAs that have historically been most challenging, such as CNS diseases, may experience the greatest relative benefit.

6. What can pharmaceutical R&D executives do to successfully lead genetics-enabled R&D organizations?

Given the significant industry impact of human genetics, biopharma companies must quickly develop appropriate human genetics strategies. We highlight three critical questions:

1. What is my innovation strategy? It is critical to crystallize your innovation strategy and understand how exposed you are to target-related efficacy risk. Excluding the cases already highlighted (for example, infectious-disease focus, only pursuing clinically validated targets), we believe companies that aim to compete in target discovery and validation activities will not be competitive long-term without the ability to validate targets with human genetics and increase their clinical success rates. Investors will not tolerate avoidable failures.

2. How can I access leading human genetics capabilities? Based on scale, innovation strategy, and therapeutic area focus, define the optimal approach to access human genetics capabilities. For some, this will involve significant investments, partnering with sources of samples (such as health systems) and building analytics capabilities. For others, partnering with consortia or larger biopharma will be appropriate. The right strategy is critical.

3. How do I ensure impact? Once human genetics capabilities are available, it is critical to ensure that they are deployed effectively and deliver the desired effect. Human genetic thinking must be embedded throughout the R&D organization and appropriate changes made to the discovery and development processes. It is not enough to make it core to the target selection decisions, it is also critical to consistently track effectiveness and reliability of genomics-informed methods, to be able to justify and maintain and refine the investment going forward. Significant changes to the development process will also be critical to capturing the full value. How do you redesign the time and investment in pre-clinical for targets that have human genetic validation? Are there ways to improve the trial design and decision making with better biologic understanding to reduce both time and cost? Systematically altering the end-to-end process has the potential to unlock substantial value.

Answering these three questions is the first step to winning in the era of human genetics-enabled R&D. Although the road has been long, we believe human genetics is now ready to deliver on the promise of the Human Genome Project. Enabling quicker and less costly discovery and development of effective medicines to improve the lives of patients is now an appropriate goal for many biopharma companies.

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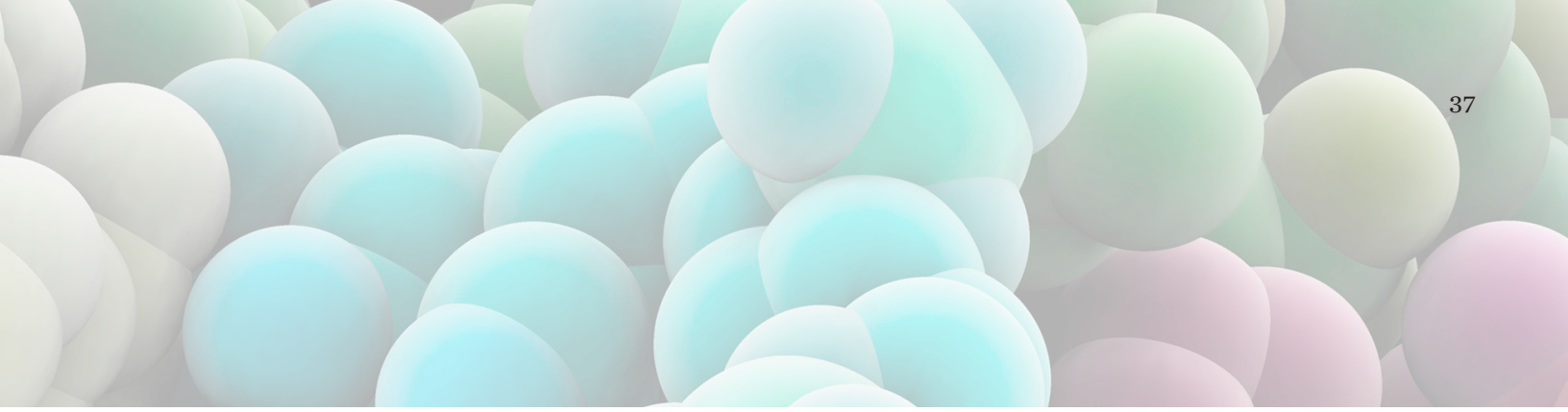


Beyond genomics: The next wave of innovation in precision medicine

Wen Wang, Simon Lee, Meredith Reichert, Kevin Webster, Laura Furstenthal

Genomic testing has proven to be a revolutionary tool in medicine, with applications including infectious disease diagnosis, cancer treatment selection, and non-invasive prenatal testing. Biomarkers and companion diagnostics are increasingly being included in FDA labeling of pharmaceuticals to guide therapy selection, a trend that is expected to accelerate, establishing genomic testing as a mainstay in the clinic.

However, while genetics is a powerful indicator of disease and reflects our individual variations, it does not necessarily inform the current biological state, which is the most predictive indicator of health. Consider that not all women with the BRCA1 mutation for breast cancer susceptibility will develop breast cancer. In addition, not all diseases are associated or caused by genetic abnormalities (for instance, diabetes, stroke, infectious diseases), limiting the adoption of genetics in precision medicine (PM). In fact, among the 3,000 drugs approved by the FDA, fewer than 10 percent of them are associated with a genomic biomarker, and approximately 40 percent of these genomic biomarkers target oncology.

Current functionality (and dysfunctionality) is better reflected in the transcriptome (RNA transcripts), proteome (proteins), and metabolome (small molecule metabolites). At their intersection is the influence of critical biological systems that research has indicated to be increasingly important, including the immune profile (the types and numbers of immune cells) and the microbiome (the types of microorganisms within an organism). The combination of these “omes”, in conjunction with genomics, form “multi-omics”, where multiple distinct analytes are used to develop a more complete picture of a patient. Beyond these, the use of non-molecular metrics such as heart rate, exercise level, and so on is also emerging in PM. In this paper, we focus on the current state of molecular measurements and potential implications for key stakeholders.

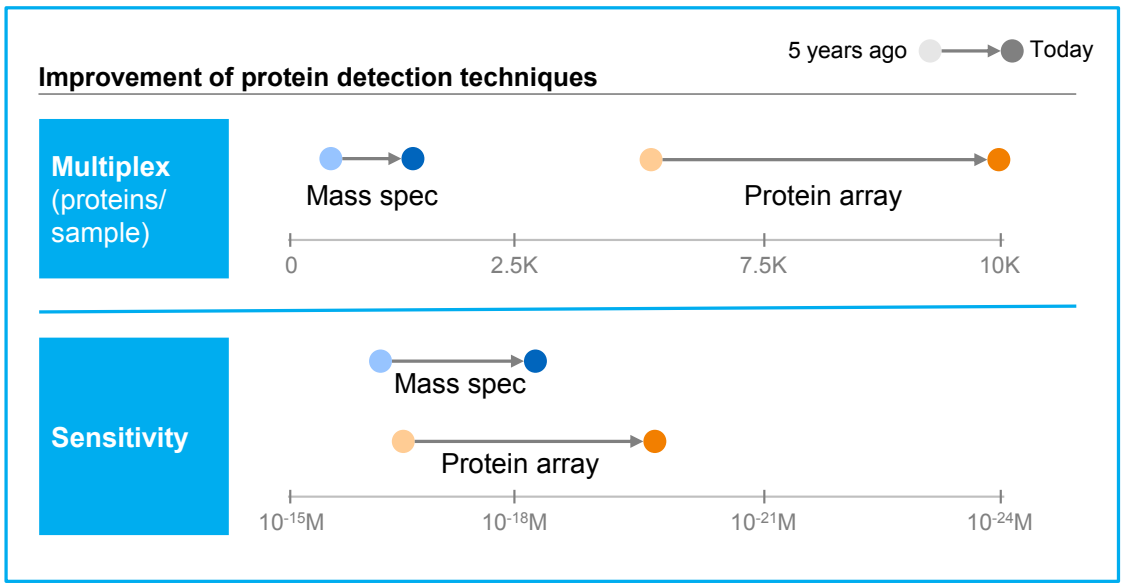
Current state of multi-omics in precision medicine

Transcriptome, proteome, and metabolome dictate true biological state, and change dynamically with time, disease, treatment, and a host of other factors. Therefore, the study of multi-omics is critical to understanding the longitudinal progression of disease and, in turn, how best to develop new therapies for treatment. The interconnectedness of these systems and biological products is nuanced and complex. Historically, they have not been a focus of personalized medicine due to the limited availability of tools and techniques. However, multiple efforts are currently underway, and we are now at a tipping point for widespread investigation beyond genomics in personalized medicine.

Innovations in omic technologies (epigenomics, metabolomics, proteomics and genomics) have now improved sensitivity and specificity, while lowering the cost to a reasonable level. These advances are unlocking the potential of omic tools to be adopted at scale, and proteomics is a case in point. As illustrated in Exhibit 1, protein array and mass spectrometry have both seen major improvements in multiplex capability and sensitivity over the past five years—the number of proteins that can be detected per sample has more than doubled, while detection sensitivity has seen almost a thousandfold improvement. Protein array technology is now approaching a tipping point to unlock scalable protein quantification in pharmaceutical research or clinical practices. In the past ten years, the cost of sequencing the human genome has dropped eight thousandfold from about $9 million per genome to around $1,000 per genome. With the advancement of technology innovation, we can reasonably estimate that the price of omic technologies will follow a similar trend to reach a price point that can drive wide adoption.

Exhibit 1

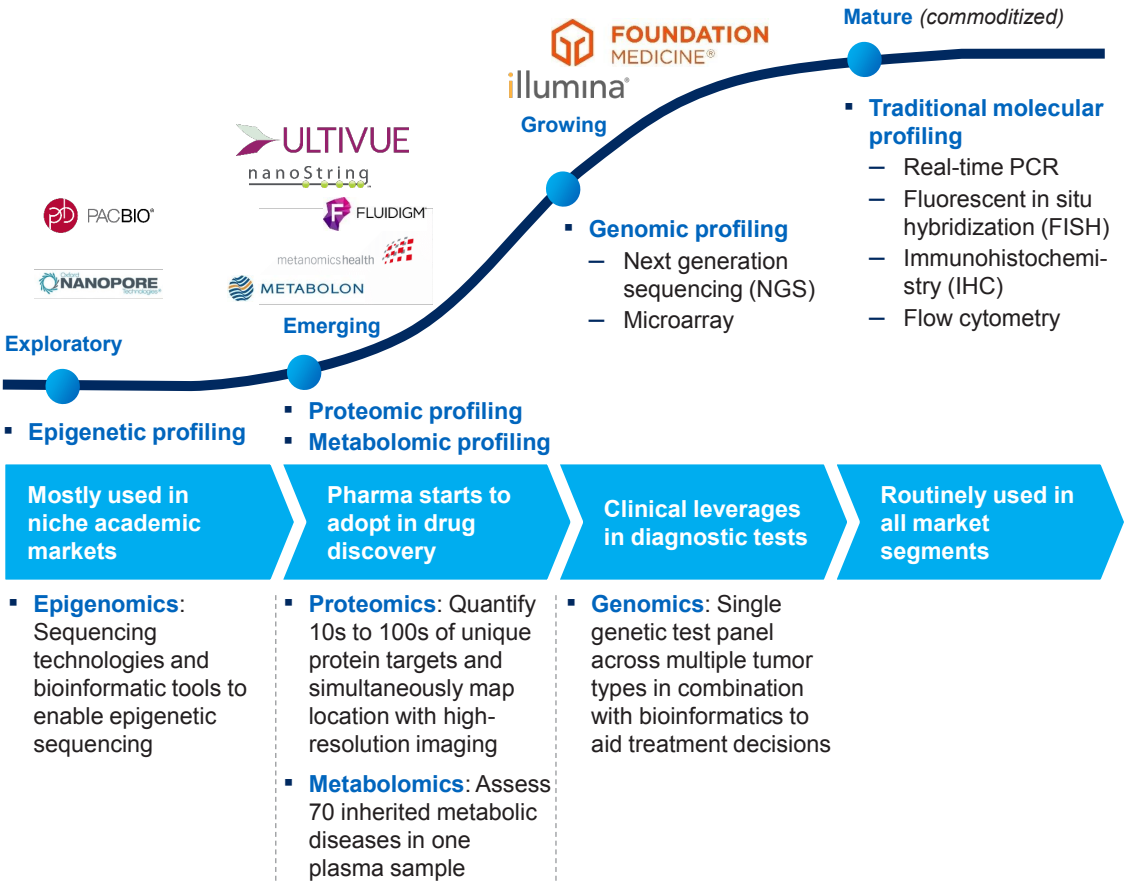
Protein detection techniques have improved significantly over the past five years



With these technological advances and better understanding of disease biology, we have now seen several beachheads emerge for multi-omics in PM. As shown in Exhibit 2, each segment of -omics has been progressing towards clinical applications.

Exhibit 2

Multiple –omics techniques are progressing toward clinical application



Epigenomics is perhaps the most naïve, but sequencing companies PacBio and Oxford Nanopore have developed the technologies and bioinformatic tools for researchers and clinicians to perform epigenetic sequencing on a routine basis. Metabolomics and proteomics have demonstrated key proof of concept examples in the clinic. Advanced mass spectrometry techniques have enabled metabolomics to be used to screen newborns for metabolic diseases from dried blood-spot specimens. Metabolon has developed a technique to test for 70 inherited metabolic diseases from a small plasma sample, and also provides a service for researchers and clinicians interested in performing metabolomics with a comprehensive set of bioinformatic tools to enable analysis and understanding. In a novel combination of techniques, multiple companies (Nanostring, Fluidigm, and Ultivue) have developed methods to quantify tens to hundreds of proteins and simultaneously map the location with high-resolution imaging (spatial profiling). This may have far-reaching implications for better understanding fundamental disease biology, as well as clinical applications to better characterize diseased tissue. While genomic testing has often focused on oncology, Somalogic has used proteomic assays combined with bioinformatic tools to develop a nine protein proteomic panel to stratify patients with cardiovascular disease (CVD) for risk of secondary events (ie. myocardial infarction, congestive heart failure, stroke and death). This assay has already been touted for use to increase the efficiency of large and expensive CVD clinical trials by identifying high-risk CVD patients who are more likely to respond. Prometheus has taken a similar approach

to develop a multi-omic diagnostic tool which combines serologic, genetic and inflammatory protein markers to differentiate between irritable bowel disease, Crohn's disease and ulcerative colitis.

As these clinical beachheads continue to show relevance in more areas and gain adoption, there are key lessons we can takeaway from genomics, as well as new challenges that each stakeholder must face. For example, new developments to make genomic testing more approachable and usable have successfully reduced complexity and boosted clinical adoption. Foundation Medicine has developed a single genetic test panel that simultaneously tests for common genetic alterations across multiple tumor types; it has also combined the genetic test with tools to distill the information for physicians to make treatment decisions. However, while the need for advanced analytics in genomics has been clear, it will be a bigger hurdle to tackle the multiple datasets involved in multi-omics. Indeed, a variety of machine learning methods have been applied to analyze large metabolite data to predict metabolic pathway dynamics over time. These advances will enable better disease understanding and prediction using multi-omics data. Here we discuss specific implications for key stakeholders in multi-omics: pharmaceutical companies, life science companies, and health systems (Exhibit 3).

Implications for pharmaceutical companies

As multi-omics becomes increasingly important in the understanding and treatment of disease, there will be profound changes in drug development, from target identification to biomarker development to clinical testing. Many of these implications are important for genomics, but going beyond to multi-omics will require specific nuances fitted to each avenue. We see three moves that pharmaceutical players can perform to prepare themselves for the future:

- **Biobanking of patient samples.** From a research perspective, understanding how the dynamics of each -ome is involved in or associated with disease progression will be critical in biomarker discovery and patient stratification. The foundation for such research is access to patient biological specimens at different timepoints of disease progression. Many pharmaceutical companies are already collaborating with independent biobanks. Pioneering players are also developing their own patient database for genomics, like the Regeneron-led consortium created earlier this year to sequence 500,000 UK patient samples. A no-regret move for all pharma players is to biobank patient samples from clinical trials and establish relationships with independent biobanks. It will also be important to consider the sample handling requirements and increase diversity of samples that new technologies will require. Longitudinal analysis will also multiply the total volume of samples. With new analytical techniques being developed, pharmaceutical companies will need to carefully choose and hedge what to biobank for future analysis.

- **Develop multi-omics abilities through selective partnerships.** Generating the data in a reliable manner will require new tools and techniques to be developed for each molecular profiling technique. While these methods likely already exist in academia, pharmaceutical companies will need to adapt them to enable studying multi-omics in a high throughput manner, at a larger scale, and often with greater reliability. Thus, to become a market

leader requires pharmaceutical players to co-develop such technologies with academia and life science instrument companies. In doing so, pharmaceutical companies will be making informed bets on which technologies will become successful and need to consider their development strategy to incorporate this view.

- **Build data and analytics capabilities.** In parallel with deciding which specific tools and assays to adopt, pharmaceutical companies will need to enhance data and analytic capabilities to store and assess new swaths of data. This will be especially important because each assay increases the total number of analytes and possible connections, rapidly increasing the complexity. The greater complexity will require new analytical tools and methods to efficiently study and filter through this ocean to determine the critical transcripts, proteins, and so on that represent actionable targets for tracking disease progression, treatment progress, and toxicity. Big-data analytics and artificial intelligence tools may be employed here to identify new potential targets or analytes of interest in the context of specific disease states. These analytes (for example, an elevated amount of protein X while possessing a certain genetic marker) could then be used to study the longitudinal impact of drugs on a patient, inform the development of biomarkers, drugs, and improvement of patient stratification.

...pharmaceutical companies will be making informed bets on which technologies will become successful

Implications for diagnostic/life sciences companies

Life science companies are already tackling multi-omics with new products and technologies. In addition to developing cutting edge tools, we see two important considerations for success:

- **Growing importance of data handling and analytical tools.** Unlike genomics, study of multi-omics often requires several disparate data dimensions to be analyzed. For example, longitudinal data is required to analyze the dynamics of metabolites and spatial information is used to indicate functionality of proteins. In addition, multi-omics data often requires quantification to reveal the associated biological activities. Conducting quantitative analysis on such complex data requires sophisticated analytical capability, which most pharmaceutical players and hospitals may not be ready for. Thus, life sciences companies can gain an edge by developing robust analytical tools to promote the adoption of instruments and link different data sets for an end-to-end bioinformatics solution.

- **Increasing importance of clinically oriented solutions.** The complexity of multi-omics data analysis and interpretation also brings opportunities to develop new business models for life sciences and diagnostics players. Software with advanced algorithms for multi-omics data analysis will be attractive for basic researchers and pharma R&D teams, particularly for those who lack the scale or ability to develop algorithms in-house. With increasing

margin and reimbursement pressure, hospitals will likely rely on diagnostics companies for patient sample analysis. Such a trend is already observed in genetic testing where hospitals outsource the molecular assay to companies like FoundationOne for patient sample analysis. Due to the data complexity, physicians will rely on these diagnostic companies or clinical support tools to interpret patient data and assist in treatment selection.

Implications for health systems

Healthcare systems will also be heavily impacted by the use of multi-omic analysis and the significant increase in total data per patient. While it is unclear if these tests will be performed on site or by third-party labs, there are clear needs that will come into play either way:

- **Requirement for data infrastructure.** Unlike a one-time genetic profile, the need to track changes in transcripts, protein, immune system, or metabolites over time will result in continual accumulation of data that will need to be stored, managed, and secured. New IT infrastructure and standards will need to be developed to perform this task and ensure proper integration with electronic health record systems.

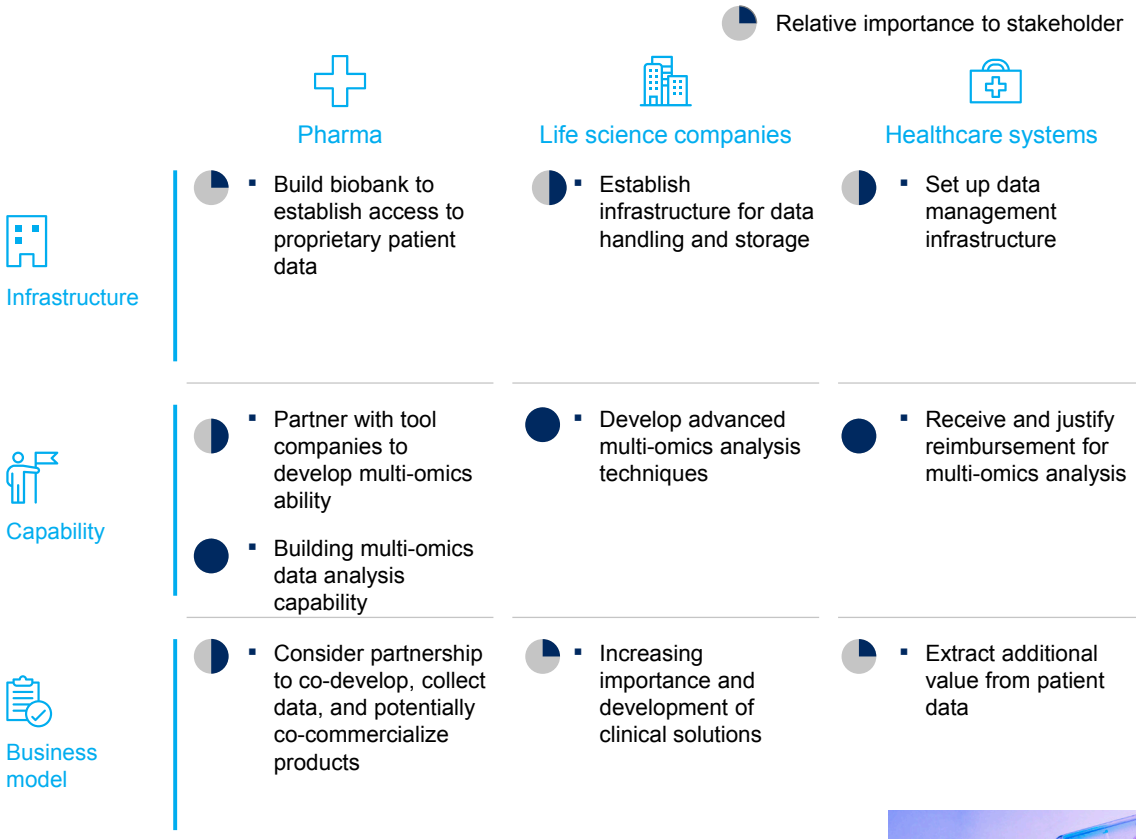
- **Payment and reimbursement complexity.** Similar to the adoption of genomics in healthcare, new products and companies will develop to provide options for performing the various multi-omic testing services that will be required. Large central labs and/or medical centers will likely only begin performing this form of testing once a critical number of tests are required by their patients *and* reimbursement is clear and robust. A clear value proposition must also be articulated to the payers and providers; such as improved patient outcomes, reduced side effects, or more efficient treatment. Until reimbursement is clearly established, the benefits of multi-omics may only be realized for a small subset of patients.

Unlike a one-time genetic profile, the need to track changes in transcripts, protein, immune system, or metabolites over time will result in continual accumulation of data

- **Value of data.** One key benefit that longitudinal multi-omic monitoring may provide is real-world evidence (RWE). Healthcare providers may be able to compare patient data against large databases containing historical data of other patients to inform treatment decisions. This is now employed in genomics (for instance, Syapse in oncology), which allows hospital networks to contribute their genomic data to an aggregated database. This database forms the basis of an analysis tool that enables healthcare providers to identify similar patients by genomic profile and disease, and which is used to determine optimal treatments. A similar database with multi-omic data may become a powerful tool that allows healthcare providers to quickly identify tailored treatments, providing truly personalized medicine.

Exhibit 3

The growth of multi-omics will have implications across the pharmaceutical industry, life science companies, and healthcare systems, particularly surrounding capability building



Conclusions

Going into the era of multi-omics in PM, stakeholders will face a number of open questions. How soon will multi-omics be widely adopted? Who in the ecosystem will capture value? Although we still need further proof of concept that these other biomolecules are critical to a breadth of diseases, with the advances in technology and research, multi-omics has the potential to revolutionize healthcare in a similar fashion to genomics. We believe recent advances place multi-omics at a tipping point, with adoption rapidly increasing in the next five years. The rise of other omic technologies will follow the trajectory of genomics to a certain extent, but much like the increasing complexity given rise by the multi-omics, rather than a few companies focusing on oncology, multi-omics will be driven by many more companies across a spectrum of therapeutic areas. Stakeholders will need to make strategic decisions in order to best face a set of unique challenges and opportunities as we enter this new era of PM. Having the foundational elements in place will allow players to establish a competitive advantage and capitalize on this next wave of innovation.

Data driven decisions in cancer care: How using analytics on EMRs and biomarkers will improve patient outcomes

David Ku, Jonathan Usuka, Arnaub Chatterjee, Ziv Yaar, Björn Albrecht

EMR- and biomarker-based diagnostics are no longer novel in oncology, but ubiquitous. As this data environment is advancing, however, several factors hinder greater use of automation and analytics-driven decisions. This paper examines these limitations and suggests solutions. Addressing these challenges will unlock a new era in cancer patient outcomes, focusing the impact of the rapidly expanding arsenal of therapies available to an oncologist on mutation-based combinations derived from expanded diagnostics.

The development of oncology treatments has grown rapidly over the last two decades. The number of active compounds in clinical development quadrupled between 1998 and 2018, and nearly doubled in the last decade alone, with more than 1,600 compounds reported today in phase I-III clinical trends data.[1]

At the same time, an unprecedented amount of data is being generated, stored, analysed, and consumed in healthcare. This data is coming from a variety of sources, including patients, providers, pharma companies, and payers. More than 13 million electronic medical records (EMRs) exist for cancer patients in the United States alone.[2]

In addition, the global market for next generation sequencing is expected to grow by 21% annually from 2017 to 2022. In particular, the cancer biomarker market is projected to reach about USD20 billion in 2022 from about USD11 billion in 2017, driven by lower

1 PharmaProjects 2017; McKinsey analysis
2 National Cancer Institute, US 2017

sequencing costs, increasing diagnostic applications of biomarkers in oncology, and a paradigm shift to one-test-one-patient.

In this environment, data use in oncology is exploding across all dimensions. Half of all drug submissions for Health Technology Assessments (HTAs) now use Real World Evidence (RWE)[3], payer spend on data and analytics has grown 20% annually in recent years, and several new oncology data aggregators have emerged with backing from major venture capitalists and partnered with large pharma companies. In one example, large healthcare technology companies have developed cloud-based platforms in oncology informatics to assist with treatment decisions and promote guideline adherence. Also, select in-vivo diagnostics companies have established partnerships with top biopharmaceutical companies to develop decision-support systems, including a dashboard for oncology care teams with combined in-vivo and in-vitro diagnostics to align on treatment decisions.

In addition, rising technologies like liquid biopsy allow minimally invasive, repeated testing along the treatment cycle that complement tissue biopsy. Ultimately, these technologies may allow for screening and early detection for high-risk patients with established biomarkers. Recent approvals of biomarker-based, indication-agnostic treatment and liquid biopsy companion diagnostics in oncology – for example, the US Food and Drug Administration (FDA) has approved the Epidermal Growth Factor Receptor (EGFR) detection test – are milestones of precision medicine. Further, detection of measurable residual disease (MRD) enables greater sensitivity to assess response to treatment, detects relapse, and can accelerate decisions.

Finally, there is a large ongoing effort to aggregate data and generate insights by creating bigger and more comprehensive and longitudinal data sets of oncology patients. Several oncology analytics partnerships are already demonstrating how individual efforts around genomic data or clinical data can combine to generate valuable insights. Also, large provider systems and academic institutions have been developing aggregated data positions with patient consent.

Amid all of this activity in oncology – from clinical development to data aggregation – a dizzying array of treatment options and pathways is emerging. Compounded by the rising costs of these technologies, a compelling opportunity arises for systems and machines that are robust and sophisticated and can help medical professionals untangle the growing complexities of oncology care.

Emerging challenges in cancer care

The increasing complexity of immuno-oncology (IO), greater stratification of cancers, and a proliferation of biomarkers will make it impossible for physicians to keep pace, making optimal clinical decisions more and more difficult. IO is an experiment of unprecedented diversity, scale, and complexity. For example, the number of companies sponsoring trials for PD-(L)1 or CTLA-4 grew 70% a year between 2011 and 2018 and the monthly diversity of major tumour indications remains high, with about 43% of major tumour types having new cohorts launched each month.[4]

Two factors are pushing the increased complexity of patient-specific biomarker information: the switch to multigene panels and the gradual lessening of reimbursement

3 Based on a sample of submissions to European HTAs, not oncology-specific
4 McKinsey MIOSS; McKinsey curated clinicaltrials.gov database as of 11/30/2017

challenges. While companion diagnostics that guide therapeutic decisions directly remain the most frequent use of biomarker generation, new emphasis is being placed on multigene panels rather than single biomarker characterisations, with 83% of oncologists using multigene panels. Payer coverage of companion diagnostics is expected to expand and drive biomarker growth, as well, yielding greater opportunities for quantifying patient response in a multiple-mutation context. Indeed, already companion diagnostics are relatively common, despite a difficult reimbursement environment: only 38% of managed care organisations (MCOs) cover FDA-approved companion diagnostics.

Taken together, these factors will provoke a data avalanche for physicians. But even as the complexity of biomarkers becomes overwhelming for physicians, oncologists are still actively seeking novel treatment opportunities. For instance, in a recent survey, 50% of oncologists said they would pursue beyond the label usage of a therapeutic that matched the patient's biomarker results, for instance EGFR mutation.

Although 97 percent of oncology practices use EMRs, only 10% of practices had EMR interoperability with hospitals in 2018

Data illiquidity adds to the difficulties in making optimal decisions. Although 97 percent of oncology practices use EMRs[5], only 10% of practices had EMR interoperability with hospitals in 2018, down from about a third in 2016. The gap creates challenges for implementing learning algorithms for the best care. Additionally, oncologists are increasingly open to automated analytics, with about a third using physician-decision support (PDS) tools. Still the report showed oncologists remained isolated from the clinical flow of information, with fewer than one in four oncologists that use PDS tools reporting access to a PDS system integrated with their EMRs.

Without EMR integration, oncologists face challenges that limit further adoption of PDS tools. Integration allows PDS tools to detect novel clinical signals and improve predictions using machine learning, a benefit greatly desired by oncologists. Integration also enables PDS applications to help oncologists visualise expected outcomes. In isolation, analytics can only deliver static results that are limited primarily to data from clinical trials with long periods needed to incorporate RWE. And finally, integration can help resolve data quality issues that plague PDS tools. Without it, patient data must often be entered repeatedly, adding to the burdens on the practice and increasing the chances for data-entry and clinical errors and the risks of liability.

Practices also face a shift in patient channels, with younger oncologists opting for online patient portals and older ones relying on email. As portal use becomes more common, these online channels will become a rich source of patient response data, complementing EMRs. Portals are particularly well-suited for data analysis and learning algorithms at scale.

5 2018 Genentech Oncology Trend Report. 10th ed. South San Francisco, CA: Genentech; 2018

This growing wealth of information provides new opportunities to create evidence-based treatment options. For example, panels that produce additional data over genotyping assays would be useful for exploratory understanding of disease mechanisms. Integration with EMR and communication portals would define machine learning approaches to predict patient response. And patient-provider communications would enrich the biological and clinical data needed to understand real-time patient outcomes.

Of course, automated decision-support analytics tools bring challenges as well as opportunities. PDS tools cannot be interpreted as recommending a therapeutic course that has not received FDA support. On the other hand, clearly linking available therapeutic options and biomarker results expands the options for life-saving therapeutic usage as clinical science and regulatory submissions catch up.

Teaching machines to learn from oncologists

Data-driven decisions can improve the outcomes for oncology patients, and to deliver these benefits quickly the broad oncology community should work together. Four measures in particular could prove very powerful.

Use biomarker data appropriately and transparently

Biomarkers have been at the forefront of oncology research and development and are expected to become requisites for the field. Combining biomarker data with clinical information in EMRs would identify complex genetic signatures linked to patient responses. Ultimately, larger sample sizes will produce phase IV-quality data and enable algorithms to be trained in a patient-care setting, with results that can be submitted to regulatory agencies and payers.

Rigorous, yet practical methods and practices are needed to define and standardise the collection, analysis, and reporting of real-world biomarker data. Today, many RWE analytics are strictly retrospective and observational, both of which are problematic. Further, any recommended decisions must be susceptible to robust analytics to confirm that data methods eliminated biases, controlled for quality, and allowed for the appropriate incorporation of disparate data sources. In addition, patient data collection, storage, and use must comply with increasingly stringent data privacy laws, such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union.

Integrate oncology decision support with the EMR

A range of capabilities will be needed to build a broader analytics platform that integrates oncology decision support with EMRs, crucially real-time data ingestion. Clinical data must be scrutinised through Health Level Seven International (HL7)-compliant interfaces and EMR-specific applications. Integration would reduce or eliminate redundant data entry and provide up-to-date information and knowledge for decisions.

At present, several burgeoning Fast Healthcare Interoperability Resources (FHIR)-enabled tools link to EMRs. Researchers at the University of Washington[6] and Vanderbilt University[7], among others, are designing applications to visualise genomic information in

6 Phillips M, Halasz L. Radiation Oncology Needs to Adopt a Comprehensive Standard for Data Transfer: The Case for HL7 FHIR. Int J Radiat Oncol Biol Phys. 2017;99(5):1073-1075

7 Warner JL, Rioth MJ, Mandl KD, et al. SMART precision cancer medicine: a FHIR-based app to provide genomic information at the point of care. J Am Med Inform Assoc. 2016;23(4):701-10

real-time, using the FHIR standard to interface with data in EMRs. Early tools can already compare a patient's genome against a distribution of thousands of other patients with links to external databases.

Oncologists will also demand that insights are displayed intuitively through effective visualisation in the EMR. The ability to visualise a patient's expected clinical outcome for a certain therapy based on clinical trial RWE data is of great interest, with 74% and 73%, respectively, of oncologists rating the two features as very important.[5] Not only will this enable clearer interpretation of results, it also minimises disruption to workflow, avoiding "click fatigue" as oncologists deal with a wealth of information on their screens.

Extract meaningful data from patient-provider communications

Portals can be powerful data tools when linked to physician-decision support algorithms. Yet similar to EMR data, data from portals would require interface between communications and the PDS. Additionally, well-designed natural language processing (NLP) tools would be needed to extract meaningful data from conversations. Once successful, a range of rich data would be available, including changes in regimen, medication adherence, patient engagement, adverse effects, and qualitative therapeutic benefit.

Link data-driven systems to post-approval monitoring and payer reimbursement

Decision-support systems tied to the EMR should not only support medical decisions, but also track the efficacy and safety of mass-produced therapeutics in the real world. New product introductions are increasingly complicated, featuring everything from more diverse usage patterns for patients and providers through drug-device combinations to advanced coating materials. Over the past two years, multiple studies have questioned the long-term impact of therapeutics on real-world quality-of-life and survival outcomes. Drugs passed by the FDA and European Medicines Agency were shown to have little follow-up once approved. These studies had clear limitations but highlighted the need for continued monitoring of approved medicines.

In addition, MCOs can link reimbursement processes to metrics tracked by a data-driven system in oncology. This would allow MCOs to manage costs amid a proliferation of treatment options for many indications with no clear leader. For instance, about 60% of projected haematology-oncology growth will come from classes with a high or medium degree of interchangeability.[8] Decision-support solutions could also be linked to quality improvement programmes, documenting response to therapeutics – including patient compliance, appropriate drug utilisation, and support for the Healthcare Effectiveness Data and Information Set (HEDIS) of the US National Committee for Quality Assurance (NCQA) – with enhanced sensitivity and accuracy.

Embracing these measures will unlock a new era in patient outcomes, enabling oncologists to effectively analyse and deploy the rising abundance of therapeutics, technology, and data in breakthrough cancer treatment.

8 Evaluate 2017

The precision medicine revolution, from oncology to large polygenic diseases

Emily Capra, Maha Prabhakaran, Erika Stanzl, Laura Furstenthal

Over the past 20 years, there has been an evolution in oncology towards precision medicine—but with little impact in other therapeutic areas. However, the growing ubiquity of information combined with advanced analytics to drive insight from that data, plus the creation of new tools to address these insights, has set the stage for personalized healthcare to be delivered across all therapeutic areas.

Introduction

The delivery of medicine can be thought of as the flow of information from data (for instance, symptoms or the genetic sequence) to insights (for example, diagnosis, clinical guidelines) and then on to actions such as therapeutic choice. Precision medicine (PM) represents the tailoring of this information flow with a view to individualized selection of treatments based on understanding of the patient and his or her condition. Personalization can occur at any of the three steps—data, insights, or action—but the ultimate PM revolution will only be obtained by marrying all three to achieve truly personalized care.

The PM revolution began in oncology, where genomic understanding of disease progression—for example, identification of cancer-causing genes—enabled development of targeted therapies based on observed mutations. These scientific advances have enabled greater understanding of the disease (data) and the targeted actions to take using this information (action). Generally, most of the advances and personalization of medicine in the field of oncology have resulted from increased understanding of the disease, improving the breadth of the input data in this paradigm. Thus, in the oncology space, we have witnessed an evolution in patient care and a slow march towards micro-segmentation of patient populations through better understanding of tumor genomics as a way to tailor treatments based on more and more biomarkers. We predict a continued emphasis on such input data, as sequencing costs continue to shrink, leading to a new scientific understanding that redefines cancer from a pathology-diagnosed disease (for

example, non-squamous cell lung cancer) to one defined by genomic mutations (such as ALK, EGFR, or KRAS mutated cancer).[1]

In rare diseases, increasing use of genomics and whole-genome sequencing has enabled the pinpointing of causal mutations. That said, the real innovation that will revolutionize treatment of such diseases comes not from improved input data, but rather from better and more targeted actions. Historically, although the genomic underpinnings of rare disease have often been well understood, technological limitations have restricted therapy to symptomatic treatment or enzyme replacement (for instance, Gaucher disease, Fabry disease, Pompe disease). More recently, advances in gene and cell therapy have opened the window to new treatment opportunities, which means that the rare disease space is poised for an acceleration in treatment and therapies.

...using PM to transform the standard of care in these polygenetic diseases, the way that it has for cancer, requires a holistic view of the patient beyond the genome—it requires a paradigm shift in the delivery of care.

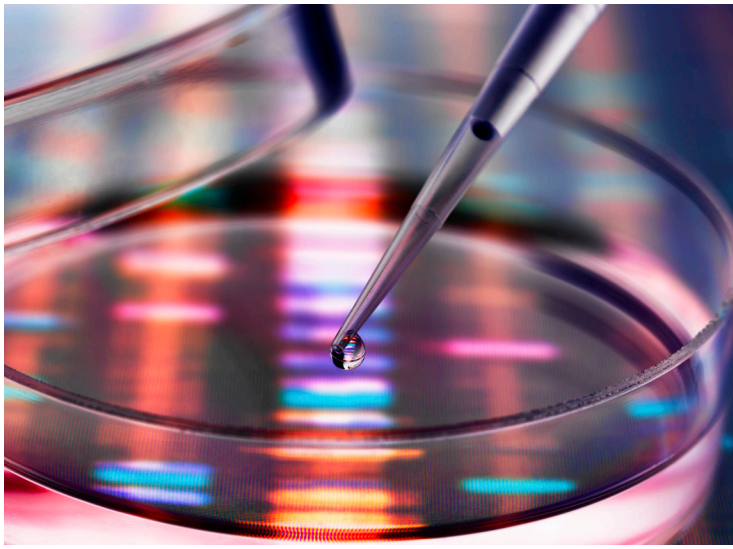
In contrast, PM in the context of large, polygenic diseases such as rheumatoid arthritis, asthma, and multiple sclerosis lags well behind. Unlike cancer and rare diseases, where the genomic underpinnings of disease are increasingly well understood, these conditions are only partially heritable; even for the genomically determined risk factors, the contribution of any given allele is relatively low. Thus, using PM to transform the standard of care in these polygenetic diseases, the way that it has for cancer, requires a holistic view of the patient beyond the genome—it requires a paradigm shift in the delivery of care. Changing the treatment paradigm to include lifestyle data, and to leverage digital platforms and advanced analytics to create personalized predictive models (for example, using data on speed of reading, accuracy of typing, and gait of the patient's walk to predict relapse or measure drug efficacy) will likely revolutionize treatment delivery and enable the delivery of precision care in large heterogeneous diseases. Widespread use of PM in these diseases will require a change in the healthcare ecosystem, with increased reliance on patient-collected data, use of new diagnostics (including digital biomarkers), and an increased focus on prevention and reduced cost of total care. Each of these factors requires a transformation in how patients, providers, and payers interact to deliver healthcare.

1 ALK: anaplastic lymphoma kinase; EGRF: epidermal growth factor receptor; KRAS: Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

The evolution of precision medicine in oncology is poised to accelerate

Oncology has been the basis for the introduction and advancement of PM. The first oncogene, or cancer-causing gene, SRC,[2] was discovered nearly 50 years ago in 1970. This was the start of significant research into the genetic underpinnings of cancer, with the discovery of p53, RAS,[3] and many others in subsequent decades. Translating this activity into a more personalized understanding of a patient's specific cancer began early as well—as early as 1996, patients could be tested for BRCA mutations. Yet, despite these early advances and a nearly 50-year history of building an understanding of the genomics behind cancer, it is still largely diagnosed through traditional means, including tumor biopsy followed by histological determination of origin. Moreover, the majority of patients still receive non-targeted, traditional chemotherapies.

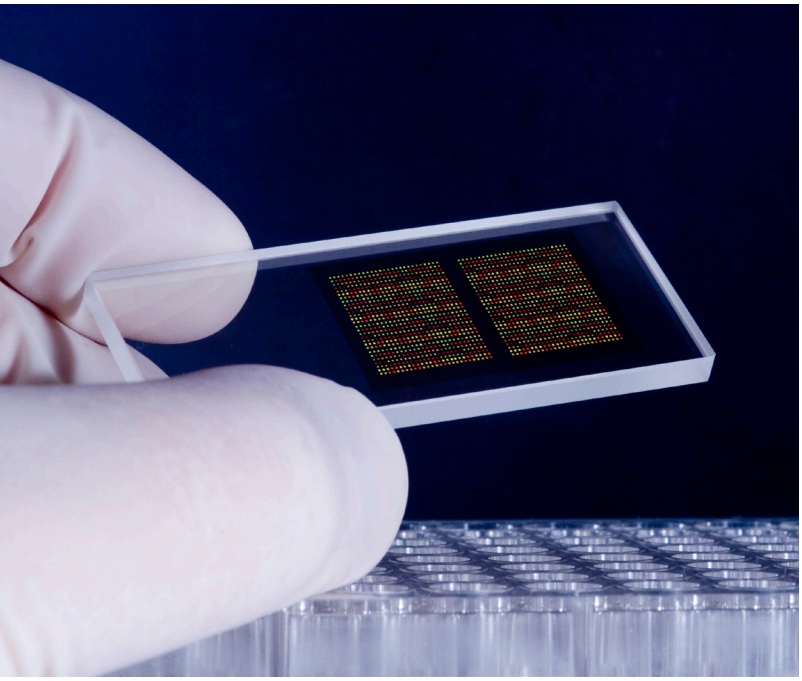
However, in just a few short years, this has begun to change rapidly. Over the past ten years, the cost of sequencing has fallen from some $10 million per genome to approximately $1,000 per genome today. This has led to a rapidly increasing wealth of sequencing data and the ability to apply next-generation sequencing for screening, with the potential to revolutionize how we think about cancer. Simultaneously, the past five years has seen an acceleration of FDA approvals for targeted therapies, with more than half of all targeted therapies approved over this period (27 out of 48 were approved between 2013 and 2017), including truly innovative cell therapies including CAR-T therapies approved in recent years. Meanwhile, diagnosis is now moving towards thinking of cancers as genomically defined diseases in contrast to the traditional pathology-defined approach. Take the example of Keytruda. In May 2017, the FDA granted accelerated approval for Keytruda to treat patients whose cancers have a specific molecular signature: Microsatellite Instability High (MSI-H) and mismatch repair deficient (dMMR). This is the first time that the agency has approved a cancer treatment based on the genomic signature rather than the tissue type where the tumor originated. Falling sequencing costs have also enabled novel diagnostic and monitoring techniques, including multigene panels, whole genome sequencing, and liquid biopsy. This has led to identification of common mechanisms of resistance and development of new treatments to target them. Several companies are exploring using liquid biopsy diagnostics to monitor healthy populations for cancer, which would permanently shift the cancer treatment paradigm. Collectively, these transformations have poised oncology to shift up from a slower evolution in PM, to a more accelerated revolution in targeted and personalized patient treatment.



2 SRC: Proto-oncogene tyrosine-protein kinase Src
3 P53: tumor protein 53

Precision medicine is on the cusp of a breakthrough in rare diseases

Like oncology, PM efforts in the rare disease space have been assisted by a clear genetic underpinning for many of the diseases. Thus, in the context of our "data to insight to action" model, data and insight have become progressively clearer through the increased level of sequencing and our understanding of Mendelian diseases. However, unlike oncology, development of targeted treatments for rare diseases has lagged behind, leading to deep understanding but few actions that can be taken based on the insights.



This has largely been due to difficulty in targeting the underlying cause of the disease in a systemic way. Until recently, most treatments for rare diseases involved enzyme replacement for metabolic diseases or factor replacement for hemophilia rather than interventions targeted to specific mutations. Among rare diseases, cystic fibrosis (CF) is one of the most striking personalized medicine success stories—Orkambi, Symdeko, and Kalydeco target specific CFTR4 mutations and collectively cover approximately 50 percent of CF patients. Kalydeco, is a particularly interesting example that started with targeting only the G551D mutation in CFTR gene, affecting some 4 percent of CF patients, but has since expanded to targeting over 40 mutations. This expansion was driven by the FDA's openness to non-standard evidence in the case of rare diseases; approval for expansion to 33 mutations was based on in vitro cell line results rather than clinical trials.

With the promise of gene therapy, RNAi,[5] and other DNA-based therapies finally coming into the clinic after years of setbacks, rare disease treatments are on the verge of transformation. Due to the high unmet need and clear genomic targets for many rare diseases, numerous companies have focused their initial "proof of concept" efforts in this space. Over the past two years, the first drugs based on antisense oligonucleotides (ASOs) (Spinraza and Exondys 51) the first true gene therapy (Luxturna), and the first RNAi-based treatment (Patisiran) have received FDA approval CRISPR[6]-based drugs are starting clinical trials in both the US and Europe, In the future, these treatments have the potential to be designed specifically for an individual-based on their personal genome sequence, but will require changes to regulatory pathways for approval.

4 CFTR: cystic fibrosis transmembrane conductance regulator
5 RNA interference.
6 CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

The coming revolution of precision medicine across all therapeutic areas

In contrast to oncology and rare disease, common diseases such as diabetes, cardiovascular disease, Alzheimer's disease, autism, and others have an array of genomic, lifestyle, and other factors that influence disease risk and progression. This lack of genomic predictability has slowed the development of differentiated genetically targeted therapies, and reduced the justification for reimbursement of genomic tests for these patients.

However, this is changing. Recent availability of hundreds of thousands, if not millions, of linked genomes through initiatives such as UK Biobank, along with advances in advanced analytics, have allowed researchers to create polygenic scores for patients in cardiovascular disease that are more predictive than traditional risk factors in risk prediction.[7] The initiatives collecting data on large numbers of patients are accelerating: the Million Vets program, All of Us, iCarbonX, and others are all expected to yield broad and deep data on hundreds of thousands of patients over the next few years. However, it remains an open question as to how quickly biopharma will be able to incorporate this information into discovery and development of novel therapies, and whether payers will reimburse for the new tools and tests.

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Biopharma is currently investing heavily in this space, with collaborations with 23andMe, Geisinger, UK Biobank, and investment into deCODE already showing promise at identifying new targets and segmenting patient populations. Once targets are identified, biopharma companies can draw on advances in nucleotide-based therapies that are currently being developed in oncology and the rare disease space to engineer therapies based on the targets. For example, Amgen mined its deCODE database to identify a variant of the ASGR1[8] gene that reduces risk of heart attacks by 34 percent,[9]

7 Joshua W. Knowles, Euan A. Ashley, "Cardiovascular disease: The rise of the genetic risk score," *PLoS Med* 15(3): e1002546, March 30, 2018, https://doi.org/10.1371/journal.pmed.1002546; Antonio Regalado, "Forecasts of genetic fate just got a lot more accurate," *MIT Technology Review*, February 21, 2018, https://www.technologyreview.com/s/610251/forecasts-of-genetic-fate-just-got-a-lot-more-accurate/.

8 ASGR1: Asialoglycoprotein Receptor 1

9 Paul Nioi et al, "Variant ASGR1 Associated with a Reduced Risk of Coronary Artery Disease," *New England Journal of Medicine*, June 2, 2016, https://www.nejm.org/doi/full/10.1056/NEJMoa1508419.

and is currently developing treatments based on the target. Likewise, Regeneron has partnered with Geisinger to create a large, linked database of genomes and medical records, identified a new target—the HSD17B13 gene—for NASH,[10] and promptly signed an agreement with Alnylam to develop an RNAi therapeutic based on the target. In increasingly competitive disease areas, biopharma will push to use genomic and other data to develop differentiated therapies, though given development timelines it will likely be another five to ten years before these drugs reach the marketplace.

In addition to collecting genomic data, as described above, there are efforts to augment genomic and electronic health record (EHR) data with lifestyle, diet, and fitness data to differentiate or sub-segment patient groups beyond the genome. This is being driven by growth in the digital health space and the prevalence of smartphones and wearables. For example, uMotif is a patient-centric comprehensive data-capture platform that has multiple partnerships to capture data across cancer, Parkinson's, and other disease states. Beyond the collection of general health and wellness data, several companies are looking to create disease-specific, but passive means to collect information on a patient's disease progression in the form of a digital biomarker. These biomarkers potentially provide mechanisms for non-invasive diagnostics, real-time measurement of symptoms, new methods of patient engagement, and the ability to identify disease in at-risk populations prior to the appearance of symptoms. For example, in multiple sclerosis, Roche released positive interim data from the FLOODLIGHT clinical study that remote patient monitoring via a smartphone app matched clinical assessment closely and could spot impairment earlier. Although digital biomarkers are currently in the developmental stage, there is interest in gaining regulatory approval for their use. Cognoa is at the forefront of this effort, with its diagnostic app for autism in children submitted for FDA approval this year.

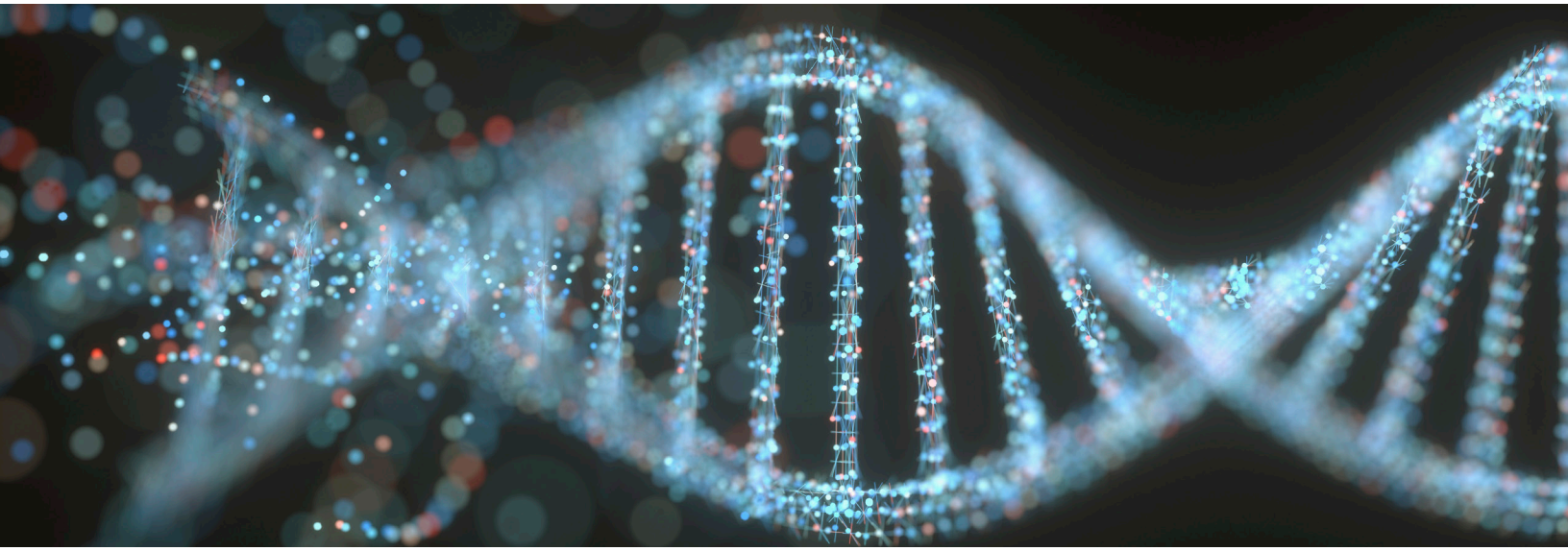
Biopharma companies are beginning to think about how to apply advanced analytics to create predictive models that include genotypic, phenotypic, lifestyle, and movement data in order to subsegment patient populations, personalize therapeutic delivery and recommendations, and create tailored and personalized therapy solutions. The ability to do this at scale has the potential to revolutionize the healthcare industry and impact all factors of drug design, production, and delivery.

While technical advances are enabling the delivery of precision care across therapeutics, the revolution

10 NASH: non-alcoholic steatohepatitis, the most severe form of non-alcoholic fatty liver disease (NAFLD).

towards precision care in these diseases requires not just individualized therapies and better understanding of disease. It needs physicians to be empowered with the right tools, and a shift in patient and physician mindset to embrace PM, and a payer willingness to reimburse large genomic panels, differentiated tests, or digital additions to monitor patients. Given this, the revolution in precision care is likely to begin in two places: (1) outside of the reimbursement context through direct-to-consumer digital health tools that empower patients to direct their health care, and (2) integrated delivery networks or single-payer countries, where the incentives are currently more closely aligned to prevent disease and manage long-term outcomes. Currently, generation of patient data and large-scale genomic testing has largely taken place outside of the reimbursed setting, using either government or private funds. However, that may be slowly changing as doctors have begun calling for the use of these polygenic risk scores in clinical practice,[11] and Geisinger has initiated a pilot to provide whole exome sequencing as standard of care.

The confluence of new data science capabilities and platforms, rapidly declining sequencing cost, and example breakthroughs like the ones described above are drawing the best minds and disruptive innovation organizations into healthcare. With rapidly increasing investment (including a near tripling of venture funding for digital health companies from $1.2 billion in 2014 to $3.5 billion by the end of 2017), we are likely to see significant acceleration and advancements in the field of PM across all therapeutic areas.



11 Antonio Regalado, “Forecasts of genetic fate just got a lot more accurate,” *MIT Technology Review*, February 21, 2018, https://www.technologyreview.com/s/610251/forecasts-of-genetic-fate-just-got-a-lot-more-accurate/.

Mobile medical apps that integrate, personalize, and predict: Unlocking potential in the healthcare value chain

Alice Zheng, George Ye, Meredith Reichert, Aliza Apple

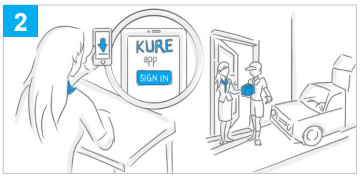
Digital applications are shaping the state of healthcare at an increasingly rapid pace. We see adoption of digital technologies across the healthcare continuum. Patients in the US are highly engaged in digitizing their healthcare needs—79 percent use online health information such as Google and WebMD, 24 percent use wearable devices, and 19 percent use telemedicine.[1] Globally, there is a surge in funding for digital health start-ups from both traditional venture capital firms and technology players, reaching over $4.9 billion in the first half of 2018.[2] The first digital pill, Abilify MyCite—a pill with a sensor that digitally tracks whether patients have ingested their medication—was recently approved and has begun a limited rollout.[3]

The largest near-term growth in digital is in the form of mobile medical applications (MMAs), which are patient-facing software programs that run on smartphones or other mobile communication devices.[4] These are a subset of mHealth (mobile health) apps, coined nearly a decade ago to also include fitness and general wellness apps, which today encompasses over 325,000 apps.[5] In our stylized example illustrated in Exhibit 1, we can see how a MMA can transform a patient's journey by delivering a highly personalized care experience to support and

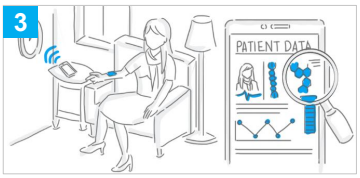
1 Mega Zweig, Jen Shen, and Lou Jug, "Healthcare consumers in a digital transition," Rock Health, 2017, https://rockhealth.com/reports/healthcare-consumers-in-a-digital-transition/.
2 *1H AND Q2 2018 Digital health (healthcare it) funding and M&A report*, Mercom Capital Group, 2018 https://mercomcapital.com/product/q2-2018-healthcare-it-digital-health-funding-and-ma-report/.
3 "FDA approves pill with sensor that digitally tracks if patients have ingested their medication," FDA News Release, November 13, 2017, *https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584933.htm.*
4 FDA Mobile Medical Applications FAQ, 2018, https://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm#a.
5 As per Research 2 Guidance 2017, releases on different platforms are counted separately. https://research2guidance.com/325000-mobile-health-apps-available-in-2017/.

In the future, MMAs will provide a highly personalized experience along the entire patient journey

- Patient Jane is diagnosed with disease X (e.g., Type 2 diabetes, lung cancer). The doctor recommends an app, ***Kure***, to manage the disease.



- Jane installs Kure on her smartphone and places an order for a biosensor kit, which arrives a few days later in the mail.



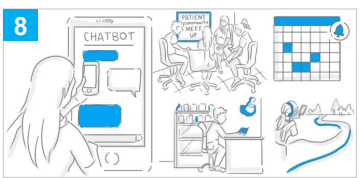
- Janes applies the biosensor to her skin, which allows Kure to track her vitals (e.g., heart rate, physical activities) and relevant medical information (e.g., blood glucose level, cell count).

- After a few weeks of data logging, Jane and her doctor set automated alerts within Kure to detect anomalies in real time. Kure has also recommended a personalized care plan including exercise and nutrition targets based on the real-world evidence of patients similar to Jane.

- By accomplishing targets in her personalized plan, Jane wins points and competes with other patients within Kure's patient community.

- Kure has a digital journal where Jane can log any changes in how she's feeling, including specific disease symptoms. With its AI-based analytics engine, the app can predict unfavorable outcomes and provide early warning and corrective measures to her care providers.

- Prior to any doctor appointments, Kure automatically generates a report for Jane and her doctor, summarizing her health condition over the past few months, including highlights from her digital journal.



- Kure's interactive AI chatbot offers helpful guidance and connects her to the drug maker's helpline. It sends out alerts for prescription renewal and automatically coordinates with the pharmacy regarding logistics. It suggests activities of potential interest, such as a forthcoming patient community meet-up or a jogging route to help her reach her targets.

manage treatment from end to end. Healthcare players, including pharma, providers and health-tech companies, are investing significantly in apps, and numerous MMAs available today are already capable of delivering components of this patient journey. MySugr, WellDoc, OneDrop, and Virta are all applications that support a diabetic patient's journey, providing monitoring, diet, and exercise suggestions. Indeed, there is no shortage of apps, with over 100,000 medical apps available to date. Rather, the issue is one of usage – approximately 70 percent of MMAs achieved less than 1,000 downloads over the past 4 years.[6] Among mHealth apps at large, a mere 7 percent have garnered over 50,000 monthly active users.[7]

How have MMAs evolved and what has been their impact on precision medicine (PM)? We surveyed the current MMA landscape[8] and interviewed digital health leaders across industry from top pharma, start-ups, hospitals, and think tanks to understand the landscape. We found three areas of major activity across the healthcare value chain: patient tracking and monitoring, digital therapy, and patient care delivery/coordination. However, the degree of sophistication of these applications varies, from simple integration to more tailored personalization, and some heading towards predictive recommendations. Here we define the different levels of personalization in MMAs today, discuss differences across the three major uses cases, and recommend key success factors for these digital apps to gain significant adoption.

The MMA landscape is increasingly sophisticated

We see fundamental differences in the degree of personalization and analytical sophistication, and data coverage across MMAs (Exhibit 2). MMAs with **integrative** features tap into existing patient data from sources such as EMR, genomics, and real-world evidence (RWE) to make suggestions to patients. **Personalized** MMAs are more sophisticated, augmenting patient data with newly generated data from tracking sensors, wearables, and patient-reported data to further personalize a recommendation based on continuously collected data. At the highest level of sophistication, **predictive** MMAs seek to incorporate and analyze all patient data on the platform and predict the individual's needs or trajectory. As such, they combine the best of population big data analytics and the personalized touch of PM. Currently, most MMAs are integrative or personalized at most, but as patient adoption increases and some of these apps reach a critical user base, more game-changing predictive MMAs may emerge.

6 Priori database 2018, Medical apps only, excludes general fitness and wellness apps. Releases on iOS and Android are counted separately. Total downloads summed from September 2014 to December 2018.
7 Among 4,200 app publishers surveyed in 2017 by Research2Guidance: *mHealth Economics – how mhealth app publishers are monetizing their apps*, March 2018, https://research2guidance.com/product/mhealth-economics-how-mhealth-app-publishers-are-monetizing-their-apps/.
8 Analysis via a proprietary, advanced analytics capability called SILA (Startup and Investment Landscape Analytics). Excludes non-sophisticated MMA such as drug companion apps developed by pharmaceutical companies that purely serve as medication reminders.

Exhibit 2

MMAs exhibit different levels of sophistication

	Integrative	Personalized	Predictive
Description	MMA integrates and consolidates existing patient data from multiple sources and makes recommendations	MMA tracks individual patient physiological metrics in real time and updates care guidance based on them	MMA analyzes all data from the patient population and predicts the individual's needs or trajectory
Data	Integrates from patient EHR/EMR, genomics, real-world evidence data	Collects patient physiological metrics in real time to environmental and medication	Compiles de-identified tracked real-world data from all patients
Analytics	Analyzes and screens for the most effective therapeutic options or related lifestyle changes	Evaluates changes in metrics and predicts prognosis and counter measures	Leverages artificial intelligence to understand potential explanatory relationship

Three MMA use cases across the healthcare value chain

To date we have seen investment into MMA across three main areas: patient tracking and monitoring, care coordination, and digital therapies. However, we expect others to evolve and become a critical part of PM in the future.

1. Patient tracking and monitoring. An average doctor's appointment lasts 13-16 minutes,[9] which provides physicians with a very limited view of patients' behavior and health status. Patient tracking and monitoring MMAs help to fill this void by giving physicians insight into patients' day-to-day lives outside the clinic, enabling them to fine-tune their care plan based on this data while empowering patients to own their own health data (Exhibit 3).

Most tracking and monitoring MMAs are integrative at the moment. However, the leading MMAs differentiate themselves from the pack by advancing into personalized capabilities. For example, OneDrop is an FDA-approved, diabetes-focused MMA that tracks patients' blood glucose levels in real time. Patients are more informed about the impact of various type of activities, food, and medication on their blood glucose level, which can create positive feedback and beneficial behavior changes. Meanwhile, doctors can also track all of their patients' glucose, food, medication, activity, weight, and HgA1C history.[10] This holistic view of their patients helps them use trends to develop a personalized treatment plan. This level of personalized care would not be possible without the data provided by such patient-tracking and monitoring MMAs.

9 Carol Peckham, *Physician compensation report 2016*, Medscape, April 1, 2016.

10 Hemoglobin A1c provides a view of average level of blood sugar over the past two to three months to assess blood sugar control.

Exhibit 3

Patient tracking/monitoring focus areas

Focus areas	Example MMA	Description
Physiology	snap 4D	▪ Wearable linked to a mobile application to continuously monitor for **vital signs** that are associated with patient deterioration
	pebble	▪ Smartwatch-based wearables connected to a mobile app that track **fitness** data
	proteus DIGITAL HEALTH	▪ Ingestible sensor and body patch for **health-tracking**, with an emphasis on the body's **physiologic** response to medications
Diabetes	ONE DROP	▪ Measures all diabetes-related data in one mobile app, including **blood glucose** data from a portable device
	sano	▪ Low-cost silicon biosensor for **glucose sensing** that is connected to a mobile app
	mySugr	▪ Mobile and web-based **diabetes** platform that is connected to a blood glucose meter to monitor glucose levels
Neuro/onco/ asthma	MyndYou	▪ Passive collection of multiple **cognitive** function markers including voice, driving, and **movement** for patients with **Alzheimer's** or other types of dementia
	SPARO	▪ Monitors **lung** function through a device connected to a mobile app to track the health conditions of asthma patients
	TUEOHEALTH	▪ Contactless sensor to monitor asthma for children, with the goal of improving **asthma control**
Cardiovascular	AliveCor	▪ Mobile **electrocardiogram** technology to improve stroke prevention through early **atrial fibrillation** detection
	COALA	▪ Small wireless **heart** monitor to measure electrocardiograms and heart sounds that are transmitted to a mobile device
	QARDIO	▪ Wearable connected to a mobile app that measures **blood pressure** and heart rate

Going forward, patient tracking and monitoring is poised to continue to grow rapidly, given the rising importance of personalized patient care, collection of real-world evidence, and the growing penetration of available mobile technologies as enablers. As tracking technology and biosensors become more advanced, less invasive, and more sensitive, the next generation of tracking and monitoring MMAs will be able to track additional relevant health and medical metrics in real time (for instance via wireless sensors).

2. Care coordination. Patient care coordination and delivery MMAs use technological solutions to enhance patient management, data management, and care delivery (see Exhibit 4). Broadly speaking, most of these MMAs are integrative, as they focus on process optimization, patient engagement, and data integration—and are less advanced in tracking patients and providing recommendations personalized to the needs of individual patients.

Exhibit 4

Patient care delivery/coordination focus areas

Focus areas	Example MMA	Description
Physiology	Eccrine Systems, Inc.	Disposable electronic patch to measure electrolyte and **stress** levels
	RDS	Wearable health-tracking device that can record, measure, and transmit data on **vital signs**
	BASIS	**Health-tracking** devices designed to improve **fitness** and **sleep**
Cardiovascular	ReThink MEDICAL	**Heartbeat** monitoring device to prevent heart attacks and other fatal heart-related conditions
	vectorious	**Cardiac** monitoring system utilizing miniature sensory implant technology to provide cardiac function measurements for heart-failure patients
	tricog	Real-time monitoring of **electrocardiography** results to monitor and detect **heart attacks**
Elderly	BLUE WILLOW Systems	Wearable and non-wearable sensor devices to offer end-to-end **senior** resident **safety** services
	UnaliWear™	Multipurpose electronic watches designed to enable senior citizens to access predictive and preemptive **support**
	CarePredict	Wearable device to increase the **quality of life** of seniors via monitoring changes in the day-to-day activities of seniors
Neuro/hemo/ ophthal/asthma	APDM	**Movement** monitoring technologies utilizing wearable sensors to monitor for **Parkinson's** disease
	injectsense	Injectable wireless pressure sensor to monitor for **glaucoma** diseases
	Atlas5D®	Smart sensor to measure **brain** and **neuromuscular** functions through tracking everyday behaviors
Diabetes	podimetrics	Remote temperature monitoring mat in order to help specifically **diabetics** who are dealing with foot ulcers

Despite the limited focus on personalization *per se*, these MMAs play a critical role in enabling PM for the broader healthcare ecosystem. In the case of electronic health records (EHR), the lack of integration of genomic and psychosocial data severely limits the potential of current EHR systems for PM applications.[11] MMAs such as Conversa Health fill this gap by providing a longitudinal patient profile derived from EHRs, biometric devices, and patient self-reported data. Apple's Health Kit offers a promising platform to manage and merge health data from multiple sources on iPhone and Apple Watch from different apps. Additionally, the health record feature is gaining traction. To date, over 75 healthcare institutions support health records on iPhone, including large, prestigious institutions such as Partners HealthCare and Kaiser Permanente. This allows aggregation of electronic records from multiple institutions with patient-generated data in health apps.[12]

11 Paul Cerrato and John Halamka, *Realizing the promise of Precision Medicine*. Cambridge: Elsevier. 2018, print.

12 Apple website accessed November 2018. https://support.apple.com/en-us/HT208647; Jeremy Horwitz, "Apple says iOS Health Records has over 75 backers, uses open standards," Xsolla, August 2018, https://venturebeat.com/2018/08/08/apple-says-ios-health-records-has-over-75-backers-uses-open-standards/

While some limitations remain (such as data representation challenges), this enhanced EHR enables novel analytics on a more integrated dataset of individual patients and allows for more precise diagnostics and treatment plan. The clinical benefit of this is evident: a study at Partners HealthCare in Boston implemented an enhanced EHR approach to identify patients with atrial fibrillation who were at greater risk of stroke and major bleeding, delivering results comparable to a gold standard (manual chart reviews by physicians).[13]

Going forward, innovation in MMA's focus on patient care delivery and coordination will likely be slow, primarily resulting from challenges involved in bringing stakeholders across the healthcare continuum under a single unified platform. Nonetheless, the improved patient engagement, increase in physician touchpoint, and enhanced EHR offered by MMAs will be significant enablers for more precise medicine, even if the MMAs themselves are not the main delivery channel. To bring these to a predictive level of personalization, strong analytics capabilities (artificial intelligence, machine learning) and proven algorithms will be required to be able to predict prognosis and suggest treatments.

3. Digital therapies. Digital therapy MMAs are a key vehicle in delivering personalized medicine to patients (Exhibit 5). Most of the digital therapy MMAs today are personalized, involving direct interaction and data collection with individual patients and, in turn, using that data to adapt and recommend behavioral or care plan changes. The leading apps in this space typically use AI and machine learning to analyze patient input and develop evidence-based, tailored care plan recommendations. Note, however, that these are currently limited to the mental health space with recommendations including games, exercises, and helpful resources to spur patients to make lifestyle changes and ultimately improve outcomes.

Going forward, MMAs will likely penetrate the chronic and psychological disease areas further, either as augmentation or complete replacement of medications

For example, Akili Interactive Labs develops immersive action video games with direct therapeutic activity to treat cognitive conditions, including attention deficit hyperactivity disorder (ADHD) and Alzheimer's. Its adaptive algorithm personalizes the treatment to individual patient in real time and, between treatment sessions, automatically adjusts the difficulty level. The personalized digital therapy pays off—its lead candidate for ADHD,

13 Wang et al., use of electronic health records to identify complex patients with atrial fibrillation for targeted intervention. *Journal of the American Medical Informatics Association* July 3, 2016.

Exhibit 5

Digital therapies focus areas

Focus areas	Example MMA	Description
CNS-focused	PEAR THERAPEUTICS DREEM BY RYTHM	▪ Developer of app-based digital therapies including **substance abuse** and **mental/behavioral** health conditions ▪ Use **AI and headband** to track sleep quality and provide advice to enhance **sleep** quality
Chronic disease prevention and treatment	omada virta	▪ Provides an integrated app and platform for promoting behavior change and healthy habits in patients with **chronic diseases** ▪ Mobile app-based platform integrates physician communication, health, and nutrition guidance, and support for improved **diabetes management**
Mental health (stress, anxiety)	pacifica Ginger.io*	▪ App-based treatments for **anxiety** and **stress** using cognitive behavioral therapy ▪ Provider of **behavioral health** analytics application designed to help people feel stronger, **happier** and fulfilled
Physical therapy and fitness	Welltok moov™	▪ Targets, engages, and guides population health behavior at the individual level with a focus on **physical activities** ▪ A **fitness wearable** that offers connection in real time to motivational coaching
Mental fitness	SenseLabs SENAPTEC	▪ Device (headset) that connects to a **smartphone** and assesses **brain performance**, develops exercise recommendations, and creates a benchmark for **improvement** ▪ Manufacturer of a smart, sensory wearable device to assess, analyze, and improve users' **vision** and **sensor-motor skills**
Platform-based digital therapy	CLICK THERAPEUTICS™ eMindful	▪ **Digital therapy platform** that offers solutions for **many diseases** including smoking cessation, depression, insomnia, and chronic pain ▪ **Evidence-based digital therapy platform** that offers trainings and courses across **multiple areas** (e.g., stress reduction, diabetes, heart, cancer)
Eye	davalor VIVID vision	▪ Uses a **device** that measures vision autonomously and automatically to explore, diagnose, and **treat** functional **visual health problems**

AKL-T01 was shown to significantly improve the Attention Performance Index (API)[14] and the predefined primary endpoint of a 20-site multicenter, randomized control trial in 348 children and adolescents with ADHD and objective attention deficits.[15]

X2AI takes a different approach in developing personalized treatment for patients with mental health conditions such as depressions and anxiety. The HIPAA-compliant app draws on AI technology and clinical psychologist expertise to develop a mental health chatbot called Tess that delivers on-demand, psychological support via automated conversations with patients. Tess customizes conversations and delivers coping strategies, which adapt to the emotions and concerns the patient expresses through the chat. In a randomized controlled trial, Tess users showed significant reduced symptoms of depression (13 percent) and anxiety (18 percent).[16]

14 The Attention Performance Index is a composite, objective measurement of attention.
15 Akili press release: "Akili achieves primary efficacy endpoint in pediatric ADHD pivotal trial," December 4, 2017, https://www.akiliinteractive.com/news-collection/akili-achieves-primary-efficacy-endpoint-in-pediatric-adhd-pivotal-trial.
16 X2AI home page: https://www.x2ai.com/.

Going forward, MMAs will likely penetrate the chronic and psychological disease areas further, either as augmentation or complete replacement of medications. Eventually, digital therapeutics technology may outpace drug companies when it comes to creating longitudinal evidence since long-term data collection can be done seamlessly. As a result, these apps are well positioned to satisfy insurance companies' desires to confirm whether a therapy works in the real world.

Criteria for winning MMA solutions

With the digital health landscape continuously evolving, how can we identify winning digital or MMA solutions? Based on our research, we have identified six critical success factors:

- Incorporate a user-centric approach
- Enable patient/physician behavior modification
- Enhance engagement by working as a digital companion for a specific disease
- Integrate relevant data sources and platforms
- Connect multiple stakeholders in the care delivery continuum
- Provide multiple uses for stakeholders

1. Incorporate a user-centric approach. User-centric digital and mobile solutions utilize user interface (UI) and user experience (UX) design approaches that focus on the patient perspective and needs. This goes beyond creating merely convenient, patient-facing solutions to offer features that are personalized at the individual patient level. The MMA must address a real patient need and be intuitive and easy (or even fun) to use to generate continued engagement. Ideally, any new data being generated or collected is effortless for the user. A user-centric approach is critical to the success of such MMAs because it increases the stickiness of their solutions—patient engagement—by offering personalized content.

2. Enable patient/physician behavior modification. Digital and MMA solutions that modify patient/physician behavior use gamification, behavior economics, and incentives to change patient interaction with the therapy or treatment plan. For instance, Omada Health designs and develops online digital health MMAs that help coordinate care for people at risk for chronic diseases such as Type 2 diabetes or heart disease, and engage with participants to help them lose weight. It personalizes its content to pinpoint individual habits and creates tailored strategies based on the preference of the patients to bring sustainable lifestyle changes. Its success has led to it being named the 2016 Technology Pioneer by the World Economic Forum. This is a strategic differentiator as behavior modification can oftentimes lead to improved patient outcomes, which is ultimately the goal of the healthcare system.

3. Enhance engagement by working as a digital companion for a specific disease. Due to the complexities involved in managing certain diseases or medications, there is tremendous value in digital and MMA solutions that provide focused, tailored offerings to help patients navigate these complexities. For example, Propeller Health provides a respiratory health management mobile platform that uses a combination of smartphone applications and snap-on inhaler sensors to track patient adherence for asthma and chronic obstructive pulmonary disease (COPD). It also incorporates local weather/air

quality data to track its effects on medication use. Since its inception in 2012, Propeller Health has raised close to $50 million in financing and has a digital collaboration with GlaxoSmithKline. The fact that these digital and MMA solutions are hyper-focused on specific diseases creates enormous value for patients and pharmaceutical companies alike and is a point of strategic differentiation. Furthermore, incorporation of features that drive daily use (such as local air-quality data) boosts the stickiness of the app for end-users by increasing satisfaction and engagement.

4. Integrate relevant data sources and platforms. With data generated from many discrete sources across the healthcare continuum, the ability to curate, integrate, and analyze relevant data sources (such as genomic, research, clinical, outcomes data) offers the potential for a holistic view of patient behavior and health from end to end of the patient journey. For example, Medisafe is an adherence platform that connects mobile apps with smart pill bottles to help patients manage treatment, in addition to serving as a broad health management app with education content and telehealth. This allows physicians to track patient adherence remotely and deliver personalized messages. Furthermore, with a view across patient populations, Medisafe can develop broader insights on adherence and market trends. Medisafe currently has a 4.5 out of 5 star rating and has collected over 6 billion data points from over 4 million users. Going forward, the integration of relevant data sources offered by such digital solutions has the potential to uncover greater unique insights.

...they simplify the care delivery process, enable a holistic view of the patient, and add an agile component to care delivery

5. Connect multiple stakeholders across the care delivery continuum. Care delivery involves multiple stakeholders—patients, caregivers, providers, payers, pharmaceutical companies, and researchers—and solutions that seamlessly integrate them offer strategic differentiation: they simplify the care delivery process, enable a holistic view of the patient, and add an agile component to care delivery. For instance, Kali Care offers an ophthalmic-focused MMA platform that connects patients with doctors, caregivers, pharmacists, CROs, university researchers, hospitals, and family members in real time. In addition to receiving reminders for medications and tracking progress, patients can share medication data with their providers to help them make more informed clinical decisions. Caregivers can also access the medication data for easy medication management. However, while experts believe that there is much potential for these solutions, innovation in this space has been slow, due to the challenge of bringing together different stakeholders across the healthcare continuum under a single platform.

6. Provide multiple uses for end-users. Digital and MMA solutions that offer multiple sources of utility (within one or across multiple diseases) generally increase the stickiness of the users by solving several of the users' problems at once. One example of such a

"one-stop shop" is HealthTap, MMA-based platform that connects patients with doctors by offering telemedicine, adherence support, and patient education all in one place. Patients on this platform are granted 24/7 immediate access to 140,000+ top doctors via video, text, or voice.[17] In addition, patients receive customized doctor reminders, checklists, newsletters, and surveys to increase adherence as well as personalized, doctor-created content for patient education. For pharmaceutical companies, Science 37 offers a MMA-based mobile technology that facilitates remote networked trial operations end-to-end. It assists with trial design for remote studies in a patient's home and facilitates care delivery for patients via telemedicine technology. By creating a high-utility solution, these digital and MMA solutions create stickiness for end-users through increased satisfaction and engagement.

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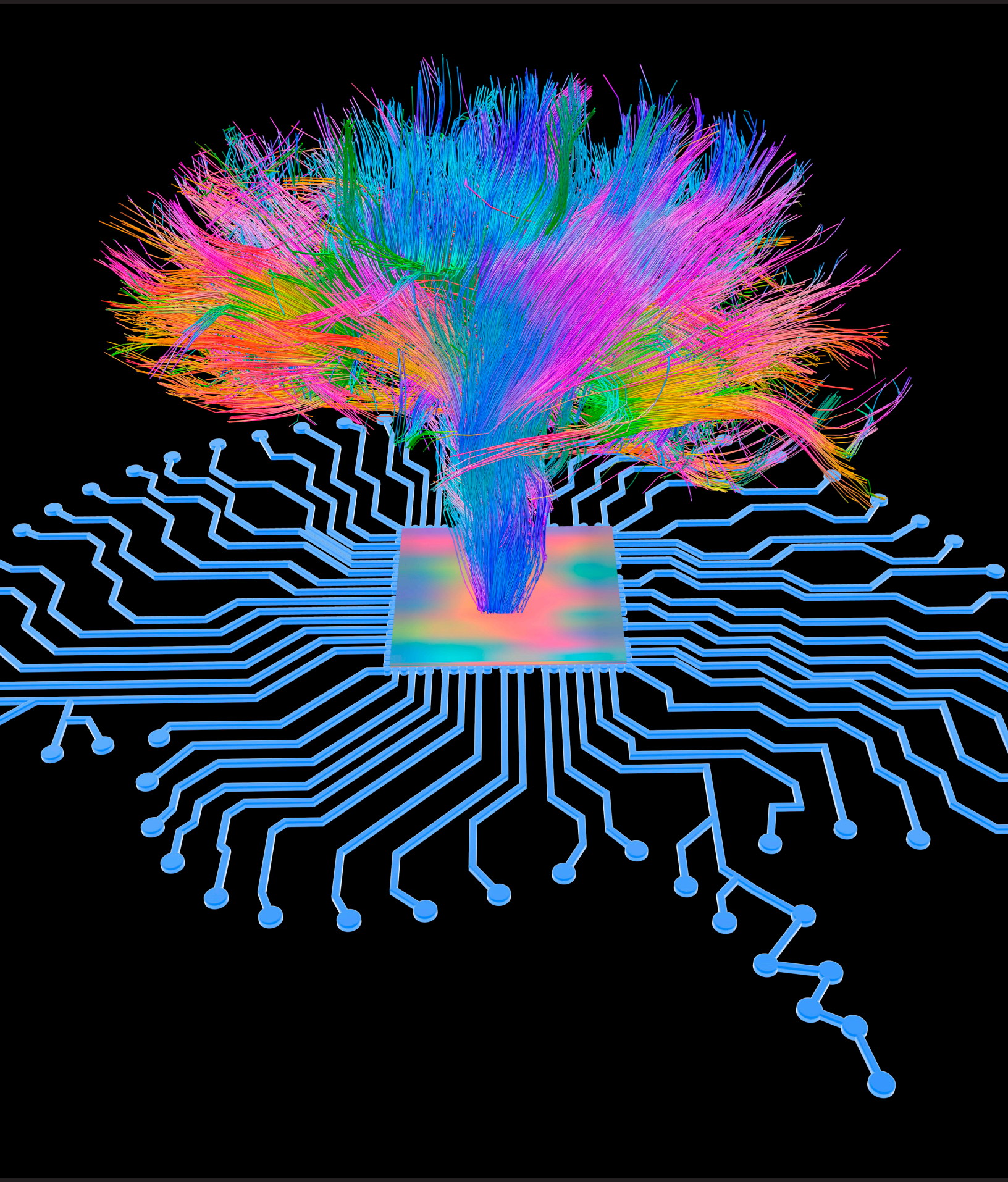
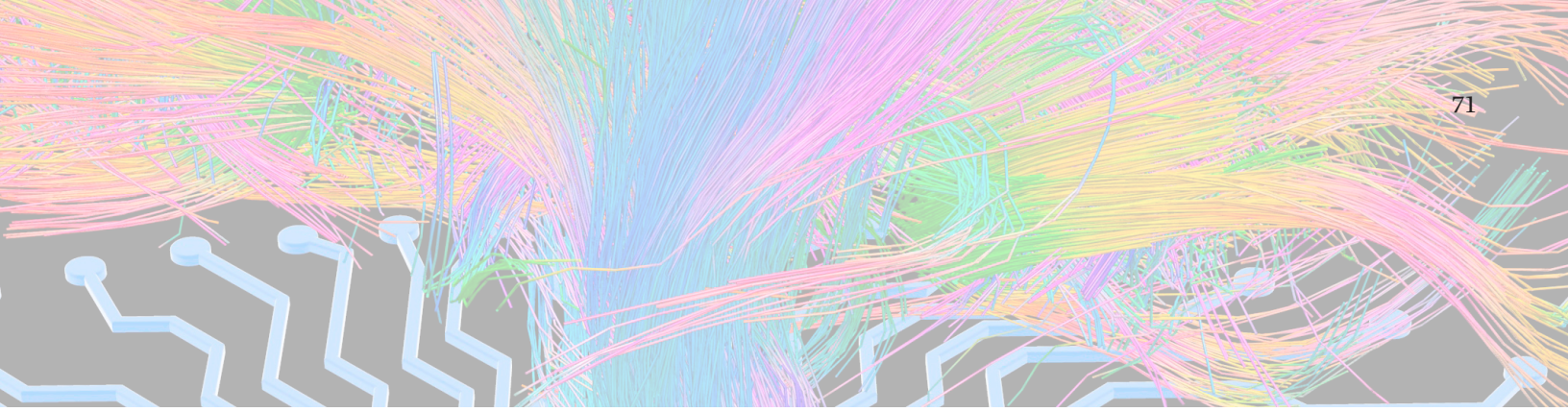
MMA solutions are a critical component for players in the health space as analytics-driven and personalized treatment become mainstream. They will boost health outcomes, allow organizations to gather new patient insights, and develop additional value-added products and services. However, more progress is required before predictive MMAs become commonplace. A threshold of patient data is needed before algorithms can deliver predictive insights. That, in turn, requires a high level of engagement with MMAs to generate the data. Other obstacles regarding the business model and sustainability of MMAs beg the question: who will pay for it, particularly if hardware such as sensors and trackers are involved? Testing one potential model, Virta recently announced 100 percent risk contracts with employers and health plans that are dependent on their ability to take patients off Type 2 diabetes medications.[18]

In conclusion, while some incumbent healthcare players (for example, payers, providers, pharma) may choose to build these capabilities in-house, many will choose to partner with technology companies or acquire capabilities from proven start-ups to mitigate risk and gain immediate access. For companies that embrace this change, MMAs can unlock enormous potential throughout the healthcare value chain and be a source of competitive advantage. As such, this vision needs to be on the CEO's agenda. We hope this overview of the MMA landscape, along with the characteristics of winning solutions, will be a useful guide on the journey toward developing transformative digital products.

17 HealthTap company website
18 Jonah Comstock, "Virta Health announces risk-based pricing for controversial diabetes management platform," *Mobile Health News*, November 14, 2018. https://www.mobihealthnews.com/content/virta-health-announces-risk-based-pricing-controversial-diabetes-management-platform.





Innovation, precision and disruption: New business models for the future of healthcare

Leigh Jansen, Erika Stanzl, Meredith Reichert, Edd Fleming, Manisha Shetty Gulati, Laura Furstenthal

Precision Medicine is ushering in rapid change for the healthcare industry, with new technological advances, both on the bioscience side (for instance, novel targeted therapies, advances in genomics and other 'omics) and the technology front (for example, improved artificial intelligence for therapy selection, wearables to better track personal health metrics). This comes with rapidly evolving expectations on the part of consumers, patients, providers, payers, medtech players, and pharma for what can and should be possible with regard to personalized care.

Despite the significant product-related innovation seen in healthcare, business models have been slow to adapt. In the United States, payers still largely earn revenue through premiums and pay for care through fee-for-service models. Pharma continues to earn revenue predominantly through direct payments for prescription medications, employing traditional sales models to support their franchises. Diagnostics companies still largely charge a test-based fee.

There are signs of change, with increasingly blurred lines between payers and providers and the adoption of new technologies. In the United States, for example, Accountable Care Organizations (ACOs) are driving value-based care. Similarly, payer models are introducing mechanisms to incent wellness, either directly or through employers (for example, through premium discounts or fitness tracker rewards). In the United Kingdom, the National Health Service (NHS) has introduced new business models that incorporate private companies and artificial intelligence, such as Babylon, to change the delivery of primary care through a subscription-based model.

The pressure to change, even for the most traditional stakeholders, is building. Though not an exhaustive list, there are several key trends converting the potential of precision medicine (PM) into a reality and spurring innovation in the healthcare business models:

- **Proliferation and availability of patient-level information**. Near ubiquitous adoption of electronic medical records, the initiation of various initiatives around collecting patient data (such as Million Vets Program, All of Us, China Precision Medicine Initiative), and the advent of wearables (among other trends) have generated hundreds of exabytes of healthcare data that is

growing at a rate of nearly 50 percent annually.[1] This massive proliferation of data, and its increasing availability to pharma, tech, payers, and other healthcare stakeholders, is rapidly transforming the ability to develop personalized therapies. For example, UK Biobank has made genomically linked healthcare data for 500,000 individuals open to researchers. While changing what's possible in terms of the development of personalized patient treatment, this data is also forcing healthcare stakeholders to rethink the value of this data, and models for how to monetize it.

The pressure to change, even for the most traditional stakeholders, is building

- **Increasing pharmaceutical focus on narrower target patient populations placing pressure on the economic model pricing.** Ever smaller and more targeted patient populations means that a newly launched drug will either generate less total revenue (given a smaller population), or per-patient charges will need to be increased. With increased attention to pricing, medtech and biotech players will need to rethink models for research and development, regulatory approval processes, and commercial execution. Higher per-patient charges will also create more impetus to shift to value-based payments for payers to justify the higher price tags with real patient outcomes.

- **Increasing demand by patients and providers for more technologically driven, customized care.** Today's patients and physicians have experienced technological innovations that have swept personalized experiences into all aspects of their lives—custom product recommendations in online shopping, custom movie recommendations, and personal banking assistance to name a few. These expectations are extending into healthcare, with demand that personal information (for example, genomics, activity data, diet) be a core part of care delivery.

- **"Hard-to-find" patient populations.** As patients are segmented into ever-slimmer "slices", their diseases are increasingly defined by molecular (for example, genomic or other 'omic) biomarkers. Without appropriate screening and testing, these patients are harder and harder to find. It can be difficult for a payer to justify reimbursing a test that identifies the 0.1 percent of patients with a given mutation, especially if the test is expensive and the body of supporting clinical evidence remains low. These tests also require up-to-date providers to know when and how to order appropriate testing for potential patients. Supporting this kind of testing will require finding an effective model that balances costs and benefits across care settings and stakeholders, including payers, providers, diagnostics companies, and pharma. It will also require new ways of building awareness of appropriate testing and treatment for small patient populations.

1 *The Digital Universe Driving Data Growth in Healthcare*, IDC, 2014, https://www.emc.com/analyst-report/digital-universe-healthcare-vertical-report-ar.pdf.

- **Blurring lines between healthtech and biotech.** Advances such as digital therapeutics and biomarkers, apps to provide real-time drug dosing feedback, and artificial intelligence-based tools for therapy selection are all testing the bounds of what would be considered a traditional therapy or diagnostic. While it's clear that these advances are welcome in medicine, what's not as clear is how they should be reimbursed. Nor is it clear who the leaders will be in the space—whether that's pharma delivering on innovative technology tools, or technology companies integrating with therapy.

- **Financial pressure to drive changes in the way care is delivered.** All of this technological innovation in precision medicine comes with a price tag, but the healthcare system is already incredibly financially taxed. A key challenge to adoption of precision medicine is affordability across global health systems that are already under significant financial constraints, adding to the need for business model innovation.

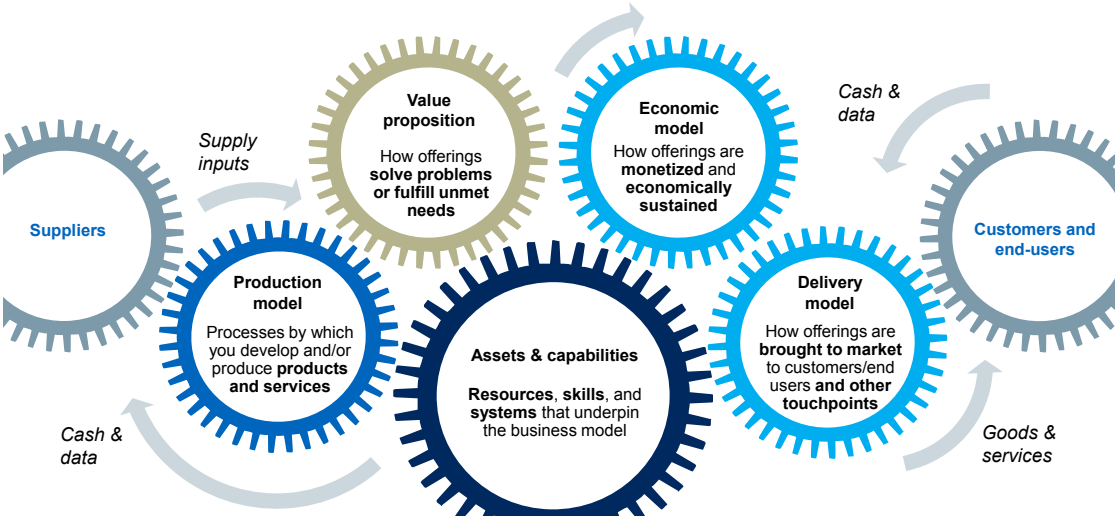
Collectively, these changes are forcing both marketplace incumbents and new entrants to reinvent the traditional business models in healthcare to deliver on the promise of precision medicine.

Business model innovation

Exhibit 1

Business models have five interconnected components

Business model innovation is led by significant change in 1–2 components, with supporting changes in the others



When we think about business models, we characterize them along five dimensions or components (Exhibit 1), all of which are important for business model innovation:

- **Value proposition**—the way that offerings solve problems or fulfill unmet needs, including new technologies such as next-generation sequencing (NGS) and artificial intelligence (AI)

- **Economic model**—the way that offerings are monetized and economically sustained, including "asset-light" offerings that are more heavily based on data and analytics

- **Delivery model**—how offerings are brought to market to customers/end-users and other touchpoints, including customer service (for example, moving to a direct-to-consumer model)
- **Production model**—which processes are used to develop and/or produce products and services, including new methods such as additive manufacturing, tissue engineering, individualized cell therapy manufacturing, and individualized ordering and tracking system development
- **Assets and capabilities**—which resources, skills, and systems underpin the business model, considering not only your own assets and capabilities but also those of others

A business model change that only involves a single gear is easily duplicated, and often outright fails. The most successful business model innovations change multiple components simultaneously, and ensure other components support those shifts.

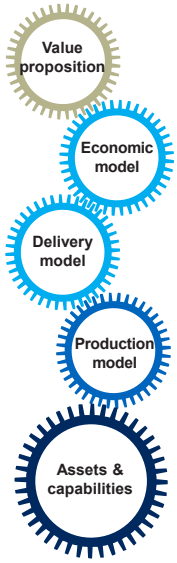
For inspiration in business model innovation, the healthcare sector can look to other industries, as well as a few pioneering examples within healthcare. By business model innovation, we mean innovating new ways to generate value by changing the value chain economics, changing delivery models for an offering, as well as using and monetizing assets and capabilities differently. Often this is catalyzed by technology, but the real value creation is through the new business model.

Take for example the classic disruptor Uber, which used existing GPS technology and an app to disrupt the taxi and ultimately the entire transportation industry, by deploying a business model that requires no assets. Dollar Shave Club disrupted the razor/razor-blade model that Gillette had perfected by moving to a subscription service, leading to a $1 billion acquisition by Unilever in 2016. Amazon took its existing Amazon Web Services storage and computing services that it used for its own online marketplace operations and sold them to other companies, ultimately becoming a key profit driver for the company.

When companies innovate their business model, there are usually one or two components that are the core of the business model shift—what we call the “lead gears”. We can categorize the business model shifts for precision medicine along these lead gears.

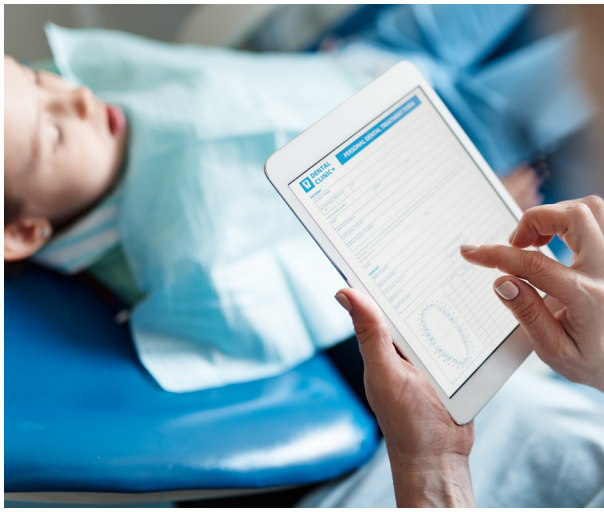
Exhibit 2

Lead gears drive the business model shift



Lead gear	Example company		Business model innovation
Value proposition	Personalis	Provider of advanced genomic sequencing and analytics to enable precision medicine for immuno-oncology	▪ Personalis moved from a high-quality whole genome sequencing offer to B2B pharmaceutical partnerships to co-develop immuno-oncology therapies
Economic model	NEBULA GENOMICS	Sequencing company that uses blockchain to allow customers to own and control their own genomic data	▪ Nebula offers free or heavily subsidized genomic sequencing to customers by allowing them to securely connect with researchers who want to use their data. Customers can get compensated for providing their genomic information
Delivery model	exact sciences	Provider of early cancer detection technologies, including Cologuard, a stool-based DNA test for colorectal cancer	▪ Exact Sciences transformed the colorectal screening delivery model by allowing consumers/patients to take the test at home, in some cases replacing a traditional physician performed colonoscopy
Production model	flatiron	Developed a shared technology platform for oncology practices, access to data for life sciences companies, and enriched data infrastructure for hospitals and academic centers	▪ Flatiron’s production model creates Real World Data from Electronic Health Records and linked datasets, with quality and scale supporting such uses as publications, drug development, market access, and regulatory submissions – in some cases reducing or avoiding the need for traditional clinical trials
Assets & capabilities	amazon BERKSHIRE HATHAWAY INC. JPMorganChase	Partnership developed to tackle waste in the healthcare industry and improve employee access to care	▪ The Amazon-JPM-Berkshire Healthcare Alliance is redefining healthcare by tapping into their expertise in logistics, technology, insurance, and finance across the partners and creating critical population scale to experiment with how to improve employee health

Companies such as those shown in Exhibit 2 are applying business model innovation across the range of lead and supporting gears, building upon trends in precision medicine. Personalis offers its pharma customers an innovative value proposition, having moved from high-quality whole-genome sequencing to B2B pharma partnerships in immuno-oncology therapy development. Exact Sciences has transformed the colorectal screening delivery model, now offering an at-home test that can, for some patients, replace a traditional physician-performed colonoscopy. Flatiron has innovated the production model, using an electronic medical records platform technology to rapidly generate data that can be used by physicians and researchers alike to support clinical decisions and run real-world or pragmatic trials.



While the lead gears drive the innovation, it is critical for a company to modify multiple gears simultaneously to ensure that the other components support lead gear shifts. This might mean changing your delivery model to support a change in an economic model. For example, Nebula Genomics, which innovated first and foremost on economic model, is offering free or deeply subsidized sequencing direct to consumers. To offer this service, it innovated on delivery model, using blockchain technology to allow consumers to securely and anonymously share data with researchers. Alternatively, it might mean a new economic model to support new assets and capabilities, as seen with the need to rethink actuarial premiums and risk-sharing in the Amazon-JPMorgan-Berkshire Hathaway Healthcare Alliance.

While the lead gears drive the innovation, it is critical for a company to modify multiple gears simultaneously to ensure that the other components support lead gear shifts

When companies don't shift the gears in parallel, there can be difficulties. Healthcare has many such examples, such as preventative care apps that improve long-term outcomes (a value proposition innovation) but lack uptake by insurers with shorter-term horizons or single-pay systems that lack the required global budgets and accompanying data and analytics to justify the costs (no accompanying innovation in economic model).

In thinking about how to innovate a business model, it can be helpful to explicitly consider existing orthodoxies about what is required to win and to think through "orthodoxy-breaking" strategies. For example, it may no longer be necessary to "own" a system—fostering an open and growing ecosystem can be much more effective (for example,

Propeller Health, which developed sensors that work with any inhaler rather than being brand-specific). Similarly, revenues do not need to come from capital equipment and disposables—a diagnostics player could give away its machines in exchange for valuable patient data. Pharma companies could rethink traditional models to biomarker testing and consider supporting consortia that bolster the entire industry's ability to identify patients.

Key success factors for business model innovation

Key success factors vary for incumbents. McKinsey has studied what makes companies successful innovators, based on a multi-year study with over 2,500 executives and 300 companies. The results show eight "essentials of innovation": these are the strategic and organizational factors that separate successful big-company innovators from the rest of the field. Of the eight essential, "evolve", which is how businesses create new business models to provide defensible and scalable profit sources, ranks the lowest, even for top innovators.[2]

It's difficult for incumbents to disrupt themselves before others do due to fear of losing key customers, the risk of cannibalizing existing business units, and the existence of entrenched incentives throughout the organization.

Apple has successfully reinvented itself multiple times. In addition to its well-known product innovations, such as the iPod, iPhone, and Apple Watch, it is strengthening its healthcare ecosystem with a broad range of partnerships including medical device players and researchers. It is now partnering with Zimmer Biomet to create a new smartwatch app to support postoperative recovery for hip and knee replacement patients, incorporating patient and physician activity reports. It is also donating its watches to aid research and strengthen its position in the health ecosystem: for example, to researchers at the University of North Carolina School of Medicine to help manage and track eating disorders.

When we look at successful business model shifts, there are a few common features for the ones that are most disruptive:

- **Restructure the existing value chain in an industry** by integrating formerly distinct steps, by disaggregating and building scale in a key step, by substituting or drawing on new capabilities from another industry. Amazon has done this in many industries, and may be poised to repeat this in healthcare with its recent acquisition of the online pharmacy PillPack.

- **Rapidly scale by incorporating virtuous cycles and feedback mechanisms**—leveraging network effects, reinforcing data and insight advantages, locking in customers, compounding cost advantage. Alphabet and Verily Life Sciences are applying their artificial intelligence expertise to assess cardiovascular risks based on retinal scans and continuously improving their algorithms with feedback loops obtained through partnerships with researchers and providers.

2 "The Eight Essentials of Innovation", *McKinsey Quarterly*, 2015.

In today's highly connected ecosystems, it is critical to consider not only how to employ your own assets and capabilities as part of your own operating model, but those of other players as well. This is true in both B2B and B2C industries. Companies that may be seen as competitors could also be collaborators, resulting in the increasing use of the broader term "coopetition".

Realizing business model innovation

How should a company think about the value at stake—both risks and opportunities—related to business model innovation? There are tactical ways to be proactive and help to sustain value through business model shifts, rather than triggering a downward spiral for your industry.

- **Assess your vulnerability.** How are value pools shifting in the industry? What are the areas where technology and business model innovations could trigger disruptions? If you "tear down" competitor business models, what do they look like, and where could they most easily move? How is your set of competitors and collaborators changing?
- **Consider opportunities for business model innovation across specific lenses.** What are the opportunities based on evolving customer needs? What are the relevant technological advances, and what could they unlock? What are the different business model innovations and how could they apply?
- **Get involved with regulators.** How can products and services be bundled, for example complementary diagnostics and the corresponding portfolio of drugs? How can data be tracked, analyzed, and used to guide care? What further changes can be made to facilitate the approval of algorithm-driven devices?

> What assumptions have become assertions? What would be possible if these orthodoxies were not true? What orthodoxies have others broken to innovate and win?

- **Increase investment in data and analytics.** What data sources could be used to improve insights, for example from wearables and other sensors? How can these be obtained? How can they be monetized? What additional capabilities are required?
- **Form partnerships with other ecosystem stakeholders.** Who is a competitor? Who is a potential collaborator? What could be unlocked by partnering with a non-traditional technology player?
- **Challenge your orthodoxies.** What assumptions have become assertions? What would be possible if these orthodoxies were not true? What orthodoxies have others broken to innovate and win?

While no one has the complete picture as to how the precision medicine ecosystem, and healthcare ecosystem more broadly, will continue to evolve, one could imagine a few paths that could disrupt the current healthcare landscape:

- Despite the slow uptake of outcomes-based contracting, to continue to capture the value they do today, pharmaceutical companies betting on PM will have to build comprehensive patient delivery solutions to ensure outcomes that justify the pricing. This could involve crossing over into active care delivery with elements like continuous monitoring of patients, active disease management, patient reported outcomes tracking and response.

- Consumer technology players leverage their expertise in data and consumer engagement to redesign care delivery algorithms and engagement. Thus these technology players become central to both clinical decision support and disease management, disrupting both the reimbursement and care delivery paradigms of today.

- Technology and data generating platform companies (for example, everything from laboratory to implantables to consumer technology) begin to sell insights from their data to consumers, providers and payers to better manage care. Insights could be from the mundane like clinical decision support to nuanced wellness input to consumers. The key difference would be that the data would be controlled by third parties who are then pushing back (at a price) to their customers across the healthcare value chain.

- Diagnostic players could move from fee per test to pay per insight to value based payments around outcomes. We are already seeing diagnostic players form at-risk partnerships with manufacturers for the drugs they indicate—this would evolve the model to increase reimbursement for appropriate therapy selection and positive outcomes while forfeiting payment for unactionable findings or poor outcomes, ensuring that patients are tracked longitudinally and managed appropriately

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Together, the product-based innovations in PM, along with changing consumer demands and increasing financial pressures are putting tremendous strain on traditional healthcare business models. Going forward, the leaders in this market will need to adapt to these pressures and innovate their business models in the way that other industries—such as transportation, retail, and finance—have to build profitable businesses based on personalized patient care.