PRECISION MEDICINE RESEARCH:
How Advanced Data Analytics Support The Journey From Clinic to Bedside

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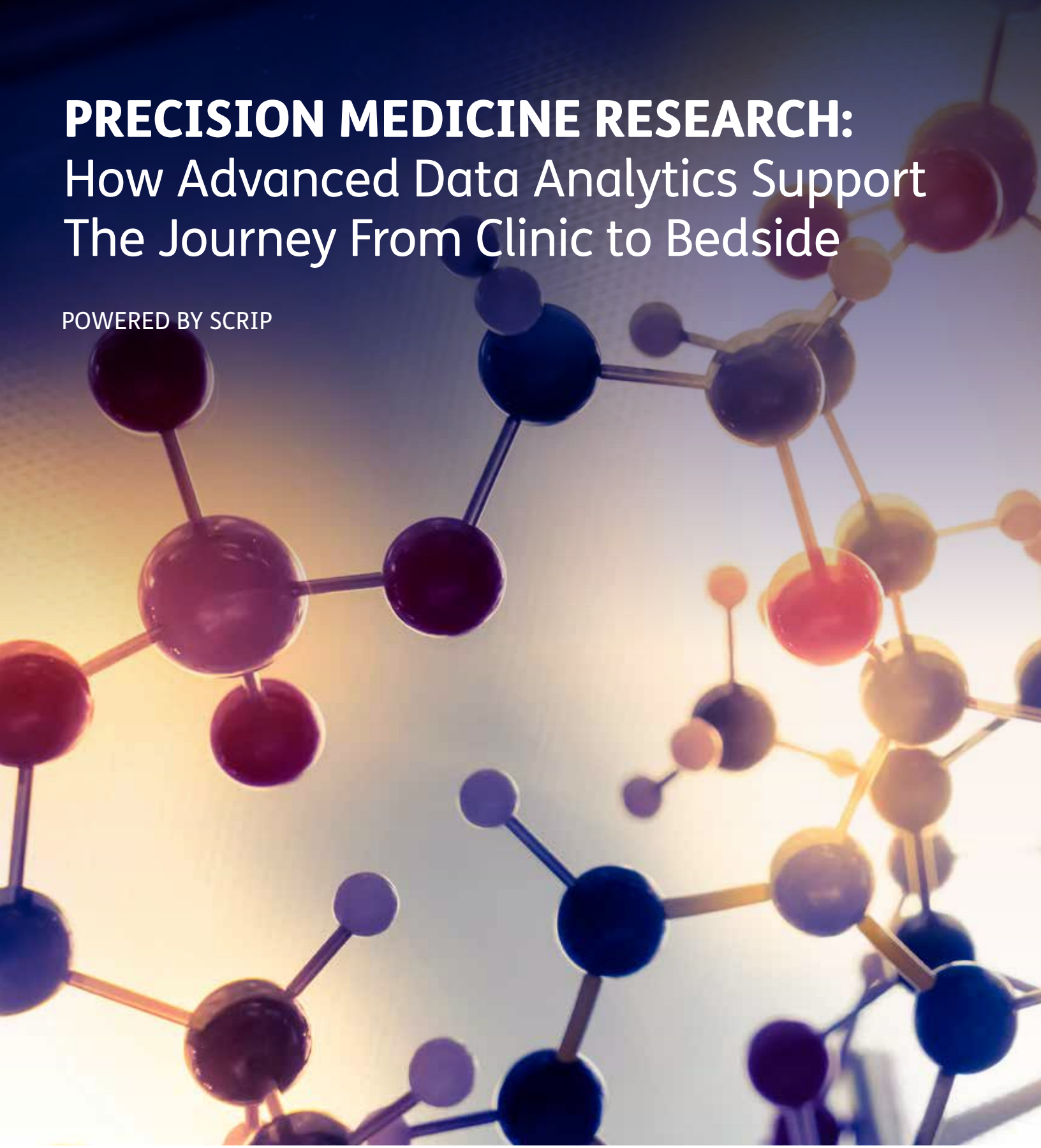

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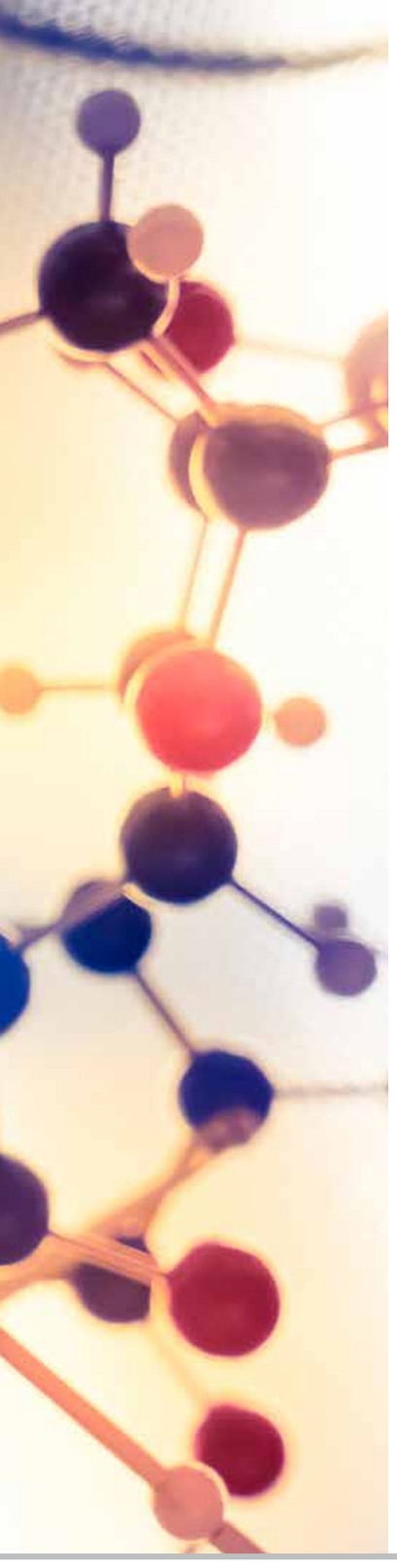

During an expert panel convened by Parexel and Pharma Intelligence in Santa Clara, industry leaders discussed the use and optimization of precision medicine trial strategies.

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PRECISION MEDICINE RESEARCH: HOW ADVANCED DATA ANALYTICS SUPPORT THE JOURNEY FROM CLINIC TO BEDSIDE

Precision medicine offers huge promise to patients and health systems. It can also substantially increase the efficiency of drug development by enabling more focused, data-rich clinical trials.

A **recent study** by The Economist Intelligence Unit (EIU), commissioned by Parexel, found that precision medicines were 10% more likely to reach the market than conventional therapies, and were adopted more rapidly onto payer formularies.[1] The report also found that the number of publication references and abstracts on precision medicine trials captured by the search engine PubMed has increased sharply since 2013, suggesting that adoption of such trials is still in a relatively early phase. On average, precision medicine studies accounted for nearly 14% of the examined 20,000 completed Phase II and III trials between 2012 and 2017, according to Informa's *Trialtrove*.

Rapid progress in genomic sequencing, biomarker identification, data capture and data analytics has helped accelerate the adoption of precision medicine. This goes beyond linking a therapy to a diagnostic. Precision medicine is a holistic approach that takes into account multiple aspects of patients' lives and health, drawing on personal data – from genomics tests, clinical records, wearables and lifestyle – as well as population-level data.

CHALLENGES

The term *precision medicine* has yet to be conclusively defined. Alternatives including *personalized health care*, *personalized medicine*, or even *stratified medicine* are used interchangeably. They all refer to tailoring a therapeutic intervention to individual patient characteristics, including (but not limited to) those that can be measured by genomics or proteomics.

In addition to attempts to standardize the definition of precision medicine, there remain multiple barriers facing its implementation, both in development and in clinical practice. Challenges lie around data infrastructure and handling, building and accessing appropriate expertise, policy development, awareness and culture change. These hurdles mean that scientific advances are not fully translating into patient benefit. *There is incredible research [into precision medicine] and a lot of really interesting hypotheses, biomarkers and clinical trials. But very few of them are actually producing direct patient benefit,"* said Minnie Sarwal, MD, PhD, Co-Founder and Chief Medical Officer for KIT Bio and Professor of Surgery at University of California, San Francisco.

Data infrastructure and standards

Data quality, consistency and transparency are key to the successful implementation of precision medicine. Yet much health data, including electronic health records (EHRs), remain fragmented, incomplete and highly variable, often with poor system interoperability.

Standards are required to ensure that appropriate tools and methods are used for handling, integrating and interpreting new data types. For instance, determining what kinds of datasets can be shared or linked, under what circumstances, or whether historical data may be used as control arms in some situations, to avoid the burden of recruiting control groups.

Building and attracting appropriately trained workforces

Precision medicine involves new skills, and new ways of working. As these

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"Today's privacy laws and guidelines can make it difficult to return results to patients outside of the clinical trial setting. It can be done, with the varying experts and a little innovation we can find a solution that enables the sharing of this sensitive information without compromising privacy and the regulations that govern it," said Anita Nelsen, Vice President of Translational Medicine at Parexel.

new skills are not yet mainstream, there is a limited workforce of trained data scientists. The industry needs appropriately trained people who can translate complex datasets into results that physicians can clearly communicate to patients. Developing these skills will involve data scientists learning more about clinical practice and physicians and clinicians becoming more data-savvy to harness the power of precision medicine to determine the best treatment.

New trial designs and funding structures

New clinical trial designs – including adaptive trials – are required to develop and employ precision medicine most fully. Such designs may involve identifying, validating and using multiple endpoints within a single study, to maximize the chances of finding meaningful data. Standards must be agreed upon around such trials, as well as around biomarkers, often used as endpoints.

These novel trials will require more flexible funding structures. Government grants often involve fixed costs and timelines, which can make it difficult to evolve adaptive trial designs as results emerge. Pharmaceutical firms may also face unpredictable trial costs as a result of collecting new kinds of data. Whole genome sequencing, for example, may require providing patients with genetic counselors, which could have long-term implications. Drug firms' interactions with patients are tightly regulated, both within and outside of trial settings, so extending this relationship beyond a clinical trial is challenging in today's environment. *"Today's privacy laws and guidelines can make it difficult to return results to patients outside of the clinical trial setting. It can be done, with the varying experts and a little innovation we can find a solution that enables the sharing of this sensitive information without compromising privacy and the regulations that govern it,"* said Anita Nelsen, Vice President of Translational Medicine at Parexel.

Data ownership and privacy

As well as challenging – and changing – the traditional pharma-patient relationship, precision medicine urgently requires a clarification of data ownership, access and privacy laws. That means working with ethics committees and engaging in a broader public debate to encourage data sharing where it is to everyone's benefit. This would require robust guidelines to protect sensitive data and minimize patient risk. *"It's really important for us to get ahead in this privacy issue. If we don't, it is going to hurt biomedical research. We need to explain the advantages of sharing certain kinds of health data to the individual,"* said Edward Abrahams, PhD, President of the Personalized Medicine Coalition.

Incentives and workflows

Implementing precision medicine means motivating patients to participate in precision medicine trials. This can be done by integrating their preferences and needs into study endpoints and implementing other measures to incorporate the patient voice. Incorporating precision medicine into workflows will also require new policies and commercial incentives for diagnostics manufacturers, who currently face challenging reimbursement conditions and unpredictable returns.

Finally, precision medicine data points must be pragmatically assimilated into the clinical workflow. Time-pressed clinicians will require, for instance, a simplified, aligned choice of biomarker-based tests and tools to help facilitate treatment decisions. This will be especially helpful for physicians who try to keep up with the latest drug-diagnostic pairs. They will be empowered to select a single test for a patient and use the results to determine the best treatment.

Adjusting the value equation

Payers must also adjust their systems to account for the value of both precision diagnostics and therapeutics. Using precision medicine tests can ultimately result in cost savings by avoiding the use of ineffective treatments. Payers must encourage greater use of precision medicine tests, even though capturing and measuring the savings may be more difficult.

Educational programs to increase patient involvement in precision medicine

Many patients do not fully appreciate what precision medicine is, or the promise it offers. Changing that, through appropriate awareness and education campaigns, will empower individuals to help drive this movement forward. Pharma and other stakeholders must continue to encourage more patients to engage in clinical trials, and to remain engaged over the course of their treatment and beyond.

SOLUTIONS

Precision medicine's promise is already driving efforts to overcome these challenges and help improve the efficiency and sustainability of drug research and development. Bringing together stakeholders from government, industry, academia and patient organizations to discuss these issues and work out how to leverage innovation in clinical trial design may help bridge the gap from bench to bedside. These efforts can then be expanded, and lessons from them shared more widely, to accelerate precision medicine's uptake and ensure that all stakeholders benefit.

Growing data infrastructure

Examples of national data-collection programs include the US Department of Veterans Affairs (VA)'s Million Veterans Program, the National Institutes of Health (NIH)'s All of US Program, the UK's 100,000 Genome Project and France's National Cancer Institute's network of diagnostic testing centers. These programs are creating the data infrastructure required for precision medicine, and highlighting implementation requirements and barriers. *"The VA has shown us what is needed to better understand the barriers, and who is needed to facilitate the use of precision medicine for patients and caregivers,"* noted Sam Hanna, Associate Dean of Graduate Programs at American University.

A growing "open data" culture exists within the research community, including through partnerships such as the NIH-supported Immunology Database and Analysis Portal (ImmPort), designed to accelerate discovery in immunologic diseases. Meanwhile, organizations such as privately owned, consumer-focused genetic testing company 23andMe are generating huge datasets from millions of individuals, which may be useful in drug discovery.

Early evidence of efficiency gains in development

Pharmaceutical firms' heavy investments in data and analytics are generating early evidence that precision medicine can make trials more efficient. Roche has publicly cited that EHR data from its Flatiron business helped at least one medicine gain faster approval by providing standard-of-care control data appropriate to local payers and regulators. Newer players like Tempus, a cancer informatics and precision medicine company, are also accelerating data collection and curation via partnerships. *"We can [use data to] create synthetic control arms across a broader population faster than what would normally be feasible for a physical trial,"* said Mark Oldroyd, SVP, Commercial Markets at Tempus. There are other, ongoing efforts to assimilate patients' EHR, longitudinal and clinical data and work out how to continually and usefully combine them. *"We are exploring mining electronic medical records to hone inclusion/exclusion criteria,"* noted Thea Sutton, Innovation Manager, Genentech Early Clinical Development.

Growing data sources and new technologies

Sources of big data, such as wearable sensors, are expanding, helping to complete the dataset for a broader precision medicine picture. Regulators' growing involvement in approving and monitoring these technologies adds validation of this informa-

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tion and is helping build and maintain data quality and consistency.

Other technologies gaining popularity, like blockchain, can facilitate data ownership, access and portability, while helping address privacy and security concerns. Technology giants such as Apple and Google are working on tools that will enable individuals to securely hold and control their personal data aggregated from across multiple real-world sources. Distributive computing algorithms allow data to be aggregated in a blinded fashion, maintaining anonymity for individual data components, yet generating powerful statistics. Such tools may mean we can *"bypass concerns around data leakage and data privacy,"* said Ying Lu, PhD, Co-Director of the Stanford Center for Innovative Study Design (CISD) and the Biostatistics Core of the Stanford Cancer Institute.

Motivated patients

Patients are increasingly involved in their health care, and in advocating for faster, more efficient drug development. The more they understand about precision medicine and its potential benefits, the more likely they are to engage in trials and help build the required datasets, experience and, ultimately, treatments. Rare disease patient groups, such as the Multiple Myeloma Research Foundation, are particularly highly motivated, well-organized communities creating useful, high-quality data. Studies like the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD)-funded Kidney Precision Medicine Project put patients front and center, encouraging adherence and interest through shared data and extensive communication.

Integrating patient preferences into endpoint selection is another emerging goal. It may also address patient recruitment, one of the biggest bottlenecks in drug development, more broadly. Studies suggest that only a tiny proportion of eligible patients – fewer than 5% – currently enroll in clinical trials.[2] As such, *"if there are ways, through precision medicine, to entice patients to get more involved, that will likely move the needle toward more efficient development more than anything,"* said Gary Gustavsen, Partner, Personalized Medicine, Health Advances.

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Progressive regulators

Precision medicine requires a progressive, flexible regulatory landscape. The US Food and Drug Administration (FDA) in 2018 approved a record 25 precision medicines (42% of the total), according to the Personalized Medicine Coalition, including the second drug based on a biomarker, rather than a tumor or tissue type. Companion diagnostic approvals have grown alongside and in 2018, the first FDA-approved direct-to-consumer genetic test for determining cancer risk arrived.

Regulators also play a key role in defining and helping validate better endpoints to facilitate precision medicine trials, through initiatives such as precisionFDA – a platform to evaluate genomic sequencing assays and explore new ways to regulate them.

Patient-centric trial designs are gaining traction among pharma firms, buoyed by government-funded initiatives such as the US Patient-Centered Outcomes Research Institute (PCORI) and the European Medicines Agency (EMA)'s proposals to better integrate patient data into benefit-risk assessments of new drugs. (These form part of EMA's draft **"EMA Regulatory Science 2025 Strategic Reflection,"** currently out for public consultation.)

More convenient, efficient diagnostic tests are being developed, including multiplex genomic tests that measure several markers at once.

Multi-stakeholder collaborations to advance precision medicine are multiplying. One recent example is a project commissioned by the Personalized Medicine Coalition and conducted by Health Advances to understand how precision medicine is being adopted across US health care systems, setting benchmarks to measure progress, highlighting lessons learned and outstanding integration challenges.

Better-adapted training and educational opportunities are also emerging, including ways for health care professionals to become more fluent in data science, so they can fully understand and clearly translate test results for their patients. The panelists identified various efforts already underway to promote skills exchange:

- Data scientists and bioinformatics or physics post-docs are embedded among scientists at Sarwal's lab at UCSF, leading to some interesting learnings.
- Hanna highlighted efforts at American University's SPExS that infuse use of critical analytical tools into medical graduates' learnings, including data programming languages like R and Python. This means "*all our students are better prepared once they get into the real world and actually work in these fields*," he said.
- Lu's team at Stanford has collaborated with the University of Chicago and begun holding "Stat4Onc" meetings, bringing together oncologists and statisticians, and organizing several other annual events bringing together regulators, statisticians and industry across the globe. *"Academia can serve as a liaison to bring people together to talk about topics of interest, avoiding conflict of interest,"* suggested Lu.

FURTHER ACTIONS FOR ADDRESSING BARRIERS

The panel identified further actions needed to promote the development and implementation of precision medicine. These include:

- Fostering coordinated, multi-stakeholder/multi-expert collaborations, including patients, across geographies to discuss new study designs that encourage patient enrollment and retention, while leveraging endpoints that align with patients' experience with a disease and their responses to treatment.
- Designating "neutral" institutions, such as academic establishments, that can serve as liaisons for pharma, physicians, statisticians, patients and regulators to introduce ideas and facilitate consensus and acceptance on both sides. *"I think the onus lies upon us in academia to really get pharma engaged*," said UCSF's Sarwal.
- Producing a master "cheat sheet" for physicians faced with multiple diagnostic tests and drugs to help inform them about which test should be administered first to enhance patient outcomes faster and at lower costs.
- Communicating precision medicine's value to physicians and payers. Specifically, physicians must understand how precision medicine can change their interactions with patients. Payers must be willing and able to adjust their systems to capture the long-term benefits of precision therapies – including by prescribing them right away in certain cases, instead of after multiple rounds of standard treatment. *"Payers are in the driver's seat, and they are slow to get into the game. If they don't want to pay for it, it [PM] is not going to happen,"* warned Abrahams.
- Increasing pharma's efforts to break down internal silos among research and development and commercialization teams, and ensuring molecular/diagnostic information established in research translates to the clinic (whether via companion diagnostics or informal associated diagnostic use). *"There is often a big gap between [pharma] research teams and commercial groups that are close to clinical care,"* said Oldroyd. Pharma can help narrow that gap by interacting with clinicians and supporting appropriate use of diagnostics, including drug-specific tests.
- Aligning incentives for diagnostics and drugs, including by reducing the risks of diagnostic development, creating incentives for diagnostic reimbursement and developing new kinds of pharma-diagnostic alliances.
- Identifying and building relevant research programs for graduate students to prepare the future workforce for precision medicine needs.

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Endnotes

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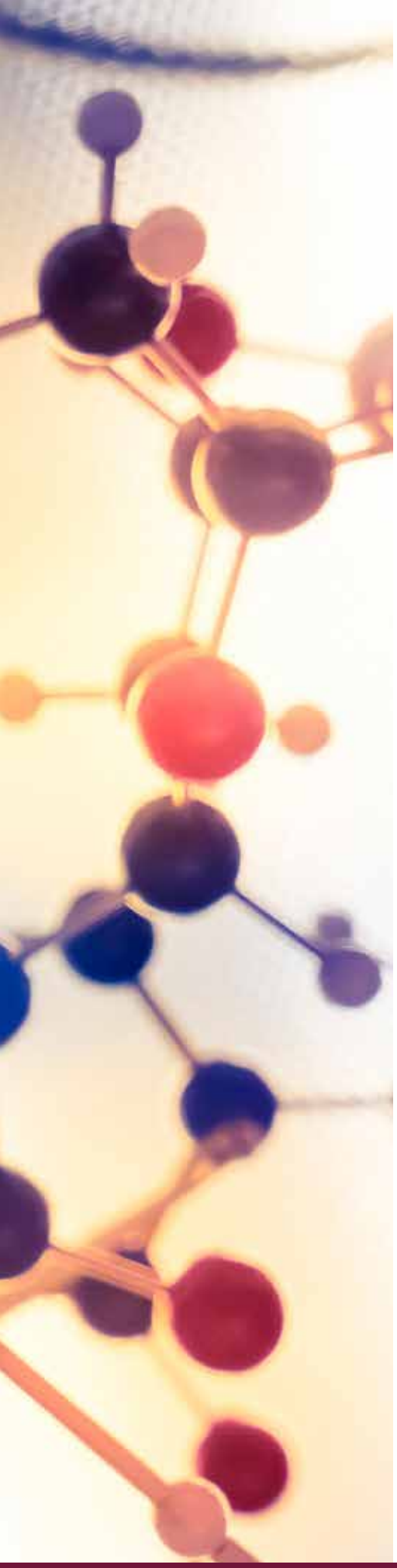
[2]http://ascopubs.org/doi/full/10.1200/jop.0922001



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