Denise Myshko

Personalized Medicine Gains Momentum

Personalized and precision medicines have the potential to change the way we think about, identify, and manage healthcare.

In the years since the completion of the Human Genome Project, advances in genome technology have led to an exponential decrease in sequencing costs. This has led to more than 100 drugs with labels that include pharmacogenomics information. Experts say the development of personalized medicine is growing because the biological targets being pursued by pharmaceutical companies are now being informed by pathway biology, genomics, and genetic data.

And as the costs of sequencing continues to decrease, an even greater understanding of the impact of genomics, epigenomics, and patterns of disease will lead to precision medicine, with more specific diagnosis and targeted treatments.

"When we talk about precision medicine, we are really talking about two things," says Patrick Flochel, global pharmaceutical leader at EY. "The first springs from the sequencing of the human genome, in 2003, which raised the possibility that as consumers of health we would soon be able to carry our genomes with us as a portable medical record. The second is more prosaic, but it is the version that — for now, at least — best represents the promise of the Human Genome Project, and that is already a reality. In this version, life-sciences companies are adopting biomarker technology to allow them to develop therapies with better specificity. This has major implications for the future of treatment, not just in terms of drug therapies, but throughout the care continuum."

The age of personalized medicine is already here, says Tyler Marciniak, director of oncology communications and advocacy, at Astellas US.

"It was not long ago that medical treatment simply relieved symptoms without altering the underlying disease," he says. "Today, we are on the verge of identifying every disease based on the underlying molecular processes that cause it."

Deeper understanding of phenotype and genotype differences is allowing healthcare stakeholders to stratify populations more finely and inform patients more accurately about their personal disease diagnosis and prognosis, says John Doyle, Dr.P.H., senior VP and managing director, Consulting Value and Outcomes Center of Excellence, at Quintiles.

"Companies will need to adapt and scale their sales and marketing functions to reach a broad, heterogeneous market with tailored messaging," he says. "It will be imperative for biopharma to partner in this capacity to better understand stakeholder preferences for information channels and content. In this way, a personalized product is matched with a personalized brand, and reaches those patients who can benefit most in terms of survivorship."

Personalized medicine is one of the most exciting areas of healthcare right now, says Matthew Howes, senior VP, head of strategic services, Palio+Ignite, an inVentiv Health company.

"Competition is intense even without well-defined markets," he says. "There could be a disruptive technology at any point. Winners will leverage disruptions to their advantage, and today's market leader could be forgotten in a couple of years. But if we look at some of the more unexpected partnerships that have been forged lately, we see that many well-established players are banking on personalized medicine becoming a reality."

Paula Brown Stafford, president, clinical development at Quintiles, says industry apprehension about moving away from the blockbuster model to a more segmented and targeted approach is evolving to a more thoughtful strategy with greater investments in the development of biomarkers, biomarker assays and pathway analysis, genomic tests, and specialized safety evaluations.

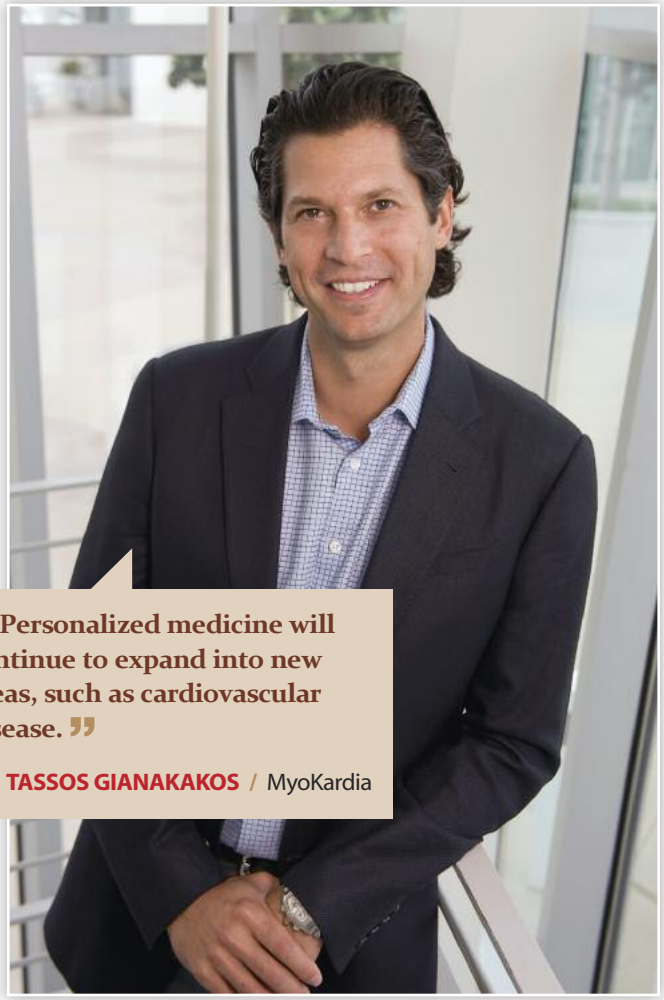
"As this model continues to evolve, a precision medicine strategy will help integrate and guide development teams from discovery and early clinical development all the way through to commercialization," she says.

The importance of personalized medicine and the necessity for biomarkers and companion diagnostics is increasingly being accepted by the pharmaceutical industry, says Richard Kennedy, M.D., Ph.D., VP and medical director, at Almac.

"It is not unusual now to hear from pharma companies that every drug in their pipeline has an associated biomarker and we are seeing a significant increase in companion diagnostic approvals," Dr. Kennedy says. "While there are costs associated with the development of biomarker strategies, the overall benefit is not just to the patients, clinicians, and payers; the pharmaceutical companies benefit too as having a predictive biomarker linked to their drug should lead to a higher likelihood of FDA approval and a reduction in costs associated with failed drugs."

More than 60% of Phase I pharmacologics are being studied with a companion device or diagnostic, says Kim Johnson, president, of Palio+Ignite.

"This boom in healthcare technology is the new trend in R&D and will re-structure the entire industry," she says. "These targeted diagnostics, monitoring devices, or technology innovations that increase care in hospitals and laboratories will change the way healthcare practitioners treat disease and how patients consume treatments. Risk aversion is an obstacle companies face in bringing innovations to market that are unproven. In many cases, adoption will require paradigm shifts that delay return on R&D investment. A long-term view should be considered as technology



> "Personalized medicine will continue to expand into new areas, such as cardiovascular disease."
>
> **TASSOS GIANAKAKOS** / MyoKardia

> "A greater emphasis on genetically validated targets is likely to reduce pipeline attrition due to lack of efficacy."
>
> **MARK DEPRISTO** / SynapDx

is changing the playing field. And the companies who fail in this area, will fail big."

Personalized Medicine for Cancer

Oncology has been the main area of research attention. Patients with melanoma, metastatic lung, breast, or brain cancers, and leukemia are now being routinely offered a molecular diagnosis to allow their physicians to select tailored treatments.

By 2025, sophisticated genomics-based tools will have transformed cancer care, according to a report issued this year by Quintiles.

Next-generation sequencing technologies are already playing a role in providing that broader understanding and helping medical researchers and drug developers address the challenges posed by the molecular complexity of cancer. The diverse population of tumor types and the complex molecular mechanisms involved in cancer drive the need for characterized biomarkers, which can distinguish tumors molecularly. These biomarkers must be reliable and easily accessible.

Decision Resources predicts oncology therapies will continue to dominate the predictive personalized medicine market, capturing 88% of U.S. sales in 2019.

In addition, predictive personalized drugs to treat cancer indications are forecast to account for more than one-third of total U.S. oncology sales in 2019.

For new therapies in oncology, a biomarker test will likely be a driver of sales. A separate study by Decision Resources finds that biomarker driven prescribing is likely to positively influence perceptions of emerging drugs for both oncologists and payers. Results of a survey of 100 medical oncologists and 30 medical directors and pharmacy directors of managed care organizations reveal that the majority of oncologists and payers look favorably on companion-biomarker testing.

Decision Resources researchers say payers will look favorably on biomarker-driven prescribing, and this can positively affect tier placement on formularies. Biomarker testing is expected by payers to be included in clinical pathways programs.

Cancer is a disease of the DNA and specific genetic mutations are responsible for driving the development, growth, and resistance of tumors, says Toni Schuh, Ph.D., CEO of Trovagene.

"The advancement of technology has enabled us to go forward in harvesting the value of the early work performed in sequencing the human genome," Dr. Schuh says. "The use of diagnostics is playing an integral role in developing treatments that can prolong life for those afflicted with complex diseases such as cancer. In the future, DNA analysis will become routine and provide a total genomic work up, from detection all the way to monitoring of disease, significantly improving the patient continuum of care."

Personalized medicine offers great promise in oncology clinical development and represents a significant paradigm shift, particularly with combined targeted therapies, says Nicholas Kenny, Ph.D., executive VP and general manager global oncology and hematology, at INC Research.

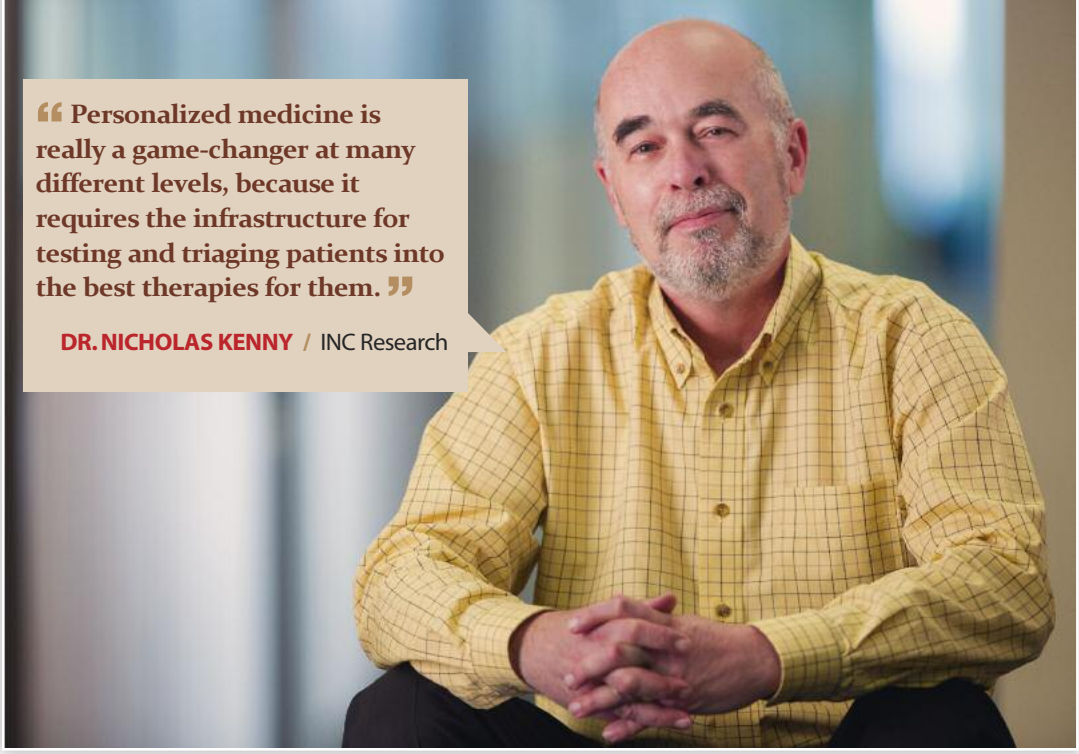
"For rare indications or particular tumor mutations that may be resistant to particular therapies, a more personalized approach is invaluable," he says. "It allows us to develop for patients better treatment options specifically matched/targeted to the unique molecular profile of their tumor."

Dr. Kenny says personalized medicine and combined targeted therapies are game changers at many different levels because it requires updates to infrastructure for testing and triaging patients into specific best-fit therapies.

"It will be about working together to determine which therapy or combination of therapies would most benefit each individual patient," he says. "There are certainly some obstacles in place that need to be overcome, such as the sharing of diagnostic data, but we as an industry are making progress."

Stephan de la Motte, chief medical advisor at SynteractHCR, says comparison of the DNA of cancer cells with the DNA of healthy tissue of the same person will help to develop therapies that are not only personalized but also disease-entity-specific.

"Therapies of the future will target cancer cells much better, and leave healthy cells less affected," he says. "DNA analysis should be able to newly identify some diseases that are caused by a single gene variant. Knowledge of



Consumer Perception of Personalized Medicine

The general public does not fully understand personalized medicine but Americans recognize the importance of choosing a treatment that is most likely to work for them and the potential to prevent illness, according to a recent survey by the Personalized Medicine Coalition.

Other findings from the survey include:

- Two-thirds (62%) have not heard of personalized medicine but the majority (65%) react positively when it is described to them and seven in 10 (69%) are interested in learning more.
- Most are excited about the potential benefits of personalized medicine and recognize the value. More than seven in 10 say major benefits are that the information gained could help them and their doctors choose a treatment that is most likely to be effective for them (76%) and give them more control to prevent or treat illness (72%).
- Almost eight in 10 would have a diagnostic test for the purposes of personalizing prevention or treatment if their doctor recommended it.
- Two-thirds (63%) immediately see the value of these emerging technologies and believe that personalized tests and treatments should be covered by insurance.

Source: Personalized Medicine Coalition

the protein products of single genes may lead to a new or better therapy. The vast majority of diseases, however, are caused by multiple factors: intrinsic, environmental, and behavioral. Once emerged, several diseases can become independent of the cause. DNA analysis alone will not be able to contribute much to improve the outcomes of those such diseases.”

Mark Goldberg, M.D., president and chief operating officer, Parexel, says with more personalized therapies, patients are receiving a medication specifically targeted to the underlying pathophysiology of their disease.

“In the case of oncology, this is dramatically different from traditional chemotherapeutic regimens,” he says. “With targeted treatments, ‘off-target’ effects are much less common, resulting in fewer side effects. In the past, chemotherapy relied upon the survival advantage of normal cells over cancer cells, but the drugs often affected healthy cells as well, resulting in significant side effects.”

Personalized Medicine Beyond Cancer

Personalized and precision medicine is expected to have an impact across many disease areas. Thomson Reuters researchers predict that DNA analysis will impact healthcare for older people as well. Analysis and understanding of the human genome will have far-reaching effects in 2025. As baby boomers begin to reach their 80s, more and more scientific research funds will be directed toward afflictions they may encounter.

“Personalized medicine will continue its expansion into new areas, such as cardiovascular disease,” says Tassos Gianakakos, CEO of MyoKardia. “By combining genetic information with existing tools for phenotyping the cardiovascular system, previously heterogenous diseases will be reclassified into subgroups, a series of rare genetic disorders. With an improved understanding of disease mechanisms, and mechanistically-informed biomarkers, companies will be able to develop molecules far more efficiently than traditional cardiovascular drugs.”

Rapid advances in DNA analysis have dramatically expanded the universe of potential genetic targets for drug development, particularly for gene-silencing technologies designed to treat disease by modulating the translation of RNA, says Sudhir Agrawal, D.Phil., president and CEO of Idera Pharmaceuticals.

“While drug candidates using these technologies can be rapidly designed to address various genetic targets with minor sequence modifications, there are few approved RNA-based drugs today largely due to very significant challenges with therapeutic index and delivery,” he says. “Over the next decade, next-generation technology platforms that effectively address these challenges may have the vast potential to exploit the growing universe of genetic targets, while reducing the time it takes to move a medicine from the lab bench to the patient’s bedside compared with the traditional development approach used with small molecule and biologic drugs.”

A Thomson Reuters report released in June

Personalized Medicine by the Numbers

- 30% of all treatments in late clinical development rely on biomarker data
- 30% of all biopharmaceutical companies surveyed require all compounds in development to have a biomarker
- 50% of all treatments in early clinical development rely on biomarker data
- 50% of all clinical trials collect DNA from patients to aid in biomarker development
- 137 FDA-approved drugs have pharmacogenomic inform in their labeling
- 155 pharmacogenomic biomarkers are included on FDA-approved drug label
- In 2014, 113 personalized medicine drugs, treatments, and diagnostics products were available compared with 13 in 2006

Source: Personalized Medicine Coalition

> **"We are just scratching the surface of the potential offered by better understanding the genome, but the potential is already apparent in targeted drugs approved for diseases such as cystic fibrosis, lung cancer, and melanoma."**
>
> **DR. MARK GOLDBERG** / Parexel

> **"The opportunity for pharma companies resides in harnessing the plummeting cost of next-generation sequencing, adopting emerging technologies and process changes, and accessing the big data revolution in healthcare."**
>
> **DR. ANNE-MARIE MARTIN**
> GlaxoSmithKline

predicted that with the proliferation of individual gene mapping and big data yielding an increasing store of information on gene expression and variation and their role in disease, the medical processes of screening and prevention will be transformed. In fact, they predict that by 2025, people will have their DNA mapped at birth and checked annually to identify any changes that could point to the onset of autoimmune diseases.

As individual genomic profiling costs continue to be reduced to a practical price, each patient should have the opportunity to have their genome fully profiled and analyzed, says Jean-Pierre Wery, Ph.D., president of Crown Bioscience.

"This will allow each person's particular disease — and the disease driver — to be better characterized and understood," he says. "Hopefully, at some point in the not-too-distant future we will then be able to use this profiling to guide the use of targeted therapies on a patient-by-patient and genome-by-genome basis."

Stephen Turner, CEO of Protea Biosciences, says DNA analysis holds great promise to identify the aberrant genetic changes that drive molecular disease processes and to identify risk factors to monitor patients to maintain wellness.

"New technology is needed that will rapidly provide molecular profiles on clinical samples, especially cell-based analysis, as this is data that defines some of the most expensive medical interventions, including cancer treatments, auto-immune diseases, and others," he says. "Data need to be provided at point of care and at significantly reduced expense."

Opportunities for Development

Experts say there are many opportunities to improve drug development with DNA analysis.

Making Personalized Medicine a Reality

In 2012, the top 10 pharmaceutical companies spent more than $70 billion annually on research and development, says Adam Simpson, president and chief operating officer of Cypher Genomics.

"Clinical trials are an incredibly expensive part of R&D," he says. "Studies have shown that validated biomarkers can significantly reduce the clinical trial risk and costs of drug development. In particular, biomarkers can identify subpopulations of patients that are more likely to respond to a particular drug and facilitate smaller and possibly shorter clinical trials, which is leading to personalized medicine becoming a reality. New technologies will be essential to quickly and accurately identify, in small sample sizes, genetic markers and their correlation with disease and therapeutic responses."

Mr. Simpson says to make personalized and precision medicine a reality, new technologies are needed that can quickly and accurately analyze and decipher clinically relevant genomic information.

"In the case of genomic-based biomarkers, there is tremendous value in markers discovered outside of the gene panels used today, as evidenced by the recent discovery of a highly predictive non-coding genetic variant for response to lithium treatment," he says. "However, only a few technologies have the potential to identify true signals from the noise of tens of millions of genetic variants detected when using the broader, yet more biologically relevant, exome or whole genome data sets for biomarker discovery in the small sample sizes typical of drug development studies."

Pieter van Rooyen, Ph.D., founder and CEO of Edico Genome, says as a result of the great demand for genomic-based tests, the amount of genomics data has skyrocketed and will only continue to surge, creating a new bottleneck: data analysis.

"There is a great opportunity for data analysis solutions that are fast and cost-effective, which will enable genomics to successfully enter the clinic and be widely used by patients around the world," he says. "Faster and cheaper data analysis solutions would have a big impact on guiding cancer treatment and diagnosis of rare diseases, where quicker results enable faster clinical decision making and decrease patient stress."

Software and cloud-based solutions for analyzing next-generation sequencing data are under development, however there are limitations, including requiring large, expensive servers and privacy issues, respectively.

Industry leaders say there will likely be regulatory challenges as well. Fundamentally, regulators have a public health imperative to bring safe and effective medicines to market to treat human disease and therefore, by necessity, they will have to adapt to be able to effectively and efficiently evaluate new technologies and treatments, along with using innovative approaches to bringing effective therapies to patients more quickly, says Karen Kaucic, M.D., VP, global head, PPD Consulting.

"Agencies will be challenged to recruit and retain appropriate technical experts, collaborate effectively with the scientific community to fully understand rapidly evolving technologies, and develop processes and procedures that provide an efficient path to approval both of drugs and companion diagnostics or novel delivery devices," she says. "But regulators don't operate in a vacuum: scientists, pharmaceutical companies, physicians, and patients operate in an ecosystem that is more closely linked than we sometimes realize. We are in an era that has seen closer collaboration among stakeholders than ever before, as evidenced by the extensive public discussion about precision medicine. At the end of the day, the most effective mechanism to build capabilities across the ecosystem is for pharmaceutical companies to continue to present novel therapies and new approaches to drug development and clinical trial design to regulators."

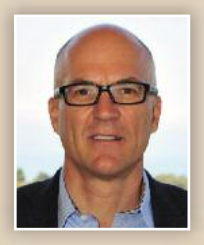
ADAM SIMPSON
Cypher Genomics

Studies have shown that validated biomarkers can significantly reduce the clinical trial risk and costs of drug development.

DR. KAREN KAUCIC
PPD Consulting

We are in an era that has seen closer collaboration among stakeholders than ever before, as evidenced by the extensive public discussion about precision medicine.

DR. PIETER VAN ROOYEN
Edico Genome

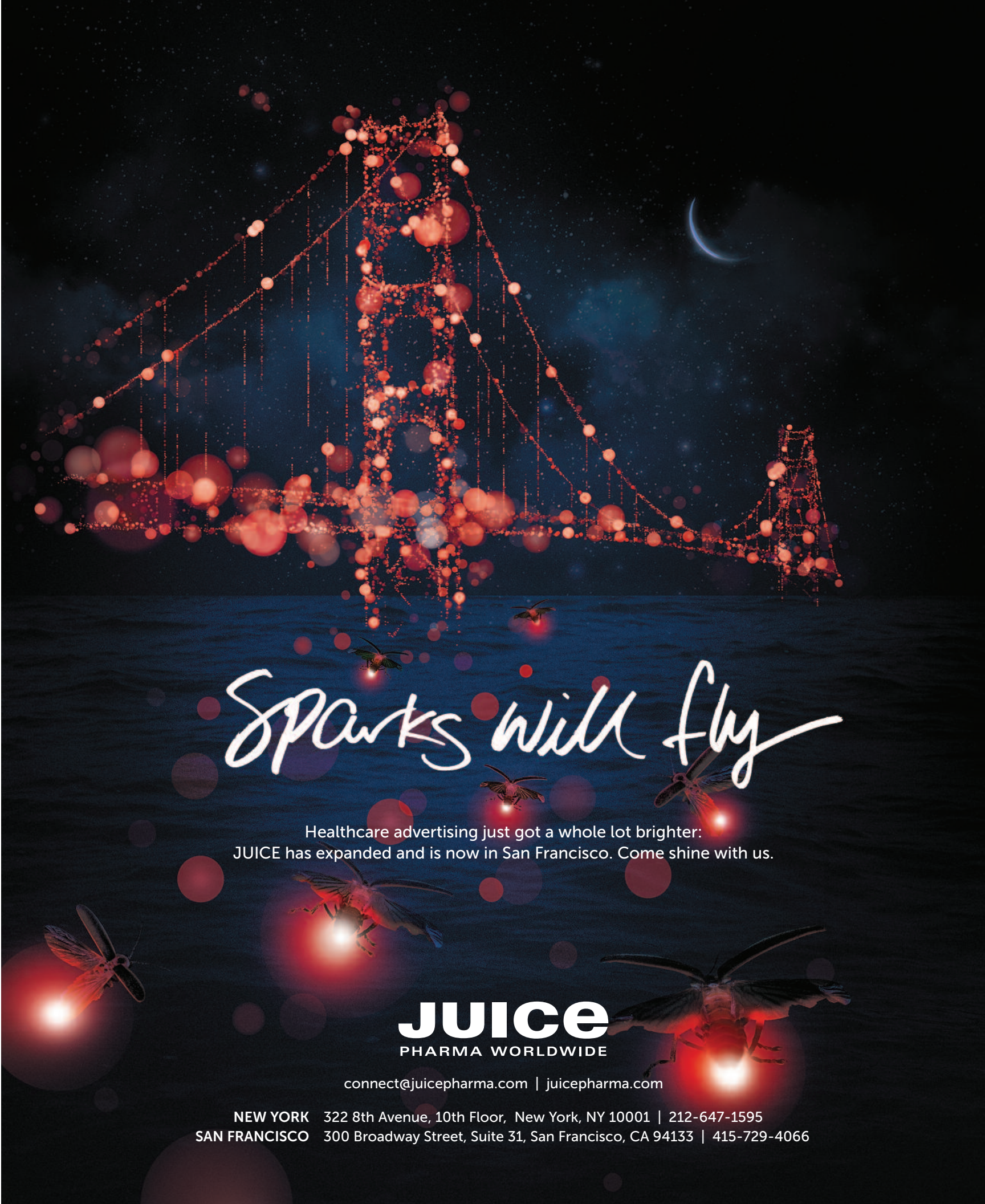


Creating industry standards is a key step that will have a big impact on the ultimate success of the space as genomic tests enter the market.

"A greater emphasis on genetically-validated targets is likely to reduce pipeline attrition due to lack of efficacy," says Mark DePristo, VP of informatics, at SynapDx. "Lower costs and increased availability of sequencing will enable us to effectively characterize the genetic profile of those who benefit most from a drug or those who experience adverse events."

The opportunity for pharma companies resides in harnessing the plummeting cost of next-generation sequencing, adopting emerging technologies, and process changes, and accessing the big data revolution in healthcare, says Anne-Marie Martin, Ph.D., head of molecular medicine and head of precision medicine and diagnostics, R&D, at GlaxoSmithKline.

"These changes mean that molecular information, combined with electronic medical records, is increasingly available to patients and their physicians for medical decision-making," she says. "In addition, the emergence of these data and the hope that it can lead to something meaningful for patients is impacting existing business models and driving the expectations whereby patients, physicians, regulators, and payers expect that the data will lead to actionable outcomes for patients. And being able to have a more comprehensive molecular snap-shot of their tumor may inform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> **“DNA analysis holds great promise to identify the aberrant genetic changes that drive molecular disease processes and to identify risk factors to monitor patients to maintain wellness.”**
>
> **STEPHEN TURNER** / Protea Biosciences

additional courses of treatment leading to greater clinical outcomes for patients.”

Martin Lee, M.D., VP, investigator relations, at PRA Health Sciences, says the costs and structures of R&D organizations will need to adapt in many ways, including improving the ability to terminate projects that have a low potential for success, forming collaborative relationships with other drug developers and service providers, and by conducting smaller and more focused clinical trials.

“High-speed computational technologies also hold the promise of accelerating innovation through big data approaches, including analysis of large amounts of patient data from electronic health records and more thorough analysis of data from the scientific literature,” Dr. Lee says.

Ms. Stafford says today’s technologies offer greater opportunities to harness real-world data and perform advanced analytics to inform better medical decisions, identify new uses, as well as improve drug development timelines and success rates.

“To capitalize on these opportunities, public and private entities must continue to enable the evolution of clinical trial design from the traditional ‘analogue and local’ model to a ‘digital and global’ one,” she says. “This includes continued investment in technologies, expedited validation and use of new tools, and importantly, improved collection and accessibility of data through the implementation of data standards. By working together to improve the quality and accessibility of data, biopharmaceutical companies and regulators can maximize the benefits of technology and analytics to advance public health and speed drug development.”

Previously, the ability to perform gene sequencing was limited, but this is no longer the case as the cost of genome and transcriptome sequencing has dropped dramatically with the availability of next-generation sequencing.

“The potential benefits of NGS in drug development include identification of previously unknown drug targets, insights into disease-related process and drug mechanisms of action, as well as the identification of polymorphisms that may impact drug metabolism or activity,” Dr. Lee says.

In the diagnostic space, the most disruptive technology is next generation sequencing, says Scott Gleason, head of investor relations at Myriad Genetics.

“The cost of sequencing a patient’s whole genome has decreased from around $100 million in the early 2000s to a few thousand dollars when we look at reagent and capital equipment costs today,” he says. “But when we incorporate the costs of performing the data analysis, and other costs, the true cost of sequencing a human genome today is probably between $10,000 and $20,000.”

Mr. Gleason says while individual whole exome and whole genome sequencing are not ready for commercial clinical use, targeted gene panels can now be run cost-effectively and accurately enough to support their use for clinical applications.

“In our core market, the hereditary cancer testing market, this has allowed for companies such as Myriad to launch next-generation gene panels that incorporate significantly more actionable genes that lead to more accurate test results, improved patient care, and lower healthcare costs,” Mr. Gleason says.

The arrival of new technologies that lower the cost of sequencing will enable genomic medicine to transform from primarily research focused to clinical applications, says Pieter van Rooyen, Ph.D., founder and CEO of Edico Genome.

“The ability to analyze DNA at lowered costs has already transformed cancer diagnosis and treatment,” he says. “Currently, patients at many of the large cancer centers have their tumor sequenced as soon as they walk in the door. Sequencing of a patient’s tumor will only improve cancer care and subsequently patient outcomes.”

Incorporating biomarkers in clinical trials supports the accelerated development of new personalized therapies and medical diagnostics, while enhancing patient safety and reducing R&D costs, says James Streeter, senior director, life sciences product strategy, at Oracle Health Sciences.

“But the use of biomarkers is creating its own set of big data challenges, especially around how to effectively collect, manage, and analyze genomic data in a trial,” he says. “Key to extending the benefits of DNA analysis into clinical research and development will be operationalizing the processes, including genomic profiling integrated with electronic data capture systems, providing decision-making insight and options for both data managers and scientists to build, conduct, and analyze these trials. The benefits are significant and include accelerated and more credible submissions to regulatory authorities; cross-study analysis of generated trial data against public domain reference data to discover new biomarkers and new indications for existing therapies; opportunities to uncover new combination therapies; and greater insight into why a trial failed.” PV

> **“Having a predictive biomarker linked to a drug should lead to a higher likelihood of FDA approval and a reduction in costs associated with failed drugs.”**
>
> **DR. RICHARD KENNEDY** / Almac

> **“At some point in the not-too-distant future, we will be able to use profiling to guide the use of targeted therapies on a patient-by-patient and genome-by-genome basis.”**
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> **DR. JEAN-PIERRE WERY**
> Crown Bioscience

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Personalized Medicine *and the* Impact on Stakeholders

As pharma companies move toward developing more targeted and tailored therapies and personalized medicine, patients, payers, and caregivers will feel the impact.

Industry experts agree personalized and precision medicine is expected to have a tremendous impact throughout the healthcare industry.

The most important consideration is the patient, says Richard Kennedy, M.D., Ph.D., VP and medical director, at Almac.

"From the patients' perspective, personalized medicine will enable improved response rates and reduced toxicity through the selection of therapies based on the molecular testing," he says. "When we look at this from the payers' perspective, targeted and tailored therapies are more economically viable as it is more likely that the drug being reimbursed will be effective. Finally, from the caregivers perspective, better therapies lead to improved patient care and reduced burden on the healthcare system."

The trend toward highly targeted therapies offering a personalized approach to treatment presents opportunities to improve patient outcomes, but also challenges in identifying patients eligible for treatment, says Sudhir Agrawal, D.Phil., president and CEO of Idera Pharmaceuticals.

"For example, despite recent advances in genetic analysis, patients and physicians often struggle with payer reimbursement of diagnostic genetic testing in certain disease areas," he says. "This problem may be particularly acute during the development phase and early lifecycle of a targeted therapy, before the rationale for reimbursement of a new diagnostic test is clearly established with payers. Therefore, to ensure that patients have access to a highly targeted therapy upon approval, it is increasingly important for companies to focus on a companion diagnostic early in the development process, and to work with disease communities and payers to incorporate them in the treatment paradigm."

Stephan de la Motte, chief medical advisor at SynteractHCR, says caregivers will face a broader variety of therapies, requiring more training.

"This will lead to a greater flexibility and diversity of delivered care, which will make caregiving more demanding but also more satisfactory, because the individuality of each human being will become more recognized and treatments will have greater success," he says.

Payer Perspective

"For payers there are also a lot of potential benefits," says Jean-Pierre Wery, Ph.D., president of Crown Bioscience. "If we can cure deadly diseases, or at least turn them into manageable chronic diseases that can be handled at home by the patient — instead of having long hospital stays — then this will in turn decrease overall healthcare costs," he says.

Tyler Marciniak, director of oncology communications and advocacy, at Astellas US, says personalized medicine has the incredible potential to impact payers, patients, and their loved ones in distinct and important ways.

"The beauty of personalized medicine lies in its efficiency and effectiveness," he says. "For payers, there is greater efficiency gained by ruling out specific treatments for patients who will not benefit from them, and instead focusing resources on finding the right treatment for the right patient. Most importantly, patients and caregivers may have access to more effective treatments to their specific disease with fewer side effects, which has an incredible impact on their quality of life."

For both payers and patients, the costs of new drugs will increase progressively as prices must necessarily reflect overall R&D spend regardless of the size of the population that may benefit, says Martin Lee, M.D., VP, investigator relations, PRA Health Sciences.

"This is counterbalanced only partially by decreased use of drugs in patients who are unlikely to benefit and the fact that personalized medicine may identify the right drug as an inexpensive generic medication," he says. "This progressive increase in costs is unsustainable in the long term, and thus major efforts will be needed to focus on reducing R&D costs in order to provide the required return on investment for pharma."

Mark Goldberg, M.D., president and chief operating officer, at Parexel, says reimbursement is a particularly vexing issue.

"More personalized therapies raise challenges for payers by virtue of the fact that the drugs are highly targeted, meaning patient populations are smaller," he says. "However, sufficient revenue must be generated to justify the R&D costs of bringing these drugs to market, a cost that must be spread across fewer patients. The result is that many highly effective medications may have price tags of tens of thousands of dollars per year. Payers are then faced with the challenge of determining the cost/benefit ratio of these treatments. For example, how does improved efficacy translate into lower costs for long-term care of a chronic disease."

Medicare will likely be influential in the area of reimbursement, say researchers at the Personalized Medicine Coalition. Medicare normally prices payments (other than for drugs, which are paid for by average market prices) as closely as possible to the marginal

Policy Concerns Impacting Personalized Medicine

1. Imminent Federal Pricing of Highly Innovative Molecular Tests

Between 2012 and 2014, there has been a wave of administrative changes in the coding and pricing paradigms for genomic tests. For many traditional genetic diagnostic tests, Medicare lowered its effective payments between 2012 and 2013. Under new legislation passed in April 2014, Medicare will establish new rules that will generally set Medicare payments equivalent to market rates for all laboratory tests.

2. Inconsistent Standards and Paradigms for Evaluating Diagnostic, Prognostic, and Predictive Genomic Tests

Health technology assessments represent a rapidly growing area of international government policy, which has accelerated in the past several years as governments seek to contain costs. Although most agree that genomic tests create a benefit by having an impact both on patient management and the delivery of treatments, many are still concerned that processes for "clinical utility" assessments are neither clear nor predictable. More objective and reliable standards for these evaluation processes need to become broadly accepted.

3. Lack of Incentives for Genomic Medicine

Unfortunately, traditional funding, pricing, or reimbursement systems fail to provide enough incentive for development of genomic medicine. These areas include funding the education of physicians and patients in personalized medicine, funding allied professionals such as genetic counselors, and creating incentives to develop new tools that could revolutionize some therapeutic areas. Initial attempts are being made to create new technologies, such as gene panel tests, for choosing among panels of generic drugs (e.g. statins and antidepressants). To the extent that such tests or processes may be difficult to patent or protect from rapid copying, it remains uncertain how these areas of personalized medicine will attract sufficient investment capital and research and development funds to permit their commercialization.

Source: Personalized Medicine Coalition

cost of the provider. Under new legislation passed in April 2014, Medicare will establish new rules that will generally set Medicare payments equivalent to market rates for all laboratory tests. Executives at the Personalized Medicine Coalition predict pricing and reimbursement issues to become worse.

Payers must look at the larger perspective, Mr. de la Motte says.

"For personalized medicine, the price per treatment will be much higher than for an off-the-shelf mass product, but there are overall cost savings," he says. "Non-responders are known in advance, and won't need the expensive treatment. Fewer unnecessary treatments mean, also, fewer unnecessary side-effects, which translates to further secondary cost savings in the treatment of side-effects."

Biopharmaceutical companies can help payers address these issues by preparing dossiers for payers that support the economic argument for their new drugs, much like dossiers of safety and efficacy data that are prepared for the FDA and other regulators, Dr. Goldberg says.

"This has given rise to a greater focus on pharmacoeconomics and commercialization strategies," he says. "We have seen growing interest in our commercialization solutions to help clients address this reimbursement challenge."

Impact on Regulators

Dr. Goldberg says personalized treatments also raise some interesting regulatory issues.

"On the encouraging side, many of these personalized treatments represent significant progress in addressing an unmet medical need," he says. "These treatments are well-suited to a number of accelerated approval pathways that have been created by the FDA and other regulators around the world. These pathways are designed to promote breakthrough treatments and allow developers to take a shorter path to market. Compelling data may be generated using smaller patient populations because of the targeted nature of the trials."

He says about 60% of drugs approved in the last 18 months used at least one of these pathways.

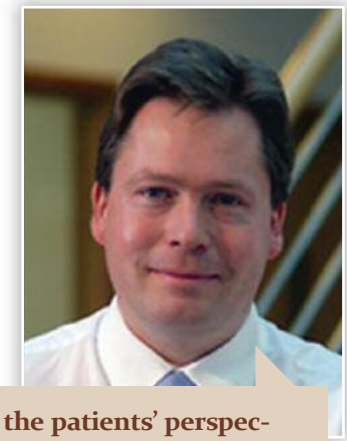
> **"Caregivers will face a broader variety of therapies, requiring more training, which will lead to a greater flexibility and diversity of delivered care. This will make caregiving more demanding but also more satisfactory, because the individuality of each human being will become more recognized and treatments will have greater success."**
>
> **STEPHAN DE LA MOTTE**
> SynteractHCR

"To make precision medicine a reality, these accelerated regulatory pathways should continue," Dr. Goldberg says. "At the same time, it is necessary to clarify the process of securing reimbursement once regulatory approval is obtained in the different markets around the world."

Mr. Marciniak says the quickly evolving science of personalized medicine has in many ways outpaced health policies and regulatory frameworks. In order to address this potential issue directly, industry leaders need to work with regulators to provide clear guidance for the evaluation and approval of personalized medicines and companion diagnostic combinations. Finding ways to increase communication and synergy between these sectors is the best way to stay on track with these developments. For example, the FDA weighed in on this when they issued guidance on companion diagnostic devices in August, which is a positive sign for further collaboration in the future.

The FDA has been more than willing to engage and collaborate on initiatives that will incorporate NGS technologies for development of cDx assays, Dr. Martin says.

"Furthermore, they are exploring ways to allow all multi analyte data to be accessible to



> **“From the patients’ perspective, personalized medicine will enable improved response rates and reduced toxicity through the selection of therapies based on molecular testing.”**
>
> **DR. RICHARD KENNEDY** / Almac

the patient and physician, even if only a small number of analysts have clinical claims,” she says. “This is a huge step forward to enable availability of more comprehensive data for patient diagnosis, treatment, and disease management, while at the same time maintaining standards and quality so that patients are not at risk. Other health authorities are following suit and I believe there is a concerted effort for regulators, pharma companies, and other PM stakeholders to find a pragmatic path forward.”

Dr. Kennedy says regulators, and particularly the FDA, are keen to keep abreast with new technologies especially as they relate to personalized medicine.

“There are FDA approved tests being delivered using qPCR, microarrays and by next generation sequencing,” he says. “There are FDA cleared platforms available for all these technologies and we have met with the FDA on a number of occasions about multiplex test both for our internal R&D work and for that of our clients in companion diagnostics development studies. All of these interactions have been very positive and shown that the agencies are keeping pace well with the industry.”

Dr. Goldberg says another interesting regulatory wrinkle in personalized medicine is the issue of companion diagnostics.

“Some, but not all, targeted therapies are approved in conjunction with new diagnostic tests that are used to qualify a patient for the treatment,” he says. “In these cases, the use of diagnostics may become part of the labeling for a new drug. The FDA has published draft guidance on the co-development of drugs and companion diagnostics. CDER and CDRH are working together to help companies wishing to undertake these types of development programs. On the business side, it is likely that new collaborations and partnerships may be required between biopharmaceutical and diagnostic companies.”

Pieter van Rooyen, Ph.D., founder and CEO of Edico Genome, says there is a great need for standards, which supports regulatory oversight of the space as well payer reimbursement.

“Well-defined guidelines, ranging from outlining the best approach for storing samples to standards for variant calling and format of reports, are greatly needed and will support regulatory and payer efforts,” he says. “Creating industry standards is a key step that will have a big impact on the ultimate success of the space as genomic tests enter the market. A comparison can be made to the cell phone industry when early technologies first became commercialized, and the space subsequently adopted industry-wide standards that enabled successful commercialization.” PV

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