Denise Myshko and Robin Robinson

Personalized Medicine From BENCH TO BEDSIDE

Pharmaceutical companies are embracing the concept of personalized medicine from research and development to commercialization.

Personalized medicine is the future of medicine. It will become standard in every hospital, clinic, and medical practice, supported by electronic records, decision support systems, and tests that analyze disease for specific genetic markers.

Traditionally, the pharmaceutical R&D path has involved testing large numbers of patients to evaluate the therapeutic effect of a molecule; now companies are narrowing their focus and determining mutations and genomics of diseases through companion diagnostics and biomarkers. Companies are interested in discovering and developing medicines that are much more targeted and personalized to specific sub-classes of patients.

And there have been successes. There are now more than 85 companion diagnostics on the market and more than 500 clinically relevant biomarkers, according to the Food and Drug Administration. Patients with melanoma, metastatic lung, breast, or brain cancers, and leukemia are now being routinely offered a molecular diagnosis that allow their physicians to select tailored treatments. While oncology has received the lion's share of research attention and funding, other therapeutic areas will benefit as well.

FAST FACT

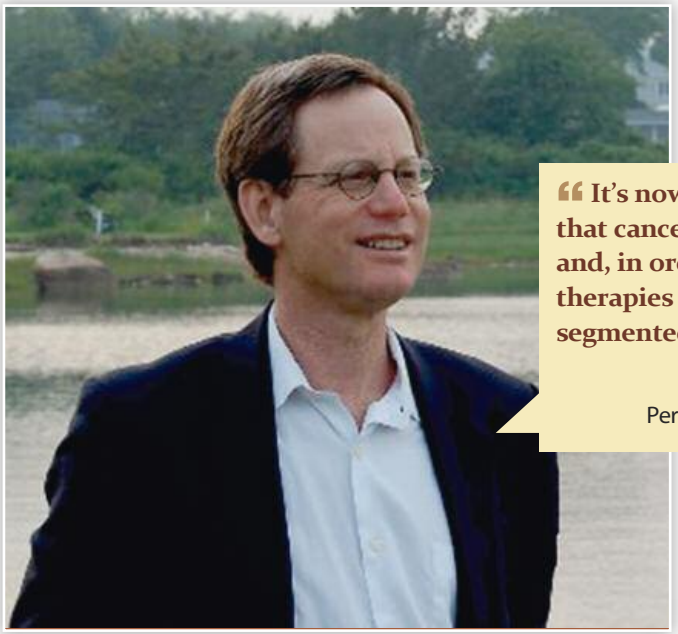
THE U.S. MARKET FOR PREDICTIVE PERSONALIZED DRUGS IS FORECASTED TO DOUBLE, INCREASING FROM $9.2 BILLION IN 2013 TO $18.2 BILLION IN 2019.

Source: Decision Resources

Long term, experts predict immunology, CNS, infectious diseases, and cardiovascular disease will be active areas of research in the area of personalized medicine. McKinsey researchers revealed several key factors that will be important for potential research, including understanding the basis of disease heterogeneity, the clinical relevance of markers, the technical feasibility, and the relative economics of diagnostics.

The President's Council of Advisors on Science and Technology defined personalized medicine as "the tailoring of medical treatment to the specific characteristics of each patient." This includes the ability to classify individuals into subpopulations who are susceptible to a particular disease or responsive to a specific treatment.

Targeted therapeutics and companion diagnostics are two important components that enable personalized medicine. Targeted therapeutics are treatments designed to benefit a particular subpopulation, or whose use in another subpopulation might be ineffective or



> "It's now well-understood that cancer is a genetic disease and, in order to be effective, therapies have to target segmented populations."
>
> **DR. EDWARD ABRAHAMS**
> Personalized Medicine Coalition

lead to side effects. Companion diagnostics are accompanying tests that can identify or measure genes and proteins associated with a targeted therapeutic. (See the digital edition of PharmaVOICE for more on companion diagnostics.)

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 genetics, says Jeff Elton, managing director at Accenture Life Sciences.

"This started in the mid- to late-1990s, but researchers found their understanding of the real underlying mechanism of disease states was not that great," he says. "Since then, the understanding of disease has grown and that is the foundation for using pathway biology and genetically determined targets when looking for new therapeutic programs. As we gain more competence and learn more about disease, therapies can be more targeted."

Economics is also a positive driver for the growing research into personalized medicines, experts say.

"The more targeted the therapy is, the higher the likelihood patients will derive real benefit," Mr. Elton says. "Historically, a therapeutic has only been 25% to 30% successful. But with targeted therapies, there is a potential 80% or 90% positive response rate. The value to the patient and health system is higher but that demands understanding in advance which patient is going to be a responder and what the response looks like."

Anecdotal examples indicate that the personalized medicine approach is working and will be successful, says Paul Harkin, president of Almac Diagnostics.

"I can only imagine that in the future the majority of new therapeutics will be delivered following some type of genomic test," he says. "Payers and health authorities are taking a harder look at the proposed value of new therapeutics, especially when the overall benefit to a specific patient population may be minimal."

"Our ability to even consider personalized medicine as a viable approach is rooted in the great progress that we have made in understanding the biology of human diseases and the realization that the underlying causes of a given disease state can be dramatically different in different patients," says Jean-Pierre Wery, Ph.D., president, Crown Bioscience. "The greatest successes have expanded our understanding of cancer biology. This is due in no small part to the progresses that have been made in genomics technologies and in the ability to characterize in great detail the genomes of cancer cells."

In addition, data and information are now available that allow for even greater learning about disease and patients.

"Because of electronic medical records and other technologies, it is much easier to bring in detailed longitudinal patient-specific data, family histories, and increasingly more affordable and actionable genomic sequence-based data," Mr. Elton says. "We are more easily able to link the work being done in therapeutics and the knowledge of who may be a potential responder to drive benefit to patients and value to the health system."

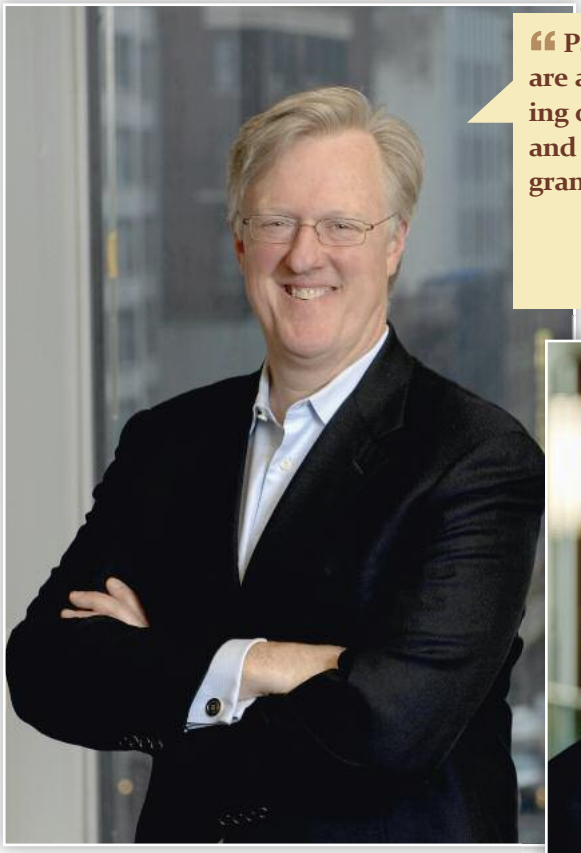
Research of Personalized Medicine

The promise of personalized medicine is

Four Steps to Integrating Prescription and Device Commercial Strategies

According to Scott Rairigh, global marketing leader, companion diagnostics at Janssen, and Peter Hoehn, global business leader at Janssen Diagnostics, there are four major elements they consider when integrating commercial strategies.

1. **Ubiquitous Access:** Make sure the diagnostic is available everywhere in the world. This includes access to technology, lab services, and favorable reimbursement. Some companies may have a diagnostic test developed for a platform that is not available in all regions.
2. **Strategy Integration:** The development of the diagnostic commercial strategy must be aligned with the pharmaceutical brand strategy. Considerations should start early in the process and include the branding of the diagnostic, the target product profile, and the positioning to make sure it is well-integrated into the commercialization strategy of the brand.
3. **Adoption Strategy:** Diagnostics require more time to be adopted into the marketplace than drugs do, for several reasons, but one is that they don't get the same promotional effort as a drug. Another reason is there are many more questions and more complexity around processing a diagnostic, so this must be considered and invested in through medical education, key opinion leader support, guidelines, etc.
4. **Postmarket Support:** Just like with drugs, there are many elements that can go awry postmarket for diagnostics, but they are different issues from those for drugs, so pharma companies may not be aware of the need for postmarket support. For instance, test results may be erroneous or there may be supply issues with the diagnostic test kits and there may be reimbursement issues or challenges, or problems with sample delivery. All these issues with diagnostic tests need to be supported in the marketplace to provide a positive experience during launch.



> "Pathway biology and genetics are accelerating our understanding of disease, and accelerating and growing new therapeutic programs across the industry."
>
> **JEFF ELTON** / Accenture Life Sciences

> "Biomarkers, when placed at the core of R&D programs, can reveal essential information about a drug's potential earlier in the development life cycle."
>
> **JOEL HASPEL** / Oracle

> "There have been a lot of recent successes that further highlight the utility of a personalized medicine approach."
>
> **DR. JEFF LEGOS**
> GlaxoSmithKline

having a tremendous impact on R&D conducted within pharmaceutical companies, particularly in the use of biomarkers and genomic information. Today, a majority of companies embrace personalized medicine, and nearly half of the preclinical and Phase I assets in the pharma pipeline have associated diagnostics, especially in oncology, immunology, and CNS, according to a 2013 analysis by McKinsey.

Biomarkers are playing a more critical role in the pharmaceutical research and development process, and as a result their use in clinical trials is growing, says Joel Haspel, director EMEA healthcare strategy, at Oracle.

"This is because through biomarkers, upcoming drugs will target new mechanisms of action, address specific subpopulations, and fill the need for safer and more effective treatments," he says. "Biomarkers, when placed at the core of R&D programs, can reveal essential information about a drug's potential earlier in the development life cycle."

Oncology: A Major Personalized Medicine Driver

Oncology is one of the most active areas of research of personalized medicines. Oncology has enjoyed tremendous success in developing targeted therapies that are addressing very specific molecular targets or pathways in cancer cells and therefore work extremely well for patients whose cancer is driven by alteration in these targets or pathways. Examples of such targeted therapies on the market include Novartis' Gleevec, AstraZeneca's Iressa, and Genentech's Tarceva.

"It is clear that in cancer, genomics technologies have played a great role in helping to unravel underlying mechanisms of cell transformation," Dr. Wery says.

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.

"My guess is that almost all of the drugs in oncology have companion biomarker strategies incorporated into their development plans," says Edward Abrahams, Ph.D., president of the Personalized Medicine Coalition. "It's been well-understood that cancer is a genetic disease. In order for these drugs to receive approval, they have to be effective and to be effective they have to target segmented populations. We're seeing an increased commitment from the industry, especially in oncology, but not only oncology, to personalize medicine."

Jeffrey Weisberg, VP of medical affairs, oncology at Worldwide Clinical Trials, says after the sequencing of the human genome, researchers realized that cancer was a lot more heterogeneous than originally thought.

"Some cancers have specific mutations and some do not," he says. "As a result of that heterogeneity, tumors respond to drugs differently. That is why there is a great need in the field of oncology to personalize the treatment. While patients may have the same tumor, the mutations of that tumor will influence the success or failure of many drugs."

Ronnie Morris, M.D., president of Champions Oncology, says the companies he works with are looking at genomic information for all the participants of their trials and they're all trying to come up with a genetic level hypotheses for the drugs they are developing.

Dr. Wery says the key is to gain a greater understanding of the biology underlying each sub-type of cancer.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> "As more and more therapies are being designated with breakthrough status or expedited consideration for approval, there is a need for a similar path for linked diagnostics."
>
> **DR. WALTER KOCH**
> Roche Molecular Diagnostics

"That understanding helps research groups identify novel targets and pathways and novel intervention approaches that eventually can be turned into novel targeted therapies," he says.

Oncology, historically, has received a disproportionate share of funding from the National Institutes of Health, Mr. Elton says.

"'The War on Cancer' that began 40 years ago led to more research in cancer and that has created a lot more insight about the disease," he says. "We know that a cancer doesn't just have one mutation. Oftentimes, tumors have multiple mutations driving the cancer. Now that we understand that, we can adjust treatment strategy."

Mr. Elton says the technology to interpret genomic data is improving over time.

"We're now seeing community oncology sites that are employing next-generation sequencing," he says. "We're seeing regional hospital systems in areas that are geographically dispersed deploying sequencing technology. At one point in time, this would have been found in academic medical and comprehensive cancer centers. Now, this technology is available to any oncology patient anywhere."

A Personalized Approach to Combination Products

Industry leaders say combination products will likely be an important part of the personalized medicine strategy. For example, GlaxoSmithKline's combination therapy of Mekinist (trametinib) and Tafinlar (dafrafenib) received accelerated approval in January 2014 in the United States for use to treat patients with melanoma with a BRAF V600 mutation. Both were approved as single agents in May 2013 for treatment of BRAF V600 mutation-positive metastatic melanoma.

"While these medicines represent a significant advancement for the treatment of metastatic melanoma, the limitation of these single agent inhibitors is that after six to seven months disease continues to progress in about half of the patients," says Jeff Legos, Ph.D., VP and medicine development leader at GlaxoSmithKline. "Over the past two to three years, there have been numerous publications showing various mechanisms of acquired drug resistance, meaning the tumor acquires new modalities to continue to grow, and the majority of these rely on reactivation of the MAP Kinase pathway."

Dr. Legos says GSK tested these two drugs in combination to evaluate whether they could delay the development of this resistance that may be mediated through this important pathway.

"The Phase II data, which was the basis for approving these drugs in combination in the United States, showed improved response rates and duration of response for the combination relative to the single agents," he says.

Dr. Legos says while combination therapies are nothing new for oncology, what's novel about what GSK has done is to combine these agents in Phase I development when neither single-agent drug was approved nor had confirmatory Phase III data.

"This was a very scientifically driven approach," he says. "We are now seeing that combination programs are starting much earlier in Phase I development in individual companies, as well as across companies, based on science."

(Editor's note: In April, GlaxoSmithKline announced an agreement to divest its marketed oncology products to Novartis, and Mekinist and Tafinlar are part of this transaction. GSK continues with it research in the oncology area, and Novartis will have the opportunity to commercialize future products that come from GSK's pipeline.)

Research is beginning to move away from the concept of a single drug being a silver bullet for addressing many diseases, says Jeffrey Spaeder, M.D., chief medical and scientific officer, at Quintiles.

"This is especially true in the oncology area, and there is more focus toward identifying specific pathways that may be affected in individual patients and developing therapies specifically for those pathways," he says. "We are seeing a lot of work with customers increasingly developing combination approaches."

Mr. Haspel says for personalized medicine to be fully realized there is a need to collect enormous amounts of data, including medical history, lifestyle information, genomics, and environmental influences.

"Then we need to truly understand all the information and how it relates to disease," Mr. Haspel says. "A first step is to create a stratified medicine program that collects and integrates the available phenol- and genotype data to identify a new class of patient subgroups. This new real-world data will help in the reclassification of diseases at the molecular level,

Precision vs. Personalized Medicine

Precision medicine is the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment. Precision medicine conveys a more accurate image of diagnosis that is person-centered and multifaceted.

Personalized medicine has been defined by President's Council of Advisors on Science and Technology as the tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Products and diagnostics developed through precision medicine facilitate the practice of personalized medicine.

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Physicians Not Ready for Impact of Personalized Medicine, But Patients Are

Bioceutics, in association with Adelphi group and Medefield, conducted a study on attitudes, awareness, challenges, and opportunities regarding personalized medicine. The results signify multiple opportunities for all stakeholders to develop resources that help accelerate the incorporation of personalized medicine into clinical practice.

They surveyed 443 physicians in the United States and European Union, including primary care physicians (PCPs), cardiologists, oncologists, and neurologists in the fourth quarter of 2012. Questions covered a broad range of topics on genomics, molecular diagnostics, targeted therapies, and physician-patient interactions. The results revealed significant gaps in knowledge, confidence, patient engagement, and communication regarding personalized medicine.

- Across all specialties in the U.S. and EU, close to 90% of physicians expect personalized medicine to have a significant impact on their practice.
- Despite their optimistic attitude, only one out of 10 physicians believe they are up to date with current advancements in personalized medicine, with the exception of oncologists.
- One-third of oncologists said they were "very familiar" with current issues in personalized medicine.

Bioceutics has also been tracking social media sentiment to new therapy launches and reports that Pfizer's Xalkori, approved for ALK+ non-small cell lung cancer that has spread to other parts of the body, received 10 times greater positive or neutral sentiment than untargeted treatment launches, indicating that testing clearly provides a new opportunity for both patients and physician communication. In fact, despite the lack of major corporate investment in diagnostic communication, research shows there are three times more Internet discussions on diagnostics than on therapy. Pfizer's cancer patient site — canceritspersonal.com — is an example of how pharma can reach beyond the physician to engage patients in a dialogue about testing and treatment choices.

Source: Bioceutics. For more information, visit bioceutics.com.

enable innovation in how to demonstrate clinical efficacy, and enable the right therapeutic combination for each patient and encourage novel partnerships and collaborations."

Dr. Wery says the biggest challenge with personalized medicine is the overall low efficiency of the drug discovery and development process.

"There is a very great need for the pharmaceutical industry to become more efficient," he says. "When we analyze the underlying causes of inefficiencies, we find that one of the major hurdles is the poor record of translating exciting preclinical discoveries into clinical successes. To address this situation many pharmaceutical companies have started translational sciences initiatives. One of the great tools that has emerged is the development of more predictive animal models."

Chuck Baum, M.D., Ph.D., CEO of Mirati Therapeutics, says an additional challenge of developing personalized medicines is the lack of a diagnostic test that can be used broadly.

"In most cases, the physician and clinical sites have to do a separate assay for every different drug rather than have a single assay that can pick up the different mutations," Dr. Baum says. "If there could be a single assay, this would make it a lot easier and more cost-effective for sites. Within oncology, sites are doing more sequencing, but it is still a hurdle."

Mirati Therapeutics' lead programs are MGCD265, a kinase inhibitor for solid tumors in Phase I trials, and mocetinostat, a spectrum-selective HDAC inhibitor in Phase II trials. Because there isn't an existing assay to identify these patients, the company has had to develop its own prototype test and will partner for approval of the test.

GSK partnered with BioMerieux to develop the companion diagnostic test required to support the FDA approvals for Mekinist and Tafinlar.

As science and technology continue to evolve, Dr. Legos agrees that the future of diagnostic testing will expand beyond a single test for a single mutation toward a multiplexed approach of evaluating large numbers of genes simultaneously.

"One of the biggest breakthroughs in terms of technology is the decrease in turnaround time and the cost of sequencing, which may eventually help identify additional genes of interest to inform personalized treatment for patients," he says.

The Holy Grail of personalized medicine is considered to be the ability to sequence the entire genome. And with the costs of whole-genome sequencing falling — $100 million to $300 million in 2001 and $1,000 in 2013 — the industry is moving ever-closer to revolutionizing the practice of medicine. Illumina,

> **"Research is beginning to move away from the concept of a single drug being a silver bullet for addressing many diseases."**
>
> **DR. JEFFREY SPAEDER** / Quintiles

which develops tools for DNA and RNA analysis, announced a new technology to sequence a patient's entire genome for $1,000 — when used at large scale.

But experts say whole-genome sequencing won't provide all the answers.

"Sequencing cancer cells requires a different approach; we have to do much deeper sequencing in order to detect the alterations that are in low abundance," says Walter Koch, Ph.D., VP, head of molecular research, at Roche Molecular Diagnostics. "Even the best centers are primarily still sequencing panels of genes. This makes more sense initially than trying to sequence everything."

Another limitation of sequencing the entire genome is that the science has not yet evolved to make sense of those genomes.

"We don't know what to do with an entire genome today," Dr. Koch says. "This is a wonderful discovery tool and will continue to be used in genome centers around the world to learn not only more about cancer but also diseases that have a genetic origin. But for myself, who is developing actionable diagnostic tests to try to gain regulatory approval, it does not make sense to sequence the whole genome.

"For those developing therapeutics, it makes sense to focus on the particular pathways that are being targeted and to sequence those genes whose proteins are known to play a role upstream or downstream or that interface with the particular enzyme or receptor that is being targeted," he continues.

New Development Models

The development of personalized medicine is spearheading new approaches to clinical trials that use a more adaptive model.

"This new transformative process helps to generate targeted treatments that lead to more effective trials resulting in faster times to market with improved safety at an overall lower cost," Mr. Haspel says.

Dr. Weisberg says it is because of the heterogeneity of cancer tumors that researchers are now using mutation-specific designs for protocols involving oncology medicines. One of the big challenges of developing personalized medicines is finding the subset of patients who have the mutation a drug candidate can address.

These trials involve many sites and include many companies contributing their pipeline products.

"One biopsy could be used to test for 200 mutations and then investigators can match up the mutation with the appropriate drug," Dr. Weisberg says. "Before the advent of next-generation sequencing, the cost of doing clinical trials with so many screen failures was unsustainable. But with this new model of using one biopsy to test for many possible mutations, it's now become feasible to do such a trial for these mutations."

As companies move from a linear to a biomarker based R&D process, data are being integrated across the discovery, development, and postmarket analysis phases. (See our bonus digital text for more about biomarker-driven trials.)

Addressing the Commercialization Strategy of Personalized Medicine

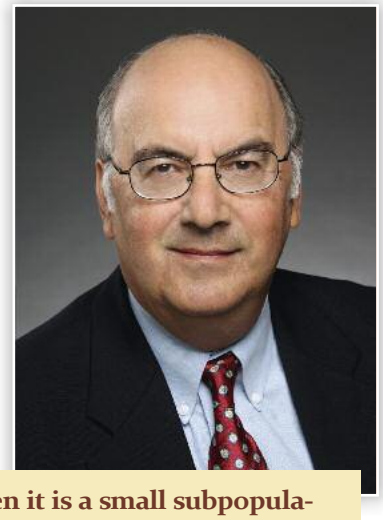
The emergence of personalized healthcare is changing the marketing landscape forever. Since 2011, the FDA has approved four cancer drugs that use a companion diagnostic test to target appropriate patients, signaling an emerging era of medical product development. The field of oncology has been using diagnostics for decades, but as more pharma companies look outside the cancer field to apply personalized medicine to other disease states, the need for pharma and diagnostics companies to work together on marketing strategies only increases.

According to analysis by Bioceutics, a marketing and education consultancy focused on personalized healthcare, the top 40 companies studied have about 400 assets in development that are currently moving through Phase II and III. If approved, they will have a biomarker in their therapy label. Of these, 80% of the products are in oncology, and the remaining 20% are spread across mostly the cardiovascular, infectious disease, and central nervous system areas. Bioceutics predicts that the convergence of prescription and diagnostics combined with the new communication channels available to personalized medicine will transform the commercial landscape in the next three to five years.

This new personalized medicine marketplace will require two traditionally separate business organizations — pharmaceutical and diagnostics — to become close partners. In response to the emerging personalized medicine market, the industry is starting to integrate its diagnostic efforts with its drug development efforts, by creating specific teams in-house and developing partnerships externally to promote a more cohesive commercialization process between the two. Uptake has been slow, although some companies such as Roche and Janssen are out in front with the creation of their own in-house capabilities. Other companies are still struggling to understand how personalized medicine applies to their pipeline and if there is a scientific opportunity for a diagnostic. Our experts say this lack of clarity is slowing adoption and execution across the industry and it may take as much as another 10 years before full integration of the two commercial strategies becomes the norm.

"The future will require integrated solutions, but historically pharma commercialization and diagnostic commercialization have happened in isolation," says Peter Hoehn, global business leader, Janssen Diagnostics.

> **"We have implemented a competency model to help our pharmaceutical partners understand the complexities of the diagnostics industry."**
>
> **SCOTT RAIRIGH** / Janssen



> **"Often it is a small subpopulation that harbors a mutation, and finding those patients with that mutation is a challenge for personalized medicine trials."**
>
> **DR. JEFFREY WEISBERG**
> Worldwide Clinical Trials

"As an industry we must bring the two together, because there will be no success if a company just focuses on the pharma piece and assumes the diagnostic piece will fall into place."

To capitalize on the rise in personalized medicine products coming down the pipeline, pharmaceutical companies need to start now to consider companion diagnostics along the decision-making process of their marketing strategies.

"We believe that 50 non-oncology targeted therapies will be arriving into the market in the 2016 to 2017 timeframe," says Sanna Paakkonen, senior VP, managing director at Bioceutics. "Considering it takes two to three years of detailed prelaunch planning to integrate a biomarker well into a personalized medicine commercialization strategy, then most pharma companies should be in planning today."

"The traditional pharma education, communications, and marketing rules no longer apply," Ms. Paakkonen says. "New disruptive thinking is needed to fully leverage the opportunities around targeted therapies and companion/complementary diagnostics and to break away from the traditional pharma commercialization approach."

Creating a better understanding of what changes when a diagnostic is added to a therapy is crucial to adoption, she adds.

"If you ask many commercial executives outside of oncology if therapy targeting with a biomarker is a plus or a negative to commercialization, they will talk about the downsides of subsetting markets and complexities of partnering with diagnostic companies," she says. "This avoidance bias is born from a poor understanding of where and when a diagnostic can be leveraged to deliver greater brand equity."

In 2012, Janssen Pharmaceuticals R&D rose to meet these challenges by establishing its own diagnostic company, Janssen Diagnostics. The goal was to create a group that focuses specifically on developing, integrating, and openly commercializing diagnostics that support its therapeutic areas, strategy teams, and specific compounds.

"Janssen Diagnostics was developed to make sure we had in-house capabilities around the diagnostic components of personalized medicine, particularly around diagnostic development, diagnostic technology, reimbursement, regulatory, business development, commercialization, and even policy," Mr. Hoehn says. "We work with our development teams and commercial strategy teams to help identify, develop, and commercialize diagnostics that support our compounds and disease area strategies."

Janssen Diagnostics had determined that getting all stakeholders across all functions on the same page in terms of integrating the two commercialization processes would be key to success. Partnering with Diaceutics, Bioceutics' parent company, Janssen developed a Dx-Excellence Toolkit to ensure employees understood the key business questions across the development pathways of both the drug and the diagnostic. The toolkit includes a custom competency module, a personalized medicine glossary, functional area route maps, and key business questions that are contextualized with case studies and tutorials. Scott Rairigh, global marketing leader, companion diagnostics at Janssen, was instrumental in developing the toolkit and integrating diagnostics training and education within the organization.

"The point of the diagnostics toolkit is to ensure there is consistency in approach among all the teams," Mr. Rairigh says. "The template with the key business questions for diagnostics is aligned with the pharma development process and that was really important to make sure our pharma partners really understand the complexities of the diagnostics industry."

The toolkit creates an awareness on how diagnostic products are developed, how they are used in the marketplace, how patient blood or other tissues used for diagnostics must travel in various markets of the world, as well as an understanding of the regulatory and reimbursement landscape associated with diagnostics.

"There is a whole realm of complexity within diagnostics that is really important for our pharma colleagues to appreciate," Mr. Rairigh says.

> **"Pharmaceutical marketing needs to adapt to the fact that the patient journey often starts with testing first and treatment second."**
>
> **SANNA PAAKKONEN** / Bioceutics

This type of alignment in-house helps alleviate the challenge of silos that often result in the drug and the companion diagnostic being marketed separately.

"There needs to be commercial acknowledgement that when a diagnostic is added to a therapy, it fundamentally changes the product," Ms. Paakkonen says. "Most pharma commercial teams do not automatically accept that interdependence and are creating a one-size-fits-all marketing strategy for a targeted drug, which actually distances the targeted drug from the relevant test."

In May 2013, the FDA approved Roche Holding's cobas EGFR Mutation Test as a companion diagnostic for Tarceva, or erlotinib, a nonsmall-cell lung cancer drug developed by Roche's Genentech.

Ms. Paakkonen says Genentech's promotional messaging did not emphasize the diagnostic piece to the drug, firmly separating the drug from the test it needed to be most effective. Even though Tarceva was previously approved for use in people with advanced-stage NSCLC and other indications without the mutation test, adding the test helps target the 10% to 30% of people worldwide with lung cancer tumors who test positive for EGFR mutation. Ms. Paakkonen views this as a missed opportunity in terms of the commercial strategy.

"Genentech opted for a test-independent

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positioning in its marketing materials despite the fact that competitor Iressa from AstraZeneca, with a similar mode of action, mentions the diagnostic testing in its marketing materials," she says.

AstraZeneca partnered with European DxS Diagnostics in 2009 to begin marketing its companion diagnostic, TheraScreen EGFR29 Mutation Kit, for Iressa.

Commercialization Challenges

Personalized medicine creates added value for all sides in the healthcare industry, making it a multiple win across patients, physicians, payers, and even regulators. The industry must gain competency and understanding in this new arena, and appreciate the value this approach has beyond its therapeutic products.

Companies will want to think more broadly around diagnostics and expand beyond the field of oncology to determine how these can be used in other disease areas to help change and improve the patient journey.

"Companies will need to think more expansively about the opportunity of diagnostics to support pharma strategies," Mr. Hoehn says. "For example, complementary diagnostics — as opposed to companion diagnostics — may not directly relate to a specific compound, but still can provide a lot of value to the patient, which can bring more value to the drug and the disease area."

Before the industry can go too far with this concept, the science needs to be available to bear out the diagnostic. These days most development teams with a discovery target or drug in early development look for response markers that might clearly identify who will respond best to the drug, but sometimes the science does not exist to provide that, Mr. Hoehn says.

"There is a lot of talk internally and externally about whether pharma is ready for personalized medicine and diagnostics, and I think the industry is ready, but still the biggest challenge is that the science is not always there," he says. "The science of oncology, for example, is much more advanced than in other therapeutic areas."

Each market is different in terms of the market preparation needed in advance of launching a targeted therapy and the diagnostic, but one challenge that remains consistent is that diagnostics are not being considered early enough in the commercialization process. A major challenge for both commercial and R&D teams is to think strategically about these initiatives early on in the pharma development process, Mr. Rairigh says.

"Opportunities can be found and potential breakthrough innovation can take place when all of these issues are considered earlier in the pharma development process," he says. "As we as an industry move closer to disease interceptive therapies, personalized disease strategies and identifying patients who will best respond to treatment, we need to integrate the diagnostic process at the start of the drug development process."

"Not everyone appreciates that diagnostic development also takes years and if a diagnostic combination is the goal, preparation needs to be done early, " Mr. Hoehn says. "A diagnostic component can't be added in Phase III of the therapeutic development."

But that is exactly what happens in most cases, says Ms. Paakkonen, and this strategy will not meet with success.

"Our experience with oncology suggests that most pharma commercial teams leave the diagnostic strategy until late in Phase III, when frankly it is too late to ensure an efficient diagnostic market is available to support the therapy at launch," she says.

"For example, Pfizer did not manage the test communications well on the therapy launch with Selzentry and CCR5 testing, because of late planning, and this eventually damaged the brand and triggered all sorts of post-launch diagnostic rescue strategies."

Each market has its own nuances where the brand may be loose or gain share in terms of these opportunities, and careful monitoring must take place to identify any gaps. For example, if the laboratory footprint is suboptimal for the therapy needs or is poorly communicated, the lost opportunity is measured in terms of lost prescriptions as not all potentially eligible patients will be tested. By identifying, early in the process, what the potential leaks around the opportunities are, the leaks can be avoided or minimized.

"Pharma marketing will need to adapt to the fact that the patient journey often starts with testing first and treatment second and the manner and quality of that interaction between the patient and the test will have an impact in their dialogue with physicians," Ms. Paakkonen says.

The pharma organization also needs to support the diagnostic through the entire commercial process, or else the diagnostic will lag behind in awareness and adoption from the drug.

"The diagnostic market is very fragmented, the returns are much lower, reimbursements are lower, so a diagnostics company is not going to develop and commercialize a diagnostic on its own, especially for small populations," Mr. Hoehn adds. "Once pharma has identified a potential diagnostic that could support its therapeutic strategy, then pharma has to make that happen, because it won't happen on its own."

Another challenge to consider when integrating commercialization strategies is the increased pressure and scrutiny of healthcare expenditures and narrowing reimbursement.

> **"Companies will have to reconcile their strategies with the reality that only those patients who will benefit from a particular therapy will receive coverage for it."**
>
> **GREG RICHARD**
> Interpace Diagnostics, PDI

According to Greg Richard, general manager, Interpace Diagnostics, PDI, companies will have to reconcile their strategies with the reality that only those patients who will benefit from a particular therapy will receive coverage for it.

"At some point, payers whether government or private, will insist that the tools to determine which therapy will be most effective in a given patient are used before providing coverage for it," Mr. Richard says. "Companies should consider using experts in molecular and companion diagnostics as well as health economics to ensure the commercialization plan adequately addresses this important element."

As companies become more committed to providing integrated solutions, long-term planning and investment will follow.

"Our pharma business is extremely committed to the idea of personalized medicine and diagnostics working together to provide better care for patients," Mr. Hoehn says. "For all of us, personalized medicine means changing the way healthcare thinks about integrating pharma and diagnostics, and this change will continue to bear out over the next decade or so." PV

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Companion Diagnostics and PERSONALIZED MEDICINE

Companion diagnostic tests are a vital part of personalized medicine that can yield crucial information necessary for guiding therapeutic treatment decisions.

There is growing acceptance of the need to work with diagnostic company partners early on in the development of personalized medicines. Experts say they have to have a strategic approach for targeted therapeutics that is combined with the biomarker test. This requires an organizational change and an awareness of the need for an integrated approach.

Walter Koch, Ph.D., VP, head of molecular research, at Roche Molecular Diagnostics, says he sees more companies approach the development of the companion diagnostic earlier in the process.

"If companies wait until they are completing Phase II trials to start a pivotal Phase III with an assay and a biomarker, that's problematic," he says. "It takes time to have an assay locked down and verified to the extent that it can gain registration approval at the same as the drug. This means that both programs need to be aligned in both the development process and the regulatory approval process."

Biomarkers are playing increasingly important roles, and one disease area, cancer, is getting much attention.

In 2012, the global DNA diagnostics market was valued at more than $17.3 billion, according to BCC Research. The total market is projected to grow at a CAGR of 12.6% from 2013 through 2018 to reach $36.5 billion by 2018.

Within the global DNA diagnostics market, the market for polymerase chain reaction-based diagnostic assays claimed the largest share in 2012 with an estimated $8.3 billion. The PCR diagnostics market is projected to grow at a five-year CAGR of 11.5% to reach $16.3 billion by 2018.

Molecular screens for oncology applications will be one of the key drivers for the clinical use of diagnostics. Total demand for products in this area is projected to grow at a CAGR of 13.4% from 2013 to 2018, BCC Research predicts. While microarrays are and will remain the top revenue contributors, the highest growth will be seen in the development and approval of novel biochips. Microarray revenue equaled $1.8 billion in 2012 and will grow by a CAGR of 13.2% to reach $4 billion in 2018. Biochips are projected to increase at a CAGR of 19.9% and reach $2.5 billion in 2018.

McKinsey experts say payers, even though they are pushing back on tests that have limited clinical actionability, are beginning to mandate diagnostics to ensure proper use of therapeutics. In the long term, McKinsey predicts that the advances in understanding the linkages between genotype markers and diseases will make these tests clinically relevant and impact healthcare outcomes.

Regulatory Environment

A draft guidance by the FDA's Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and Center for Biologics Evaluation and Research defined a companion diagnostic device as an in vitro diagnostic that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

Personalized medicine diagnostic tests can be either IVD products, regulated by the FDA under the device authorities, and/or laboratory tests regulated under the Centers for Medicare and Medicaid Services under the Clinical Laboratory Improvement Amendments (CLIA).

"Any diagnostic test that is used to make a therapeutic decision is elevated to the highest risk category because we take on the same risks in terms of safety and efficacy as the therapeutic," Dr. Koch says. "We are governed by the FDA's regulations, so we have to obtain premarket approval for these in vitro diagnostics, which can then be broadly distributed to high-complexity laboratories. Those laboratories are regulated by CLIA whereas our IVD tests are regulated by the FDA."

In 2011, the FDA issued a draft guidance document pertaining to the process for approving targeted therapeutics and their accompanying companion diagnostics. According to this guidance, where a companion diagnostic is essential for the safe and effective use of a targeted therapeutic, the FDA would regulate the companion diagnostic as a medical device and subject that test to the FDA premarket review process.

More recently, in April 2014, the CDRH issued two draft guidances to address devices for unmet needs for life-threatening diseases. In the first, the FDA plans to provide more interactive communications during device development and more interactive review of investigational device exemption applications and PMA applications. In addition, the FDA intends to work with the sponsor to create a data development plan specific to the device.

The second draft guidance addressed post-marketing collection of data for those given devices on this expedited path.

"As more and more therapies are being given breakthrough status or expedited consideration for approval, there is a need for a similar path for a linked diagnostic," Dr. Koch says. "You wouldn't want the diagnostic to languish behind and not be available at a time when a breakthrough therapy is being made available for a patient that has a serious condition. A new draft guidance would provide a similar expedited access for premarket approval of medical devices that are intended to address these unmet medical needs for life threatening disease." PV

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