The Innovation CHALLENGE

Innovation continues to be a hot topic in pharma R&D. But developing truly innovative medicines will require companies to embrace nontraditional partnerships, have a focus on genomics to get a better understanding of disease, and adopt systems biology and big data approaches to create a more efficient environment.

Pharmaceutical companies have been trying to address the innovation gap for some time now. They are working with smaller biotech companies as sources for new products. They are exploring targeted therapies. They are seeking out new kinds of collaborations. They are focusing on orphan drugs. They've outsourced and optimized R&D.

Still, the innovation gap persists.

Companies are innovating less in comparison with 10 to 20 years ago, says David Rear, president of Advanced Clinical Concepts.

"Larger pharma companies seem to be more focused on managing costs, so they remain risk averse," he says. "Instead of developing new drugs, they are focusing on the licensing of products from smaller companies. While this approach reduces their risk and investment into new products, they are also innovating less. Less innovation means fewer new products, more me-toos, and greater competition for physician attention. Ultimately, patients lose."

Mr. Rear says innovation today is coming out of smaller or specialty-oriented companies.

"They are the ones taking the risk and pushing the envelope to create new drugs," he says. "They also tend to be more niched, focusing only on specific areas, such as antibiotics or immunology."

Industry experts say new types of partnerships will be required to address the industry's innovation gap. Alliances, collaborations, and consortia will continue to drive improvements in clinical success, while reducing total spending, with drug developers retaining only those functions they consider core competencies, according to leaders recently convened by the Tufts Center for the Study of Drug Development.

A growing emphasis on academic and nonprofit organization partnerships could rescue the pharmaceutical industry from the redundancy of an inefficient R&D model and plug the so-called innovation gap, according to an April 2013 report from GlobalData.

FAST FACT

THERE WILL BE A RETURN TO GROWTH FOR THE PHARMACEUTICAL INDUSTRY THROUGH 2018, WITH NEW DRUG APPROVALS AND INCREASED R&D PRODUCTIVITY.

Source: EvaluatePharma

GlobalData analysts argue that collaboration in drug development benefits both parties, with academia constantly looking for sources of research funding while the pharmaceutical industry would gain a partner to share in the high risks and substantial costs of bringing new medicines to market.

Focus on Biotech and Orphan Drugs

Industry experts also point to an increased focus on the development of biotech products and therapies for orphan diseases.

Bhaskar Sambasivan, VP and head of life sciences at Cognizant, says the advancement of scientific discovery, the inflow of VC/entrepreneurs, and unique barriers to entry for biosimilars have made this a renewed priority for pharma companies.

Jamie Macdonald, CEO of INC Research, says there is a real resurgence in the biotech sector and those companies are generating more interest and funding from investors.

"This sector is still responsible for a good deal of the innovation we see in terms of new molecules, so this is a welcome development," he says.

"The analysis of genomics data enables researchers to better understand complex diseases and to uncover disease biomarkers, disease-related pathways, and ultimately new and effective drug targets."

DR. SZILARD VOROS
Global Genomics Group

According to EY, in 2012 R&D spending by public companies in the four established biotechnology centers (the United States, Europe, Canada, and Australia) grew by 5%, below the 9% growth rate achieved in 2011. Across these major markets, R&D spending by commercial leaders remained strong, while smaller, pre-commercial entities substantially reduced the pace of growth.

The biotech industry's revenue grew by 8% in 2012, compared with the 10% growth (after adjusting for large acquisitions) achieved in 2011. In 2012, a handful of up-and-coming firms in the United States and Europe grew their product revenue to enter the ranks of commercial leaders. The number of FDA approvals increased to levels not seen since 1997,

> **"Mobile devices are poised to facilitate patient-initiated interactions with clinical researchers, doctors, payers, and other stakeholders, and a new research paradigm will emerge that has the potential to improve R&D."**
>
> **PAULA BROWN STAFFORD** / Quintiles

> **"The next generation of biologics and advanced therapeutics offers new opportunities to target disease processes that could not be addressed by traditional small molecule strategies."**
>
> **DR. TIMOTHY WRIGHT** / Novartis

> **"Advanced solutions will incorporate multi-disciplinary capabilities and technologies that will become the enabling tools to generate a cell-based industry."**
>
> **ZAMI ABERMAN** / Pluristem Therapeutics

according to EY analysts. Many of the year's approvals were not me-too offerings but first-in-class treatments that seek to address genuine unmet needs.

Industry experts stress the need for pharma pipelines to address neglected and orphan diseases. The annual R&D spending to treat neglected diseases is currently $3 billion, according to a July 2013 analysis from the Tufts Center for the Study of Drug Development. The annual number of new drug approvals worldwide to treat neglected diseases has nearly doubled in recent years, with HIV/AIDS and malaria drugs accounting for 60% of the most recent approvals, according to Tufts CSDD.

Martin McGlynn, president and CEO of StemCells, says there is now a funding priority for underserved diseases.

"Good-bye me-too products," he says.

Tariq Kassum, VP of corporate development, oncology at Millennium: the Takeda Oncology Company, says dozens of small private biotechnology companies have gone public this year.

"In addition, many small public biotechs have had great success raising public equity capital," he says. "Last year's small fledgling biotech is this year's newly public, well-capitalized success story. As a result, these companies have a lot more strategic latitude. They don't have to partner their drugs out or sell the company; they can follow a course of independence for much longer. Working with pharma can still be helpful for these companies, but in a much different way than before; we will need to adapt to this new reality."

This is enabling a new strategy to target the underlying disease mechanism and thereby offer breakthrough therapies that are truly disease modifying and potentially curative, rather than merely improving symptoms, says Timothy Wright, M.D., global head of development at Novartis.

"Finally, the next generation of biologics and advanced therapeutics offers new opportunities to target disease processes that could not be addressed by traditional small molecule strategies," he says.

Fran DeGrazio, VP of global research and development, pharmaceutical packaging systems at West Pharmaceutical Services, points out that biologics may be more challenging for another reason.

"Biologics tend to be more sensitive," she says. "They also tend to be manufactured in smaller quantities. So packaging and delivery systems need to meet the unique needs of biologics. There is opportunity in the market from that perspective.

She says delivery systems for biologics will continue to be important as a means to drive patient compliance and lower overall cost.

"As new systems are developed, we will see treatment move away from the hospital or clinical setting and closer to the patient," she says. "Such change will, in the long run, save money and increase compliance."

Dr. Wright says advancements in the understanding of genetics and disease pathways are already leading to major R&D breakthroughs.

"Since up to 95% of the variability in patient drug response may be due to genetic differences, determining the right treatments for individual patients at the right time based on a patient's genetics and underlying biology can lead to significantly improved patient responses, and better tolerated therapies," he says.

Mr. Macdonald says there are also interesting new technologies in development on the diagnostic side, including biomarkers, genotyping, and more.

"This is significant because the better we understand patients and disease progression the better we can design treatments," he says.

Paula Brown Stafford, president, clinical development at Quintiles, says evolving technologies and approaches to medicine — genomics, biomarkers, biologics, biosimilars, personalized medicine — are advancing how medicines are discovered, developed, and delivered and will continue to impact research and development in a big way.

Based on patent findings and products in development, personalized medicine will be part of 25% of all trials by 2016, says John Potthoff, president and CEO of Theorem Clinical Research.

"This trend has begun to introduce new partners to sponsors and CROs, for example, mobile applications development companies and telecommunications companies, who need both execution expertise as well as regulatory guidance," he says. "Already, these companies are in partnership with traditional biopharmaceutical and medical device companies for development of combination therapies."

Within the oncology market, the identification of biomarkers and companion diagnostics has grown in importance over the years, says Takashi Owa, Ph.D., chief innovation officer at Eisai Product Creation Systems.

"Now, the emergence of new DNA sequencing technologies will take that to the next level," he says. "Currently many agents in the clinic each have one companion diagnostic that is used to help determine the appropriate patient for treatment with that particular

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DR. WILLIAM PRATHER / Pluristem Therapeutics

drug. With new DNA sequencing technologies, researchers will soon be able to identify all relevant gene mutation simultaneously versus having to use separate companion diagnostics to identify each mutation. This offers increased value to physicians, payers, and patients. This is why Eisai and many other pharma companies are continuing to make significant investments in companion diagnostics."

In recent years, researchers have made enormous progress in understanding the origin of disease and disease progression, says Szilard Voros, M.D., CEO and co-founder of Global Genomics Group (G3).

"New and advanced technologies including whole genome sequencing have helped to decipher common variants that are found in patients with late-onset diseases and that determine drug response," he says. "Nevertheless, complex diseases such as cardiovascular disease are multifactorial, and biological pathways involved in its development are not well understood."

Dr. Voros says genomics provides very important information, but the analysis of multidimensional biological networks require more.

"The collective use of multi-tissue genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, lipoprotein proteomics and glycomics, called pan-omics, is a more rigorous method for elucidating the complex processes underlying disease," he says. "The analysis of this data enables researchers to better understand complex diseases and to uncover disease biomarkers, disease-related pathways and ultimately new and effective drug targets."

R&D Needs to Focus on Value

Demonstrating the value of new medicines to physicians and payers will be just as important for biotech drugs as it is for small molecules, industry experts say. Dr. Wright of Novartis says payer requirements are shaping the clinical development programs more than ever with the inclusion of endpoints and comparators required for pricing and reimbursement in many Phase III programs.

According to EY analysts, most biotech companies are not adequately prepared for this focus on value.

Specialty drugs are often a driver of costs in drug spending. Two recent studies conducted by pharmacy benefit manager Prime Therapeutics and Blue Cross and Blue Shield of Minnesota forecast that specialty drugs will account for 50% of all drug costs by 2018, up from 20% in 2009. Since many of the diseases on which biotech firms focus are treated using specialty drugs, those developing biotech products will also to need to take value into account.

"There is a growing imperative for the industry, and specifically R&D, to play a more integrated role in the broader healthcare ecosystem as pressures intensify to reduce development costs, contain reimbursement, and deliver better health outcomes overall for patients and governments," says Charmaine Gittleson, VP, clinical R&D, global, at CSL Behring. "Health technology assessment (HTA) is likely to have a significant impact on the way we operate in R&D. In the past, R&D focused on the science and development aspects of bringing new products to market. But today with HTA it's essential that new products are differentiated or meet unmet medical needs to achieve a positive HTA outcome. And while R&D has not historically taken this into consideration, it will need to do so now and do it fairly early in the development process. This is going to require a new way of operating, partnering with commercial, and even learning new skills."

R&D needs to evolve, agrees Steven Gilman, Ph.D., executive VP of research and development and chief scientific officer at Cubist Pharmaceuticals.

"No longer is it sufficient to be so centered on drug approvability as the key outcome, which focuses primarily on clinical safety and efficacy," he says. "The industry needs to focus on providing accessible drugs to patients, which not only encompasses clinical safety and efficacy but also provides a unique health outcome value that healthcare providers will support and payers will reimburse. This demands that a new set of clinical and health economics and outcomes research skills be applied to clinical development."

FAST FACT

TOTAL U.S. LIFE-SCIENCES R&D SPENDING IS EXPECTED TO REACH $82.7 BILLION IN 2013, UP 1.4% FROM 2012.

Source: Battelle

"2014 will be the year when we hear more about the advances that the universal biomolecule mRNA has made in many different therapeutic and prophylactic areas."

DR. INGMAR HOERR / CureVac

Continued Focus on Efficiency

At the same time, biopharmaceutical companies are being challenged to find ways to lower development costs and make drug development more efficient.

There is a definite trend in the increasing pressures on pharmaceutical and biotech companies as it relates to the ability to bring new products to market quickly, cost-effectively, and with an optimum patient outcome, says Graham Reynolds, VP, marketing and innovation, pharmaceutical delivery systems, at West Pharmaceutical Services.

"This often means that there are more things to be considered in early phases of R&D to ensure that companies optimize their chance of success," he says.

While lack of commercial viability is the leading cause of Phase I failures for new drug candidates, efficacy issues dominate as the reason for Phase II failures, according to a new analysis from the Tufts Center for the Study of Drug Development.

Based on a study of products that entered clinical development from 2000 through 2009, Tufts CSDD found that commercial reasons accounted for 40.9% of all Phase I failures, but only 27.3% of Phase II failures. Efficacy issues explained 50.9% of Phase II failures. Safety issues accounted for nearly twice as many Phase III failures as did commercial reasons: 29.5% vs. 15.9%. Efficacy issues accounted for 54.3% of respiratory drug failures and 48.3% of drug candidates to treat central nervous system diseases.

Clinical study failures also vary widely by

therapeutic class of drugs being investigated, the Tufts CSDD analysis showed. Cardiovascular drugs experienced the highest prevalence of commercial failures (46.7%) among all classes of compounds analyzed.

The study, based on investigational drugs in the pipelines of the top 50 firms in terms of pharmaceutical sales, examined the development histories of 812 compounds, which had 1,369 failed indications, and established reasons for failure by clinical phase for 410 of these compounds and 659 indications.

Dave Meek, chief commercial officer at Endocyte, says the ability to identify factors that will increase the success of a drug candidate is critical for R&D.

"Approaches that help improve clinical success will be increasingly important, including the use of predictive and prognostic biomarkers, to clinical outcomes," he says. "Another exciting realm is the use of companion

Hot Technologies

Stem cell therapeutics will continue to be an area of high interest for the industry because of promising clinical results that have been seen to date, and the potential the approach holds overall. Human stem cells hold particular promise for treating serious neurological diseases, including spinal cord injury, dry age-related macular degeneration, and Alzheimer's disease. Industry experts say these indications are particularly attractive for stem cell therapeutics, as these are all devastating diseases for which no effective therapeutic options currently exist.

The market for stem cells was valued at $26.23 billion in 2011 and is expected to reach an estimated value of $119.51 billion in 2018, growing at a CAGR of 24.2% from 2012 to 2018, according to a June 2013 report from Transparency Market Research. The market will be driven by a rising proportion of patients with neurological and other chronic conditions and rising disposable incomes of patients induced by economic growth of Asian regions in the next five years. In addition, increasing dependence on stem cells for drug discovery and screening will boost the growth of the market in the future. Increased outsourcing of contract research and clinical trials to developing Asian regions will further encourage growth of the stem cells market.

Cell-based therapies have always held much promise, and this year the space has begun to mature, as evidenced by a number of product approvals of cell-based therapies. These include Dendreon's Provenge, Osiris' Prochymal, and Genzyme's MACI, as well as Fibrocell Science's laViv, an aesthetic product.

Cell therapy has been accepted and proven to be effective in laboratories worldwide for over two decades, says Zami Aberman, chairman and CEO of Pluristem Therapeutics.

"Furthermore, numerous early stage clinical trials for a wide range of indications have been successful," he says. "Nevertheless, this therapy has not yet been commercialized and will face many unmet challenges. These challenges begin with the cell source, manufacturing, up-scaling, up and downstream challenges, aseptic processing, storage, shipment, handling and proper thawing at the site. Advanced solutions will incorporate multi-disciplinary capabilities and technologies that will become the enabling tools to generate a cell based industry.

2014 may be the year of cell therapy, says William Prather, M.D., senior VP, corporate development, at Pluristem Therapeutics.

"The lack of well-designed, placebo-controlled clinical trials has hindered the acceptance of cell therapies," he says. "This may change in 2014. A recent report from PhRMA indicates there are 69 cell therapy-related clinical trials under review with the FDA, including 15 in Phase III clinical trials. There are a number of indications being addressed with these trials, including cardiovascular disease, cancer, and musculoskeletal and GI disorders. A number of these Phase III trials will be completed in 2014. If these trials are successful, there will be a re-awakening of interest in cell therapies, especially with large pharma whose pipelines are starving."

For the cell therapy space, a key focus for the year ahead will be to continue to present meaningful results from clinical trials, which will enable the area to continue to mature, says Martin McGlynn, president and CEO of StemCells.

"The clinical results reported to date have been very promising, and additions to this growing body of data only continue to provide rationale for increased investment to support translational efforts in the clinic," he says. "According to the Alliance for Regenerative Medicine, there are 54 companies with late-stage clinical trials under way evaluating various cell and tissue-based therapeutics, another 114 in mid-stage trials and about 65 others involved in earlier stages."

Mr. McGlynn says companies in the cell therapy space should go the extra mile to publish well-written, peer-reviewed, articles in well-respected journals describing the scientific and preclinical rationale for the clinical trials they have undertaken, and also publish the results of the trials once they have been completed.

"I believe that this is an effective strategy to counter the criticism that companies overreach with regard to the potential for their respective technologies," he says. "I believe the investment community will develop a greater degree of understanding and confidence in technology as a whole."

mRNA Research

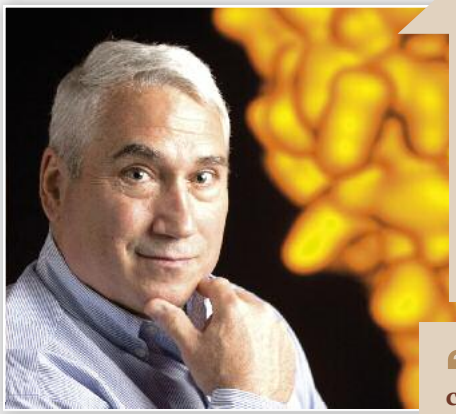
Another hot technology identified by industry experts is mRNA. Messenger RNA are molecules that transfer genetic, protein-building information from the nucleus to the protein-building mechanism of the cells.

Ingmar Hoerr, Ph.D., CEO and co-founder of CureVac, says researchers have been able to unlock the potential of messenger (m) RNA.

"Currently, novel therapeutics based on mRNA are being developed as transformative treatment options across a broad range of human diseases and disorders," he says. "The biomolecule mRNA is known for its instability, and for a long time it was overshadowed by DNA-based therapeutics and, of course, protein-based drugs. But a number of researchers worldwide have continued to investigate mRNA and have been able to overcome these hurdles, making the clinical application of mRNA feasible."

Cancer immunotherapy based on mRNA has already demonstrated promise in clinical trials, but the potential of mRNA-based approaches goes far beyond cancer vaccines.

"mRNA-based therapies provide an excellent safety profile — no genomic integration, enormous flexibility with regard to the sequence, and they can be produced very quickly and cost efficiently, all attributes that make them ideal candidates for prophylactic vaccines as well as for the in vivo production of recombinant therapeutic proteins and as a method for gene replacement therapy," Dr. Hoerr says. "These are all approaches that are currently being investigated. 2014 will be the year when we hear more about the advances the universal biomolecule mRNA has made in many different therapeutic and prophylactic areas."



> **"Providing a unique health outcome value that healthcare providers will support and payers will reimburse demands that a new set of clinical and health economics and outcomes research skills be applied to clinical development."**
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> **"Approaches that help improve clinical success will be increasingly important, including the use of predictive and prognostic biomarkers, to clinical outcomes. Another exciting realm is the use of companion imaging agents for biomarker selection."**
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> **FRAN DEGRAZIO** / West Pharmaceutical Services

imaging agents for biomarker selection and ultimately, the selection of a therapeutic."

Dr. Wright says more targeted, effective treatment approaches have the potential (based on much higher efficacy) to reduce the size of clinical trials and thereby shorten development timelines and potentially to accelerate regulatory approval (e.g. "breakthrough therapies").

The status quo of R&D is done, says Eric Silberstein, co-founder and CEO of TrialNetworks.

"Historically, pharma companies have been hesitant to adopt modern technology," he says. "Fortunately, a new generation of clinical trial managers and leaders are injecting a welcome understanding and willingness to use new tools into the pharma culture. We have seen this with customers ranging from biotech startups to top 10 pharmas running the largest clinical trials in the world. As pharma's attitudes toward adopting positive change evolves and matures, we will see the results in quality and process efficiency improvements such technologies are proven to provide on a wider scale."

Much has been said about the perceived sub-optimal R&D productivity within pharma and the volume of R&D assets not being pursued because of the enormous risks and costs of developing new drugs, Ms. Gittleson says.

"I think the industry has taken note and reflected and we will start to see the impact of resultant changes made to R&D operations," she says. "In recent years, our R&D team at CSL Behring has introduced a record number of new products and indications in North America, Europe, America, and Japan, all while keeping a close eye on cost vs. value. This imperative — to remain productive while also being smart in our capital spending and R&D investments — will remain an important trend for us and the industry. This will continue to take place while we preserve our future productivity and value to shareholders.

Dr. Wright says Novartis continues to revolutionize its approach to conduct clinical trials by pioneering new approaches as well as developing and leveraging emerging technologies

"At Novartis, we have been using diagnostics to identify patients with cancers and other diseases that are most likely to benefit from certain treatments," he says. "In oncology specifically, Novartis is using genetic approaches to help ensure that those patients with the highest potential for therapeutic response can be identified."

Novartis is also now capturing clinical trial data through handheld smart tablet devices, as well as using e-sensors to monitor patients' vital signs and developing mobile apps to help improve patient compliance with trial protocols, he says.

"Among other benefits, this approach prompts investigators directly entering trial data to correct out-of-range data, ultimately minimizing errors, and providing access to the data in real time, versus the usual time of weeks, using the traditional data entry process," Dr. Wright says. "We believe that these e-technologies will also help to address the current challenges individuals face in being able to participate in clinical trials by allowing patients to be monitored remotely. Through this approach we bring clinical trials to the patient, making it easier and more convenient to participate in clinical research. As tools like these are developed and become more widely used, we expect that the industry will significantly accelerate clinical development timelines and improve efficiencies."

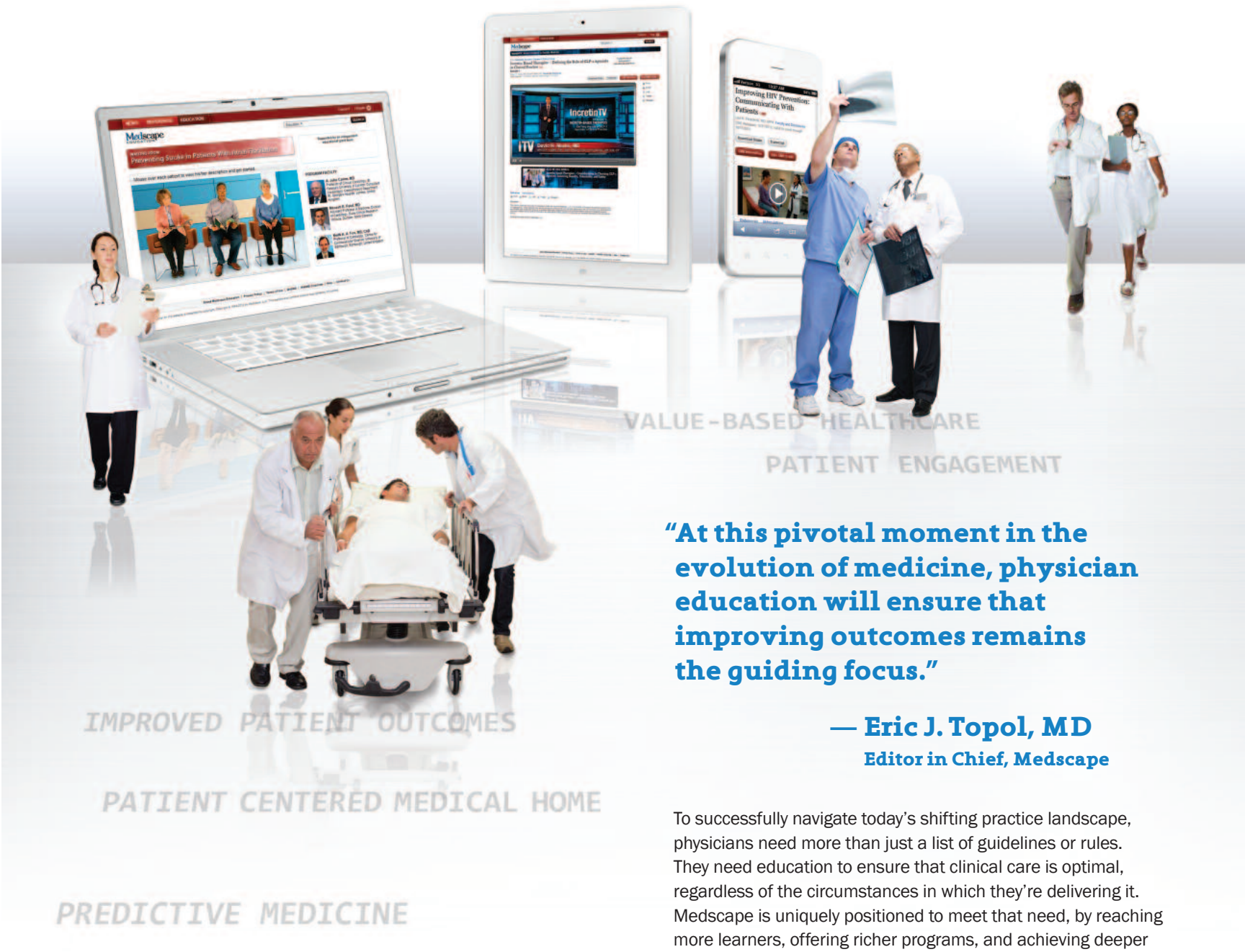
Ms. Brown Stafford says mobile devices, including wearable devices, will have a positive impact on R&D.

"Mobile interactions with patients are now becoming more mainstream through the uptake of mobile devices and new wearable devices such as FitBit and Jawbone," she says. "This trend is poised to facilitate patient-initiated interactions with clinical researchers, doctors, payers, and other stakeholders. Once the industry can adjust to the impact of live, streaming patient data on protocols, efficacy, endpoints, etc., then a new research paradigm will emerge that has potential to improve R&D in terms of trial duration, measurements, monitoring, cost and, ultimately, time to market."

Mark Penniston, senior VP and general manager of clinical analytics for Theorem Clinical Research, says another technology that can be used to address clinical trial efficiency is electronic medical records.

"I would hope that in five years the industry will have come to an agreement on data standards for electronic medical records," he says. "At a minimum, mobile apps should help with the capture of standard data — vital signs, physical exams — so that CRAs can focus on the capture of study-specific data." PV

AS THE HEALTHCARE SYSTEM EVOLVES, THERE IS ONE CONSTANT—PHYSICIAN EDUCATION



"At this pivotal moment in the evolution of medicine, physician education will ensure that improving outcomes remains the guiding focus."

— Eric J. Topol, MD
Editor in Chief, Medscape

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