That the pharmaceutical industry is committed to delivering on the promise of personalized medicine is actually old news. Data compiled by the Tufts Center for the Study of Drug Development regarding the industry’s commitment to personalized medicine in 2014 and 2015, along with the Personalized Medicine Coalition’s analyses of the U.S. Food and Drug Administration’s recent approvals of novel new drugs, demonstrate that the pharmaceutical industry has embraced personalized medicine, despite the absence of a tried and tested business model that ensures success. Nevertheless, conventional wisdom fades slowly. Many policymakers and some members of the media still believe, as Mara Aspinall and Richard Hamermesh wrote in Harvard Business Review in 2007, that the single biggest obstacle “hindering the transition from trial-and-error medicine to personalized medicine” is the pharmaceutical industry’s devotion to its “historically successful blockbuster model,” which discourages targeted therapeutics aimed at segmented populations. In fact, the chief obstacles slowing the realization of personalized medicine, in addition to the inherent biological complexity of targeting treatments to the right patients, do not include reluctance on the part of industry. Rather, they are, as Aspinall and Hamermesh also contend, regulatory and payment systems that do not keep pace with the implications of the new discoveries regarding individual variation and the development of new technologies that facilitate more precise diagnoses.

Introduction

The father of modern medicine, William Osler, once observed, “Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.” From this insight arose the fundamental principle of personalized medicine: providing only the specific care an individual needs based on defined characteristics of that patient. Rather than a generalized pattern of medical care based on population averages, personalized medicine assumes that physicians will use sophisticated diagnostic tests to determine which medical treatments will work best for each patient. Only by combining the results from those tests with a patient’s medical history, circumstances, and values, can health care providers develop targeted treatment and prevention plans. These plans offer patients better care and more certain outcomes. In theory, the health care system will also benefit from the movement of resources towards individuals for whom an intervention will provide a better outcome and away from others for whom it will not, thus resulting in an economic advantage when medical resources are scarce or expensive. In other words, by treating the right patient at the right time with the right
therapy, health care can become more efficacious and efficient. As simple as this may seem though, personalized medicine has proven difficult to implement, and its development and adoption have been slower than many would wish. But the pace has quickened, and is likely to accelerate with profound implications for the pharmaceutical industry as well as health care generally.

To succeed, personalized medicine requires two major transformations. First, we need to better understand at the molecular level why individuals with the same disease differ in their response to the same therapy. This is well illustrated by the current molecular characterization of lung cancer, which evolved from prior characterizations of lung cancer based on clinical examination, microscopic morphology and radiographic findings. Descriptive observations of lung cancer, however, could not be clearly linked to biological pathways for which a medicine could be invented. In contrast, the current molecular characterization of lung cancer describes aberrant biology based on specific gene mutations for which several highly effective mutation-targeted medicines are now available. Thus, the nosology of medicine must be revamped to clearly segment clinically similar diseases that have markedly different biological characteristics, and would therefore be better served by different medications. Despite the progress in diseases such as lung cancer, most indications outside of oncology are still unfortunately characterized by subjective clinical observation, including highly prevalent mental health conditions such as schizophrenia, depression, and autism.

Second, better medicines need to be developed to target the unique biology of newly discovered disease segments. Such new medicines have to come from an industry that has historically discovered and developed drugs for large, undifferentiated markets. Some, as noted, have questioned whether the pharmaceutical industry could, or was even willing to, shift from its historic “one-size-fits-all” model to one in which companies discover and develop medications for much smaller medical indications that would be expected to generate smaller returns based on a limited number of patients with a much more narrowly defined disease segment.

However, much has changed in the last decade. Today, pharmaceutical companies large and small are eagerly pursuing personalized medicine strategies as a core part of their research and development efforts.

**Data Supporting Current Widespread Adoption of Personalized Medicine**

The first line of evidence, a leading indicator of significant adoption, comes from the percentage of new drug approvals that were personalized medicines; that is, they include biomarker strategies on their respective labels.

In 2014, 20 percent of new medicines approved by the FDA’s Center for Drug Evaluation and Research were personalized medicines. See Figure 1 for a complete list of the personalized medicines FDA approved in 2014.

In 2015, FDA approved 13 targeted therapeutics, which accounted for 28 percent of the year’s total approvals. In contrast, the agency approved only one personalized medicine in 2005. See Figure 2 for a complete list of the personalized medicines FDA approved in 2015.

<table>
<thead>
<tr>
<th>Personalized Medicine</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynparza (olaparib)</td>
<td>for the treatment of advanced ovarian cancer. The decision to treat with this product is affected by the BRCA biomarker status in patients.</td>
</tr>
<tr>
<td>Vimizim (elosulfase alpha)</td>
<td>for the treatment of Mucopolysaccharidosis Type IV (Morquio Syndrome). The decision to treat with this product is affected by the type A or B biomarker status in patients.</td>
</tr>
<tr>
<td>Cyramza (ramucirumab)</td>
<td>for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma or non-small cell lung cancer (NSCLC). Treatment procedures are influenced by the EGFR or ALK biomarker status in patients.</td>
</tr>
<tr>
<td>Zykadia (ceritinib)</td>
<td>for the treatment of NSCLC. The decision to treat with this product is affected by the ALK biomarker status in patients.</td>
</tr>
<tr>
<td>Beleodaq (belinostat)</td>
<td>for the treatment of peripheral T-cell lymphoma. Treatment procedures are influenced by the UGT1A1 biomarker status in patients.</td>
</tr>
<tr>
<td>Cerdelga (eliglustat)</td>
<td>for the long-term treatment of Gaucher disease type 1. Treatment procedures are influenced by the CYP2D6 biomarker status in patients.</td>
</tr>
<tr>
<td>Harvoni (ledipasvir and sofosbuvir)</td>
<td>for the treatment of chronic hepatitis C infection. The decision to treat with this product is affected by the genotype 1 biomarker status of the viral infection in patients.</td>
</tr>
<tr>
<td>Viekira Pak (ombitasvir, paritaprevir, and ritonavir; dasabuvir)</td>
<td>for the treatment of chronic hepatitis C infection. The decision to treat with this product is affected by the genotype 1 biomarker status of the viral infection in patients.</td>
</tr>
<tr>
<td>Blincyto (blinatumomab)</td>
<td>for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL). The decision to treat with this product is affected by the Philadelphia chromosome biomarker status in patients.</td>
</tr>
</tbody>
</table>

**Figure 1.** New Personalized Medicines FDA Approved in 2014
The same trend is illustrated in Figure 3. The diagram, compiled by L.E.K. Consulting, illustrates the quickening pace of new, targeted therapeutics with required or recommended companion diagnostics in their respective labels.8

L.E.K. also estimates that in 2015 the market value for drugs reliant on a companion diagnostic was $25 billion, up 12 percent from $22 billion the year before (see Figure 4).9,10 That this is more than a short-term trend can be seen by looking at research and development strategies in an industry known for its long discovery and development timelines. A 2015 survey of pharmaceutical executives conducted by the Tufts Center for the Study of Drug Development found that 42 percent of current biopharmaceutical company pipelines include biomarker strategies. In oncology that figure rises to 73 percent. Biopharmaceutical companies, the researchers found, have nearly doubled their research and development investment in personalized medicine since 2005, and they expect to increase it again by an additional third in the next five years.11

Finally, if there is any doubt remaining about the pharmaceutical industry’s commitment to personalized medicine, it should be noted that as of 2014 personalized medicines account for 13 percent of all approved medicines as judged by their inclusion of a reference to biomarkers to guide their administration, and 137 approved drugs have genomic information in their labels.12

The reasons explaining the shift in focus are not hard to understand. According to Paul Hudson, President, AstraZeneca U.S. and Executive Vice President, North America, “As the biopharmaceutical industry investigates and earns FDA approval for more targeted therapies in oncology and other disease states, the benefits are clear: better diagnoses, fewer adverse drug reactions, increased patient adherence, improved quality of life and, ultimately, significant savings in overall U.S. health care costs.” He noted that

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Indication</th>
<th>Biomarker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alecensa (alectinib)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>ALK</td>
</tr>
<tr>
<td>Tagrisso (osimertinib)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>EGFR</td>
</tr>
<tr>
<td>Cotell (cobimetinib)</td>
<td>Advanced melanoma</td>
<td>BRAF</td>
</tr>
<tr>
<td>Nucala (mepolizumab)</td>
<td>Maintenance treatment of asthma</td>
<td>Eosinophil</td>
</tr>
<tr>
<td>Aristada (aripiprazole lauroxil)</td>
<td>Treatment of schizophrenia</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Lonsurf (trifluridine and tipiracil)</td>
<td>Treatment of advanced colorectal cancer.</td>
<td>VEGF, RAS, EGFR biomarker statuses</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>Treatment of high cholesterol</td>
<td>Biomarkers that indicate familial hypercholesterolemia</td>
</tr>
<tr>
<td>Daklinza (daclatasvir)</td>
<td>Chronic hepatitis C infection</td>
<td>Genotype 3 biomarker status of the viral infection in patients</td>
</tr>
<tr>
<td>Praluent (alirocumab)</td>
<td>Treatment of high cholesterol</td>
<td>Biomarkers that indicate familial hypercholesterolemia</td>
</tr>
<tr>
<td>Rexulti (brexpiprazole)</td>
<td>Schizophrenia and major depressive disorder</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Orkambi (lumacaftor and ivacaftor)</td>
<td>Treatment of cystic fibrosis.</td>
<td>F508del/CFTR biomarker status in patients</td>
</tr>
<tr>
<td>Cholbam (cholic acid)</td>
<td>Bile acid synthesis disorders</td>
<td>Various single enzyme defect biomarker statuses in patients</td>
</tr>
<tr>
<td>Ibrance (palbociclib)</td>
<td>Advanced breast cancer</td>
<td>ER and HER2 biomarker statuses in patients</td>
</tr>
</tbody>
</table>

**Figure 2. New Personalized Medicines FDA Approved in 2015**
Figure 3. Recent Personalized Therapeutic Launches Have Relyed on Well-Validated Biomarkers (BRAF, EGFR) and First-in-Class Biomarkers Including BRCA and PD-L1

Note: * EU approval in 2009 and FDA approval for EGFR+ NSCLC in 2015
** While Tarceva had already been launched, it was approved for first-line treatment for EGFR+ NSCLC patients in 2013


Figure 4. Marketed Therapeutics Reliant on a CDx Generated ~$25B in Therapeutic Revenues in 2015

Note: * 2015 revenues are actual or analyst estimates; PHC products include those with labels that require/recommend CDx test for candidacy
** Includes all Tarceva revenues, not just those from first-line treatment for EGFR+ NSCLC patients
*** Other includes Alecensa, Aristada, Blincyto, Bosulif, Cholbam, Cotellic, Gilotrif, Ibrance, Iressa, Kadcyla, Lonsurf, Lynparza, Mekinist, Nucala, Orkambi, Praluent, Repatha, Rexulti, Selzentry, Tafinlar, Tagrisso, Tykerb / Tyverb, Vectibix, Victrelis, Xalkori, Zelboraf and Zykdia drug revenues
**** Other includes Infectious Disease, Neurology, Cardiology, Pediatrics, Respiratory, and Gastroenterology therapeutic areas

In addition, FDA has, according to Janet Woodcock, Director of the agency’s Center for Drug Evaluation and Research, “been pushing for targeted drug therapies...for a long time.” She has pointed out that 60 percent of the targeted therapies approved in recent years were cleared based on data from a single trial, and that 90 percent used one or more of FDA’s expedited programs. 14

Other indicators suggest that the trend towards personalized medicine will continue. In his State of the Union Address last year, President Obama launched a new Precision Medicine Initiative (PMI) to, in his words, “bring us closer to curing diseases like cancer and diabetes.” Essentially a research program with multiple components, the initiative presumes that diseases will be defined based on their molecular characteristics and that, in turn, the pharmaceutical industry will develop targeted therapeutics to address them. As an example, the President noted progress in treating cystic fibrosis based on an emerging understanding of the genetic basis of that disease.15 Although he did not mention it, that progress also depended on the ability of a biotechnology company in Massachusetts, Vertex, to translate that understanding into the development of new drugs to treat specific subsets of cystic fibrosis patients.

Obstacles
While the pharmaceutical industry’s fear of the segmented markets that personalized medicine presumes is not among them, three major obstacles still slow personalized medicine’s progress. According to the Tufts survey of both the pharmaceutical and diagnostics industries, most executives expressed concern about the uncertain regulatory environment for diagnostics, challenging payment policies for both diagnostic and therapeutic products, and the ease with which the health care system can adopt personalized medicine practices.

Regulation of Diagnostic Tests
First, the regulatory environment for diagnostics remains unclear and unsettled, which in turn deters investment in linking therapy to individual variation. With two separate agencies of government overseeing diagnostic products in the United States, uncertainty remains regarding the best path to the largest market in the world. Although FDA has proposed ending its “enforcement discretion” in regulating laboratory developed tests, which represent the overwhelming majority of diagnostic tests and are overseen by the Centers for Medicare and Medicaid Services (CMS), it has yet to demonstrate its capacity to regulate them, thereby causing increased confusion for both the diagnostic as well as the pharmaceutical industries. That confusion is compounded by the fact that to develop targeted therapies, the pharmaceutical industry relies on a diagnostic industry, which employs a different business model and is subject to the decisions of public and private payers, which may or may not value its products. Because public and private insurance companies typically want to pay as little as possible for diagnostic tests, diagnostic companies, especially absent expensive-to-develop evidence that demonstrates the underlying value of their products, have less control over production and pricing.

Payment
Perhaps even more challenging than the price pressures on diagnostics are the looming ones on drugs. Last year, for example, 118 oncologists published a widely reported letter calling for a grassroots movement to oppose the high cost of new cancer drugs, some of which are targeted therapeutics that are extraordinarily effective in prolonging life. They stated in their letter that many new cancer drugs average more than $100,000 a year, with copays of up to one-third of that amount, or about half the average household annual income in the United States. These oncologists want FDA to define a “fair price” for drugs and also encourage importation of drugs across national borders to deflate current prices.16 Their views are finding their way into the public arena, with many in the media now echoing the contention made by the New York Times on its editorial page on December 20, 2015 that there is “no justification for high drug prices.” That opinion, if it leads to price controls, could slow progress towards the development of personalized medicines, which are targeted at smaller populations and therefore will be more expensive than less effective, one-size-fits-all therapies that can be marketed to all patients whether they work or not. Unless the pharmaceutical industry can differentiate targeted therapeutics from one-size-fits-all/ trial-and-error medicines and demonstrate the increased efficacy and safety of personalized medicines, along with their capacity to reduce overall systemic costs to the health system, pricing pressure will be a hard headwind to navigate.

Adoption
Even when manufacturers of personalized medicine products complete the obstacle course of researching and developing targeted therapies and getting them approved and reimbursed, there is no guarantee that physicians will change their behavior and prescribe the new medicines. In the Tufts survey of diagnostic and drug manufacturers, for example, very few respondents believed that doctors were “very comfortable” in prescribing tests underpinning genomic medicine. The majority considered physicians only “somewhat” comfortable with practicing personalized medicine. As one noted, “It is learning not just new stuff, but all the stuff that is foundational that you never learned before.”17
Conclusion

Henry Ford, remarking on the Model T, said “Any customer can have a car painted any colour that he wants so long as it is black.” 8 While this approach worked for the new car industry at the beginning of the twentieth century, as the industry matured, market segmentation followed. By dividing a broad target market into subsets of consumers with common needs, one could design products to target them. This concept is familiar to most businesses, but has arrived later in drug development due to the difficulty of identifying the biology of various patient segments within larger, typically undifferentiated disease categories. Since patient preferences are strongly tied to clinical outcomes, which in turn are based on patient biology, a new biological understanding was needed before more sophisticated marketing strategies could be advanced.

Now, however, pharmaceutical companies, led by the science and encouraged by FDA, have embraced personalized medicine (a form of market segmentation), which benefits patients and will also help make the health care system more efficient. It therefore comes as no surprise that pharmaceutical companies are moving towards targeted therapeutics at an increased rate, given that science and technology now provide the tools necessary to design and develop these drugs.

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Note: This article represents the personal opinions of the authors and not necessarily those of Astellas or PMC.

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17. From previously unpublished interview data provided in July 2015 by Christopher Milne and Joshua Cohen, the researchers who conducted the study on behalf of the Tufts Center for the Study of Drug Development.