Within our lifetimes, we may look back at chemotherapy and group it with insulin shock therapy, electric baths, bloodletting, and other barbaric medical practices discredited long ago. Today, advances in identifying biomarkers that may predict who will or won’t respond to a treatment offer vast potential for reducing the use of ineffective or even harmful therapies. These biomarkers, typically genetic (prognostic) or genomic (predictive), are propelling the evolution of precision medicine from pipe dream to work-in-progress to clinical reality.

Biomarker science is, perhaps, having its most pronounced effect on the development of new drugs, and that has gotten most of the attention. In some cases, biomarkers have resurrected drugs that were pulled off the market. Biomarkers that predict treatment success change how a disease is viewed, subdividing it into smaller and smaller therapeutic categories.

All of this is forcing the pharmaceutical industry to rethink drug lifecycles in concert with academics, repurposers, and diagnostics companies. None of this is happening in a vacuum; the power of predictive biomarkers

Right biomarker, right definition

Not so long ago, biomarker meant vital signs: body temperature, pulse, and blood pressure. Today, the term refers to a host of things that are objective and measurable. The FDA’s 2014 guidance on qualification of drug-development tools defines several types of biomarkers:

- **Diagnostic** biomarkers are characteristics that suggest disease, such as the presence of the ZnT8 antibody in people with Type 1 diabetes.
- **Pharmacodynamic** biomarkers measure a patient’s biological response to a medication, such as changes in HbA1c levels in people with diabetes.
- **Prognostic** biomarkers indicate a patient’s risk of disease occurrence or progression. The presence of a BRAF gene mutation, for instance, is a strong prognostic factor for recurrence of colorectal cancer.
- **Predictive** biomarkers categorize patients by their likelihood of responding to a treatment. Predictive biomarkers are established through the ability to measure gene expression, such as protein production and cell replication.

In clinical trials, showing the presence of a predictive biomarker can be a strategy for identifying groups of people who are most likely to respond to a treatment or regimen.
to alter the treatment of subpopulations has handed the FDA and payers complex considerations about how to approach drug approval, coverage, and payment.

Biomarkers can be a boon for patients, says Edmund Pezalla, MD, Aetna’s national medical director for pharmacy policy and strategy. But he offers two cautions. First, all the talk of precision notwithstanding, today’s generation of biomarkers are not perfect. Immuno-oncology drugs, for instance, work by blocking cellular pathways, like PD-1, that inhibit the immune system from attacking cancer cells, yet some patients may have an immune response that defeats the drug. “That would have nothing to do with the marker but rather some other genetic component of the patient we don’t understand,” Pezalla says.

Second, biomarkers that limit a drug’s patient population shouldn’t be expected to generate big savings to the health care system. In fact, just the opposite could happen. “Personalized medicine is more efficient, but I don’t think it will necessarily lower costs,” says Pezalla. If a company produces a cancer drug that is effective in only 10% of patients that a biomarker has identified, then the manufacturer may price the drug much higher than another drug that is effective in a broader group of patients, he notes.

That is what happened with gefitinib (Iressa), introduced in 2003 for metastatic non–small-cell lung cancer (NSCLC). At the time, its annual cost was $20,000. Today, gefitinib is limited to patients with a specific biomarker who fared much better in clinical studies than did a broader population (see “3 off the scrap heap,” page 13). Its annual cost today: $80,000.

With the advent of biomarkers, can the American health care system absorb the costs of drugs that are effective in smaller and smaller groups of patients? “It’s one of the questions we have to ask,” says Pezalla.

Still, these are early days. Just 18 of the 113 drugs approved from 2013 to 2015 had a prognostic or predictive biomarker in their indication. Those drugs and others to come are pushing pharmaceutical companies
into new territory, forcing them to collaborate with diagnostics manufacturers. In 2010, when the FDA rejected omacetaxine (Omapro), a leukemia drug for patients with a certain genetic mutation, regulators made it clear to pharma: Don’t bring us a drug for a molecularly defined subset of patients without a validated test for the biomarker. ChemGenex, maker of omacetaxine, had no such test.

With new drug applications increasingly coupled with in vitro diagnostics, the FDA has paid closer attention to the accuracy and validity of each test. A faulty companion diagnostic “could deprive a patient of a potentially lifesaving therapeutic or could cause a patient to be given an ineffective drug, delaying treatment with the appropriate therapy,” Jeffrey Shuren, MD, director of the FDA’s Center for Devices and Radiological Health, testified to Congress last November. In 2014, the FDA issued guidance describing a regulatory pathway for collaboration on the development of companion diagnostics and, to date, the agency has approved 27 tests. Together, pharma and diagnostics companies develop practical ways to detect the biomarker in clinical practice.

**Liquid biopsies** can circumvent traditional diagnostic challenges by capturing rare cells of interest in a test tube of blood, says Peggy Robinson of the diagnostics company Angle.

The relevant biomarker, however, may be a moving target. In metastatic breast cancer, for example, a woman’s HER2 status may change and with it, the most effective therapy, notes Peggy Robinson, a U.S.-based vice president for Angle, a British diagnostics company. The German SUCCESS study group, she says, is looking at HER2 expression and FISH gene copy expression on circulating tumor cells (CTCs) in women whose breast cancer metastasized.

Typically, the presence of a biomarker would be confirmed through a biopsy and molecular characterization of the cancerous cells, which shows which genes are expressed. As a means for tracking disease, however, frequent biopsies are impractical, and biopsies can be difficult to perform when cancer metastasizes. Diagnostics companies recognize the practical and cost challenges associated with biomarker detection and confirmation, however, and are racing to develop simpler techniques that may reveal clues through metabolites and blood.

Angle is one of a number of companies working on “liquid biopsies” that circumvent traditional diagnostic challenges by capturing rare cells of interest, such as CTCs, in a test tube of blood. When coupled with a gene-expression profile, a CTC harvest can help with the selection of therapy, says Robinson. “Drawing the tube of blood and doing the appropriate characterization can be much more cost effective” than a biopsy, she adds. Angle plans to seek FDA 510(k) clearance for this technology, called Parsortix, later this year.

Angle’s business plan is to work with pharmaceutical companies during preclinical development to detect relevant biomarkers. “If the pharma company knows that a cellular pathway causes cell proliferation, it may target something in one of those pathways to stop cancer cells from reproducing,” says Robinson. “So, by looking at CTCs, we can see the impact of that target on those circulating tumor cells.”

**Parsortix**, she says, may help drug developers understand therapeutic response better by stratifying the patient population. “It comes down to what is the biomarker that they are using, and how does that relate back to the rare cell?”

**The niche–population conundrum**

Biomarkers have splintered diseases we once thought of as single entities into several distinct conditions. Once biomarkers have disaggregated a disease, different treatment may be needed for the various subsets. Cystic fibrosis (CF)—an inherited, genetically determined condition—is an interesting illustration. When it was initially approved in 2012, ivacaftor (Kalydeco) was indicated only for CF patients with a particular mutation in the CFTR gene. That’s just the kind of precision that biomarkers are supposed to bring to the table. The manufacturer, Vertex, has since been successful in getting the FDA to add indications for patients with other CFTR mutations.

Finding and treating those slivers of patients was at the heart of one of several recommendations in 2012 by the President’s Council of Advisors on Science and Technology. The council endorsed creation of a drug-approval pathway called Special Medical Use (SMU), which would grant an agent provisional approval for use in narrow populations on the basis of small and rapid trials. Approval would be contingent on risk–benefit data from larger subsequent studies. FDA Center for Drug Evaluation and Research Director Janet Woodcock later testified to Congress in favor of the SMU pathway, and authority for this sort of microapproval is written into the 21st Century Cures legislation circulating in Congress.

Pezalla, an invited expert who contributed to the development of the council’s report, is generally supportive of regulatory pathways that validate the promise of biomarkers. But he’s concerned about
3 off the scrap heap

Iressa: We didn’t know what we didn’t know
Gefitinib (Iressa) received FDA approval in 2003 as third-line treatment for metastatic non–small-cell lung cancer (mNSCLC). In phase 3 trials, the tyrosine kinase inhibitor shrunk tumors in only 11% of the efficacy population, but the change in that 11% was dramatic enough to warrant approval. When postmarketing studies showed no meaningful increase in response in a broader population, however, AstraZeneca voluntarily pulled gefitinib off the market. In 2012, the FDA withdrew its approval.

When gefitinib was approved, nobody knew why those 11% did so well. But in 2009, physicians at Massachusetts General Hospital and Harvard Medical School sequenced the EGFR genes in trial participants. Nearly all patients whose tumors had responded to gefitinib had mutations in the tyrosine kinase domain of the EGFR gene. No such mutations existed in nonresponders. This gave rise to the hypothesis that responders could be predicted if selected carefully.

AstraZeneca readied new clinical trials in patients with the relevant biomarkers. This time, response rates reached as high as 70%, and the duration of response exceeded that of the original studies. In July 2015, the FDA granted first-line approval to gefitinib in mNSCLC patients whose EGFR gene shows deletions on exon 19 or mutations on exon 21. The drug’s indication statement requires that these mutations be detected by an FDA-approved test.

Lynparza: Back from the depths—twice
On the heels of a disappointing phase 2 trial, AstraZeneca decided to end development of olaparib (Lynparza) as maintenance therapy for women with ovarian cancer. The placebo-controlled study of 265 patients whose cancer had relapsed produced a modest 3.6-month progression-free survival (PFS) advantage in the olaparib arm. AstraZeneca’s announcement in 2012 that it would terminate the program came even before the company learned that it would terminate the program even before investigators published their work in the New England Journal of Medicine.

But the investigators sensed that the outcomes weren’t telling the whole story. A subgroup of study participants with known BRCA gene mutations had shown a more promising response. Noting that their study was not designed to address differences among patients on the basis of BRCA status, the NEJM authors wrote that “there is a need to identify biomarkers to select patients for this therapy.”

Two years later, AstraZeneca retrospectively identified BRCA status for 97% of the women in the study. In 137 participants with BRCA mutations, the progression-free survival benefit was seven months, prompting AstraZeneca to request accelerated approval. Concerned about the sample size, however, an FDA advisory committee voted 11–2 against approval.

But in December 2014, the FDA recognized the underlying mechanism of disease and overruled the committee. It approved olaparib for women with germline BRCA mutations detected by an FDA-approved test. Continued approval may be contingent on the clinical benefit reported in ongoing phase 3 trials.

Payers are likely to watch these outcomes closely. At a cost of about $7,000 per month, olaparib exceeds conventional standards of cost-effectiveness, even when restricted to patients with BRCA mutations, according to a study presented at last year’s Society of Gynecologic Oncology annual meeting.

Iclusig: Dot all the (T315)i’s
Ten months after the FDA approved ponatinib (Iclusig) as second-line treatment for some leukemias, the agency ordered Ariad Pharmaceuticals to stop sales and marketing. Real-world incidence of blood clots hit 27%, far higher than what the labeling showed, and fatal and serious events occurred in some patients just two weeks after starting therapy. “FDA cannot identify a dose level or exposure duration that is safe,” the agency warned in October 2013.

In the phase 2 trial that led to ponatinib’s approval, 54% of patients given the BCR-ABL inhibitor had achieved major cytogenic response (MCyR). But in a subset of patients—those with a BCR-ABL kinase domain mutation called T315i—MCyR reached 70%. This subgroup was no less at risk for vascular occlusion, but given its high response rate and the fact that the T315i mutation causes resistance to other kinase inhibitors (nilotinib [Tasigna], imatinib [Gleevec], and dasatinib [Sprycel]), the FDA knew that ponatinib addressed an unmet need.

Ultimately, the agency limited ponatinib’s indication to patients with a T315i mutation and approved a Risk Evaluation and Mitigation Strategy before sales resumed. Though the biomarker requirement cut ponatinib’s market to about 1,300 eligible patients in the United States, it may have saved the product and assured its availability to a handful of patients with few other options.

In returning to a market that has shriveled to a fraction of its original size, however, Ariad was forced to recoup R&D costs from a smaller group of patients. When ponatinib was first approved, its wholesale acquisition cost (WAC) was $9,580 for a 1-month supply. When it reintroduced the drug, Ariad increased the WAC price of ponatinib to $10,350, an 8% hike.
Call it repurposing, repositioning, or recycling, it’s a fast-growing strategy

Drug repurposing goes by a lot of names—some less flattering than others—but put simply, repurposing involves applying a drug’s mechanism of action to an indication far from its original intended use. The best-known example may be sildenafil (Viagra), which failed in early trials as a hypertension agent but became a household word after men in those studies enjoyed, well, a certain side effect.

With the cost to bring a drug to market north of $1 billion, finding a use for a once-promising compound collecting dust on a shelf but has nonetheless cleared preclinical and early safety studies may make strategic sense. Numbers on the size of the repurposing industry are hard to come by, but the existence of several repurposing conferences—when just a few years ago none were held—is a testament to its growth.

Some repurposing involves a bit of serendipity, albeit high-tech serendipity. Using complex computational methods, researchers pair the medicinal effects of a drug with molecular features of disease, such as cellular pathways, to predict usefulness for a given purpose. This approach led researchers at Johns Hopkins and the University of Texas to the discovery that itraconazole, the common antifungal agent, inhibits the Hedgehog signaling pathway. In a subsequent phase 2 study published in the Journal of Clinical Oncology, the researchers reported that itraconazole reduced Hedgehog pathway activity and cell growth in patients with basal cell carcinoma. In January, Japanese researchers published evidence of itraconazole’s effectiveness against endometrial cancer cell proliferation.

Other efforts take a personalized medicine approach. For example, Almac, a Northern Ireland company with U.S. operations, works with pharmaceutical clients to examine databases to identify subgroups that might signal the presence of a predictive biomarker.

NIH gets into the game
The National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health, puts a new twist on repurposing. In its Discovering New Therapeutic Uses for Existing Molecules program, NCATS uses the power of crowdsourcing to match pharmaceutical company-donated assets with scientists who envision new conditions for which they may be effective. The program funds repurposing projects for drugs with an established safety profile and that once advanced to clinical studies, but are no longer under commercial development. Christine Colvis, director of drug development partnership programs at NCATS, says the primary focus is improving the efficiency of addressing unmet needs, not the commercial viability of a molecule.

“The program demonstrates that public posting of industry assets to solicit new therapeutic use ideas from the academic community via crowdsourcing is an effective way to launch new collaborations,” says Colvis. She points to one project in which a team at Yale found that saracatinib—originally developed as a cancer therapy—could be used to treat Alzheimer’s disease.

“By repurposing an existing drug, investigators were able to begin testing it in humans within three months of receiving their award. Typically, it would take more than a decade from the discovery of a promising compound to its readiness for clinical trials.”

The project is one of the early successes of the New Therapeutic Uses program. Shortly before AstraZeneca made saracatinib—a Fyn kinase inhibitor—available for study, the Yale team had discovered that activation of the Fyn kinase protein triggers a process that leads to synapse loss, a characteristic of Alzheimer’s. The team, led by Stephen Strittmatter, MD, hypothesized that blocking Fyn activity may modify the course of Alzheimer’s. After four weeks, saracatinib reversed synapse and memory loss in mice. Strittmatter’s team went on to complete a successful phase 1b trial and has advanced to a multisite phase 2a study of saracatinib.

NCATS has funded 13 projects, with another round of funding likely next year. “Some of our projects will use a personalized medicine approach to identify patients that are most likely to respond to therapy,” says Colvis. Those studies are ongoing now, so details are not yet publicly available.

For a drug already on the market, a successful repurposing may or may not boost its cost. A 2014 analysis in the Journal of Market Access and Health Policy found that potential for cost increases is greatest when the treatment setting shifts from outpatient to hospital, route of administration changes, an unmet need is addressed, or if the drug is classified as orphan.
off-label use of drugs with narrow indications, saying “it’s incumbent on the provider to use the drug appropriately.” His concern is founded; a 2015 study, for instance, found that 60% of oncologists do not make NSCLC treatment decisions based on EGFR mutation subtype. EGFR mutations are believed to exist in as many as 30% of NSCLC patients, and they are an important prognostic factor for guiding treatment choice. As with breast cancer patients who are tested for hormone receptor of HER status before initiation of treatment, guidelines recommend EGFR mutation testing when a patient is diagnosed with NSCLC.

Yet both the president’s council and 21st Century Cures legislation explicitly forbid prohibition of off-label use of drugs that are approved under a new accelerated pathway. The council called for strong limitations, perhaps through insurers, in the SMU pathway. For indications provisionally approved for small populations on the basis of a biomarker, Aetna would like to see confirmatory evidence supporting a link between surrogate endpoints and meaningful improvements, according to Pezalla. “In the cancer trials, it might be progression-free survival, overall survival, or improvements in patient quality of life,” he says. In relatively short trials, “some of those data are lacking or not statistically significant because of the small number of patients.”

A biomarker that shows with reasonable certainty why a drug will or won’t work in populations, says Pezalla, “is really going to help patients and help doctors talk about therapy, and it may also help therapies that have been reserved for the more advanced cancers to be used earlier in the disease, perhaps with better outcomes.” But because not every biomarker is promising, he adds, “it’s great if the FDA looks at these as part of their approval pathway, because it helps us understand just how well a biomarker works.”

**New life for old molecules**

One of the side benefits of biomarker discovery is the reintroduction of a handful of currently approved drugs that were either once taken off the market or shelved halfway through development. Gefitinib, the lung cancer drug, is the prime example. Tested on more than 1,500 people with metastatic NSCLC, the kinase inhibitor was approved in 2003 because of its dramatic performance in a small subpopulation. But when postmarketing studies failed to confirm the drug’s benefit in a broader population, gefitinib was pulled from the market.

What researchers didn’t know then was that gefitinib wasn’t originally tested on enough of the right people. Six years after gefitinib’s approval, researchers identified genetic abnormalities in those original responders. In 2015, the drug made it back to market after being studied in 106 patients whose EGFR gene expressed the same abnormalities. Today, it is indicated specifically for that population.

Gefitinib’s rebirth is a cold, hard lesson in missed opportunity, lost time, and wasted resources. “If you have success in a broad population but it’s all due to a subgroup, you’re exposing that whole population to determine that subgroup until you have the right biomarker,” says Pezalla. “That’s not only expensive, but for some people, their cancers may progress and it may be difficult to regain that ground.”

That realization has led the FDA to scale back the indications for a handful of other targeted drugs, such as cetuximab (Erbitux) and panitumumab (Vectibix), that reached the market before science fleshed out our understanding of their biomarkers. Panitumumab was approved by the FDA in 2006 for metastatic colorectal cancer but was rejected in 2007 by the European Medicines Agency (EMA), the European analog to the FDA, for lack of efficacy. Amgen subsequently showed EMA that the drug doubled progression-free survival in a subset of patients without a KRAS mutation. As a result, the FDA changed panitumumab’s indication in 2009 to warn that the drug was “not recommended” in patients with KRAS mutations, changed it again in 2012 to say it was specifically “not indicated” for this group, and again in 2014 to require use of an FDA-approved test to confirm that a patient does not have a KRAS gene mutation.

As biomarkers transform cancer and turn other diseases into niche conditions, some treatment decisions are becoming more clear cut. But they are something of a lesson in systems theory—introducing complexities that will fuel dialogue about cost and access for years to come.

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