WHEN ONE SIZE DOESN'T FIT ALL:
Targeted treatments can improve outcomes // But at great cost //
Can we afford to each have our own?

The Price of Personalization

BY TIMOTHY GOWER // PHOTOGRAPHS BY ADAM VOORHES

Brian O'Sullivan considers Kalydeco (ivacaftor) an invaluable medicine. "For me, as a clinician who cares for kids with cystic fibrosis, this drug has been wonderful," says O'Sullivan, a pediatric pulmonologist at UMass Memorial Medical Center in Worcester, Mass. Kalydeco is the first drug to target a gene mutation that causes CF, an inherited chronic disease that produces thick mucus in the lungs, digestive problems and other symptoms. It afflicts about 30,000 children and adults in the United States. O'Sullivan has seen dramatic improvements in breathing, digestion and overall quality of life in patients treated with Kalydeco.

Yet Kalydeco only treats just the 4% of patients with CF who carry the G551D gene mutation—a total of about 1,200 people in the United States. Studies to see if Kalydeco could benefit patients with other mutations only recently began. And then there's the price tag: $300,000 per patient for a year of treatment, which must continue for life. "We weren't expecting it to be cheap, but this is so outrageous," says O'Sullivan.

Last year, O'Sullivan and several colleagues wrote an editorial in *JAMA* that asked, in essence: How many more Kalydecos can the U.S. health care system afford? It's a pressing question in the emerging era of personalized medicine, as the list of so-called targeted therapies—which are designed for a fraction of patients within a disease category and inevitably carry huge price tags—continues to grow.

The concept of personalized medicine takes many forms, but the most promising may be the goal of replacing "one size fits all" drugs made to treat broad swaths of patients with new medicines designed to pinpoint genetic mutations and other molecular abnormalities that occur within patient subpopulations. Because researchers have learned a great deal about the genetic origins of cancers, oncologists have the largest number of targeted drugs to call upon. At Massachusetts General Hospital Cancer Center, all malignant tumors now are studied for genetic mutations that might make the patient one of the 10% of candidates for whom there is a drug that precisely fits their needs, says director Daniel Haber.

But targeted cancer drugs routinely cost $100,000 or more per course of treatment. When pharmaceutical companies make drugs for small groups of patients, they compensate for low-volume sales by charging a lot. Lofty price tags are also common for so-called orphan drugs that treat rare diseases. Insurers have generally not balked at the high cost of orphan drugs because relatively few patients need them. But in the pursuit of personalizing medicine there will be an ever-expanding formulary of expensive drugs that critics believe will strain the U.S. health care system. "This is not sustainable," says O'Sullivan.

The rise of premium-priced targeted therapies is occurring at a time when the overall cost of drugs is increasing, and signs of resistance within the medical community are stirring. For example, the high price tag of a new hepatitis C drug, Sovaldi (sofosbuvir)—which costs $84,000 for a 12-week treatment—has come under protest by patients and payers alike. But while Sovaldi is considered a major advance in the treatment of


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hepatitis, that's not the case for all recently approved drugs with sky-high prices, and some hospitals and insurers are refusing to use or cover high-ticket medicines that don't provide patients with significant benefits. But even if personalized medicine yields therapies that improve patient care and prolong life, is this an advance we can afford?

The idea of tailoring therapies to individual patients isn't new. Hippocrates observed that two people could respond very differently to the same drug. Indeed, scientists have long known that variations in enzymes that help patients metabolize compounds can influence how a particular patient responds to a given medication, which may fail to have the desired effect or could cause potentially serious side effects. According to an oft-cited 2001 study, analgesics work for about 80% of users, for instance, while conventional oncology therapies are effective only for roughly one in four patients. Response rates for most other drug classes are in the 50% range. Moreover, 2.2 million Americans suffer adverse effects from drug treatment each year, and 100,000 die.

The rise of molecular medicine has seemed to promise that we could do better, and efforts toward personalizing medical therapies, primarily for treating cancer, have accelerated. For several decades researchers have known that about two-thirds of breast cancer patients have tumors with estrogen receptors, and many of those patients respond well to estrogen-blocking drugs such as tamoxifen. The widely used drug Herceptin (trastuzumab) is considered another early success story in personalized medicine. Roughly 15% to 20% of women with invasive breast cancer whose tumors have overactive HER2/neu genes are candidates for Herceptin, which blocks signals that cause abnormal cell growth and help cancer spread to other organs. Adding Herceptin to chemotherapy decreases the risk of death in women with early breast cancer by a third.

Spurred by the publication of the Human Genome Project in 2001, more and more drugs and diagnostic tests that fall under the rubric of personalized medicine have become available in the United States—from 13 in 2006 to over 100 today, according to the Personalized Medicine Coalition, an education and advocacy group whose members include pharmaceutical firms, biotechnology companies, hospitals and developers of diagnostic tools. "Personalized medicine has made significant progress in reshaping the way we think about how medicine should be practiced," says Edward Abrahams, president of the PMC.

There are signs that drug developers concur. A 2010 survey by the Tufts Center for the Study of Drug Development estimated that as many as half of new medications in the drug industry pipeline were targeted therapies, and some firms have been particularly aggressive. One example is the Swiss pharmaceutical company Roche; according to a spokesperson, 75% of the drugs under development at Roche will have accompanying biomarker tests to be used for identifying proper candidates.

A few targeted therapies have had a profound impact on care. Gleevec (imatinib mesylate), approved in 2001 for the treatment of chronic myeloid leukemia, is often held up as one of the earliest and most successful of these drugs. Unlike conventional chemotherapy, which attacks all cells in a malignant tumor, Gleevec targets a mutation that promotes tumor growth. (Because most CML patients carry that mutation, it's debatable whether Gleevec really qualifies as personalized medicine, a fact that underscores the lack of clear definitions in this field.) Before Gleevec, a diagnosis of CML was usually fatal, but now 95% of patients treated with the drug survive at least five years.

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Meanwhile, Gleevec has been approved for treating several other forms of cancer—and its price has tripled to more than $90,000 per year since it was introduced in 2001.

But a number of new cancer drugs have price tags comparable to Gleevec's, or higher, despite offering more modest benefits. Consider Xalkori (crizotinib), a drug designed for approximately 3% to 5% of patients with advanced non-small-cell lung cancer who have fused EML4 and ALK genes, which produce a protein that drives tumor growth. MGH thoracic oncologist Alice Shaw and colleagues compared Xalkori with standard chemotherapy in patients with ALK-positive NSCLC and found that it tripled the number who responded to therapy, and more than doubled the length of time patients remained cancer-free, from slightly more than three months to almost eight months. Though there was no difference in overall survival because of the fact that patients randomized to receive chemotherapy were allowed to "cross over" to receive crizotinib, the trial showed significantly greater improvements in quality of life with crizotinib compared with chemotherapy.

Last year, Xalkori was labeled "not recommended" by the United Kingdom's National Institute for Health and Care Excellence. NICE deemed the drug not cost effective at a price that could run as high as £51,579, or about $86,500, for a course of treatment.

A number of other new cancer drugs—some, though not all of them, targeted therapies—cost between $8,000 and $10,000 a month, and are only incrementally better than traditional chemotherapy, says Lowell Schnipper, chief of oncology and hematology at Beth Israel Deaconess Medical Center in Boston, and chair of the American Society of Clinical Oncology's Task Force on Value. A few extra months of life may be extremely valuable to a patient, Schnipper acknowledges. But he says the "financial impact" of high-priced medications can be devastating to patients and their families, to the point of being the primary cause of declaring personal bankruptcy. Even those who have health insurance may face huge co-payments. "We talk about the medical marketplace, but there isn't one," Schnipper says. "If there were, patients wouldn't pay the same for a curative therapy as they do for something that gives them only a couple of extra months."

Cancer drugs don't have a monopoly on sticker shock. "We're turning out too many super-expensive drugs that have marginal benefits," says health economist Joshua P. Cohen of the Tufts Center for the Study of Drug Development. Cohen cites Soliris (eculizumab), which treats a rare chronic blood disease called atypical hemolytic uremic syndrome, at a cost of about $500,000 per year; and Juxtapid (lomitapide), for patients with homozygous familial hypercholesterolemia, at $250,000 per year.

Yet Cohen believes the health care system can afford targeted drugs if they work well. "This is not just about the pharmacy budget," says Cohen, noting that someone treated with an effective targeted therapy may require fewer office visits or trips to the emergency room because of serious drug-induced side effects. A person on a targeted drug may cost the system less than a similar patient taking conventional medications.

Some research suggests that personalized approaches can

benefit both patients and health care budgets. For example, a preliminary 2011 study at MD Anderson Cancer Center in Houston found that using biomarkers to select drugs likely to help particular patients resulted in better responses to treatment. In a non-randomized trial, researchers at the hospital's Clinical Center for Targeted Therapy identified 175 patients with various forms of advanced cancer whose tumors had molecular abnormalities that could be matched to specific targeted oncology drugs. More than 25% of patients responded to treatment with those drugs, compared with just 5% of those who got conventional cancer therapies. Patients who received targeted therapies also remained in remission and survived longer.

In some cases, even very high-priced medications might ultimately save money. The drug Erbitux (cetuximab), for example, is designed to slow the spread of colorectal cancer in patients who carry the common form of the KRAS gene, at a cost of about $95,000 per course. Yet a Northwestern University analysis determined that if all Americans with metastatic colorectal cancer underwent testing for the KRAS mutation, and if only those who tested positive were treated with Erbitux, the U.S. health care system could save $604 million a year. "If we see more relatively cost-effective drug-diagnostic combinations, we won't lower costs, but we'll bend the cost curve downward," says Cohen. That could happen, he says, "if we have more Gleevecs—drugs that are expensive but do a really good job."

There's also the argument that higher prices may simply be the cost of better medicine. "We have paid large amounts of money to do trial-and-error medicine, without very good results for patients," says Henri Termeer, the former president and CEO of Genzyme Corporation, who with his wife donated $10 million to create the Henri and Belinda Termeer Center for Targeted Therapies at Mass General Cancer Center in 2011. "The cost of treating a disease effectively could be higher than treating a disease ineffectively."

Indeed, Vertex, the maker of Kalydeco, defended the drug's $300,000 annual cost in a statement: "The price of Kalydeco reflects how well this medicine works, the time and cost it took to develop, and our commitment to reinvest to help many more people with CF—work that is highly expensive, risky, and takes the dedication of hundreds of people over decades." Vertex added that most patients in the United States who take Kalydeco have monthly out-of-pocket costs of $50 or less, and that the company offers financial assistance and free medicine to patients who meet certain criteria.

In a similar statement, Pfizer, maker of Xalkori, noted that targeted therapies may be more cost efficient than conventional medicines because they're administered only to patients who are more likely to respond to them. When NICE rejected Xalkori, Pfizer chided it for its "limited and slow-paced adoption of innovative medicines."

Targeted therapies often cost more to develop than conventional medications because they require an accompanying test to identify candidates, says Daryl Pritchard, director of policy research for the National Pharmaceutical Council, a trade group supported by biopharmaceutical companies. "There are substantial costs associated with co-development," says Pritchard, regardless of whether a drug company designs the test on its own or hires a diagnostics firm to create one.

Yet there are a number of ways to reduce the cost of producing targeted therapies, savings that could be passed on in the form of lower prices, says Kevin A. Schulman, director of the Center for Clinical and Genetic Economics at the Duke Clinical Research Institute. For one, the long, expensive process of gaining Food and Drug Administration approval for a new drug

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could be faster and more efficient. Instead of paying clinicians and institutions to recruit volunteers for a clinical trial, a quest that can take years, drug developers might find participants by collaborating with disease foundations and support groups.

It may also be that targeted therapies need not be tested in traditional trials that include large numbers of patients. "That is inconsistent with the very idea of targeted therapies," says Christof Koelsch, executive vice president of Diaceutics, a global firm supporting the drug industry in commercializing personalized medicines. Koelsch and others note that most targeted therapies usually have much higher response rates in their targeted population than a comparable conventional drug would have, which means that targeted therapies can be shown to have statistically significant benefits in a relatively small number of patients. "With targeted therapies, you don't need 10,000 patients for a clinical trial—you need 100, as long as they have the mutation of interest," says MGH's Haber.

Will the FDA accept smaller clinical trials for targeted therapies? In a statement to *Proto*, the FDA's Center for Drug Evaluation and Research said that all approved medications must meet high standards to prove efficacy and safety, yet the agency "exercises flexibility and scientific judgment in applying those standards, and the FDA has a long and well-documented history of applying this flexibility to the development of new products for small patient populations."

Schulman says it would also help if drug companies spent less to market their products. The pharmaceutical industry spent $27 billion on promotion in 2012, according to the Pew Charitable Trusts. With more and more targeted therapies, large and expensive advertising campaigns make less sense, and Schulman suggests that drugmakers might market personalized medicines more efficiently through social media and direct interaction with patient advocacy groups.

The federal government could also help keep costs down by offering grants to small biotechnology firms to help fund development of new drugs, in return for a promise from drugmakers that they'll cap prices. Schulman and colleagues estimated in a 2012 *Health Affairs* article that the price of a drug that was funded solely through private equity at a cost of $329,000 per year could still be profitable for investors when priced at $35,000 a year if it was developed with 90% of funding coming from public grants. The government, in turn, would save money by no longer paying for expensive drugs through Medicare. "Clearly it would be cheaper to use public resources for clinical trials than to pay current personalized medicine drug prices for large numbers of people," says Schulman.

Whether drugmakers would indeed pass savings along to consumers is an open question. Regardless, Termeer doesn't believe that the high prices currently charged for these products will persist. "Markets don't work that way," says Termeer. The business of making personalized medicines may be expensive today, he argues, but as pharmaceutical companies fill their portfolios with targeted drugs, the development process will become more efficient while the need for a huge return on investment for each product will diminish. "In the future," says Termeer, "with the economies that will become available, as with any industry, we'll bring the price down." ■

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1. ***Me Medicine vs. We Medicine: Reclaiming Biotechnology for the Common Good*, by Donna Dickenson (Columbia University Press, 2013).** A medical ethicist argues that the promise of personalized health care has been overstated and that focusing on the individual distracts from the importance of proven public health interventions, such as vaccination programs.
2. **"Towards a Balanced Value Business Model for Personalized Medicine: An Outlook," by Christof Koelsch et al., *Pharmacogenomics*, January 2013.** To bring down the high cost of personalized medicine, drug developers need to adopt new strategies, such as shorter, smaller clinical trials, Koelsch and colleagues argue, stating that "not all targeted therapies must inevitably cost a fortune."
3. **"Can Genomics Bend the Cost Curve?" by Katrina Armstrong, *JAMA*, March 14, 2012.** Like most medical innovations, targeted therapies and companion diagnostic tests add to health care costs. However, Armstrong argues that personalized medicine has the potential to improve the value of health care by reducing the use of ineffective treatments.