care defies conventional market logic.[5] Health care is entangled in complex pricing systems that even most health care professionals do not understand. Trained in diagnosis and treatment, physicians have little education in counseling patients on options and economic issues. With more of their own dollars at risk, however, patients will eventually insist that health care providers deliver the value they expect from other businesses.

This surge in consumerism has already stimulated the growth of retail delivery models. Companies including Wal-Mart, CVS Caremark, and Walgreens have entered the world of health care delivery, with capital, information technology, and national distribution systems. These firms offer convenient locations with standardized processes and are expert at managing cost and price. They are likely to be powerful change agents in this new era of health care consumerism and may encourage other companies to enter this large segment of the U.S. economy.

As patients become more sophisticated purchasers of health care, they will push competition in health care delivery to look increasingly like that in consumer-goods industries. This competition could lead to product offerings that appeal to consumers with different needs. While some patients may seek greater odds of survival, others may seek a faster return to work or lower out-of-pocket costs. These options are at the core of "patient-centered" care.

To move health care in this direction, public reporting must shift from "one size somewhat fits all" to an approach that reports metrics reflecting the varied concerns and preferences of consumers. With better information, millions more patients can become smart shoppers and, in the process, help bend the health care cost curve.

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Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation

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Many people with serious or life-threatening illnesses for which there are no satisfactory treatments are understandably eager to gain access to new therapies and are willing to trade off greater certainty about a drug's performance for speed of access. Because the typical clinical drug-development program takes about 7 years, during which a substantial body of safety and efficacy data is generated, the Food and Drug Administration (FDA) has long-standing expedited pathways available for drugs being studied for such illnesses. However, many patients and their advocates continue to believe that clinical development is sometimes prolonged beyond what is necessary. During the congressional considerations leading up to passage of the FDA Safety and Innovation Act of 2012 (FDASIA), a variety of provisions related to this theme were put on the table. When the bill was enacted, two modifications of the Federal Food, Drug, and Cosmetic Act addressed the issue of drug development for serious illnesses: a new "breakthrough therapy" designation for investigational drugs and expansion of the statute regarding accelerated approval. The breakthrough-therapy designation has since been introduced into the FDA portfolio of expedited programs for serious conditions.

The genesis of the new designation can be traced to several emerging trends in drug discovery and development. Most notable is the rise of molecularly targeted therapies, often paired with companion diagnostics, for treatment of cancer, genetic diseases, and increasingly, other serious illnesses. These therapies are directed at subgroups of patients (within the larger population with a given disease) who are predicted to benefit from

Table 1. Drugs with Breakthrough-Therapy Designations Announced as of September 30, 2013.*

Investigational Drug Designated as Breakthrough Therapy	Indication	Sponsor	Date Announced
Ivacaftor	Cystic fibrosis	Vertex	January 6, 2013
Ivacaftor–lumacaftor combination	Cystic fibrosis	Vertex	January 6, 2013
LDK378	Metastatic non–small-cell lung cancer	Novartis	March 15, 2013
Ibrutinib	Mantle-cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, small lymphocytic lymphoma	Pharmacyclics	April 8, 2013†
Palbociclib	Breast cancer	Pfizer	April 10, 2013
Lambrolizumab	Advanced melanoma	Merck	April 24, 2013
Daclatasvir–asunaprevir–BMS-791325 triple combination	Chronic hepatitis C	Bristol-Myers Squibb	April 25, 2013
SD-101	Epidermolysis bullosa	Scioderm	April 29, 2013
Daratumumab	Multiple myeloma	Janssen	May 1, 2013
ABT-450/r–ABT-267–ABT-333 triple combination	Genotype 1 hepatitis C	AbbVie	May 6, 2013
Obinutuzumab	Chronic lymphocytic leukemia	Genentech	May 15, 2013
Sebelipase alfa	Lysosomal acid lipase deficiency	Synageva	May 20, 2013
Asfotase alfa	Hypophosphatasia	Alexion	May 28, 2013
Serelaxin	Acute heart failure	Novartis	June 21, 2013
Drisapersen	Duchenne's muscular dystrophy	GSK	June 27, 2013
Sofosbuvir–ledipasvir combination	Hepatitis C	Gilead	July 25, 2013
Bimagrumab	Sporadic inclusion-body myositis	Novartis	August 20, 2013
Amifampridine phosphate	Lambert–Eaton myasthenic syndrome	Catalyst	August 27, 2013
Entinostat	Advanced breast cancer	Syndax	September 11, 2013
Ofatumumab	Chronic lymphocytic leukemia	Genmab and GSK	September 13, 2013
Volasertib	Acute myeloid leukemia	Boehringer Ingelheim	September 17, 2013
Alectinib	Advanced non–small-cell lung cancer	Roche	September 23, 2013

* Some sponsors do not publicly announce the receipt of a breakthrough-therapy designation.
† Multiple breakthrough-therapy designations were announced.

them. Some of these targeted therapies achieve a much larger treatment effect than currently available therapies — effects that are obvious even in the initial trials in humans. When a large effect in a serious disease is observed early in drug development, it seems excessive to conduct a prolonged clinical development program that encompasses traditional trial phases; approaches to expediting drug development in this circumstance, however, have not been well defined. Responding to this problem, the advocacy organization Friends of Cancer Research and the Brookings Institution sponsored workshops on possible development pathways for such drugs. After extensive discussion in the drug-development community, the concept was embodied in law.

Section 902 of the FDASIA articulates two general criteria according to which the FDA may designate an investigational drug as a breakthrough therapy. First, this designation can be applied only within the context of a "serious or life-threatening disease or condition." Second, it must be predicated on "preliminary clinical evidence indicat[ing] that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints." The FDA has interpreted the second criterion to mean that data from studies in animals or conducted in vitro showing that a drug has promise are not sufficient to justify this designation; data from clinical trials in humans are needed.

Once a drug is designated as a breakthrough therapy, the FDA commits to working particularly closely with the drug sponsor to devise the most efficient pathway for generating additional evidence needed about safety and efficacy. The amount of additional data needed will vary, depending on the disease, the magnitude and robustness of the initial data, and the availability of alternative therapies. The statute also calls for reducing exposure of patients to a potentially less-effective active control drug (i.e., when clini-

Table 2. Comparison of the FDA's Various Expedited Programs for Serious Conditions.*

Variable	Fast-Track Designation	Breakthrough-Therapy Designation	Accelerated-Approval Pathway	Priority-Review Designation
Qualifying criteria	A drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need†	A drug that is intended to treat a serious condition and that preliminary clinical evidence indicates may demonstrate substantial improvement over available therapies on a clinically significant end point or end points	A drug that treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that is reasonably likely to predict an effect on "irreversible morbidity or mortality" or other clinical benefit	An application (original or efficacy supplement) for a drug that treats a serious condition and that if approved would provide a significant improvement in safety or effectiveness‡
Features	Opportunities for frequent interactions with FDA; possible eligibility for priority review; rolling review	All fast-track designation features; intensive guidance on an efficient drug-development program, beginning as early as phase 1; organizational commitment involving FDA senior managers	Approval based on an effect on a surrogate or intermediate clinical end point that is reasonably likely to predict a drug's clinical benefit	Shorter period for review of marketing application (6 months, as compared with the 10-month standard review)

* Information in the table is from the FDA draft guidance regarding expedited programs for serious conditions.[1]
† Certain antibacterial and antifungal drugs are eligible for fast-track designation by law even if they do not otherwise meet the qualifying criteria.
‡ Certain applications and supplements are eligible for priority-review designation by law even if they do not otherwise meet the qualifying criteria.

cal equipoise is not present). Although this ethical principle is applicable to all development programs, it is especially pertinent to drug development under the breakthrough-therapy program in cases in which impressive early clinical data are available. In such cases, the immediate needs of patients must be balanced on an ongoing basis against the need to generate reliable data to inform therapy. In addition, rapid clinical development for breakthrough-therapy drugs will put more pressure on other components of drug development, such as drug manufacturing: development of a final formulation and scale-up of processes will have to occur more rapidly than they traditionally do. It is possible that manufacturing will become the rate-limiting step in some breakthrough-therapy drug-development programs.

It is not expected that all products designated as breakthrough therapies will in fact turn out to have the potential suggested by the early clinical data. Subsequent trials may reveal a smaller treatment effect, or unacceptable adverse effects may occur. It is also important to recognize that a breakthrough-therapy designation is not a drug approval. Like all drugs in development, drugs designated as breakthrough therapies will be reviewed by the FDA to determine whether they are safe and effective for the intended use before they can be approved for marketing. This review will be expedited for drugs designated as breakthrough therapies, if the clinical findings warrant doing so. Since enactment of the FDASIA about 1 year ago, more than 80 requests for a breakthrough-therapy designation have been submitted to the FDA, and 26 have been granted. The designations that have been publicly announced by drug sponsors, along with the conditions being studied, are listed in Table 1.

How does the breakthrough-therapy designation differ from other FDA programs that expedite drug development? Fast track, which was implemented under the FDA Modernization Act of 1997, is for drugs that are intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need. This tool allows applicants opportunities for frequent interactions with the FDA review team and permits the applicant to submit portions of an application to the FDA for review before submitting the complete application. Priority-review status is given when a new drug application is filed for a drug that, if approved, would provide a significant improvement in safety or effectiveness for a serious condition. Priority review shortens the target period for FDA review by 4 months. Accelerated approval allows for approval of drugs, again in the context of serious illness, that demonstrate an effect on a surrogate end point or intermediate clinical end point that is reasonably likely to predict clinical benefit and that also provide a meaningful advantage over available therapies. The FDASIA included language that provided flexibility

in application of the accelerated-approval pathway and clarified the use of an intermediate clinical end point as a basis for accelerated approval. In Table 2, we compare the qualifying criteria and features of each of the four expedited programs.

The FDA has recently released draft guidance on expedited programs for drugs for serious conditions, including the breakthrough-therapy designation.[1] The draft guidance outlines the qualifying criteria and the process for requesting a breakthrough-therapy designation for investigational drugs, and it describes features of the program that are intended to streamline drug development for highly promising agents.

The breakthrough-therapy designation program is of great interest to patients and patient advocates. Because designations are given to drugs in development, it will be some time before the program's effect on access to important therapies can be assessed. This program may represent the initiation of a new paradigm for investigational drugs undergoing development in a setting of extensive mechanistic understanding of disease pathogenesis. As the pace of scientific discovery continues to increase, drug-development pathways will need to evolve in parallel.

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From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

1. Guidance for industry: expedited programs for serious conditions — drugs and biologics. Silver Spring, MD: Food and Drug Administration (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

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Dead Man Walking

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"Shocked" wouldn't be accurate, since we were accustomed to our uninsured patients' receiving inadequate medical care. "Saddened" wasn't right, either, only pecking at the edge of our response. And "disheartened" just smacked of victimhood. After hearing this story, we were neither shocked nor saddened nor disheartened. We were simply appalled.

We met Tommy Davis in our hospital's clinic for indigent persons in March 2013 (the name and date have been changed to protect the patient's privacy). He and his wife had been chronically uninsured despite working full-time jobs and were now facing disastrous consequences.

The week before this appointment, Mr. Davis had come to our emergency department with abdominal pain and obstipation. His examination, laboratory tests, and CT scan had cost him $10,000 (his entire life savings), and at evening's end he'd been sent home with a diagnosis of metastatic colon cancer.

The year before, he'd had similar symptoms and visited a primary care physician, who had taken a cursory history, told Mr. Davis he'd need insurance to be adequately evaluated, and billed him $200 for the appointment. Since Mr. Davis was poor and ineligible for Kentucky Medicaid, however, he'd simply used enemas until he was unable to defecate. By the time of his emergency department evaluation, he had a fully obstructed colon and widespread disease and chose to forgo treatment.

Mr. Davis had had an inkling that something was awry, but he'd been unable to pay for an evaluation. As his wife sobbed next to him in our examination room, he recounted his months of weight loss, the unbearable pain of his bowel movements, and his gnawing suspicion that he had cancer. "If we'd found it sooner," he contended, "it would have made a difference. But now I'm just a dead man walking."

For many of our patients, poverty alone limits access to care. We recently saw a man with AIDS and a full-body rash who couldn't afford bus fare to a dermatology appointment. We sometimes pay for our patients' medications because they are unable to cover even a $4 copayment. But a fair number of our patients — the medical "have-nots" — are denied basic services simply because they lack insurance, and our country's response to this problem has, at times, seemed toothless.

In our clinic, uninsured patients frequently find necessary care unobtainable. An obese 60-year-old woman with symptoms and signs of congestive heart failure was recently evaluated in the clinic. She couldn't afford the echocardiogram and evaluation for ischemic heart disease that most internists would have ordered, so furosemide treatment was initiated and adjusted to relieve her symptoms. This past spring, our colleagues saw a woman with a newly discovered lung nodule that was highly suspicious for cancer. She was referred to a thoracic surgeon, but he insisted that she first have a PET scan — a test for which she couldn't possibly pay.