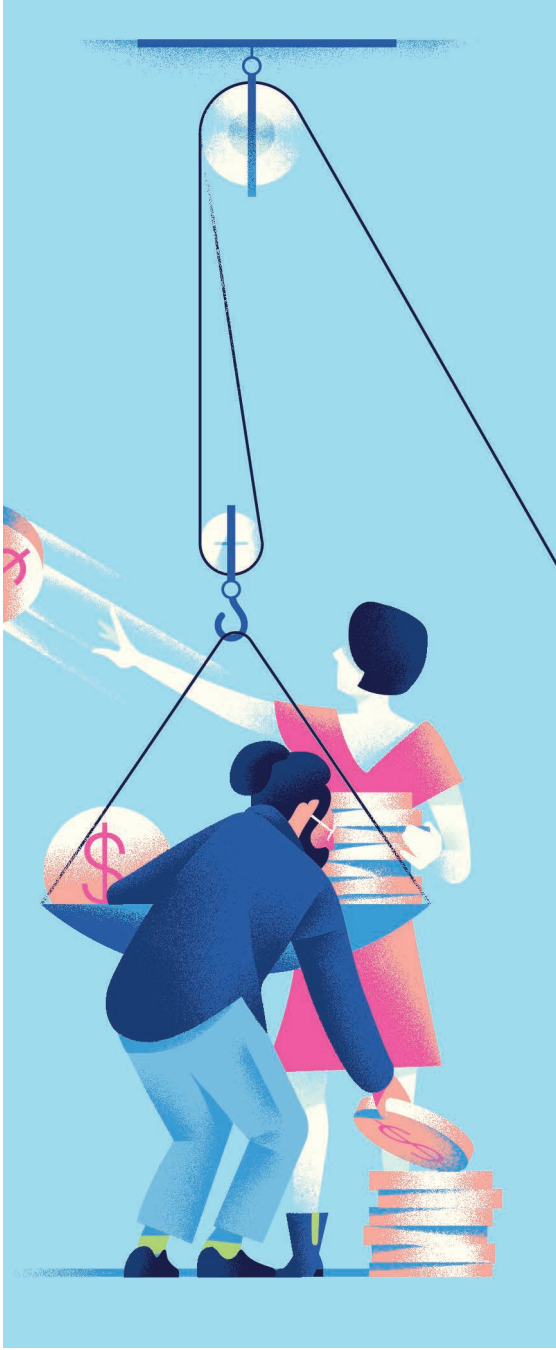
HEALTH ECONOMICS

Cancer's cost conundrum

The price trajectory of oncology drugs is unsustainable — but fixes are in the works.

BY ELIE DOLGIN



MICHELE MARCONI

The year 2011 was a watershed for cancer medicines in the United States. In the space of five months, federal regulators approved the first checkpoint-inhibitor immunotherapy, the first treatment for an aggressive form of thyroid cancer, the first personalized drug for the skin cancer melanoma, the first in an innovative class of targeted agents for lung cancer, and a 'weaponized' antibody therapy that delivers a drug to tumour cells in people with lymphoma.

The potency, complexity and innovative nature of these treatments were noteworthy. But so was the price. Each cost more than US$100,000 per person when taken for a year — a rarity at the time for oncology drugs.

The prices seemed staggering to doctors, patients and health-care providers alike. But quickly, they became normal. By 2014, the average cost of a new orally administered cancer medicine exceeded $135,000 a year — up to six times the cost of similar drugs approved in the early 2000s, after adjusting for inflation[1]. 2017 brought the most eye-popping price tag in oncology yet: a one-time cost of $475,000 per patient for a personalized cell-based therapy for childhood leukaemia.

This generation of treatment promises to transform the field of cancer, yielding more cures and long-term remissions than ever before. But as medicine's ability to tackle tumours races ahead, health-care systems worldwide are struggling to deliver the benefits. If the affordability of drugs is not addressed soon, many people with cancer might not be able to reap the rewards of cutting-edge therapies. "We're on a trajectory that's really unsustainable," says Ameet Sarpatwari, an epidemiologist and legal scholar who studies drug pricing at Brigham and Women's Hospital in Boston, Massachusetts.

"It's really a major issue," says Sabine Vogler, a health economist at the Austrian Public Health Institute in Vienna. Drugs are unaffordable in many parts of the world[2]. "We have to ask ourselves," she says, "how long can we continue paying these high prices?"

STRATEGIES OF CONTAINMENT

New drugs are not the only aspect of cancer care that is getting more expensive. The costs associated with doctors' salaries, diagnostic tests, radiotherapy and surgery are all rising, says Darius Lakdawalla, a health economist at the University of Southern California in Los Angeles. Collectively, they continue to make up the lion's share of cancer-care expenditure. "This is a systemic problem," he says.

And as Daniel Goldstein, an oncologist and health economist at the Rabin Medical Center in Petah Tikva, Israel, and his colleagues reported last year, even the cost of existing cancer drugs has been increasing precipitously — well above the rate of inflation and much faster than other aspects of health care[3]. This price creep, as Goldstein calls it, can cause harm to patients, with a large number of them delaying or skipping treatments that they can no longer afford. Health-care costs are then compounded, Sarpatwari says, because people who don't take their drugs as scheduled are more likely to require hospitalization at a later point. "If people can afford their drugs, it can decrease downstream spending," he says.

The catalyst for spiralling costs starts in the United States, where the price of a drug "is not linked to anything rational", says Vinay Prasad, a cancer specialist at Oregon Health & Science University in Portland. This, he suggests, enables drug companies to charge exorbitant amounts for new treatments that are often not much better than older, cheaper options. And although other countries can usually negotiate a discount, the prices paid are often benchmarked against those in the United States. "What happens in America really has an impact on the rest of the world," Goldstein says.

One idea for lowering prices is to tie them to the level of clinical benefit provided. Peter Bach, a physician and cancer-drug pricing theorist at Memorial Sloan Kettering Cancer Center in New York City, has developed one such calculator of value-based prices: DrugAbacus. This online tool lets users calculate drug prices on the basis of their views on the relative importance of factors such as tolerability, new mechanisms of action, research and development costs and disease rarity — as well as the monetary value that they place on a year of life. Under reasonable economic assumptions, DrugAbacus shows that 80–85% of cancer drugs are overpriced in the United States (see 'Over the odds').

Most countries with nationalized health care already have a value-based price-negotiation system in place — but even then, there are loopholes. In England, for example, the National Health Service spent almost £1.3 billion (US$1.8 billion) between 2010 and 2016 on the Cancer Drugs Fund, a pot of money set aside to improve access to innovative treatments that ended up being used to pay for medicines that the country's drug-pricing watchdog, the National Institute for Health and Care Excellence (NICE), did not deem to be cost-effective.

An analysis[4] conducted in 2017 by Richard Sullivan, director of the Institute of Cancer Policy at King's College London, and his colleagues found that the fund had "not delivered meaningful value to patients or society". It has since stopped paying for drugs that were rejected by

NICE, although it still covers medicines for which the institute's appraisal was inconclusive and further real-world data are required.

An alternative cost-cutting proposal takes the form of a money-back guarantee. Under such an arrangement, only those who obtain medical benefit from a drug have to pay for it. This kind of success fee could eliminate wasteful spending on drugs that do not work for a lot of people, but it has yet to do so in practice.

The best data on this sort of scheme come from AIFA, the Italian Medicines Agency, which introduced performance-based reimbursement for 25 cancer drugs in 2006. Two independent analyses[5,6] of the scheme suggest that it introduced extra layers of administration for little financial benefit. But the money-back guarantees "are still in place, despite their poor performance", says Livio Garattini, a health economist at the Mario Negri Institute for Pharmacological Research in Bergamo, Italy.

Some pharmaceutical companies are also beginning to offer this kind of guarantee on a voluntary basis. Novartis of Basel, Switzerland, for example, has said that people who receive tisagenlecleucel (sold as Kymriah), the company's $475,000 therapy for leukaemia (available only in the United States, at present), can get a full refund if they show no improvement in the first 30 days after treatment.

"We are proud to offer this outcomes-based approach for Kymriah, which is unprecedented in this disease area," says Eric Althoff, head of global media relations at Novartis. He cites independent analyses by NICE and the Institute for Clinical and Economic Review in Boston, as well as evidence from economists at Novartis, to show that the price, even without a discount, is cost-effective for health-care systems. "We recognize our responsibility to ensure patient access and the need for a holistic, evidence-driven approach which incorporates clinical outcomes, patient experience, benefit to the health-care system and societal value," Althoff says.

Goldstein, however, brushes off the guarantee as a public-relations stunt, rather than a real cost-containment measure. He points out that the treatment fails in about 20% of people in the first month, which makes the average cost per person treated, after refunds, about $380,000. That's almost the same as a similarly effective treatment from Gilead Sciences in Foster City, California, which was approved in the United States just weeks after Kymriah, and has a price tag of $373,000 per patient but no money-back guarantee.

"What happens in America really has an impact on the rest of the world."

"It becomes mathematical gymnastics," Goldstein says, with the cost of the guarantee baked into the list price. "It's all basically a little bit of a trick."

A Nepalese man receives cancer drugs provided through an access programme.

VIJI VENKATESH/THE MAX FOUNDATION 2018

GOVERNMENT INTERVENTION

More-radical steps could be taken to force down drug prices, even in the United States, where health care is largely a private, decentralized affair. Under federal law, the US government has the right to procure generic versions of patented drugs in exchange for 'reasonable' royalties that compensate patent holders.

According to a 2017 analysis[7] by Hannah Brennan and her colleagues at Yale Law School in New Haven, Connecticut, the US Department of Defense relied on this to obtain antibiotics and other drugs at steep discounts throughout the 1960s and early 1970s. And the threat alone of such action has been enough to rein in excessive drug pricing: in the wake of the 2001 anthrax attacks, a drug company fended off federal intervention by halving the price of its anthrax medicine.

"It's time to reconsider how the government provides medications," says Brennan, now an associate at the consumer-rights law firm Hagens Berman Sobol Shapiro in Cambridge, Massachusetts. "If drug companies are going to continue making up list prices and completely untethering them to anything," she adds, "then this is an appropriate and proportionate response."

The governments of countries in the European Union might be able to negotiate with drug companies to set prices, but they tend to do so in isolation, "which weakens the purchasing power", says Vogler. To address the problem, some EU countries have banded together to create a united front against pharmaceutical companies. The Netherlands, Belgium, Austria and Luxembourg have formed one such union. Half a dozen Mediterranean countries hope to do the same.

But even when drug companies do offer large discounts, there are many places in which cancer medicines remain out of reach. In several parts of Africa, for example, Swiss pharmaceutical giant Roche has engaged with governments and patient groups to provide its breast-cancer drug trastuzumab (Herceptin) at half the usual price. That markdown was enough for the government of Kenya to agree in 2016 to foot the other half of the bill, at least for a small group of people. The country's Ministry of Health last year committed around 20 million Kenyan shillings (US$195,000) to the effort.

The cost was too high for the government of the much poorer nation Rwanda, however. A 50% concession is "still so beyond what they can afford", says Lawrence Shulman, director of the Center for Global Cancer Medicine at the University of Pennsylvania Abramson Cancer Center in Philadelphia, who works in the East African country.

In a bid to pressure pharmaceutical companies into making expensive medications available to all people in low- and middle-income countries — as happened with HIV drugs in the 2000s — Shulman and an international team of leading cancer researchers worked with the World Health Organization (WHO) in 2015 to expand its list of essential medicines[8]. That helped to prompt two large pharmaceutical companies — Pfizer of New York City and Cipla of Mumbai, India — to agree in June 2017 to offer 16 medicines, most of which are on the WHO list and some of which were advocated by Shulman's group, at rock-bottom prices for people in Rwanda, Kenya and four other low-income countries in Africa.

But the drugs were all staples of chemotherapy treatment that are available as generic versions. Neither trastuzumab nor any other branded medicine from the list was included in the deal. For the most part, the newest therapies continue to elude those in need in the developing world, where a diagnosis of cancer means a painful and distressing death for most people (see 'The diagnosis differential').

One notable exception is imatinib (Glivec). Since 2001, and essentially in parallel with the drug's first approval for use in chronic myeloid leukaemia (CML), Novartis has made the treatment available — at no cost — to the poorest people of the developing world through the Glivec International Patient Assistance Program. "This is a drug that gave people a normal life back," says David Epstein, a former chief executive at Novartis who is now at Flagship Pioneering, a venture-capital firm based in Cambridge, Massachusetts.

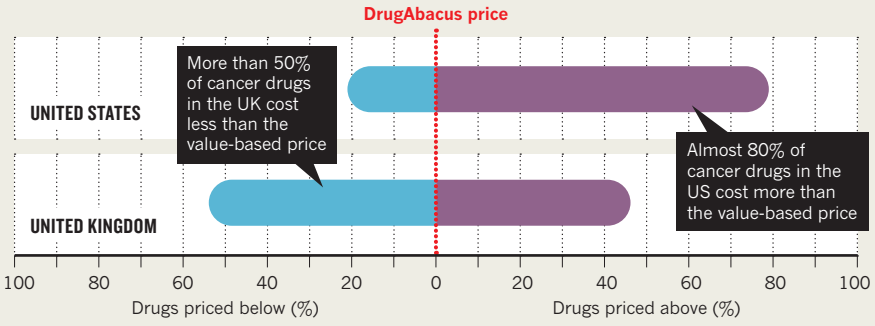
"We felt this obligation to try to make the drug reach as many people as needed."

"We felt this obligation to try to make the drug reach as many people as needed," he says. The programme has handed out around 2.3 million monthly doses of the drug to more than 50,000 people in 80 countries[9].

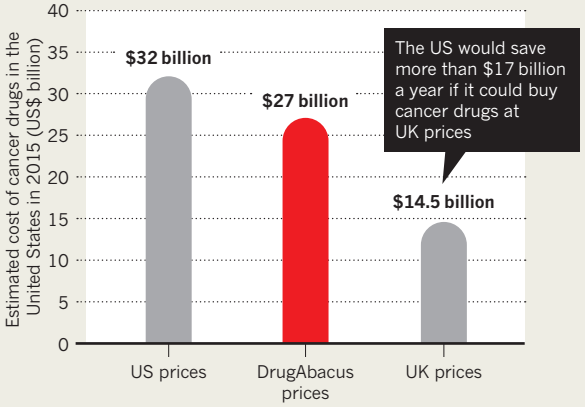
Building on that success, the Max

OVER THE ODDS

Linking a drug's price to the clinical benefit that the medication provides — a practice known as value-based pricing — has the potential to reduce spending on cancer drugs. The DrugAbacus tool provides reasonable estimates of value-based prices* and can be used to indicate whether cancer drugs are priced appropriately.



The total estimated spend on cancer drugs in the United States in 2015 was US$32 billion — almost $5 billion more than if the drugs had been purchased at the prices suggested by DrugAbacus. The same drugs would have cost only $14.5 billion at UK prices.



*The value-based pricing ('DrugAbacus price') used in the analysis assumes that an extra year of life is worth $132,000 and that a 15% discount should be applied to drugs with severe side effects. Increasing the value of an extra year of life increases the percentage of drugs that are available at or below the DrugAbacus price. The data cover the prices of 52 cancer drugs in the US Medicare system and the UK National Health Service.

SOURCE: DRUGABACUS

Foundation — a non-profit organization in Seattle, Washington, that runs the imatinib access programme in partnership with Novartis — has worked with three other manufacturers to make all five of the CML-targeted treatments on the market available in the same way. "Today, if you live in the lowest-income economies of the world and you're diagnosed with CML, you can have access to any drug that you need," says Pat Garcia-Gonzalez, the foundation's chief executive.

"My next goal," Garcia-Gonzalez adds, "is to make that possible for all oncology products." So far, however, the foundation has expanded only into targeted treatments for multiple myeloma and a few types of solid tumour.

BREAKFAST BENEFITS

Although most of the proposed fixes for the cancer-drug cost conundrum have focused on large-scale systemic change, which often requires buy-in from governments, the pharmaceutical industry and doctor and patient groups, small tweaks also have the potential to make a big difference.

An idea championed by Mark Ratain, director of the Center for Personalized Therapeutics at the University of Chicago in Illinois, is to give expensive cancer drugs with food, rather than on an empty stomach as prescribed. This, he hopes, will improve absorption of the drugs, enabling recipients to lower the dose needed and, therefore, to reduce the cost of treatment.

There are several commonly prescribed cancer pills for which food is known to increase the fraction of the dose that enters the bloodstream, including the lung-cancer drug erlotinib and the melanoma drug vemurafenib. So far, however, Ratain has tested his idea only with the prostate-cancer drug abiraterone.

During abiraterone's development, trials showed that the concentration and kinetics of the drug differed between people who took it at mealtimes and those who took it without food. The company behind the drug, Janssen Biotech in Raritan, New Jersey, therefore decided to conduct further testing only in the absence of food, to minimize variability between study participants and to reduce the risk of diet-related complications.

The prescribing information for abiraterone, which is marketed as Zytiga, reflects that decision. "Take Zytiga on an empty stomach," it reads. "Taking Zytiga with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects."

In a pilot study[10] involving 72 people, Ratain and his colleague Russell Szmulewitz, a medical oncologist at the University of Chicago, confirmed this warning by showing that a similar amount of the drug was absorbed when taken as a low dose with a low-fat breakfast as was received with a full dose when fasting. Participants could therefore take one-quarter of the normal dose and still receive the same anti-cancer effects after 12 weeks of treatment, as measured by changes in the level of prostate-specific antigen, a proxy for tumour burden.

If the results hold up to scrutiny, people taking abiraterone will be able to spread the cost of one month's worth of pills — about $9,000 — over four months. That could lower US health-care spending by as much as $20 billion in the next decade, estimates Allen Lichter, former chief executive of the American Society of Clinical Oncology. "The savings that would come simply from taking this with your Cheerios is pretty compelling," he says.

Last year, with Ratain and others, Lichter co-founded a non-profit organization called the Value in Cancer Care Consortium, which aims to find better and cheaper ways of using existing medicines. The hope is to start by conducting a larger, confirmatory trial of Ratain's abiraterone study but, according to Lichter, the consortium is struggling to raise the $5 million needed for a 300-participant trial.

"There's just a tremendous disconnect at times between what people say is important and what they're willing to step up to the plate and make happen," Lichter notes. "If we can take billions and billions of dollars out of the equation, it cannot help but do good for the cancer patients of the world and for the health-care systems of the world." Unfortunately, he laments, "Not enough people are focused on value." ■

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IMPROVING CANCER CARE

The diagnosis differential

In 2015, cancer took the lives of 6 million people in low- and middle-income countries — more than HIV, tuberculosis and malaria combined. Limited access to life-saving medications at an affordable price contributes to this burden. But even if oncologists in these countries could prescribe the same medicines as their better-funded colleagues in the West, it might not reduce the death rate by much.

That's because, in contrast to residents of wealthier countries, more people with cancer in places such as sub-Saharan Africa seek medical attention only after their tumours have metastasized — the point at which outcomes become poor regardless of the intervention. As David Kerr, a cancer researcher at the University of Oxford, UK, points out: "Unless we can diagnose patients at an earlier stage of presentation, all these 'fancy-schmancy' new drugs will have very little impact."

Early detection is useless, however, if there's no one who is trained to treat those affected, notes Lawrence Shulman, director of the Center for Global Cancer Medicine at the University of Pennsylvania Abramson Cancer Center in Philadelphia — many developing countries have only a small number of cancer specialists, if any.

To build capacity, since 2011, Shulman has worked with Partners In Health, a non-profit organization based in Boston, Massachusetts, to develop cancer-treatment programmes in Rwanda and Haiti. He has also engaged in similar work in Botswana.

"You need well-trained nurses. You need appropriate physician expertise," Shulman says. "You need a certain number of those pieces in place before you can shoot the starting gun and get going."

A requirement for better training is not limited to countries that are low on resources. The increasing complexity of cancer treatment means that, even in the wealthiest nations, oncologists must work across specialities to achieve optimal outcomes for their patients. That's why, in 2017, the European Commission's Expert Group on Cancer Control endorsed the recommendation that all doctors involved in cancer care should undergo a period of cross-disciplinary learning.

Medical oncologists, radiation oncologists and surgical oncologists already collaborate on the day-to-day management of patients through meetings known as tumour boards; such panels of multidisciplinary teams have been shown to increase diagnostic accuracy and to improve patient care.

But Jesper Eriksen, a clinical oncologist at Aarhus University Hospital in Denmark who spearheaded the European recommendation[11], thinks that there's still room for improvement. He has called for doctors to complete clinical rotations across disciplines — to enhance the value of meeting other specialists. "Hopefully that will result in a shorter time from diagnosis to treatment," he says. E.D.