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Opportunities for Precision Cancer

Reflections from the Gant Consortium

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About Us

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THE LEONARD DAVIS INSTITUTE OF HEALTH ECONOMICS

Since 1967, the University of Pennsylvania's Leonard Davis Institute of Health Economics has been the leading university institute dedicated to data-driven, policy-focused research that improves our nation's health and health care. It catalyzes and facilitates multidisciplinary work on issues concerning health care reform, health care delivery, healthy behaviors, and vulnerable populations. The Institute connects all of Penn's schools and the Children's Hospital of Philadelphia through its more than 250 Senior Fellows.

About the Gant Consortium

The Gant Precision Cancer Medicine Consortium was an expert work group charged to develop a policy framework that addresses the economic viability and sustainability of precision cancer medicine. In keeping with its multidisciplinary and collaborative principles, the Gant Consortium was comprised of more than 20 individuals with diverse viewpoints and scholarship from both within and outside the University of Pennsylvania. While the Consortium members made important contributions to the discussion, the views expressed in this report are those of the authors alone.

The Consortium was funded by an unrestricted philanthropic gift to the University of Pennsylvania from Donald R. Gant, Wharton Class of 1952, and the Gant Family. It was staffed by the Department of Medical Ethics and Health Policy at the Perelman School of Medicine and the Leonard Davis Institute of Health Economics, both at the University of Pennsylvania.

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Introduction: It Takes a Consortium

There is substantial interest in targeted cancer therapies, spurred by recent biomedical research in genomics and oncology. Targeted cancer therapies, in which prevention and treatment of cancer are based on genomic and biologic analyses, hold promise for cancer care. However, the rising costs of such therapies may threaten that promise.

In an effort to meet the future challenges of targeted cancer medicine head-on, the University of Pennsylvania convened the Gant Family Precision Cancer Medicine Consortium, a multidisciplinary work group of experts from health care economics, policy, law, regulation, cancer research and medicine, patient advocacy, and the pharmaceutical and insurance industry. The Gant Consortium sought answers to a central question: what approaches should stakeholders take to foster the economic viability and sustainability of targeted cancer drugs?

The Consortium literature review was conducted from August through November 2016. The expert committee met regularly from October 2016 to May 2017 to identify points of contention and consensus, outline the issues at the core of sustainable targeted cancer medicine, and inform potential policy recommendations. The literature presented in this report does not include therapies developed afterwards, such as CAR-T.

The views expressed in this White Paper reflect the discussions of the Gant Consortium but do not necessarily represent the views of either any individual member or of the Consortium as a whole.

What is Targeted Oncology?

PERSONALIZED MEDICINE, PRECISION MEDICINE, AND TRENDS IN ONCOLOGY

Understanding and applying genomic and biologic analyses holds promise for cancer, a disease defined by abnormal cell growth brought on by genetic mutation. As genetic testing and genomic data have informed cancer care, the perception of cancer as a limited number of tissue– and organ–specific diseases has given way to a paradigm of hundreds of different diseases, defined, in part, by their underlying genomic alterations. Different diseases require novel treatments, and some observers view targeted therapy as the future of cancer care. A 2015 study found that the percentage of patients who received targeted cancer therapies increased from 11% in 2001 to 42% in 2011.[1]

Targeted cancer therapies rely on the diagnostic identification of biologic (including but not limited to genomic) targets within cancer cells. Targeted therapies can include inhibitors that block the growth of tumor cells, immunotherapies that stimulate the body's immune system to destroy cancer cells, therapies that block the production or action of hormones that stimulate tumor growth, and antibodies that bind to and attack cancer cells.[2]

TARGETED CANCER THERAPY: A DEFINITION

References to targeted cancer therapies often label them "precision medicine," but the definition of precision medicine is often imprecise. Personalized medicine may be a useful umbrella term for tailoring health care to the needs of individual patients, but the relevant factors for customization—genetics and biomarkers, socioeconomic, lifestyle, the focus on prevention versus treatment—are infrequently aligned across definitions. As part of the national Precision Medicine Initiative (PMI), now called "All of Us," the National Institutes of Health (NIH) define precision medicine broadly as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."[3]

A more narrow definition of precision cancer therapies, from Doug Lowy of the National Cancer Institute, is: "Interventions to prevent, diagnose, or treat cancer, based on a molecular and/or mechanistic understanding of the causes, pathogenesis, and/or pathology of the disease. Where the individual characteristics of the patient are sufficiently distinct, interventions can be concentrated on those who will benefit, sparing expense and side effects for those who will not." In contrast to "All of Us," this view focuses on leveraging genomic information to treat and prevent cancer. The Gant Consortium used a more direct term, "targeted cancer therapies," defined as cancer treatments that rely on diagnostic identification of targets within cancer cells—such as small molecules, monoclonal antibodies, and other therapies—and require genomic and related analyses.

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THE PROMISE OF TARGETED CANCER MEDICINE

Visions of curing cancer are an American mainstay. Cancer treatment is expensive, has substantial side effects, and is emotionally and physically taxing. Thus, targeting treatments to individuals who are most likely to benefit has become a commonly held goal. A recent article from the American Society of Clinical Oncology presents this vision: "As our deepening understanding of tumor biology converges with rapid advances in measurement science and technology and computational analysis, we have an enormous opportunity to create a future for precision medicine in oncology that provides for highly specific, minimally toxic, and dramatically effective treatment for each patient."[4]

National programs, such as the Cancer Moonshot, All of Us, and the Biden Cancer Initiative demonstrate renewed interest in cancer research and treatment. Targeted oncology is the focus of much of this research: The 21st Century Cures Act of 2016 authorized $1.8 billion in funding for the Cancer Moonshot over seven years. Recent cancer drug approvals reflect this focus: The average number of approved new cancer therapies rose from 4.9 from 2001-2010 to 10.3 from 2011-2013, largely driven by approvals of targeted therapies.[5]

Targeted approaches have led to a number of breakthroughs in oncology. Imatinib (Gleevec) has dramatically improved care for chronic myelogenous leukemia (CML), turning a deadly disease into a managed condition for many patients.[6] For patients with HER2 positive breast cancer (approximately 30% of patients), Trastuzumab (Herceptin) significantly cuts the risk of recurrence and death.[7] In 2017, the FDA approved Keytruda (pembrolizumab), which was already approved for melanoma, non-small-cell lung cancer, and head and neck cancer, for tumors with certain biomarkers—the first time the FDA approved a cancer drug based on its molecular target, regardless of where the tumor originated.

THE SKEPTIC'S TAKE: INSUFFICIENT EVIDENCE, LIMITED RELEVANCE, AND SKYROCKETING PRICES

Some stakeholders are skeptical that targeted cancer medicine will ever fulfill its promise. At least three factors contribute to pushback: the relative infrequency of identifiable, actionable genetic mutations in tumors, the lack of evidence for increased long-term efficacy of targeted drugs as compared to non-targeted treatments, and the cost of targeted cancer medications.

Targeted therapy may help only a small subset of cancer patients. A sequencing program at the MD Anderson Cancer Center in Houston found that only 6.4% of cancer patients had tumor mutations that could pair with a targeted drug. Complicated cancers may have several mutations, and increased response rates do not guarantee improved overall survival. A recent meta-analysis found that while the use of biomarkers to select patients for phase 1 trials was associated with improved treatment response rates (30.6% vs. 4.9%), progression-free survival increased only from 2.95 to 5.7 months.[8] For many therapies, there is insufficient evidence from randomized control trials to claim that a targeted approach can dramatically improve survival above benefits from non-targeted therapies.[9] Targeted therapies to inhibit tumor growth may extend median survival in the short term, but further mutations within the tumor may result in cancers that are resistant to those treatments in the long term.

Mixed evidence has not slowed down the rate of research and drug development. Targeted therapies have become the norm in much of cancer care,[1] and a recent study found that the number of new targeted drugs approved for cancer doubled in the 1990s, and increased again more than two-fold in the 2000s.[5] In 2016, the FDA approved six new cancer drugs out of 22 total new drugs, four of which were targeted therapies.[10]

For many, the growth of research interest and shifts in approaches to chemotherapy represent a paradigm shift in cancer care. To others, the velocity of research and development of targeted cancer drugs, along with their prices, appears to be out of step with the available evidence. What all sides may agree on, however, is that cancer as a disease appears to occupy a unique position in society.

Is Cancer Special?

The Emperor of All Maladies: A Biography of Cancer won the 2011 Pulitzer Prize for Non-Fiction and became a New York Times best seller. The runaway success of a nearly 600-page medical history raises a question: is cancer special? From a policy perspective, diseases are exceptional if they are treated differently than other comparable conditions. Exceptional treatment includes a willingness to commit more financial and social resources, per unit of burden, than other diseases. The Gant Consortium considered two interlocking claims: first, is cancer treated differently than other, similar diseases, and second, should it be?

CANCER IN THE PUBLIC EYE

Cancer evokes great concern in public opinion and mass media. Public opinion surveys suggest that cancer is a widely feared disease. A Mayo Clinic survey found that most Americans believe that the country's most significant health care challenge is cancer.[11] Media coverage of cancer features headlines such as: "Report: Cancer will be No. 1 killer in U.S."[12] The language around cancer often includes metaphors of "battle," "war," and "struggle." Unlike most conditions, the first question doctors hear after giving a cancer diagnosis is, "how long do I have?"

Much of this anxiety is justified. Cancer is the second leading cause of death in the United States, causing approximately 590,000 deaths in 2017.[13] As Americans live longer, cancer incidence rates continue to rise, and nearly 40% of Americans will be diagnosed with cancer at some point.[14] Almost every American has been personally touched by cancer through either a friend or family member. However, the diversity of cancer complicates the narrative of cancer as a widespread, debilitating cause of mortality. Some cancers are very early stage and grow too slowly to warrant treatment. For example, NIH guidelines suggest that many men with Grade I localized low-risk prostate cancer may forgo or delay treatment in favor of surveillance.[15]

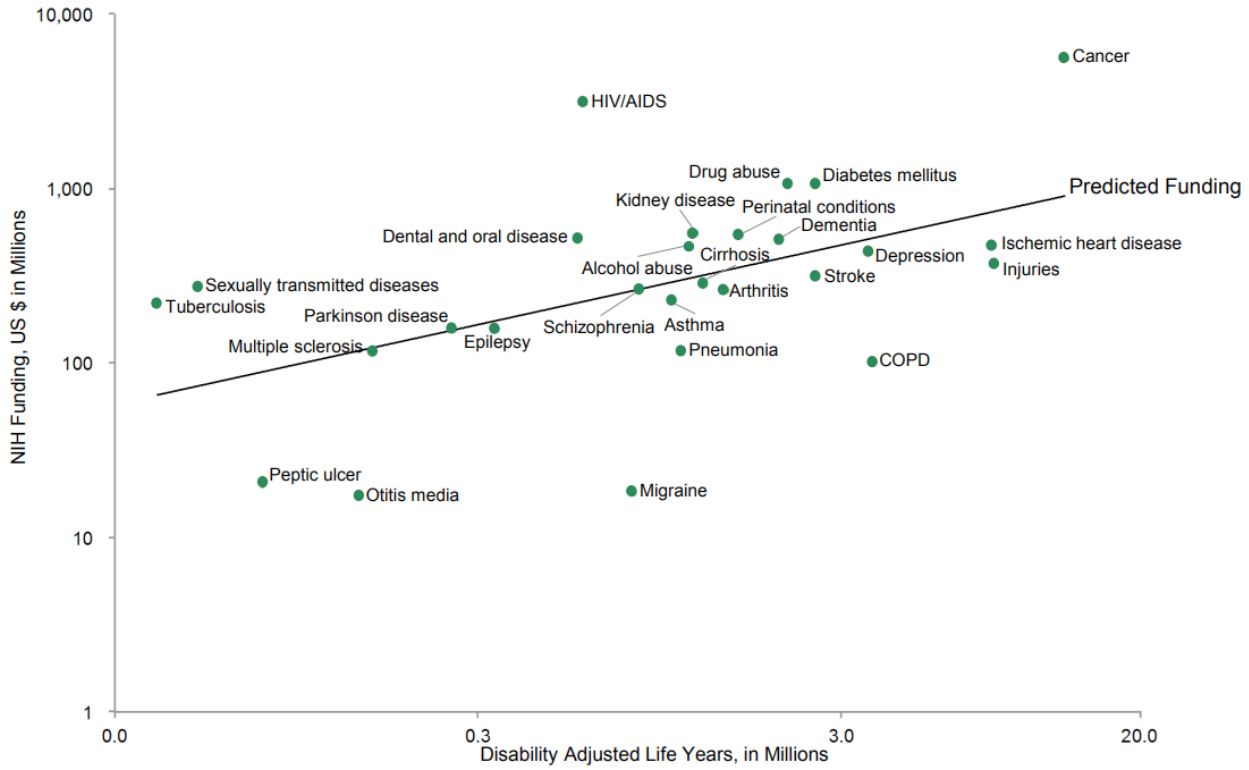
CANCER FUNDING FOR RESEARCH AND DRUG DEVELOPMENT

Public attention to cancer is matched by considerable research attention. The Cancer Moonshot and 21st Century Cures Act, which appropriated billions of dollars of federal funding for cancer research, are only the most recent examples of a high-profile focus on cancer. Sustained attention to cancer dates back to Nixon's 1971 "War on Cancer." The research interest stretches across the public and private sectors: A 2015 JAMA study found that cancer accounted for 16% of all NIH funding ($5.6 billion) in 2013, and 25% of all drugs in clinical trials.[16] In addition to funding across the spectrum of biomedical research, cancer accounts for a substantial share of drug development; in one review of trends, 32.6% of all drugs in development in 2017 had an oncologic target.[17]

Some experts argue that the allocation of research resources should be matched to the societal burden of each disease. The quantitative tools used to measure population-level disease burden include aggregate Quality Adjusted Life Years (QALYs), Disability Adjusted Life Years (DALYs), Years of Life Lost (YLLs), and number of deaths. In theory, the allocation of scarce resources, they argue, ought to track with the societal disease burden. However, it seldom does.

Public and private funding for cancer research is higher than most measures of disease burden would predict. A recent study of funding trends modeled expected public funding for research based on disease burden, measured in lost disability adjusted life years (DALYs). Among a set of 27 diseases, public funding was only marginally associated with US disease burden, and cancer was overfunded—only HIV/AIDS had a larger deviation.[16]

Figure 1. Relationship Between NIH Disease-Specific Research Funding and Burden of Disease for Selected Conditions



Source: The anatomy of medical research: US and international comparisons. JAMA. 2015;313(2):174-189. doi:10.1001/jama.2014.15939. (Online Appendix)

Funding variations also exist across different types of cancer. A study evaluated the National Cancer Institute's distribution of funding and revealed a mismatch within cancer between funding levels and disease burden. Leukemia, breast cancer, and prostate cancer were overfunded, while liver cancer, pancreatic cancer, and esophageal cancer were underfunded. Lung cancer receives only 10% of cancer research funding, despite accounting for 32% of all cancer deaths.[18]

Many researchers question whether the disease burden approach can capture the full value of cancer research, including its external social and scientific benefits. Cancer research often lies at the leading edge of biomedical research—including hematology, immunology, and genomics—and potential for breakthrough treatments for cancer may have downstream effects for other diseases. Just as NASA-led research in the 1960s yielded scientific breakthroughs beyond space travel, funding for biomedical research, and especially cancer research, may not fit into neatly defined buckets. Furthermore, some argue that resource allocation should reflect patient and public values. If, for example, Americans value avoiding a year of life lost to cancer more than a year of life lost to other diseases because of fears specific to cancer, those preferences ought to be reflected in resource allocation. Such a holistic framework towards value of research is attractive, but it is difficult to define.

SPENDING ON CANCER TREATMENT

Disproportionate spending on cancer continues once treatments come to market. A recent review of 54 studies compared incremental cost-effectiveness ratios (ICERs) of cancer drugs and non-cancer drugs. Cancer drugs had mean and median ICERs of $138,582/QALY and $55,000/QALY, respectively, while non-cancer drugs had mean and median ICERs of $49,913/QALY and $31,000/QALY, respectively. Among cancer drugs, 30% of treatments had ICERs above $100,000/QALY, compared to 10% of non-cancer drugs.[19] This suggests that when cancer is the diagnosis, consumers and third-party payers will pay twice as much for the identical therapeutic benefit.

These value thresholds for cancer drugs have increased over time. A study in the Journal of Economic Perspectives evaluated pricing trends for 58 cancer drugs from 1995 to 2013 and found that approval prices per life-year gained had nearly quadrupled, after adjusting for inflation.[20] A more detailed discussion of costs and spending on targeted cancer drugs is found in the next chapter.

SPECIAL FUNDING CARVE-OUTS INTERNATIONALLY

The exceptional nature of cancer is reflected in the proliferation of "ring fencing" in some countries, in which assessment, approval, and payment for cancer drugs lie outside the normal cost-efficacy and drug approval processes. Proponents of ring fencing argue that the practice is protective. The argument assumes that cancer is a unique disease, and the typical measures of value and cost-efficacy do not apply. Patients are not seeking a median overall survival benefit; rather, they are seeking a chance to do better than average given their diagnosis. Because cancer drugs are unusually expensive, and the way society values them is qualitatively different, ring fencing protects budgets for cancer from being whittled away by other diseases, and vice versa. Skeptics claim that, from an economic perspective, there is no rationale for separating out cancer drugs for resource allocation purposes. Any ring fencing will impede a payer's ability to maximize aggregate health benefits.

RING FENCING: THE UK CANCER DRUGS FUND (CDF)

Cancer's status is controversial in the United Kingdom, where the socialized National Health Service (NHS) has struggled to balance cost-effectiveness, equity, and the unique demands of cancer. NHS relies on the National Institute for Health and Care Excellence (NICE) to conduct cost-effectiveness analyses for approval of new drugs and technologies. Generally, NHS will only cover pharmaceuticals with a recommendation from NICE, which has a maximum threshold of £100,000 per QALY. In 2010, widespread concern that cancer patients were not given access to potentially life-saving drugs—because NICE had either not approved, not appraised, or too slowly studied the drugs—led to the establishment of the Cancer Drug Fund (CDF) in England. The CDF had a ring fenced budget and a distinct approval process for drugs. In short, the CDF allowed patients to access drugs before receiving NICE approval.

A 2014 study in the British Journal of Cancer found that the CDF had a substantial impact on prescribing patterns for cancer drugs in England. The CDF was associated with increased prescribing for drugs that NICE had either rejected or given a mixed recommendation, but not for drugs that NICE had deemed cost-effective. The early evidence suggested that the CDF was primarily used to access drugs that were eventually not deemed cost-effective by NICE, rather than expedite access to new, cost-effective cancer treatments that were stalled in the NICE/NHS approval process.[21]

Despite a strategic vision of moving towards value-based pricing schemes, the CDF could not keep up with the cost of drug approvals: Its original budget of £50 million per year grew to £340 million within 5 years. By the time it was folded back in to NICE, the CDF had overspent its budget by an order of magnitude, paying out £1.27 billion on cancer drugs. The CDF remains controversial, and recent literature suggests that it may have been counterproductive for cancer patients and English society at large.[22]

SHOULD CANCER BE SPECIAL?

The argument over whether cancer ought to be treated as special remains far from settled. On the one hand, some claim that resources should be directed to diseases and treatments in proportion to their empirically demonstrated impact on individual patients and population health. Using this framework, the fact that some diseases carry the name "cancer" should not be a consideration. On the other hand, many stakeholders contend that cancer is a unique disease in clinically salient ways. It demands coordination among surgeons, pathologists, geneticists, and oncologists. From a research perspective, the complexity of cancer treatment reflects an interconnected research agenda. Cancer research is not a tidy work plan with clearly delineated objectives; it is a multidisciplinary biomedical endeavor under study on multiple fronts. According to this line of thinking, cancer is the "emperor of all maladies," and it requires a different paradigm for resource allocation.

Recent Spending Trends for Targeted Cancer Drugs

PRESCRIPTION DRUG SPENDING IN THE UNITED STATES

In 2013, Americans spent an average of $858 per capita on prescription drugs—more than double the average of similar industrialized countries.[23] The $450 billion spent on drugs account for approximately 17% of overall health care spending,[24] and $37 billion of drug spending was devoted to cancer.[20] High costs for prescription drugs can have important clinical and economic effects. A quarter of Americans have failed to fill or take medications due to cost,[25] and a diverse literature links high drug costs and cost sharing with poor medication adherence and worse health outcomes.[26]

THE FOCUS ON CANCER DRUG PRICES

Average prices for new cancer drugs routinely exceed $100,000 per year.[27] Studies confirm an upward trend in prices and spending on cancer drugs: A review of commercial claims found that monthly spending on new cancer drugs during the year of product launch increased from $1,869 in 2000 to $11,325 in 2014.[28] Monthly out-of-pocket expenses can reach nearly $1,000 per month. For many families, the financial burden that accompanies health care can be substantial. A Commonwealth Fund study found that over 25% of Medicare beneficiaries spent at least 20% of their income on health care in 2016.[29]

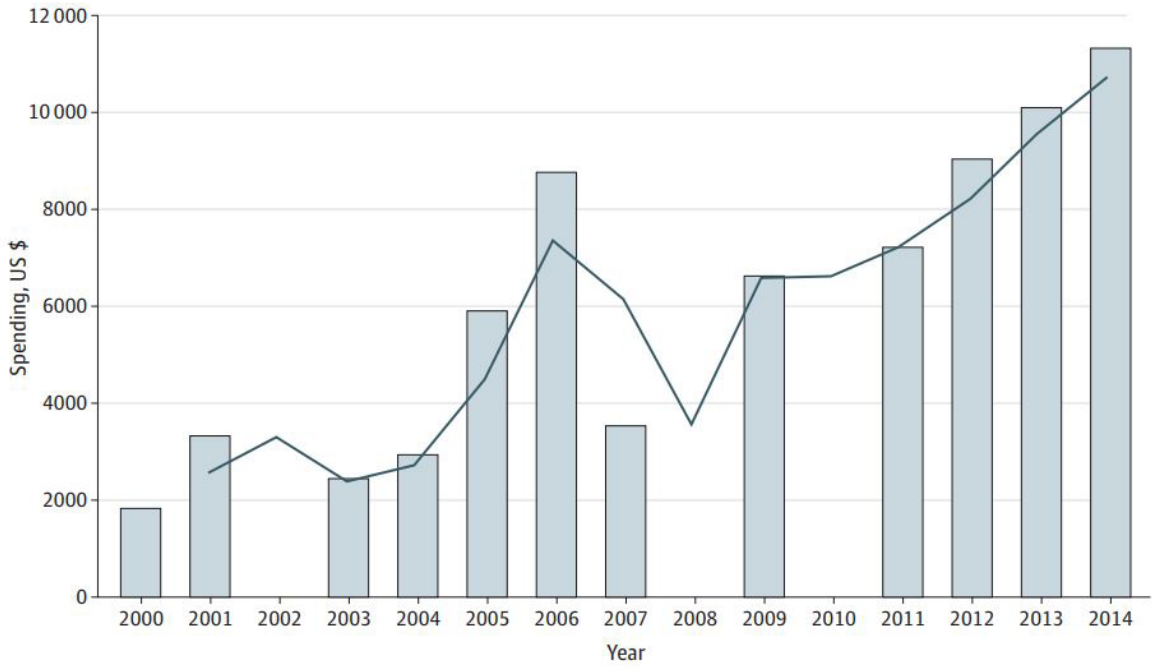
High costs for patients may reduce medication adherence as well. A recent study in the Journal of Clinical Oncology found that cancer patients with greater than $500 in cost-sharing expenses were four times more likely to abandon their prescriptions as patients with less than $100 in out-of-pocket costs, and over half of patients with more than $500 in cost-sharing failed to fill prescriptions for cancer medications.[26] Thus, physicians, patients, and policymakers all have an interest in understanding what is driving the growth in spending on cancer drugs. The Gant Consortium examined two sustained trends driving spending growth in targeted cancer drugs: higher launch prices and compounding annual price hikes.

LAUNCH PRICES AND YEARLY PRICE HIKES

Prices for new cancer drugs have reliably risen on a yearly basis. A recent economic analysis of cancer drugs found that launch prices for cancer drugs increased by 10% annually—an average of $8,500 per year—from 1995 to 2013.[20] While some cancer drugs may be steadily delivering improved survival, some researchers argue that price inflation has outstripped health benefits. As an economic study from Howard et al. notes, "in 1995 patients and their insurers paid $54,100 for a year of life. A decade later, 2005, they paid $139,000 for the same benefit. By 2013, they were paying $207,000."[20]

After cancer drugs hit the market, prices tend to continue to increase. These yearly price hikes of FDA-approved drugs significantly outpace inflation, suggesting an absence of competition. A recent analysis found that inflation-adjusted per-person monthly prices increased an average of 5% per year from 2007 through 2013.[30] The prices of Imatinib and Erlotinib have risen an average of 7.5% per year since 2001, though the drugs' efficacy and use have not changed.[28] Critics of high prices frequently cite small average survival benefits, but this claim may fail to account for important context. Because targeted therapies focus on subsets of patients, looking at average survival across an unselected population may be misleading. For the responding patient subset, targeted drugs may be far more effective. As responding groups provide data, more effective targeting can take place—an iterative process not reflected in aggregated survival data. On the other hand, as the relevant subset of

Figure 2. Mean Monthly Spending for Orally Administered Anticancer Medications During the Year of Product Launch, 2000-2014



Spending, US $	1869	3346		2464	2943	5951	8764	3553		6603		7246	9051	10049	11325
No. of products	1	1	0	1	1	1	4	2	0	2	0	5	5	7	2

Source: Drug Pricing Trends for Orally Administered Anticancer Medications Reimbursed by Commercial Health Plans, 2000-2014, JAMA Oncology, 2016;2(7):960-961.

patients that will most respond to a given treatment shrinks, prices are likely to continue to spike as pharmaceutical companies seek to meet revenue benchmarks in rarified markets.

MARKET DRIVERS OF PRESCRIPTION DRUG PRICES: MONOPOLISTIC REFERENCE PRICING

It is difficult to disaggregate drivers of targeted cancer drug prices from trends in the larger pharmaceutical market. Federal regulation grants patents and market exclusivity to drug companies for new and reformulated drugs, and prices appear to be whatever the market will bear. Drug makers have monopolistic pricing power during periods of exclusivity, private payers are fragmented, and Medicare is barred from directly negotiating drug prices. In such a market, prices can appear disconnected from value. Rather, prices reflect a calculation based on price elasticity and market size: Manufacturers set the highest price that consumers, including third-party payers, are willing to pay in order to generate the most revenue. In the United States, some argue that pharmaceutical companies set launch prices for new cancer drugs within 10% of previous drugs, regardless of comparative effectiveness or competition.

MARKET DRIVERS OF PRESCRIPTION DRUG PRICES: DISCOUNT OFFSETTING

List prices for prescription drugs rarely reflect the price paid by patients and payers. Many observers contend that discounts and rebates in the private and public sector incentivize higher launch prices to offset future write-offs. At the federal level, the government mandates discounts for certain classes of buyers—such as federally qualified health centers and hospitals with a high proportion of low income patients—through the 340B program. The 340B discount is based on the drug's average price, which incentivizes setting higher launch prices to offset those discounts. Medicaid has its own idiosyncratic pricing rules. Manufacturers must give rebates to the federal government on sales to Medicaid patients, which may provide an additional incentive for

high prices. Insurers and employers hire pharmacy benefit managers (PBMs) to create drug formularies, negotiate discounts, and set up rebates with drug manufacturers. Given the complicated and non-transparent discount and rebate structure, launch prices may simply represent a high opening bid for a protracted negotiation.

MARKET DRIVERS OF PRESCRIPTION DRUG PRICES: PRICE INELASTICITY, PHYSICIAN INCENTIVES, AND DRUG DEVELOPMENT

There may be demand-induced causes of regular drug price increases as well. As families hit their deductibles and out-of-pocket maximums, they tend to become indifferent to the cost of a drug. High deductible health plans may have an impact, but patients in general and those with cancer in particular tend to be inelastic purchasers.

Supply-induced drivers, such as physician incentives, may also play a role. In Medicare Part B's "buy and bill" payment structure, physicians are paid based on a percentage of the drug sales prices, which incentivizes physicians to use expensive drugs. Thus, many physicians have little to no financial incentive to seek out lower cost, clinically equivalent treatment options.

Finally, pharmaceutical companies argue that barriers to market entry, production costs, and research and development investment require high prices to recoup outlays. Drug manufacturers argue that they must recoup all of their costs during the marketing exclusivity period, which requires hitting the market with high launch prices. Critics of these explanations suggest that the widely publicized figure of $2.7 billion per drug from the Tufts Center for the Study of Drug Development remains unverified. Public Citizen estimates the cost of developing a single drug to be $320 million, and a recent study in JAMA Internal Medicine estimates the cost of developing a single cancer drug to be $648 million on average, while median revenue since approval is $1.65 billion.[31] Whatever the actual average cost of drug development is, new drug development is a multi-year process with high rates of failure that carry financial downside risk, and once an effective drug hits the market manufacturers must derive enough revenue to pay for ongoing research and development.

Value Frameworks

Paying for value, instead of volume, has become the focus of health reform efforts. Value is more than a political buzzword. In response to rising costs, payers, physicians, and patients have considered value assessment frameworks to inform treatment plans and design sustainable budgets. Due to the relatively high number of new drugs reaching the market each year, cancer drugs have become a focus of many new frameworks aimed at capturing the value of therapies.

Early movers include the American Society of Clinical Oncology (ASCO) Value Framework,[32] National Comprehensive Cancer Network (NCCN) Evidence Blocks,[33] and the Institute for Clinical and Economic Review (ICER) Value Assessment Framework.[34] While these tools share a goal of creating a rigorous framework for thinking about the value of drugs, they differ in mission, methodology, and scope. ASCO and NCCN's tools are designed for shared medical decision making, while ICER helps insurers negotiate drug prices and develop sustainable drug formularies.

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) VALUE FRAMEWORK

ASCO developed a framework for shared decision making between physicians and patients. The ASCO value framework generates a Net Health Benefit (NHB) score based on clinical benefit, toxicity, symptom palliation, and quality of life measures. The NHB synthesizes useful assessments of relevant data, which can be weighted according to patient preferences.

The first component of NHB is the clinical benefit score, which is calculated with overall survival (OS), progression-free survival (PFS), or response rate (RR). OS is the preferred outcome measure, followed by PFS and RR if OS is unavailable. The ASCO framework then assigns a toxicity score based on the severity and likelihood of side effects. If the new treatment regime is more toxic than the comparator treatment, the toxicity score is subtracted from the clinical benefit score. For new treatments with a lower toxicity than the comparator, the toxicity score is added to the clinical benefit score.

Finally, the ASCO framework adds several sets of bonus points: "tail of the curve" survival, patient-reported quality of life, palliation of symptoms, and treatment-free intervals. The weight of these metrics can be increased based on patient values, in an acknowledgement that improved survival or disease control are not the only important measures of a cancer drug's value. Bonus points for the tail of the curve address a particular concern for cancer: how to account for a novel treatment that leads to a survival benefit in a sizable minority of patients, even though most patients will not see much benefit.

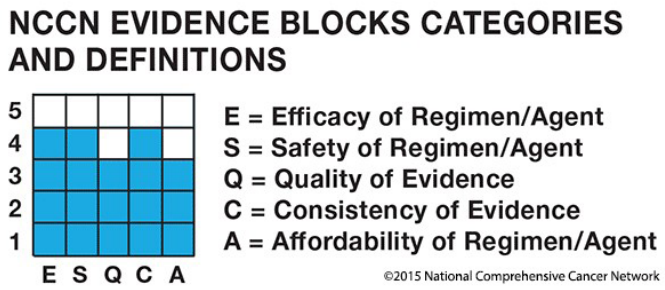
ASCO's value framework does not consider the cost of a drug to the health system. Rather, it lists a drug acquisition cost (DAC) for the patient as the relevant measure, a cost that each patient and family must define themselves. Presenting net health benefit scores alongside the DAC allows physicians and patients to determine the relative value of different courses of treatment. Some researchers have taken up the task pre-emptively: A recent study in the Journal of Oncology Practice used ASCO's value framework to construct a value-based ranking of frontline treatments for ovarian cancer.[35]

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) EVIDENCE BLOCKS

NCCN's Evidence Blocks are also designed as shared decision making tools. NCCN measures five aspects of a treatment: efficacy, safety, quality of evidence, consistency of evidence, and affordability. Unlike ASCO, each aspect of a treatment is assessed by a panel of NCCN members, not physicians at the bedside.

NCCN Evidence Blocks provide visual snapshots of treatment options for different types of cancer. Each measure is rated from 1 to 5, with 1 being the lowest score. For

Figure 3. NCCN Evidence Blocks Categories and Definitions



Source: 2015 National Comprehensive Cancer Network

efficacy, a score of 1 indicates only palliative, while a score of 5 indicates a drug that often provides long-term survival or curative advantage. Similarly, toxicity scores range from highly toxic to no meaningful toxicity, quality of evidence scores range from little to no evidence to multiple well-designed randomized trials and/or meta-analyses, and consistency of evidence ranges from anecdotal to highly consistent across trials.

While NCCN evidence blocks produce a simple output, the methodology is relatively opaque. NCCN panel members make their own assessment for each drug, and the methodology is not open to other stakeholders or open comment. Notably, affordability does not speak to individual patient situations. Ultimately, it is up to the physician and patient to make sense of the evidence blocks as they relate to their own treatment preferences.

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW (ICER)

The ICER value framework can inform population-level perspectives and support evidence-based guidelines for appropriate care, drug pricing, insurance coverage determinations, and payment methods. For new drugs, ICER delivers reports on value and affordability, with the stated end goal of providing sustainable access to quality drugs for patients.

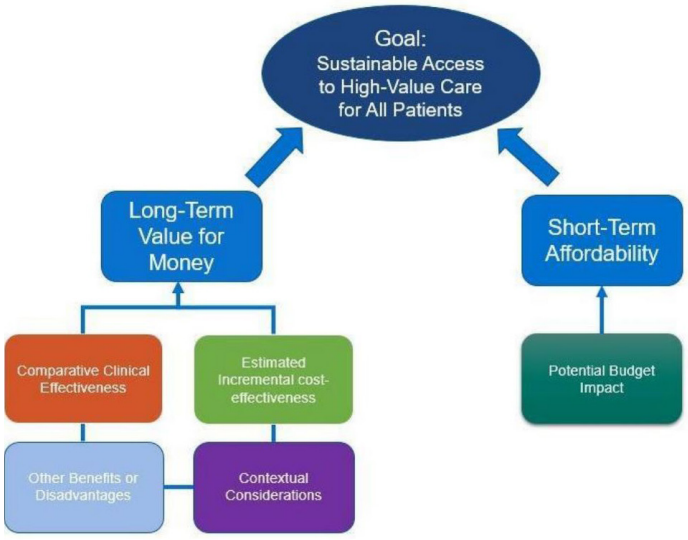
ICER uses four frames to assess the long-term population-level value for money of a new drug: comparative clinical effectiveness, estimated incremental cost-effectiveness, other benefits or disadvantages, and contextual considerations. The long-term value for money judgement is paired with a short-term potential budget impact assessment in ICER's reports.

These measures translate into a care value designation, which informs the assessment of potential short-term budget impact and long-term value for money.[34]

When judging comparative clinical effectiveness, ICER evaluates evidence of clinical benefit from multiple sources—although randomized control trials are preferred—and assigns a grade for new drug benefit over comparator, ranging from negative net benefit to substantial net benefit. ICER lists seven potential benefits or disadvantages and five contextual considerations to include, such as bonuses for drugs that reduce health disparities, lessen caregiver burden, or provide novel mechanisms of action that may treat patients who were previously unable to be successfully treated.[34] With a clinical benefit assessment in hand, ICER drafts incremental cost-effectiveness analyses. These reports primarily use cost per additional quality adjusted life year, with a benchmark with a willingness to pay of $50,000 to $150,000 per QALY. Drugs coming in above the threshold are listed as "low value," and drugs below the threshold are listed as "high value."[34]

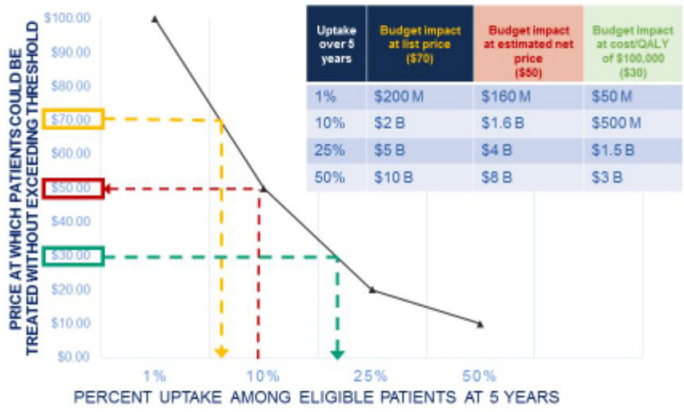
ICER's potential budget impact is treated separately from questions of value to a health system. Rather, the budget impact models estimate impacts of a drug at different prices and uptake rates. Thus, ICER assumes that health systems and payers will use the impact analysis and local knowledge to ascertain sustainable drug prices.

Figure 4. ICER Value Framework



Source: Final Value Assessment Framework for 2017-2019. Institute for Clinical and Economic Review, available online at https://icer-review.org/final-vaf-2017-2019.

Figure 5. ICER Potential Budget Impact Scenarios



Source: Final Value Assessment Framework for 2017-2019. Institute for Clinical and Economic Review, available online at https://icer-review.org/final-vaf-2017-2019.

COMPARING VALUE FRAMEWORKS: DEVELOPMENT, AUDIENCE, AND OUTPUTS

Each framework differs in terms of its audience, development process, and measures of benefit and cost. NCCN and ASCO are patient/provider facing, but ICER is targeted to payers. Methodological transparency also varies: ICER and ASCO have open comment periods and update their approaches based on stakeholder input, while NCCN has no formal public comment process. A comparison of the frameworks on multiple dimensions appears in Tables 1 and 2.

FRAMEWORKS IN THE FIELD

Early evidence suggests that value frameworks hold promise in providing reliable, consistent measures of quality. A recent study applied the NCCN, ASCO, and ICER frameworks to five advanced lung cancer drugs to assess the rankings across frameworks and the degree to which they provide consistent determinations of drug quality. The frameworks ranked each of the drugs similarly, with stronger agreement between ASCO and NCCN than ICER and NCCN. Inter-rater reliability for each drug was highest for ASCO, and lowest for ICER.[36]

However, value frameworks are far from industry standard. The primary users of the ICER framework have been payers, with the goal of informing coverage decision processes. Physicians have yet to adopt NCCN and ASCO in a systematic way. One optimistic take voiced by members of the Gant Consortium was that as outcomes-based risk sharing agreements between drug manufacturers and payers gain in popularity, value frameworks may establish guardrails for contract negotiations.

TABLE 1: DEVELOPMENT OF VALUE FRAMEWORKS

	ICER	NCCN	ASCO
Developers	ICER staff, committee of payers, patient organizations, physician organizations. Input from pharmaceutical industry	NCCN staff and disease specialists	ASCO Value in Cancer Care Task Force, committee of payers, patient organizations, physician organizations. Input from pharmaceutical industry
Open Comment?	Yes	No	Yes
Audience	Payers	Patients and Providers	Patients and Providers

TABLE 2: MEASURES OF BENEFIT AND COST

	ICER	NCCN	ASCO
Clinical Efficacy Measures	Variable, based on available data	Panel assessment based on overall survival, progression free survival, or palliation of symptoms	Overall survival, progression free survival, response rate. Bonuses for palliation of symptoms, tail of the curve survival, quality of life, and treatment free interval
Safety/Toxicity	Variable, based on available data	5 point scale based on assessment of likelihood of adverse event	Grade based on frequency and severity of toxicity
Patient-Centered Benefits	Yes, qualitative bonuses for quality of life improvements	Not separately evaluated	Yes, bonuses for quality of life and treatment-free interval
Indirect Benefits	Yes, qualitative bonus for ability to return to work, reduced caregiver burden	No	No
Social Consideration	Yes, qualitative bonus for reducing health disparities, unmet need, novel mechanism of action	No	No
Cost Measures	Cost-effectiveness analysis and budget impact analyses	Reported as affordability to patient	Reported as drug acquisition cost to patient
Outputs	Value based price and value assessment (high/low)	Visual representation of 1-5 scores for efficacy, safety, quality of evidence, consistency of evidence, affordability	Quantified net health benefit score, drug cost to patient

International Drug Pricing

Americans are not alone in the struggle to define "fair prices" for cancer drugs. Variation in prices and spending have no single cause, but differing regulatory approaches to drug pricing can provide some lessons for policymakers in the United States. With no illusions about the barriers to policy change, the Gant Consortium looked beyond America's national boundaries to learn how other nations have sought to balance cost, access, and innovation.

Drug prices vary internationally. A recent study in Lancet of ex-factory prices (i.e., before discounts) in 16 European countries, Australia, and New Zealand uncovered several-fold variation in prices of individual cancer drugs, with the average priced country and lowest priced country varying by up to 388%. Although the study could not determine the actual prices paid after discounts to payers were applied, it did suggest that prices for the same drug change across borders.[37] Another study of price variation for eight patented cancer drugs in seven countries found that median monthly prices ranged from approximately $2,500 in the UK to $8,694 in the United States. Put another way, patented median monthly drug prices were 78% of GDP per capita in the UK, but 192% of GDP per capita in the United States.[38]

Although there are many approaches to drug regulation, Managed Entry Agreements (MEAs) are the most commonly employed abroad. These agreements between payers and manufacturers are among the most common regulatory levers used by public and private payers to balance incentivizing innovation with controlling price inflation, value-based pricing, and sustainable budgets. Although dozens of countries use such agreements, the Gant Consortium focused on three countries that differ in the structure and implementation of MEAs—the UK, Canada, and Germany.

A TAXONOMY OF MANAGED ENTRY AGREEMENTS

A study of MEAs in 12 OECD countries provides a useful typology of these agreements. Broadly speaking, MEAs are legal risk sharing arrangements between a drug or device manufacturer and a funding authority to enable faster access (i.e., reimbursement) to new drugs and technologies. They are typically used when the clinical value of a treatment is uncertain. MEAs tend to focus on either budget impact or health outcomes, although some combine the two.[39]

MEAs that focus on budget impact typically use specific levers to control cost. These levers include initial price discounts for new patients, price-volume agreements that apply discounts after a certain spending or volume threshold is reached, and per-patient price caps that limit the total cost per patient—after which the manufacturer assumes the cost of the drug. MEAs that focus on health outcomes also use financial risk sharing, but the financial downsides for manufacturers are triggered by pre-set clinical performance indicators. These schemes include conditional coverage, in which payers cover a drug during a trial period as further clinical efficacy data are gathered for a reassessment—which may lead to a further price change. Other performance-linked agreements use outcome guarantees to make manufacturers financially liable for drugs that fail to perform as expected. Finally, conditional treatment mechanisms focus on cost-effectiveness, in which payers are only responsible for covering patients for whom a new drug is effective.[39]

MEAs often rely on international or domestic "reference pricing" systems. External reference pricing directly or indirectly links reimbursement for a drug to the price paid for the same drug in another country. Reference pricing can also limit prices based on the cost of similar classes of drugs. On

the one hand, benchmarking prices to low-cost countries and tying new drugs' prices to existing therapies makes reference pricing an attractive tool for price control. On the other hand, international reference pricing can incentivize manufacturers to limit or delay the release of new treatments in low-income countries due to secondary effects in higher income countries. Furthermore, reference pricing may limit the ability to differentiate prices.[40] Because most EU member states engage in some form of international reference pricing, MEAs in one country can have international ripple effects.[41]

CASE STUDIES: UK-NICE CANCER DRUG FUND

As discussed earlier, the original UK Cancer Drug Fund (CDF) folded into NICE in 2016 after it overspent its budget. The new CDF operates as a managed access fund. The process for drug coverage approval in the UK is:

- Initial review by NICE, which includes cost-effectiveness analysis with prices set by the manufacturer. NICE either approves, denies coverage, or recommends provisional approval.
- Under provisional approval, NICE establishes a short-term coverage and data collection period with a confidential, negotiated price.
- After the data collection period, NICE reappraises the drug, which can either be approved for coverage or denied.

NICE recommends a new cancer drug for interim funding through the CDF when there is some evidence of benefit, but the clinical and cost-efficacy data are too uncertain for full approval. The CDF covers cancer drugs during the provisional approval period as more data are collected. Importantly, the managed access period utilizes both health outcomes based conditional coverage provisions and price-volume agreements. To keep the fund from overspending its budget, the CDF uses price-volume agreements with manufacturers. Furthermore, to receive provisional funding through the CDF, manufacturers must agree to a proportional rebate system if the CDF overspends its budget.[42]

Some members of the Gant Consortium were skeptical that the NICE-CDF system could be widely adopted in the United States. First, the MEA and drug coverage system relies on the ability for public payers to say "no" to certain drugs, and public payers have little appetite for denying coverage for cancer drugs, even ones with limited effectiveness. By statute, Medicare is required to cover any FDA-approved drug prescribed by a licensed physician. In the case of Avastin, Medicare continued to pay for its use even after the FDA removed the drug's approval for use in breast cancer patients. In contrast, NICE has shown more willingness to not recommend drugs: The institution approved 37 of 47 of cancer drug submissions since July 2016, and recommended 5 more to a managed entry agreement via CDF in that time.[43]

CANADA: PAN-CANADIAN ONCOLOGY DRUG REVIEW (PCODR)

Canadians spend more per capita on prescription drugs than any other OECD country except the United States.[23] Canada's system for covering drugs is decentralized. In-hospital drugs are covered through the universal, publically funded Medicare program, but outpatient and prescription drugs are not included in national insurance. Individual provinces and territories are responsible for public drug coverage benefits, and about two-thirds of Canadians have some form of private insurance for prescription drugs. Although final reimbursement and pricing decisions are decentralized, Canada does employ a centralized system that issues recommendations for public insurers, though the final review and decision is made by each individual public drug plan.[44]

Drugs in Canada must be reviewed by the Canadian Agency for Drugs and Technology in Health (CADTH) before they can be covered by provincial and territorial health plans. CADTH conducts evidence reviews and cost-effectiveness analyses of drugs, diagnostic tests, medical procedures and devices. Much like the National Academy of Medicine in the United States, CADTH provides advice and recommendations (i.e., best practices) for the delivery of health care. CADTH has two arms for assessing drugs: The Common Drug Review (CDR) reviews non-oncologic drugs, while cancer drugs fall under the purview of the pan-Canadian Oncology Drug Review (pCODR).[45]

pCODR is tasked with assessing the clinical evidence, cost-effectiveness, and patient perspectives to make recommendations to Canadian provinces about covering new drugs. The keystone of pCODR's health technology assessment is the pCODR Expert Review Committee (pERC). pERC's deliberative framework (Table 3) has four criteria: overall clinical benefit, alignment with patient values, cost-effectiveness, and feasibility of adoption into health systems (budget impact). pERC's recommendations synthesize reports from other advisory committees, including

TABLE 3: DELIBERATIVE FRAMEWORK FOR PAN-CANADIAN ONCOLOGY DRUG REVIEW

Criteria	Measures	Sources
Overall clinical benefit	**Efficacy –** health impact based on mortality, morbidity, and quality of life. Assessment of direction of effect, magnitude, and level of uncertainty **Safety –** frequency and severity of adverse events **Burden of Illness –** incidence of disease in population **Need –** current availability of effective alternatives	Clinical Guidance Report from relevant Clinical Guidance Panel. Systemic literature reviews and registered clinician input.
Alignment with patient values	Measures of social value (e.g., social desire for cures for cancer)	Patient group input
Cost-effectiveness	Net efficacy compared to other drugs — costs, cost per QALY or event avoided, uncertainty about net health benefits	Economic Guidance Report from Economic Guidance Panel, review of pharmacoeconomic models
Feasibility of adoption	Overall assessment of budget impact	Provincial advisory group input and economic guidance reports

clinical guidance panels for specific diseases, provincial advisory groups that provide input from each province's health agency, patient advocacy groups, and economic guidance panels.[46]

Despite the well-delineated process for recommending drugs for coverage, Canada has the second highest drug spending in the world. Furthermore, because coverage decisions are ultimately made at the provincial level and by private insurers, the actual negotiated prices and discounts are kept confidential. Coverage for cancer drugs varies by province and insurer, both in terms of formulary decisions and out-of-pocket costs.

Canada has a national stopgap to protect consumers from price gouging. The Patient Medicine Prices Review Board (PMPRB), a consumer protection agency, has the authority to impose sanctions and price reductions for patented products deemed excessively priced. However, the PMPRB is hobbled in its ability to keep Canada's drug spending low. PMPRB allows companies to set prices for new patented drugs up to the highest amount paid for other medicines in the same therapeutic class (an internal reference price), which incentivizes manufacturers to avoid lowering prices for older patented drugs. Furthermore, the countries the PMPRB uses to compare drug prices are some of the highest-priced countries in the world, which raises the ceiling for Canadian prices.[47]

CASE STUDIES: GERMANY (AMNOG)

In 2010 the German government passed the Pharmaceutical Market Restructuring Act, or Arzneimittelmarkt-Neuordnungsgesetz (AMNOG), to regulate drug prices. AMNOG went into effect in 2011, and the legal process attempts to balance paying for innovative drug development with making decisions based on clinical efficacy. Germany's compulsory health insurance system is publicly financed from wage taxes. Tightly regulated, independent, competing, non-

profit, non-governmental insurance funds (known as sickness funds), pay for the majority of health care services. Similarly, AMNOG relies on non-governmental bodies to conduct clinical efficacy reviews and allows drug makers to set their own prices for specified review periods, but it avoids paying on a cost per QALY basis.[48]

The AMNOG process takes approximately 15 months. Once a new drug is approved (i.e., deemed safe and effective) by the European Medicines Agency, drug makers may set any price—and German health plans will fully reimburse the cost of the drug. Manufacturers must submit a benefits dossier within 3 months to the Federal Joint Commission (G-BA), a non-governmental body of payers, providers, and patient representatives. G-BA is ultimately responsible for assessing the clinical benefit of new treatments, but the organization typically commissions a clinical comparative effectiveness review by another non-profit organization, the Institute of Quality and Efficiency in Healthcare (IQWiG). Within six months, IQWiG returns its assessment to the G-BA based on a 1 through 6 scale.

1. Major added benefit – sustained and great improvement, cures or major increase in survival time/avoidance of serious side effects
2. Considerable added benefit – marked improvement, alleviation of disease, moderate increase in survival time, relevant avoidance of adverse events
3. Minor added benefit – moderate improvement or reduction in non-serious symptoms
4. Added benefit, but not quantifiable
5. No added benefit proven
6. Lower benefit than current therapies

Benefit ratings take into account survival time, symptom palliation and adverse events, and improvements in quality of life. IQWiG may give differential rankings for distinct patient subpopulations and grade the quality of data provided. In the case of orphan drugs for rare diseases, the initial approval for sale is assumed to be evidence of added benefit. Therefore, IQWiG only assesses the expected cost of coverage. G-BA makes the final determination, with additional input, and it has shown a willingness to differ from IQWiG, mainly because G-BA has a wider focus beyond the scientific evidence and may have different interpretations of efficacy measures.

The assessment by IQWiG and G-BA prompt a reevaluation of the drug price. For drugs without a demonstrated benefit over previously available drugs (rankings 4 through 6), payers will only reimburse at prices currently paid for existing drugs for the same conditions—an internal reference price. If drug manufacturers do not lower the price, patients must make up the difference out-of-pocket. Furthermore, if the drug company is deemed to have charged excessive prices for a lower ranked drug during the conditional coverage period, the manufacturer must return extra revenue as a rebate.[49]

Treatments with demonstrated efficacy above existing therapies trigger a structured negotiation between drug makers and insurers. Payers and manufacturers are expected to agree on a discounted price within six months. If parties cannot reach an agreement, the decision is moved to an arbitration panel, which decides based on international prices and cost-effectiveness evaluations.[50]

There is insufficient evidence to fully appraise AMNOG's effects on drug pricing, access, and the development of new treatments, but early data suggest that price cuts for drugs have significantly increased since the law's passage.[51] A recent study suggests that Germany saved at least $1 billion on new drugs in 2015.[52] Structurally, many aspects of the AMNOG process may be attractive for American policymakers. First, the system gives manufacturers the benefit of the doubt to set an appropriate price in the first year a drug comes to market. The health benefit assessment does not rely on controversial cost per QALY cost-effectiveness analysis, but it is a step towards evidence-based pay for value schemes. Finally, the process is relatively open, with disagreements about appropriate measures of clinical efficacy and benefit aired in transparent forums.

WHAT LESSONS CAN THE UNITED STATES DRAW FROM OTHER SYSTEMS?

Regulatory systems for drugs cannot be copied from one country to the next—political and economic histories are both path dependent and contingent, so a system of rules that works in one national context may have unintended consequences in other places. But policymakers can still learn from other national regulatory experiences. Table 4 summarizes the strategies and levers used by the highlighted nations to implement value-based drug pricing.

TABLE 4: COMPARISON OF INTERNATIONAL DRUG PRICING REGULATIONS

	Lever	Germany	UK	Canada	US
Non-health outcome based	**Initial discount**	Yes	Yes	Yes – provincial level	340B program, VA, Medicaid
Non-health outcome based	**Price-volume agreements**	Yes	Yes	No	No
Health outcome based	**Conditional coverage**	Yes (clinical not cost-effectiveness)	Yes (clinical not cost-effectiveness)	Yes (clinical not cost-effectiveness)	No (very limited)
Health outcome based	**Performance-linked**	Yes	No	No	No
	International reference pricing	Yes	No	Yes	No

Studies of international regulations of drug prices and the Gant Consortium's own analysis of the Canadian, English, and German experiences suggest that there are several "necessary but not sufficient" components of value-based drug regulations. One study of MEAs argues that key components of successful agreements include:

1. Willingness to say no – either de-list, not list, or reprice drugs that show little clinical or cost-efficacy
2. Transparent and robust methodologies for assessing cost-efficacy and clinical effectiveness – otherwise payers, manufacturers, or patient advocates may view funding decisions as illegitimate
3. Value assessment and coverage decisions that are binding, rather than arbitrary
4. Funding recommendations that are insulated from politicians
5. Legislation that allows payers to negotiate prices and deny coverage for low-value treatments
6. Assessment of both cost-effectiveness and global budget impact
7. Adequate funding for cost-effectiveness and clinical effectiveness analyses[53]

Ultimately, managed entry agreements require political consensus and considerable practical effort. American payers have typically been reticent to say no to covering drugs, and MEAs are built on the capacity to deny coverage for some treatments. The technical complexity of MEAs present additional implementation barriers; for example, the administrative burdens and complexity of collecting data and managing agreements with different manufacturers are considerable. Should MEAs be adopted more widely by private insurers, the discounted prices are likely to remain confidential. Finally, MEAs do not resolve underlying controversies regarding appropriate comparator drugs, measures of clinical efficacy, or how to build in other patient considerations.

Orphan Drugs

INTRODUCTION

While cancer is a common condition in aggregate, targeted therapies increasingly slice cancer into smaller subsets of diseases. These biomarker-defined subsets can be classified as rare diseases, affecting only a small number of patients. Thus, it is helpful to review the previously trodden path of policy problems specific to rare conditions.

Historically, diseases that only affect a small number of patients have posed unique drug development and access challenges. Typically, small markets fail to attract many entrants or competition. In the case of pharmaceuticals, diseases that only affect a small number of people have limited prospects for revenue generation and attract little investment.[54] When a drug does come to market, the lack of competition tends to increase the cost of treatment. The US has previously grappled with market failure for treating rare diseases with the 1983 Orphan Drugs Act (ODA), and the use of the law holds both promise and cautionary tales for targeted oncology.

THE 1983 ORPHAN DRUGS ACT

The passage of the Orphan Drugs Act of 1983 marked a concerted federal effort to increase access to therapies for people with rare diseases. At the time, drug companies lacked financial incentives to develop drugs for small populations. But the general public had an interest in incentivizing such drugs—because taken together, orphan diseases affect millions of Americans. A 1984 amendment to the ODA defined an "orphan" disease as affecting less than 200,000 persons in the US, or approximately 1 in 1,500 people. [54,55] Researchers note that this is an arbitrary definition, as the notion of an orphan disease is a construct. Drug companies can apply for orphan designation for any drug, and the designation unlocks several benefits, including:

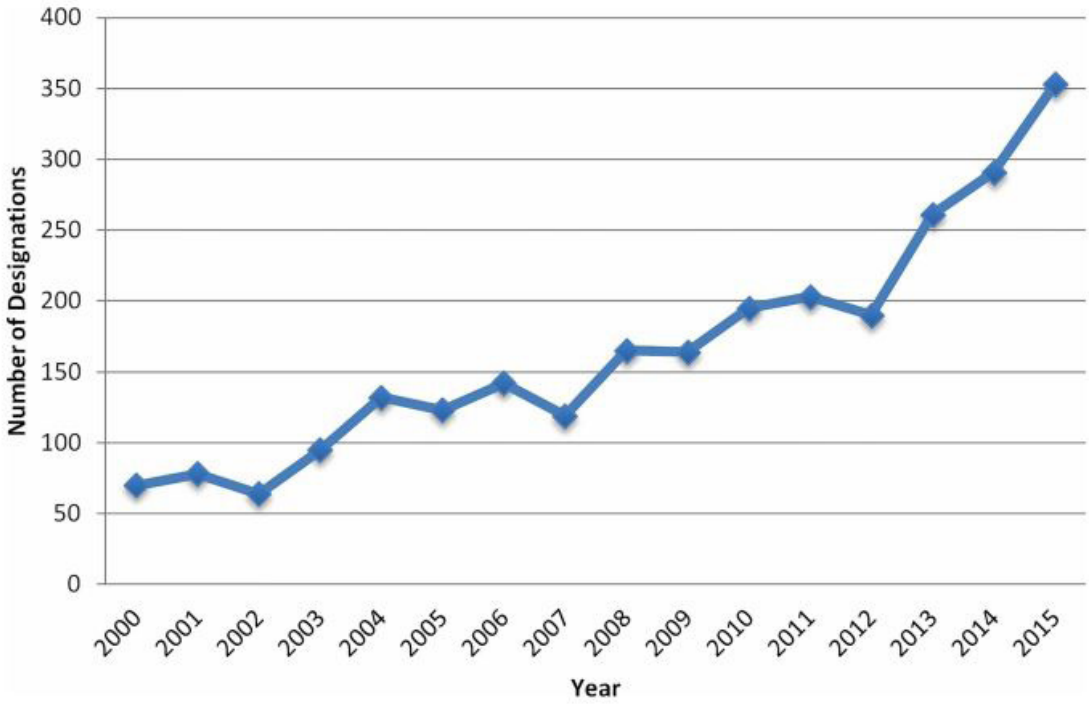
- Access to a pool of research grants ($15.5 million budgeted per fiscal year)[56]
- Tax credits for clinical research costs (50% of clinical trial expenses until 2017, when they were lowered to 25% of expenses)
- Waiver of FDA approval fee (approximately $2 million)
- Seven years of post-approval market exclusivity for approved indication (i.e., an additional 2 years)[57]

Furthermore, the ODA calls on the FDA to display "flexibility" when considering the approval of drugs. Proponents of the law argue that it has successfully hastened the development of dozens of effective treatments for rare diseases. At least 450 orphan drugs have come to market since the law took effect,[58] and the number of orphan drug designations has increased from an average of 63 per year to over 200 per year since 2010.[57] A recent study in 1984 of drug approvals between 2009 and 2015 found that 84 of 229 approved drugs had an orphan designation.[57]

Critics, on the other hand, argue the law is being abused. Despite an explosion in orphan designations, 95% of rare diseases still have no therapy, and multiple orphan designations for individual drugs may be inflating the data. Some observers attribute the apparent discrepancy to the "salami slicing" of common diseases into subsets of rare disease based on genetic biomarkers. Gleevec, for example, has nine orphan designations, and recent studies suggest that orphan drug approvals cluster around a small set of conditions, including cancer. Furthermore, critics contend that the approval process for orphan drugs is less rigorous. One 2011 study of drugs approved to treat cancer between 2004 and 2010 found that trials used to approve orphan drugs were less likely to use blinding and double-blinding, had smaller participant numbers, and tended to use surrogate outcomes (such as disease response) rather than overall survival.[57]

Worldwide sales of orphan drugs have grown at double the rate of the overall drug sales growth, becoming increasingly dominant in the pharmaceutical industry. In 2000, orphan

Figure 6. Orphan drug designations per year.



Source: Kesselheim AS, Treasure CL, Joffe S. (2017) Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage. PLoS Med 14(1):e1002190. doi:10.1371/journal.pmed.1002190

drugs accounted for 6% of all prescription sales. By 2015 they were 16.4% of prescription sales.[59] Supporters of the law cite the growth in orphan drug sales as evidence of the law's success. Critics argue that because of the lax designation rules and the easier approval process, US taxpayers may be subsidizing research into an already lucrative market.

Targeted cancer therapies bring these debates into sharp focus. They hold out the possibility that many common cancers (such as breast, prostate, and colon cancer) will turn into amalgams of "rare" biomarker-defined diseases, each qualifying for orphan status and commanding a price premium. The budget-busting potential of this process is concerning. A recent article lays out the economic factors that exert upward pressure on drug prices in precision medicine: Limited competition in small markets, followed by delayed generic competition when market exclusivity is extended beyond the patent expiration, can cause unsustainable pricing.[53] Furthermore, targeted medicines are often biologics, which are more costly to develop and produce than traditional small molecule drugs and face limited competition from biosimilar drugs.

On the other hand, higher drug prices for targeted medicines may be warranted if they are more effective than treatments in unselected populations. The fundamental challenge that remains is how to make targeted cancer medicine economically sustainable as more of the population is treated with biomarker-defined therapies, each commanding a higher price than its non-targeted predecessor.

Conclusion

The Gant Consortium's literature review surfaced several themes that are likely to persist as targeted therapies continue to define cancer care and research. Targeted cancer therapies are at the cutting edge of biomedical research, and the price of drugs has to be sufficient to make the risks involved in drug development worthwhile. For a number of reasons, the cost of cancer therapy is likely to continue to rise. However, these high prices may carry concerns over the distribution of benefits, as high prices may limit access to patients without significant disposable income.

Furthermore, targeted therapies are likely to sharpen the debate over paying for the value of drugs. Although several stakeholders have laid the groundwork for formal value assessments, the methodologies and outputs remain different, and targeted therapies may require differential value propositions for each subpopulation. While paying for value is likely to remain a goal for many policymakers, contentious debates remain on the horizon regarding how to factor in global payer budgets, patient preferences, and provider flexibility.

Additionally, the struggle to create a sustainable targeted cancer paradigm is not a uniquely American experience. A review of managed entry agreements abroad finds that several countries are struggling to balance access and innovation, and different regulatory approaches have not landed on a singular solution. The complexity of the American health care system—with dozens of payers, drug manufacturers, and care providers—is likely to complicate "one size fits all" regulatory fixes.

Finally, keeping the voices of patients and families well represented in discourse is likely to remain a challenge for payers, providers, and drug manufacturers. As the biological science of cancer care becomes more rarified and ways of measuring value become increasingly complex, asking meaningful questions and getting useful input from patients will likely grow more difficult. Ultimately, the goal of targeted cancer should be to relieve suffering for cancer patients and families, and their voices should be heard at many steps of policy development.

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