Drug Pricing and Value in Oncology

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Abstract

This paper first reviews the evidence on price levels, price growth, and value for cancer drugs. The available evidence suggests that prices for originator (brand-name) drugs are rising significantly more rapidly than general inflation, but the available data are inadequate for robust comparisons between cancer and other categories of specialty drugs. We then examine the factors contributing to high and rising prices for cancer drugs. This analysis focuses mainly on the USA, which accounts for 46% of global expenditures on cancer drugs. It is the country of first launch for most cancer and other specialty drugs and frequently has the highest prices for drugs.

Keywords

Cancer drugs · Pricing · Reimbursement · Affordability · R&D

1 Introduction

Concerns over pricing and value pervade healthcare systems, but are nowhere more acute than in the case of cancer drugs. For payers, the rapidly growing number and cost of cancer drugs challenge affordability, threatening to crowd out other valued services from limited healthcare budgets. Faced with high prices, payers routinely restrict access or, in some cases, simply refuse to provide coverage of high-priced drugs. High prices also raise questions of value-for-money, that is, whether the sometimes modest incremental survival and quality-of-life benefits delivered by

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these drugs justify their high prices. For patients, high prices can entail significant out-of-pocket costs in countries that lack comprehensive insurance coverage, including the USA and many middle- and low-income countries. Perhaps of greatest concern is that no end is in sight to the underlying factors that drive prices upward, with primary drivers in the USA and spillover effects to other countries.

This paper first reviews the evidence on price levels, price growth, and value for cancer drugs. The available evidence suggests that prices for originator (brand-name) drugs are rising significantly more rapidly than general inflation, but the available data are inadequate for robust comparisons between cancer and other categories of specialty drugs. We then examine the factors contributing to high and rising prices for cancer drugs. This analysis focuses mainly on the USA, which accounts for 46% of global expenditures on cancer drugs. It is the country of first launch for most cancer and other specialty drugs and frequently has the highest prices for drugs. Pricing strategies therefore tend to be developed with the US market in mind and then adapted to other countries. We argue that the design of public and private insurance coverage and reimbursement for cancer drugs in the USA is a major contributor to high and rising prices. This is illustrated by a review of the reimbursement rules of Medicare, the public insurance for all seniors over 65, which are similar to reimbursement rules for private insurance plans. Reimbursement rules are reviewed for both physician-dispensed drugs (which includes infused and injected drugs) and oral, pharmacy-dispensed medications. The basic approach relies on market forces to constrain prices. However, market forces work poorly for differentiated, highly priced drugs for which patients have insurance coverage with cost-sharing but protection through catastrophic caps, supplementary insurance, and other programs. The federal government is barred by statute from negotiating drug prices or using cost-effectiveness as the basis for coverage decisions. This reimbursement regime provides little if any constraint on the upward drift of prices.

High drug prices, including for cancer drugs, are sometimes attributed to high costs of research and development (R&D). Economic theory and evidence support the view that investors must anticipate a reasonable return on their investment (ROI), in order to continue investing. However, this does not imply that drug prices are based on the cost of R&D, which would be irrational. Producers in any profit-driven industry rationally set prices based on what customers are willing to pay. In the case of pharmaceuticals, this depends on the effectiveness, safety, and other characteristics of alternative treatments and, importantly, on payer reimbursement rules when drugs are largely covered by insurance. The evidence of strong investment flows into cancer compared to other therapeutic areas strongly suggests that cancer is perceived to offer relatively profitable investment opportunities, given current R&D costs and pricing environments.

In this paper, Sect. 1 reviews the evidence on rising prices, costs, and value for cancer drugs. Section 2 then reviews the main causes of rising prices and costs for cancer drugs. Section 3 briefly reviews the evidence on R&D costs and pricing. Section 4 discusses policy solutions.

2 Evidence on Expenditures and Price Growth for Cancer Drugs

2.1 Expenditures

Global expenditures on cancer drugs increased from $91b in 2012 to $113b in 2016 and are projected to grow to $150b by 2020 (QuintilesIMS Institute 2017). The USA accounts for 46% of global spending on cancer drugs, whereas the USA accounts for roughly 15% of global GDP, adjusted for purchasing power parities (PPPs).[1] The disproportionate US share of global drug spending, compared to its share of global GDP, applies to drugs in general and is not confined to cancer drugs. It reflects primarily that the USA has quicker and broader uptake of new drugs and higher prices, but not necessarily higher total volume of drug use (Danzon and Furukawa 2003, 2006). Illustrating the more rapid US uptake of new drugs in the case of cancer: Of the 42 cancer drugs launched globally between 2011 and 2015, the number available by 2016 was 37 in the USA, 35 in Germany, 33 in the UK, 25 in France, 22 in Japan, and 4 in India, China, and Indonesia (QuintilesIMS 2017).

Several recently published surveys provide overviews of the literature and accumulating evidence on trends in prices of cancer drugs (e.g., Prasad et al. 2017). Novel anticancer drugs routinely cost over $100,000 per year or course of treatment in the USA, less in other countries (Prasad et al. 2017; Vogler et al. 2016). However, when national cancer prices are compared to average per capita income (as a rough measure of affordability), prices are highest, relative to income, in emerging markets such as India (Goldstein et al. 2016). Simple theory and evidence from pharmaceutical markets more generally indicate that high prices, relative to average per capita income, contribute to the limited availability of the newest drugs in middle- and low-income countries (MLICs), as payers refuse to reimburse and/or patients cannot afford to pay out-of-pocket for these products (Danzon et al. 2013a).

Growth in the cost of cancer drugs reflects at least three factors: growth in launch prices of new drugs; price growth post-launch once drugs are on the market; and changing mix of drugs used, including increased use of drug combinations.

2.2 Launch Price Trends

Median launch prices for new cancer drugs increased between 1960 and 2016 from $100 to $10,000 per month of treatment (Bach 2009). In a study of trends in launch prices of orally administered cancer drugs, Dusetzina (2016) found that average cost per month increased from $1,869 in 2000 to $11,325 in 2014, after adjusting for inflation. Of course, this is not an apples-to-apples comparison, because the more recent drugs on average provide greater health benefits. However, when cost

[1] https://www.statista.com/statistics/270267/united-states-share-of-global-gross-domestic-product-gdp/.

is measured per unit of benefit gained, measured in terms of life-years saved, this standardized cost rose by an average of $8,500 per year since 1995 (Howard et al. 2015).

2.3 Price Growth Post-launch: Measurement Issues

Measuring post-launch trends in cancer drug prices poses several methodological challenges. Government statistical agencies in most countries report price indexes that measure the year-on-year price growth for defined baskets of major products, such as pharmaceuticals. For example, the US Bureau of Labor Statistics (BLS) publishes the pharmaceutical producer price index (PPI) that represents drugs in all therapeutic categories, weighted by use. The aggregate pharmaceutical PPI increased 83% (from 126.8 to 231.5) over the decade January 2007–December 2016, with the annual average growth rate increasing from 4.1% in 2007 to 8.8% in 2016,[2] which exceeds general inflation over the period. Unfortunately, a price index that specifically tracks cancer drug prices is not available from US government sources.

Although this aggregate US pharmaceutical PPI includes cancer and other specialty drugs, it is likely to understate price trends for such specialty drugs for several reasons. The PPI is a volume-weighted index, intended to represent drugs in proportion to their usage by patients in general and hence is more representative of widely used, primary care medications. Further, because it defines treatments by chemical name, it treats bioequivalent generic versions of chemical drugs as substitutable for the originator referent products. Thus when cheap generics enter and take a dominant market share after patent expiry for the originator, the volume-weighted average price, which includes both generic and originator prices weighted by market share, usually declines. Over the last 15 years, patent expiries and genericization of many major primary care drugs have significantly moderated the overall growth of drug prices as measured by the PPI, in which these chemical drugs carry a large weight. However, the aggregate PPI understates price growth of originator (brand-name) drugs and understates price growth for categories like cancer, with a relatively large share of biologics that are not subject to genericization comparable to chemical drugs.

To illustrate this price divergence for originator versus generic drugs, between 2008 and 2016, the Express Scripts Brand-Name Prescription Drug Price Index increased threefold, while their Generic Prescription Price Index fell over 50% (Commonwealth Fund 2017). Thus post-launch price growth has been significantly higher than general inflation for originator drugs in general in the USA, and this would include most cancer drugs.

The BLS has recently begun to produce disease-specific indexes for total cost of care (Bradley 2017) for certain diseases, including "Neoplasms" as a single disease category. For the period 2003–2013, the Neoplasm disease category is similar to other disease categories in overall expenditure growth and in each of the individual

[2]https://data.bls.gov/pdq/SurveyOutputServlet. Retrieved 8.29.17.

components of total cost growth that are identified, including overall inflation, real expenditures, population growth, prevalence growth, and per capita output growth.[3] However, drugs are not broken out separately, and price growth for drugs is not reported separately.

Measuring price change for cancer drugs is further complicated by variation across patients and over time in the definition of a dose. If price is defined as dollars per dose, e.g., price per 10 mg, and the normal dose per patient increases in terms of mg per kg body weight, then changes in dosing norms contribute to increases in cost per patient even with no change in price per mg. Studies in the literature of trends in cancer drug prices reach different conclusions, partly due to differences in data sources, products studied, dosing measure, health plan, and time period. In particular, studies that use the average price per prescription or per month of cancer therapy may confound changes in dosing and mix of drugs dispensed with change in price for a given drug mix and dosing. Of course, all three factors contribute to the rising cost of cancer care, but they suggest different causes and conclusions. Given these measurement challenges, there is no single, official, or gold standard measure of price growth for cancer drugs. The evidence summarized here reviews evidence from academic studies in the USA.

In the USA, pure post-launch price growth for cancer drugs typically exceeds general inflation with significant variation across individual drugs (e.g., Gordon et al. 2016). Prasad et al. (2016) studied both patented and off-patent drugs covered under Medicare Part B, which covers physician-administered drugs (see below). For the period 2010–2015, 64% of drugs increased in net price (net of all rebates), and 12.7% increased more than 100% over this 5-year period. Bennette et al. (2016) studied prices to commercially insured patients for 24 orally administered cancer drugs for the period 2007–13. They found that on average cancer drug prices increased 5% per year, after adjusting for general inflation. Prices rose an additional 10% with each FDA-approved indication and declined 2% with FDA approval of a competitor product. Post-launch price inflation also occurs for other on-patent specialty drugs in the USA, as noted earlier, and whether the experience is systematically different for cancer versus other therapeutic categories remains to be studied. Theory and existing evidence suggest that it would depend on the particular drugs and time period studied. However, it seems clear that on average price growth for cancer drugs in the USA exceeds general inflation. By contrast, because most other developed countries do not permit post-launch price growth, this positive post-launch US price growth contributes to divergence in prices between the USA and other countries.

[3] https://www.bls.gov/opub/btn/volume-6/pdf/cost-of-care.pdf.

3 Drivers of High Prices for Cancer Drugs: Reimbursement Rules Matter

In recent years, the majority of new drugs have been launched first in the USA, both because of the US FDA's relative speed in reviewing "novel" medicines and the US' lack of a formal price review as a condition of reimbursement, as required in other countries. Further, for strategic reasons, companies may prefer to launch first in the relatively unconstrained, high-priced US market, so that the US price becomes a benchmark from which discounts may be granted to other countries. Although the USA does not formally use external referencing to set drug prices, very large price differentials between the USA and other high-income countries can increase the political risk of calls for external referencing or drug importation in the USA. Thus, the US price plausibly influences prices in other countries indirectly, in addition to being directly referenced by a few other countries, including Canada and Japan. Thus, the factors contributing to high pricing in the USA are potentially important for pricing in other countries.

Within the pluralistic US system of public and private insurance plans, there is no overarching review process to set price and reimbursement limits for drugs, nor do individual public or private plans use formal processes to assess price relative to value created, comparable to the price and reimbursement processes used in many other countries, including individual EU countries, Canada, Japan. In the USA, the underlying presumption is that market forces should work to constrain prices, as manufacturers compete to get their drugs favorably placed on formularies and used by doctors and patients, and health plans compete for enrollees. In practice, this system does not work well to constrain prices for specialty drugs like oncologics, because of differentiation of the products, widespread insurance, and specific regulatory rules that undermine competition. The next section outlines the relevant features of this reimbursement system.

3.1 Reimbursement Rules and Pricing Incentives in the USA

Reimbursement rules for drugs in the USA depend on whether a drug is dispensed by a retail pharmacy; administered through a physician office or hospital outpatient department; or administered during an inpatient hospital episode. Although the detailed approaches in each of these contexts also differ across insurers, common features apply in each context. Retail pharmacy and physician outpatient locations are most important for cancer and are the focus here.[4]

Retail pharmacy-dispensed drugs. Drugs that a patient buys from a pharmacy for self-administration are covered by the pharmacy benefit of private insurance plans for the under-65 population and by Medicare Part D for seniors over 65. Pharmacy benefits are usually managed by specialized pharmacy benefit managers (PBMs) for private plans and by prescription drug plans (PDPs) for Medicare

[4]For more detail, see Danzon (2014).

Part D, which was modeled on and is implemented by private insurers, using very similar approaches. The basic strategy is to use a tiered formulary, offering a drug preferred tier placement in return for price rebates or discounts. Most formularies have at least four tiers: Tier 1 includes generics, with a $5–10 monthly co-pay; tier 2 includes "preferred" on-patent drugs with a modest co-pay (about $30 per script/month); tier 3 includes "non-preferred" on-patent brands, with significantly higher co-pay ($45–90 per script/month); and specialty drugs are put on tier 4 with coinsurance at 20–33% of the drug price, in addition to prior authorization (PA) and other requirements for access. PBMs/PDPs use tiered formularies with co-payment differentials and other access controls to steer patients to use preferred drugs. Because preferred formulary placement increases sales, manufacturers traditionally have been willing to grant price discounts in return for preferred tier placement.

This tiered formulary approach works reasonably well to generate manufacturer price discounts in therapeutic classes with multiple, close-substitute drugs, for which patients/physicians are willing to accept the PBM restrictions on prescribing freedom that are implied by tiered formularies. However, PBMs have less leverage to steer utilization through formulary design and hence to negotiate discounts in therapeutic classes such as cancer, where drugs are more differentiated and individual patients' conditions and preferences may influence appropriate choice of drugs. The growing number of drugs in many specialty classes has increased the drug choices and might be expected to enable PBMs/PDPs to negotiate discounts in return for preferred formulary placement. Such discounting in return for preferred placement occurred for the hepatitis C drugs, but these are similar in outcome and require relatively short treatment duration. In general, discounting in return for preferred formulary placement is not the norm for specialty drugs.

Most PDPs and PBMs place drugs costing over $600 a month on a fourth "specialty" tier with a 25–33% coinsurance rate,[5] rather than seeking discounts in return for preferred placement. This 25–33% coinsurance on such expensive drugs would be unaffordable for most patients, but few actually pay it, thanks to supplementary insurance, catastrophic caps, and/or coupons. Low-income seniors have cost-sharing assistance through Medicaid, and most higher income seniors have supplementary insurance. Moreover, under Medicare Part D, patient cost-sharing is capped at a "catastrophic threshold," above which the patient pays at most 5% (zero for low-income seniors), while the PDP pays 15% and taxpayers pick up the remaining 80%.[6] Under the Affordable Care Act, private insurance offered through exchanges must have an income-related catastrophic limit on patient cost-sharing, but health plans may no longer set annual or lifetime caps on their payments for covered benefits. For patients who do face high out-of-pocket costs, pharmaceutical companies offer patient assistance and coupon programs to cover cost-sharing.

[5]Medicare defines drugs costing at least $600 a month as "specialty drugs" and permits PDPs to place these drugs on a specialty tier with a coinsurance percentage up to 33%.

[6]In 2017, the catastrophic coverage threshold is $4,950 in True Out-of-pocket spending. http://www.kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/.

The net effect and important implication of this patchwork of coverage for drug pricing strategy are that, because most patients have a cap on their cost-sharing and significant protection below the cap (through supplementary insurance, coupons, etc.), most patients are relatively insensitive to prices. In particular, at price levels that exceed the cost-sharing cap for most patients, price elasticity or sensitivity is likely to be minimal. Most novel cancer drugs are now priced in that range where increasing price is unlikely to significantly affect utilization.[7]

Physician-dispensed drugs: Drugs that require infusion or injection are dispensed in physicians' offices or hospital outpatient departments. These drugs are covered by a private insurer's medical benefit and by Medicare Part B for seniors (Kaiser Family Foundation 2017). Physicians buy these drugs from specialty pharmacies and are reimbursed by the health plan for the drug cost plus a modest dispensing fee—the "buy and bill model." Medicare Part B's reimbursement rules set the norm followed by many private payers. Since 2005, Medicare Part B reimburses the physician for the drug at its average selling price (ASP), calculated as the volume-weighted average manufacturer selling price, net of discounts and lagged two quarters, plus 6%. This ASP + 6% formula creates incentives for manufacturers to set a high rather than low ASP at launch, because a higher price offers a larger absolute margin to the dispensing physician and this may influence prescribing, other things equal. The ASP formula also discourages discounting by manufacturers to gain market share. Although a discount given to some customers in period T increases their margin in that period, the discount reduces the average selling price and therefore reduces the reimbursement paid to *all* customers in period T + 2. Many private payers follow Medicare's ASP-based reimbursement rule, with possible modifications such as using a different add-on percentage.

Thus this Medicare Part B reimbursement rule places no constraint on launch prices and has likely contributed to high prices for oncologics and other physician-dispensed drugs, by creating incentives for manufacturers to set high prices and avoid discounting. The 2-quarter lag structure may constrain rapid price increases, because reimbursement in quarter T is based on ASP in T-2, such that rapid price increases could result in physicians being reimbursed at less than their acquisition cost for drugs. Medicare patients face 20% cost-sharing with no catastrophic cap for Part B services, which might in theory create price sensitivity and provide a countervailing constraint on prices for Part B drugs. However, many Medicare patients have supplementary insurance—either private Medigap coverage or Medicaid—that covers their cost-sharing, making them less price sensitive. Those patients who do face the 20% coinsurance out-of-pocket may simply forego the drug, unless they are referred to a patient assistance program or a hospital outpatient department that may waive the co-payment.

Oncology drugs thus illustrate that the US' market-based approach to pharmaceuticals, which works reasonably well for many primary care drug classes with

[7]Specifically, for a Medicare patient using a fourth-tier drug with 25% coinsurance, they reach the cost-sharing cap and face incremental cost-sharing of at most 5% for any price beyond $20,000 per treatment.

moderately priced, closely substitutable, products, is poorly designed to deal with high-priced, differentiated products like the cancer drugs. The market approach presumes that price-sensitive consumers and their payers/PBMs choose between similar products on the basis of price. For cancer drugs, differentiation of drugs, patient conditions, and preferences mean that choice among drugs is heavily influenced by clinical factors, as patients and their physicians determine their preferred sequencing of drugs to manage the condition. Insurance coverage further drastically reduces price sensitivity, because many patients have cost-sharing covered through supplementary public and private insurance. Although the evidence shows some patients face "financially toxic" cost-sharing even in meeting these caps, in general the significant coinsurance provisions in US private and public insurances provide little if any constraint on manufacturer pricing because most patients have supplementary insurance, coupons or other cost-sharing assistance, while those who face the full out-of-pocket payment likely drop out of the market at quite low prices, leaving only the heavily insured patients who are price insensitive in the market. Further, for physician-dispensed drugs Medicare's ASP + 6% reimbursement creates incentives for manufacturers to set high launch prices for cancer and other physician-dispensed drugs, with no constraint except the nominal 20% patient coinsurance, which appears to be an ineffective constraint due to supplementary coverages.

The failure of reliance on patient cost-sharing to create price-sensitive markets is exacerbated by the requirement that all Medicare Part D PDP plans must cover all FDA-approved cancer drugs. Further, CMS is expressly barred by statute from negotiating prices with pharmaceutical companies or from using evidence on costs or effectiveness to make coverage decisions. CMS recently proposed some modest changes in its reimbursement for Part B drugs, but was forced to drop these initiatives under industry pressure. Although biosimilars are being developed as the earlier biologic drugs reach patent expiry, the US lags the EU in number of approved biosimilars. Further, because most biosimilars will not achieve the stringent standards for substitutability with originator products and reimbursement rules treat them as distinct products, incentives for competitive pricing by biosimilars are weak, at least under current rules.

In sum, the system is designed to rely on price-sensitive choice between similar products, but this cannot work well for costly, differentiated products like cancer drugs, where clinical distinctions matter and insurance considerations have appropriately led to catastrophic limits on cost-sharing in most public and private programs. If fully insured patients are the majority of customers, while those who face the large cost-sharing either forego their drugs or apply for patient assistance programs, the coinsurance has little constraining effect on manufacturer pricing. In this environment, if payers have no leverage to control prices, the manufacturer's rational pricing strategy may be to set a high price to the highly insured majority, while offering patient assistance or coupons to those who face significant out-of-pocket costs. This status-quo system is unsustainable because ultimately patients/enrollees/taxpayers must pay the insurance premiums and taxes to fund the private and public programs. Such willingness-to-pay is eroding as prices rise out of

line with perceived value of benefits delivered and opportunity cost of other goods foregone in order to purchase these products.

3.2 Pricing in Developed Countries Ex-USA

In contrast to the USA, all EU and other developed countries have national or social health insurance (NHI or SHI) systems that evaluate price and coverage criteria for drugs, as a condition of reimbursement. Countries differ in detail of these pharmaceutical price and reimbursement systems (see, e.g., Danzon 2012; Stargardt and Vandoros 2014). The payer typically evaluates the manufacturer's proposed price, relative to such factors as: evidence of clinical benefits and risks; prices of comparator drugs in the same country (internal referencing); and/or price of the same drug in other countries (external referencing). Reimbursement is contingent on the manufacturer and payer agreeing on a price, including any rebate or "access program" to reduces costs for the payer. Price increases are generally not permitted and payers may mandate price cuts or freezes to meet budgetary goals. Cancer drugs are subject to these general price/reimbursement constraints, but may sometimes receive special treatment on such grounds as: orphan status, which may justify a higher price; treatment of terminal conditions; and strong patient/physician advocacy of medical need.

The fact that ex-US payers operate within limited health budgets and can refuse to pay for treatments that are deemed poor value at the manufacturer's price gives payers some leverage to negotiate lower prices, but can also lead to less availability of new drugs and access for patients. Manufacturers may be reluctant to cut prices in one country if such cuts could spill over to other countries, through external referencing or parallel exports, which are common in the EU (see, e.g., Danzon et al. 2005; Kyle 2007). Spillovers may be avoided if price cuts take the form of rebates paid directly to payers, which must remain confidential to avoid spillover but hence lack transparency. The non-observability of discounts and rebates means that studies based on observable prices may underestimate the extent of cross-national price differences. But the fact that low-income countries have fewer of the novel, expensive drugs is consistent with the observed data, that prices vary across countries less than in proportion to per capita income and hence that drugs are least affordable, relative to per capita income, in low-income countries. However, the limited availability and relatively high prices (compared to per capita income) of drugs in low-income countries plausibly reflects a complex mix of factors besides limited ability to pay, including other medical priorities in these countries, lack of specialist physicians, and other complementary medical services needed to assure appropriate use of complex drugs, risks to intellectual property, and other factors.

4 R&D and Pricing

High prices for cancer and other drugs are sometimes attributed to high costs of R&D. Economic theory and evidence support the view that investors must be able to anticipate a positive return on their investment (ROI), in order to continue investing. However, it does not follow that prices are based on the cost of R&D, which would be an irrational pricing strategy. Producers in any profit-driven industry rationally set prices based on what customers are willing to pay. In the case of pharmaceuticals, this depends on the effectiveness, safety, and other characteristics of alternative treatments and, importantly, on payer reimbursement rules when drugs are largely covered by insurance.

Nevertheless, recognizing the need to maintain appropriate incentives for investment in R&D, some understanding of the structure and cost of R&D is important. As with pricing, the available data and studies have limitations, but are nevertheless useful. A recent study (DiMasi et al. 2016) estimated the average cost of bringing a new drug to market at $2.7b (2017 US dollars), including the cost of capital. This study used corporate data from the 10 largest companies for their self-generated drugs (discovered and developed in-house). This is a biased sample, because these self-generated drugs were a small and declining share of total drugs approved during the study period, when novel discovery R&D was shifting to smaller companies, including for cancer.

A more recent study (Prasad et al. 2017) focused at the other extreme, on 10 small cancer-focused companies that brought a single drug to market between 2006 and 2015. Their estimate of the median cost of bringing a new cancer drug to market was $757.4 m, including the cost of capital. Although both studies have limitations and the reported estimates have large ranges, the lower estimate from the Prasad et al. (2017) study is more consistent with other evidence of trends in cancer R&D. In particular, for phase III trials (which are usually the largest element of R&D cost) between 1997 and 2016 average trial duration declined from 2000 days to 1070 days, and average enrollment declined from 671 patients to 188 patients (QuintilesIMS Institute 2017). This reflects both the focusing on smaller niche conditions and streamlining of regulatory processes and trial design. Prasad et al. also report total revenue to date for the 10 drugs of $67b. Since this is at a median of 4 years since approval, it seriously understates their full lifetime expected revenues. This partial report of total revenue far exceeds the total $9.1b in R&D expense (including 7% opportunity cost of capital).

Further evidence that oncology is perceived to offer a relatively profitable R&D investment opportunity is provided by the 45% increase in the number of oncology drugs in clinical development over the past 10 years, with 631 late-stage drugs in development (QuintilesIMS Institute 2017). The incentive from generous pricing of cancer drugs reinforces other favorable factors, including the ease of stratifying cancers to target drugs for narrow conditions that qualify for orphan status, which brings benefits of R&D tax credits, 7-years market exclusivity, relatively small trial requirements and, if granted breakthrough status, favorable regulatory review

conditions. While the robust flow of investment into oncology R&D may bring new cancer treatments, it does raise the policy issue whether cancer is disproportionately favored, to the relative neglect of other therapeutic areas, on account of the high prices and relatively low R&D costs. Such concerns reinforce the case for a value-based approach to reimbursement for all drugs, including cancer drugs, in which pricing and reimbursement coverage are linked to evidence of value created across all therapeutic areas.

5 Value-Based Pricing: A Way Forward

The US lags many other countries in developing a consensus approach to measuring the value of drugs and using such data in reimbursement decisions. Frustration over high prices that appear unrelated to clinical value has recently prompted multiple initiatives to develop "value frameworks," including the value framework developed by the American Society of Clinical Oncology (Schnipper et al. 2015) and the drug Abacus developed by Peter Bach and colleagues at Memorial Sloan Kettering (https://drugpricinglab.org/tools/drug-abacus/). The ASCO approach is designed to assist physicians and patients make clinical choices. Outcomes include overall survival or progression-free survival, with an arbitrary weighting attached to risks, while costs include on the drug cost, either the full price or the patient's out-of-pocket cost, depending on perspective taken. The Abacus allows for more elements of "value," including not only expected survival and risk, but also the drug's R&D costs, treatment population size, price charged in one or more foreign countries, etc. The analyst must supply their preferred weights for each of these dimensions, and then the Abacus calculates a weighted aggregate "value," which can be compared to the drug's price, to determine whether or not the price is "fair." These approaches may provide useful aids to clinical decision-making, but they are not designed for use by payers to assure consistency in price and reimbursement decisions, which is essential to achieve the goal of maximizing health gain from a given health budget.

5.1 Value-Based Pricing

In fact, an extensive health economics literature addresses the issue of how to measure health outcomes and other dimensions of value with a view to maximizing health gain from a fixed health budget (see, e.g., Newman et al. 2017; Drummond et al. 2015; Sculpher et al. 2017). This literature recommends using a validated outcomes metric that captures at minimum both the quality and quantity of survival, as in the quality-adjusted life year (QALY). From a payer or societal perspective, costs should include the full price of the drug plus any additional costs or cost offsets, such as hospital days required or averted due to the treatment. Calculation of an incremental cost-effectiveness ratio (ICER) in terms of incremental cost,

relative to incremental QALYs gained for a new treatment, relative to customary treatment, provides a measure of incremental cost per unit of health gain. Assuming that the payer's objective is to maximize health gain, given its available budget, the payer should set a threshold willingness-to-pay (cost per QALY) and pay for those treatments that meet this threshold. Paying for treatments that are priced above the cost-per-QALY threshold while foregoing others that priced below the threshold implies that health gain would not be maximized for the budget.

With this approach, the payer need not directly regulate drug prices. By requiring that drugs meet a cost-per-QALY limit in order to be reimbursed, the payer creates incentives for manufacturers to price their drugs to meet this limit, in order to qualify for reimbursement. This implies that the products that yield significant incremental benefit, in QALYs gained or costs saved, can charge a significant premium over the comparator product and still meet the cost-effectiveness threshold. Conversely, a new drug that offers no incremental benefit must be priced at par with the comparator or risk exceeding the threshold and being denied reimbursement. Thus, use of a cost-per-QALY threshold as a condition of reimbursement creates incentives for manufacturers to charge prices commensurate with value created and creates incentives for R&D to focus on areas where significant value can be created (Danzon et al. 2013b) .

While the approach to value-based pricing described here is structurally similar to that used by the UK's National Institute for Care Excellence (NICE), important adjustments would be needed to adapt the approach to the pluralistic and more affluent US health system. In particular, different public and private health plans could choose different ICER thresholds and might also include different items in their measure of benefits, depending on their premium levels and implied budgets. In general, since ICER thresholds reflect taxpayers/enrollees' willingness-to-pay for health gain, such thresholds are expected to be higher in countries/health plans with high income and/or a high willingness-to-pay for health. Thus US health plans would surely adopt significantly higher ICER thresholds than those used in the UK.

More generally, this basic framework to induce value-based pricing could also be used to set drug price differentials across countries at different income levels. If each country unilaterally defined its approach to measuring value and sets its ICER threshold based on its willingness/ability to pay, this would create incentives for manufacturers to differentiate prices across countries such that prices would better align with affordability across countries. Of course, implementation of such a system presupposes an institutional framework that precludes either consumers or middlemen arbitraging price differences within and between countries. In fact, technological advances make it increasingly feasible to target price differentials through electronic rebates to specific payers, bypassing intermediaries. Such electronic rebates are widely used in the USA to maintain price differences across health plans and have also been used in other countries. Thus, the main obstacle to broader use of differential pricing is not technical feasibility but political acceptance of non-transparency, which could be addressed through audit mechanisms to prevent abuse.

6 Conclusion

In conclusion, a significant driver of high and rising prices for cancer drugs is the structure of reimbursement systems in US public and private insurances, which provide no constraint on the upward drift of prices. Constraining this upward drift while preserving appropriate incentives for R&D requires a mechanism that allows prices commensurate with value. Such value-based pricing can be achieved via the relatively simple, indirect approach of using an ICER threshold as a condition of reimbursement, which could differ across health plans and across disease or patient categories within a plan, e.g., higher willingness-to-pay for treatments of terminal conditions. This value-based pricing approach creates appropriate incentives for R&D and maximizes health gain for a given budget. It can be used with different ICER thresholds across countries, based on income, which would facilitate price differentials that are reasonably affordable relative to income, while incentives for R&D are maintained.

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