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Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures

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ABSTRACT

Objectives: To analyze how value-based pricing (VBP), which grounds the price paid for pharmaceuticals in their value, can manage "affordability" challenges, defined as drugs that meet cost-effectiveness thresholds but are "unaffordable" within the short-run budget. **Methods:** Three specific contexts are examined, drawing on recent experience. First, an effective new treatment for a chronic, progressive disease, such as hepatitis C, creates a budget spike that is transitory because initial prevalence is high, relative to current incidence. Second, "cures" that potentially provide lifetime benefits may claim abnormally high VBP prices, with high immediate budget impact potentially/partially offset by deferred cost savings. Third, although orphan drugs in principle target rare diseases, in aggregate they pose affordability concerns because of the growing number of orphan indications and increasingly high prices. **Results:** For mass diseases, the transitory budget impact of treating the accumulated patient stock can be managed by stratified rollout that delays treatment of stable patients and prioritizes patients at high risk of deterioration. Delay spreads the budget impact and permits potential savings from launch of competing treatments. For cures, installment payments contingent on outcomes could align payment flows and appropriately shift risk to producers. This approach, however, entails high administrative and incentive costs, especially if applied across multiple payers in the United States. For orphan drugs, the available evidence on research and development trends and returns argues against the need for a higher VBP threshold to incentivize research and development in orphan drugs, given existing statutory benefits under orphan drug legislation.

Keywords: affordability, cures, orphan drugs, pharmaceuticals, value-based pricing.

Introduction

Value-based pricing (VBP) seeks to ground the prices paid and coverage decisions for pharmaceuticals on their value, as measured primarily by health gain to the patient (incremental efficacy and safety) plus any net savings in medical costs. (Other societal costs and benefits, such as equity and prevention of contagion, could be included if the perspective is societal.) Drugs that are priced to be cost-effective at a specified threshold (cost per quality-adjusted life-year [QALY]) should be reimbursed. In a welfarist context, the threshold and health budget reflect consumers' willingness to pay (WTP) for health-related versus non–health-related goods, given incomes, preferences, and technologies. In equilibrium, VBP can be designed to achieve the maximum health gain for a given budget (static efficiency) and create second best optimal dynamic incentives for research and development (R&D) investment in a global context [1].

In practice, changes in technology imply that application of VBP may sometimes conflict with affordability, at least in the short run. A new drug (class) is deemed "unaffordable" if paying for all eligible patients at the VBP price would force either an overrun of the payer's budget or displacement of other cost-effective treatments. In the long run, changes in health technologies can in principle be accommodated by increasing health budgets if consumers are willing to allocate more resources to health care. Thus, affordability is mainly a problem of disequilibrium. This article examines three prototypical affordability contexts and the possible approaches to deal with each. Because affordability of a treatment depends on price and disease prevalence, these three contexts correspond to different situations of high price and/or high prevalence.

First, a high-price/high-prevalence threat to affordability is likely to occur with new, highly effective treatments for chronic, progressive diseases, such as hepatitis C. For such diseases, the initial disease prevalence exceeds the annual incidence of new cases and the current treatment yields medical cost savings that accrue mainly in the future. The transitory budget impact of treating the initial patient stock can thus far exceed the steady-state annual cost of treating new cases. Stratification of treatment is potentially an effective approach to dealing with unaffordability in such high-prevalence, progressive disease contexts.

Second, affordability is a potential concern for "cures" such as gene therapies that might claim extremely high VBP prices on the

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basis of their potentially long-lived benefits (The emphasis on "cure" is to highlight the uncertainty as to actual long-term effects of such treatments.) Installment payments are evaluated as a solution. Contingent payments appropriately shift risk to producers and align payment with accrual of benefits, but also create insurance agency and transaction costs.

Third, orphan drugs raise concerns about longer term affordability because their increasingly high prices and growing numbers imply a growth in expenditures at more than twice the rate for nonorphan drugs [2]. This prospect, that current growth rates of orphan drug prices and volumes will require either abnormal budget increases or cuts in other programs, raises the issue addressed here, of whether orphan drugs should continue to be exempt from standard VBP thresholds, given the evidence that rare diseases are no longer neglected but now account for 30 to 40 of new medicines approved each year [3].

In this article, the first section summarizes the basic VBP framework. The second section examines the high-prevalence/high-price context of mass, progressive diseases and considers how the role of stratification depends on disease and drug characteristics. The third section discusses high-priced cures and evaluates proposals for installment payments. The fourth section discusses orphan drugs, with concluding remarks in the last section.

Theoretical VBP Framework

VBP is grounded in a welfarist framework in which either consumers choose among competing private health plans that offer different coverage/premium choices or taxpayers choose an annual health budget through a political process. In either case, the private/public payer has a budget that is fixed in the short run and reflects consumers'/taxpayers' expected marginal utility of spending on health care versus other consumption, given incomes and preferences. The payer—public or private—maximizes the expected health gain for enrollees by setting a threshold or marginal WTP for health (e.g., $100,000/QALY) and reimburses for drugs/indications that meet this cost-effectiveness threshold. In a market context, insurers could offer a menu of plans, with higher WTP threshold plans offering greater technology coverage and higher premiums. A consumer's choice of plan thus implies a choice of premium (budget), threshold, and coverage generosity for the year. For public plans, a similar process operates: choice of the health budget implies a threshold, given the technology set. This approach is potentially consistent with efficient use and investment in pharmaceuticals (static and dynamic efficiency), if adopted unilaterally by payers in each country [1].

This approach implies a maximum VBP price that a manufacturer can charge for a new drug and still meet the cost-effectiveness threshold, which depends on the value created (subscripts "n" and "0" denote the new and comparator treatments, respectively).

$$\mathrm{VBP}_{\mathrm{n}}^{\max} = P_0 + [(C_0 - C_n)^1 + K(Q_n - Q_0)^1] + \sum^T [(C_0 - C_n)^t + K(Q_n - Q_0)^t]. \quad (1)$$

The maximum VBP price of the new drug is the sum of 1) the price of the comparator P_0, 2) a premium that reflects cost offsets plus incremental health gain in the current period $[(C_0 - C_n)^1 + K(Q_n - Q_0)^1]$, and 3) expected future cost offsets and health gain over the patient's life, appropriately discounted $\sum^T [(C_0 - C_n)^t + K(Q_n - Q_0)^t]$. The VBP price would grant all the consumer surplus to the producer, which in theory provides optimal incentives for investment in R&D at the margin. High expected returns may encourage multiple competitors of slightly differentiated products. Whether price competition then transfers some surplus to consumers depends on payer bargaining strategies and consumer price sensitivity.

In this welfarist approach, in equilibrium the payer's health care budget (B), the WTP threshold (K), and services reimbursed are simultaneously determined, given available technologies, consumer incomes, preferences, and other factors. Over time, changes in incomes, technologies, or other factors could lead to revision of the budget, the threshold, and services reimbursed. In the long run, new cost-effective medical technologies can be accommodated by displacement of inferior technologies and by growth of the health budget, but such adjustments take time. Unanticipated expansion of the technology set can upset the budget balance for a given threshold, leading to short-run affordability problems.

Affordability and High-Prevalence, Progressive Diseases

Equation 1 implies that a VBP-priced new drug is easily "affordable" within the existing budget if it creates value solely by reducing current medical costs, with no change in future costs or current or future QALYs. In this case, the VBP premium for the new drug is accommodated by current cost offsets, resulting in budget neutrality for the payer.

In contrast, a new technology potentially increases current year expenditures when its value derives primarily from reducing future medical costs and/or providing QALY gains, current or future, because future cost savings and all QALY gains justify VBP premiums that add to current year expenditures without any current savings. The larger the potential treatment population, the more likely such technologies appear unaffordable.

This concurrence of large treatment population with high VBP price reflecting future cost savings and QALY gains is most likely to occur for highly effective new treatments of progressive diseases that entail rising medical costs and deteriorating quality and duration of life as patients age, such as hepatitis C. A treatment that stops disease progression offers large future medical savings and future QALY benefits per patient, and hence justifies a high VBP price. Moreover, slow disease progression leads to an accumulated initial prevalence of patients potentially eligible for treatment that far exceeds the annual incidence of new cases. For payers, the short-run budget impact of treating the initial patient stock far exceeds the steady-state annual cost of treating new cases, because of the diminishing number of eligible patients once the initial stock has been treated and because realization of deferred savings offsets new outlays. This "unaffordable" short-run budget impact of treating the accumulated patient stock is most severe if the new drug requires only a short treatment, as for hepatitis C. A maintenance drug that is effective at preventing further progression of a chronic disease could not justify such a high VBP price per unit. Essentially, maintenance treatment spreads the cost over many years, whereas a cure that requires a single, highly effective course of treatment concentrates the cost in the price of that short treatment, and hence is more likely to pose a transitory affordability challenge, as for hepatitis C.

Long-Run (Budget) Adjustment versus Short-Run (Stratification) Adjustment

Expansion in the set of available medical technologies may optimally require different adjustments in the long run versus the short run. In the long run, consumers may choose to increase the health budget relative to non–health-related consumption and possibly also raise or lower the WTP threshold K if the marginal utility of health care relative to non–health-related goods changes.

If the budget is fixed in the short term, the payer faces the transitory issue of how to deal with the new drug versus other services eligible to be covered within the inadequate budget. The payer could reduce the threshold *K*, which in theory should optimally allocate the budget across the now expanded technology set. Evaluation of this approach should weigh the adjustment and transaction costs to the health system and patients of changing protocols and/or discontinuing established treatments versus the incremental cost of delaying new treatment starts for some new patients.

In fact, the slow disease progression that leads to the large accumulated stock of eligible patients and large transitory budget impact also implies that patient stratification and staged treatment rollout may be an appropriate solution. For most slow progressive diseases with high costs at mid to advanced disease stages, such as hepatitis C, treatment of early-stage patients can be deferred with minimal incremental health risk, thereby spreading the transitory budget impact over several years.

Although the staged rollout strategy is likely to be feasible for most progressive diseases, the optimal strategy depends on the disease and the drug profile. For diseases that may progress rapidly to permanent physiological damage, such as joint damage in rheumatoid arthritis, treatment might optimally target early-stage patients. This applies if the drug reduces a high near-term risk of disease progression to physiological damage that is irreversible once it has occurred. Even if the drug might also reduce the risk of incremental damage for advanced stage patients, the cost per QALY is likely higher for late- versus early-stage patients. The human papillomavirus vaccination illustrates such prioritization of early-stage patients (although affordability was not a limiting factor in this rollout). The vaccine was initially shown to be effective only for patients with no previous exposure to the virus. Vaccination therefore targeted young, nonexposed patients, which greatly reduced the treatment population, compared with a vaccine that reduces disease risk for all patients. More generally, reflecting this heterogeneity of patients with a progressive disease, different disease stages are usually treated as different indications requiring separate efficacy trials for drugs. Sequential clinical trials naturally stage the rollout of treatment as approved indications expand over time.

Stratifying treatment of the initial patient stock over multiple years has a further threefold benefit for affordability and overall treatment value. First, delay aligns the increased expenditures better with cost offsets, because the more severe patients who are treated first are those at risk of significant near-term medical expense. Second, delay may allow time for competing treatment options to launch, giving payers an opportunity to negotiate discounts on prices as suppliers compete for the one-off opportunity of treating the initial patient stock. Third, the first drug to launch in a new class is not always the best, and hence patients who delay treatment may benefit from an expanded range of treatment options. Treatment staging can thus operate through volume, price, and choice adjustments to transform a potentially unaffordable budget spike into a more manageable, transitory multiyear adjustment, with minimal incremental harm and possibly incremental benefit for patients who wait.

Installment Payments for High-Priced Cures

A payment-by-installment approach has been proposed to ease the budget impact of high-priced treatments that offer a cure for a chronic condition [4,5]. Consider a gene therapy that offers a single treatment that corrects a congenital abnormality, thereby averting a lifetime of costly medical care. The VBP price, calculated as the discounted present value of expected medical savings plus QALY gains, could imply a significant budget impact in the treatment year, before the savings accrue in future years. Payment by installment could in theory align the payments to the flow of cost savings and health benefits.

Such installment payments have been compared with paying for a house with a home mortgage. Nevertheless, the home ownership analogy is weak and other major differences make the payment-by-installment approach generally inappropriate for reimbursement by insurance payers to producers of medical treatments for several reasons. This is also very different from a self-pay patient taking out a private loan to pay in full at the time of treatment.

Because long-term effects of any new technology are uncertain, the strongest case is for future payments that are contingent on the actual health outcomes and savings realized. This shifts outcome risk from the payer to the producer, aligning the producer's incentives to design a product with the best possible long-term benefit-risk structure. Because contingent installment payments shift the risk to producers, producers would prefer an upfront, lump-sum payment unless the lump-sum payment is significantly less than the discounted sum of the expected installment payments. Thus, a contingent installment contract can align the payment and benefits stream over time and shift performance risk to the producer, who is likely more informed and more able to influence the product's actual performance.

Nevertheless, contingent installment payments can distort incentives for payers if the current payer can shift payment disproportionately toward future payers who are not party to the initial contract. More generally, the current payers who draft the contracts have incentives to future-load the payment structure, if this enables current payers to compete for current patients by offering lower premiums than actuarially required for the generous benefits, while leaving future payers to pay a disproportionate share of the cost.

More generally, insurance raises incentive and administrative complications for installment payment for medical care, particularly in a pluralistic, competitive insurance market such as in the United States. Health plans and policies on offer change over time, and patients switch among plans. Although Medicare covers everyone older than 65 years, patients have choice among Medicare Advantage plans and Part D prescription drug plans. Patient mobility creates the opportunity and incentive for the patient's insurer at the time of treatment to structure an installment plan with low upfront payment and most cost shifted to future payers. Future private payers have incentives to avoid patients with accrued liabilities due on past treatment, and this might be imperfectly prevented under guaranteed issue and preexisting condition provisions. Payers might reasonably argue that they should not have to pay for previous treatment, because they were not party to previous treatment contracts and their formularies may not include the treatment at issue. Medicare and Medicaid might be required to accept patients with previous treatment liabilities, which would protect patients but potentially exacerbate the abuse of installment contracts by private payers.

Furthermore, if an insurer refuses to make the installment payments agreed by a previous insurer, or the patients default on their co-payments, the gene therapy producer cannot "repossess" the treatment and resell it to another customer just as a bank might repossess a house. Thus, nontransferability of the collateral asset (the gene therapy), combined with the cost, information, and incentive challenges of contracting between current and unspecified future insurers, makes installment payment for medical treatments radically more problematic than paying for a house with a mortgage. To enforce future payment, a gene therapy might in theory be designed such that the patient must take a pill periodically to maintain the benefit flow. The pill could then be an enforcement mechanism that is priced to reflect

benefits received. This, however, might add to cost and technical risk of therapy development.

Even if the incentive, information, and contracting issues of installment payments could be handled with modest administrative cost, the question remains as to which medical treatments should be singled out for installment payment. Many surgical treatments and drugs offer benefits that accrue for many years—for example, vaccines offer multiyear protection against contagious diseases, osteoporosis drugs reduce the risk of future bone fractures, and hip replacements provide years of mobility and pain reduction. Despite long-term benefits from many health treatments, even single-payer systems such as in the United Kingdom or Canada normally reimburse for medical treatments in the year of treatment, regardless of future benefits. This suggests that the administrative costs of contracting and measuring patient-specific outcomes outweigh any gain from improvement in producer incentives and/or alignment of payment with benefits over time, which, for large payers, average out over millions of patients/treatments covered. Consistent with this emphasis on contracting costs, contingent payment contracts that have been adopted primarily target treatments with uncertain outcomes that are easily measured in the short- to medium-term, such as progression-free survival for cancer or blood sugar for diabetes. Most patient access schemes for pharmaceuticals in the United Kingdom are simple discounts or dosage caps, with few linked to individual patient response [6]. In the United States, contracts requiring manufacturer rebates if near-term outcomes fall short have been used for cancer [7], diabetes and heart disease [8], and the recently launched gene therapy for blindness [9].

Orphan Drugs

Orphan status is assigned by regulatory authorities to drugs that target diseases affecting small populations—fewer than 200,000 patients in the United States. In 1983, the US Orphan Drug Act (ODA) was enacted to address concerns over the neglect of R&D for orphan diseases, which were perceived as relatively unprofitable. Similar legislation followed in the European Union and Japan. Orphan thresholds are roughly 6.37 patients per 10,000 population in the United States, 5 in 10,000 in the European Union, and 4 in 10,000 in Japan [2]. The US ODA provides investment incentives for R&D in orphan drugs, including tax credits equal to half of clinical development costs, R&D grants to help fund clinical trials, waiver of Food and Drug Administration (FDA) user fees, and 7 years of market exclusivity for each orphan indication. Although the ODA does not explicitly address pricing, a recent study estimates that of the top 100 drugs in the United States, the average cost per patient per year in 2016 was $140,443 for orphan drugs and $27,756 for nonorphan drugs, with the highest priced orphan drug costing more than $400,000 per patient per year [2]. These studies include in the orphan subset only those drugs that are expected to generate more than 25% of their sales from their orphan indications, thereby excluding drugs such as Avastin, Enbrel, Herceptin, Humira, and Remicade, which have both orphan and blockbuster indications. High prices have been rationalized on grounds that 1) budget impact on payers is modest because each orphan disease affects few patients and 2) higher prices are needed to offset smaller patient populations to cover R&D costs and yield a competitive return on investment (ROI) for producers.

Both these rationalizations are now being challenged [10,11]. By 2014, more than 400 orphan drugs had been approved. Orphan drugs now account for more than one-third of new drugs approved by the FDA, and the number of new orphan designations per year has increased dramatically, from 50 to 100 per year from 1987 to 2003 to 291 new designations in 2014 [12]. The increasingly high prices and growing numbers of orphan drugs imply increasing budget impact for payers and that orphan indications are far from neglected by R&D.

This shift of R&D into orphan indications strongly suggests that the expected profitability of R&D for many orphan diseases is now perceived to be greater than for nonorphan diseases. This inference from R&D trends is confirmed by other supporting evidence: mean and median price per patient-year are 4.8 and 13.8 times higher, respectively, for orphan versus nonorphan drugs; phase III orphan drug development cost is 50% lower (and 75% lower after US tax credits); and FDA approval time is 10 months versus 13 months. Overall, the expected ROI of phase III/filed orphan drugs was 1.14 times greater than that of nonorphan drugs [12]. This analysis is based on a subset of orphan drugs that were first approved for an orphan indication and are expected to derive more than 25% of sales from their orphan indications. Orphan drugs are projected to account for 21.4% of worldwide prescription drug sales (excluding generics) by 2022, compared with 6.1% in 2000, with sales growth of 11.1% per year from 2017 to 2022, roughly double of the overall prescription market growth, implying a significant budget impact for payers [2].

Let us assume that the policy goal is that investors should face a similar expected ROI if they undertake R&D for orphan versus nonorphan diseases, such that patients should face similar likelihoods of treatment availability for orphan versus nonorphan diseases. We take as given the existing ODA provisions, including R&D tax credits and market exclusivity. The issue for a VBP framework is whether a higher WTP threshold should apply to orphan versus nonorphan drugs to permit higher prices and boost the ROI for orphan drugs. The traditional rationale is that orphan drugs require higher prices per patient to offset their lower patient volumes on the presumption that some costs are fixed or imperfectly variable with patient volume. (The R&D-based orphan drug argument is distinct from the more general argument for a higher WTP threshold for severe, debilitating diseases, which may include some orphan drugs. This concern is grounded in patient preferences and is not addressed here.)

To examine the assumption that higher prices are required to offset higher average costs, consider the following cost structure:

$$C = F + dQ + mQ + vQ, \tag{2}$$

where C is the total cost of bringing a new drug to market, F and d are the fixed and variable components of R&D expense, Q is the expected patient volume, and m and v are marketing and production cost per patient, respectively (F could be defined to include any fixed production or marketing costs).

Average cost per patient, c, is as follows:

$$c = F/Q + d + m + v. \tag{3}$$

If F is quasi-fixed and other variable cost components are not lower for orphan drugs, then average cost would vary inversely and the ROI would vary positively with disease prevalence, unless the higher costs are offset by higher prices.

Detailed empirical evidence is unavailable to estimate the relationship in Equation 3 between average cost per patient and disease prevalence. Moreover, any such analysis must recognize that observed R&D choices and expenditures reflect endogenous responses to incentives. With these caveats, the limited available evidence does not support the hypothesis of large fixed R&D costs and relatively high total cost per patient for orphan drugs, as required to justify large additional price premiums, over and above ODA's provisions of R&D tax credits, grants, user-fee forgiveness, and 7-year market exclusivity per orphan indication, which we take as given. Recent estimates indicate that phase III

development cost is 75% lower, net of tax credits, for orphan versus nonorphan drugs. In addition, because many orphan drugs target unmet medical need, they qualify for FDA's breakthrough status, which can significantly reduce clinical trial costs and approval times. Many orphan indications are now approved with a single, pivotal trial, and orphan trial size is sometimes fewer than 100 patients, reflecting the small patient populations.

Moreover, many orphan drugs are approved for multiple indications, which expands treatment volume with modest incremental R&D cost, because follow-on indications require only the pivotal efficacy trial(s). A study of 45 orphan drugs available from 2012 to 2014 found that 44% of these drugs' usage was for nonorphan conditions, including 20% for nonorphan on-label uses and 24% for off-label uses [10]. Multiple approved indications as well as off-label use mean that many orphan drugs are used to treat more patients than implied by the indication for which orphan status was granted. These considerations—smaller clinical trials, shorter review time, savings from breakthrough and other priority statuses, and use for multiple indications including off-label—together with ODA's statutory benefits of tax credits, grants, user-fee forgiveness, and market exclusivity tend to undermine the presumption that orphan drugs incur significantly higher, after-tax R&D cost per patient treated compared with nonorphan drugs. Furthermore, marketing costs are minimal for orphan drugs because orphan diseases are typically managed by a small number of specialists and the market exclusivity provision eliminates competitors. Finally, in contrast to the pre-ODA 1983 payment environment of predominantly out-of-pocket payment and low prices, the growth in insurance coverage implies that orphan drugs are now virtually assured of reimbursement in the United States, regardless of price. The upward drift of orphan prices means that even ultra-orphan drugs (fewer than 10,000 patients in the United States) can achieve blockbuster sales (e.g., priced at more than $450,000 per patient, Soliris had $2.8 billion worldwide sales in 2016, despite only roughly 2,400 patients treated in the United States [2]).

Some observers point to the dramatic recent increase in orphan drugs approved and under development as evidence that the ODA is achieving its intended result and should not be changed. As noted earlier, we assume no change in ODA's statutory provisions, including R&D tax credits, grants, user-fee forgiveness, and market exclusivities. Rather, we focus on whether, in addition to these ODA statutory benefits, a VBP framework should also provide for abnormally high prices through use of a higher WTP threshold for orphan drugs. The evidence reviewed has shown a dramatic and apparently accelerating shift of R&D toward orphan indications. This R&D trend strongly suggests higher expected profitability from R&D for orphan than for most nonorphan drugs. This inference from R&D trends is supported by the data cited earlier on actual costs and returns, that clinical trial costs are 75% lower (net of tax credits), prices are on average 5 times higher, and overall profitability is higher for orphan drugs.

The shift of R&D toward orphan indications raises concern not only over affordability but more fundamentally of potential bias toward R&D in orphan drugs, to the relative neglect of therapy classes that cannot qualify for orphan drug status, such as dementia or antibiotics. The concern of pro-orphan drug bias is reinforced as advances in genetics and personalized medicine enable scientists to subdivide broader disease classes into increasingly narrow indications. Given the ODA benefits, favorable FDA treatment, and the advances in genetics, the evidence now raises concerns that the abnormally high prices for orphan indications could bias R&D toward excessive subdivision within disease classes, rather than toward developing drugs with the broadest possible application consistent with safe and effective treatment (e.g., Ref. [13] and references therein). Evidence that individual drugs are sometimes approved for multiple, closely related subdivisions within a larger disease and/or used off-label for related indications is consistent with—but not proof of—excessive subdivisions. Further research is needed to assess the clinical versus economic benefits of such strategies.

Thus, current evidence no longer supports the traditional rationalizations for higher prices for orphan drugs, that budget impact for payers is minimal and the ROI for producers would otherwise be inadequate. The evidence suggests that the simple 200,000 population threshold, defined by indication, is an arbitrary and imperfect way to identify indications that may require special incentives to achieve a normal ROI. Given the downside risks of encouraging excessive disease subdivision and biasing R&D toward high-priced orphan drugs, to the neglect of broader, nonorphan drug indications, it seems prudent to base VBP pricing on value created, with no special higher threshold or pricing premium for orphan drugs, given existing ODA provisions. Future research should consider whether the current mix of tax credits, grants, fee forgiveness, and market exclusivity is the optimal strategy to promote R&D for neglected disease classes and how such subsidies should be targeted. Whether a higher VBP threshold might be appropriate for a subset of orphan indications, which incur disproportionate R&D cost per patient and have limited opportunity for indication expansion, is also a subject for future research.

Conclusions

In a VBP regime in which consumers/taxpayers can increase health budgets in the long run, affordability is conceptually a short-run problem of dealing with treatments that are cost-effective but unaffordable within current budgets, usually because of a combination of high prices and high volumes. This article focuses on solutions that seek to avoid reducing the threshold and displacing existing, cost-effective treatments, which entails high adjustment costs.

High volume is most likely for treatments that target chronic, progressive diseases, which accumulate a large disease prevalence that far exceeds annual incidence. Such a transitory budget spike can likely be managed by stratified rollout of treatment, prioritizing treatment to patients at greatest immediate risk of irreversible deterioration, and delaying treatment for patients whose condition is stable.

High prices under VBP usually reflect highly effective treatments with long-lived benefits, which are essentially prepaid in the VBP price. Contingent installment payments can potentially align payment to benefits over time and optimize producer incentives. Nevertheless, this approach faces high incentive and transaction costs of contracting between current and future payers (or across budget years within public systems) and of identifying which of the myriad medical treatments with future benefits should be singled out for future payment.

Despite low prevalence for each drug, orphan drugs in aggregate raise affordability concerns because of rising prices and proliferation of orphan indications. A review of available evidence on R&D costs, number of approvals, and relative prices of orphan drugs concludes that orphan drugs are now a highly attractive R&D class. Given the existing ODA tax credits, grants, exclusivities, and other benefits, the evidence argues against routinely using a higher VBP threshold for orphan versus nonorphan drugs. Future research should consider the broader question of optimal use of pricing versus other policy options to stimulate R&D for currently neglected diseases.

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