Sustainable Reimbursements: Towards a Unified Framework for Pricing Drugs with Significant Uncertainties

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ABSTRACT

Recent political events have thrust the bulk negotiation of drug prices by Medicare and Medicaid back into the spotlight. Yet, even if politically feasible, there is no clear framework for negotiating prices of new drugs with uncertain target populations—for example, due to imprecise estimates or off-label use—or uncertain clinical effects—for example, due to heterogeneous patient response. We create such a framework using two-price programs developed in the economics of procurement literature. This framework delivers new payment strategies, and unifying them with theoretical advances in pharmaceutical reimbursement like capitation and value-based pricing. Two-price programs substantially reduce uncertainty for both payers and pharmaceutical companies, while still creating financial incentives for those companies that innovate and create value for patients.

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This research received no outside funding. All authors contributed to all parts of the design and execution of this research. The views expressed in this manuscript are personal and may not be understood or quoted as being made on behalf of—or reflecting—the position of EMA or AIFA or any of their committees or working parties. They are not intended to be an official and/or binding regulatory position.

Total pharmaceutical expenditures have been growing at a much faster pace than payments to physicians in the U.S. over the past 25 years. [1] This is due, in part, to experimentation with alternatives to fee-for-service, while pharmaceutical reimbursements are almost always done on a fee-per-dose basis. [2, 3, 4] A shift to bulk purchasing by Medicare and other government payers, as has recently been put back on the table by political events, may seem to be a promising start to reducing the financial challenges posed by spending on pharmaceuticals. [5] However, European governments that use bulk purchasing face similar financial challenges. [6] Thus, new tools are needed, including reimbursement strategies for large government payers. [7, 8, 9]

We present a framework using two-price reimbursement programs. These programs—with high initial prices and low continuation prices—reduce risk to both pharmaceutical companies and payers, and offer a sustainable, profitable way to guarantee patient access. In particular, these programs reduce the payer's financial uncertainties by ensuring a low cost of continuing treatment, and also reduce pharmaceutical companies' uncertainties by guaranteeing the bulk of their profit up front. We describe and explore the uncertainties faced pharmaceutical reimbursement, and show, through simulations, the stark differences between two-price programs and fee-per-dose.

Key Sources of Uncertainty

Negotiating a reimbursement program is challenging because of uncertainty over both the effects of a drug and the size of the future patient base. Total payments with a fee-per-dose program are:

Total Payments = [Number of Doses per Patient x Number of Patients] x Price per Dose.

As price per dose is relatively fixed, uncertainty over total payments will come from one of the terms in the brackets. Pharmaceutical companies face greater uncertainty than payers. Payers are uncertain about the number of doses needed, whereas a pharmaceutical company has the extra uncertainty of how many doses will be purchased from them, rather than from a competitor.

Uncertainty over the number of doses per patient comes from the limited nature of clinical trial data. In most cases, treatments are approved on the basis of a small benefit to soft endpoints. [10] But, in some cases, treatments can have radical, lasting effects on a sizeable share of treated patients. For example, a substantial number of cancer patients from the original trials of immune-checkpoint inhibitors are still alive years later. Unlike traditional chemotherapy, some of these treatments are given continuously. Together, these factors can lead to the exponential growth of treated populations. This is not predictable from the surrogate endpoints upon which approval is

based, such as the proportion of patients experiencing progression-free survival at 6 or 12 months. This, coupled with high price tags—$300,000 (nivolumab + ipilimumab) to $1,000,000 per patient, per year (pembrolizumab)—creates significant financial challenges. [7, 11] Equally, past-approval research may result in unexpected declines in usage. For example, the standard duration of treatment using trastuzumab is one year, although recent studies suggest a treatment duration as short as nine weeks may be equally effective. [12]

Uncertainty over the number of patients may come from changing demographics and medical practices. For example, the number of patients taking PCSK9 inhibitors to reduce LDL cholesterol is difficult to predict as it depends crucially on the number of patients who do not respond to statins, the number that develop statin intolerance, and the number who choose to switch because of differential side effects between the treatments. [13] Moreover, precision medicine may suddenly reduce the applicable patient populations. For example, the discovery that African American hypertensives responded better to ACE-inhibitors than β-blockers lead to a large decrease in the number of patients taking β-blockers. [14, 15]

Standard fee-per-dose reimbursement programs expose both pharmaceutical companies and payers to significant financial risks. If the treatment turns out to be unexpectedly effective, or more widely used than anticipated, the payer may have difficulty covering a rapidly expanding patient population. [6, 9] There is additional uncertainty from the pharmaceutical company's point of view: the drug may be used much less than expected. This may occur because a competitor quickly gains approval, because the treatment turns out to be much less effective than clinical trial results would predict (for example, Drotrecogin Alfa), or due to the detection of previously unknown side-effects (for example, Tetrazepam). [16, 17] These significant financial risks cause pharmaceutical companies to maximize profit on successful compounds, which creates financial challenges for payers that might compromise access for patients. [6, 10]

Two-Price Reimbursement Programs

Two-price reimbursement programs are designed to insulate against uncertainty in the number of doses per patient or the number of patients. They start with high prices for initial doses, and convert to lower prices after some number of doses have been administered. High initial prices guarantee that profits will be realized up front, in a predictable way. Low continuation prices limit the potential financial liability of payers, guaranteeing that payments do not grow exponentially,

even if the treated population does. These programs are inspired by cost-plus and price-volume discount programs that have been extensively studied by economists. [18, 19, 20, 21]

The total payments under these programs are given by:

Total Payments = High Price* Switching Time + Low Price * (T – Switching Time),

where **T** is the end of the profitable life of the treatment, for example when it goes off-patent, or is superseded by a new standard of care; or when the patient finishes treatment or dies. This formulation means that no matter how uncertainties resolve, the total cost and profits will be relatively similar. If **T** is much further in the future than anticipated, or unexpectedly soon, this has little effect on total payments.

The next section discusses two forms of two-price programs that are built to insulate against different sources of uncertainty. Both adjust the price per dose in similar ways, high to low, however, the timing of these prices differs based on whether the program is insuring against a large number of doses per patient, in the patient-based program, or a large number of patients, in the treatment-based program.

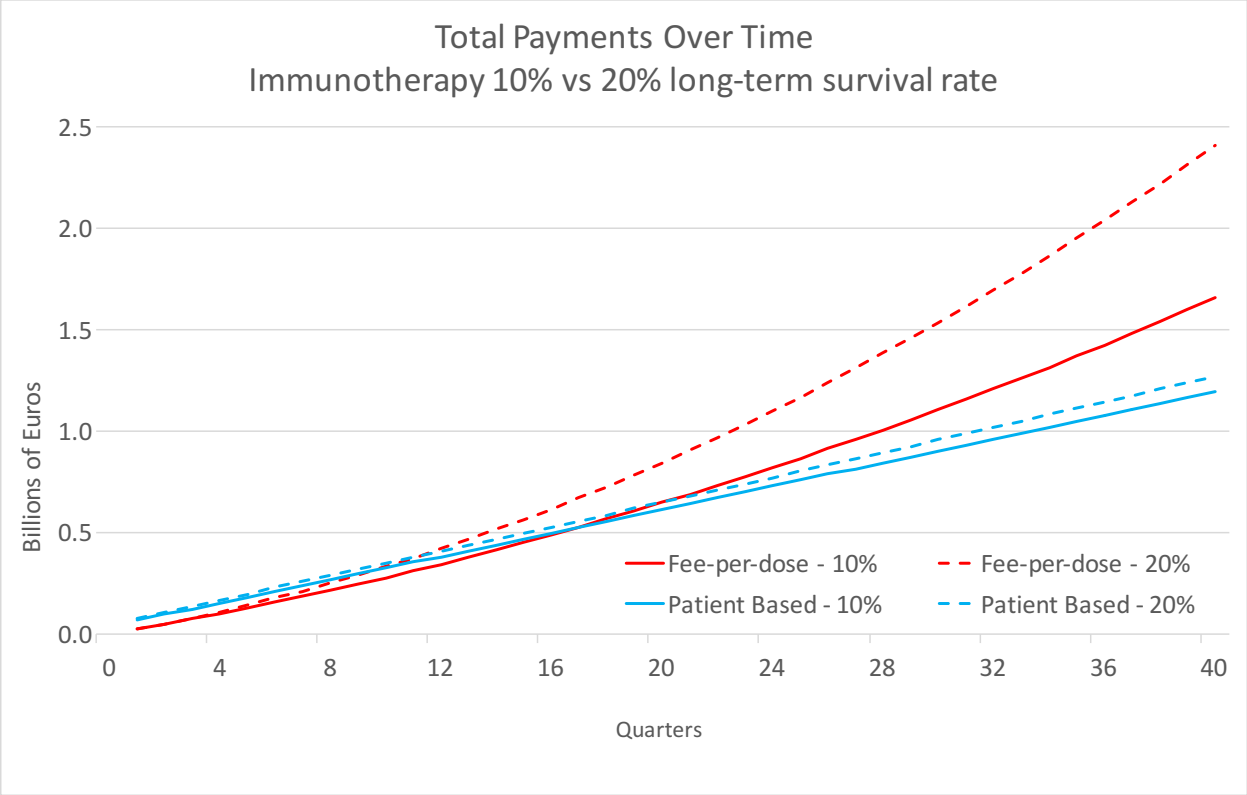
Patient-Based and Treatment-Based Programs

In the *patient-based program*, the payer pays a large initial price for the first doses *given to that patient* at some point after treatment starts, with a much smaller continuation price being paid for doses *to that patient* thereafter. A lag between the start of treatment and the start of reimbursement can be used as a check against over-prescription. The simplest implementation verifies that the treatment is appropriate to a patient's condition; reimbursement will not occur if treatment is halted, or if the patient dies, during the initial lag. More sophisticated effectiveness checks are possible during this initial period, but rely on having an effective and trusted monitoring system, such as the certified registries developed by AIFA—the Italian pharmaceutical regulator, health technology assessment (HTA) authority, and payer. [6, 22]

In *treatment-based programs*, the larger initial fee is paid on some number of initial doses covered by the payer, and the smaller continuation price is paid on all later doses. Once again, the high initial fee may be delayed, in this case to give the payer time to understand the effectiveness of the treatment in their covered population. Moreover, the payments themselves could be negotiated to depend on outcomes in that population. If this requires too long a delay, initial

payments could be made immediately, with claw-backs—or additional payments—indexed to pre-defined levels of effectiveness, as commonly done by AIFA. [23, 24]

There are three aspects to negotiate. Two are common to both programs: the high initial price and lower continuation price. In the patient-based program the lag between treatment start and payment of the initial price must also be negotiated; the analog in the treatment-based program is the number of doses that will be reimbursed at the higher initial price. These details will determine total payments, but the structure of the programs leads to fundamental differences in how uncertainties affect both the payer and pharmaceutical company. We explore these differences through examples. This leads to a general discussion of how to choose a reimbursement program.



Examples

Two examples serve to illustrate how different reimbursement programs insure payers and pharmaceutical companies against different types of uncertainties. These examples are from Italy, where access to AIFA registry data makes possible much more precise projections, although substantial uncertainty still remains. [22] Total expenditures for the U.S., assuming similar levels of disease incidence and treatment, would multiply total expenditures by about a factor of five. While neither of these assumptions is particularly plausible, total expenditures are not the object

of interest. Rather, the simulations focus on the percentage differences in expenditures between fee-per-dose and two-price payment programs, and this difference is largely robust to violations of these assumptions. For more on the assumptions that go into these simulations, and the consequences of their being violated for our results, see the Appendix.

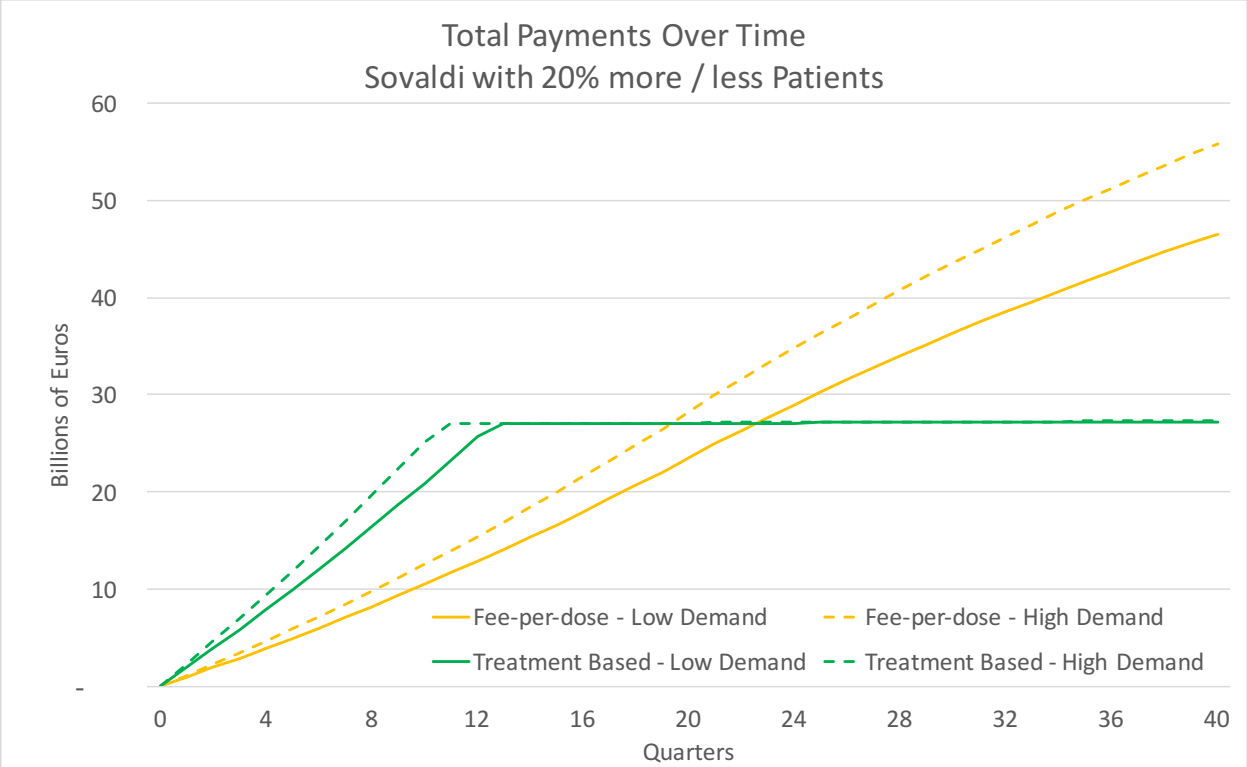
The first figure shows simulated total payments from fee-per-dose (using list prices) and a patient-based program for nivolumab + ipilimumab as a treatment for metastatic melanoma. [25] The critical uncertainty is the percentage of patients that will survive, and be treated, for a very long time. In the simulations, two different values are used: 20% represents the highest rate consistent with clinical trials, 10% is a more pessimistic rate. The fee-per-dose program is based on the average monthly price of $25,000. [11] The initial and continuation prices in the patient-based program are set so total payments in both programs are similar in year 5—the 20th quarter. These prices focus on the long-term effects of uncertainty under the different programs.

Two patterns in the figure are worth noting. First, under either assumption about the long-term-survival rate, in the fee-per-dose program total spending grows exponentially, whereas the total spending in the patient-based program is roughly linear. This is due to the fact that in the patient-based program, payments in a given year are almost completely determined by the flow of new patients, which is roughly constant across years. In contrast, under the fee-per-dose program, payments in a given year depend on the stock of existing patients, which is growing. Second, in the patient-based program misestimating the percent of long-term survivors has very little effect on cumulative spending (5%), whereas in the fee-per-dose program, a 10% error in the percentage of long-term survivors leads to a 45% difference in total payments over 10 years. Initial profits are higher, so the patient-based program also provides some insurance to the company.

Our second example uses the Hepatitis C treatment Sovaldi (sofosbuvir). [22, 26] Here, the critical uncertainty is in the number of patients. As new drug combinations are approved, the patient population may grow unexpectedly. [27, 28] The existence of a "cure" for chronic Hepatitis C may also increase testing for the disease, as well as risky behavior. [29] Thus, the second figure compares fee-per-dose and treatment-based programs for two projections of future patient populations. Both of these use current patient populations in Italy to project future demand. One takes this projection and lowers it by10%, and the other raises it by 10%.

The treatment-based program almost completely eliminates financial risk for both the payer and pharmaceutical company, as payments and profits are predictable and quickly realized. The

reduction in risk to the pharmaceutical company may allow the payer to bargain for lower prices. However, this may be offset by the fact that treatment-based programs eliminate the possibility of "blockbuster" financial performance. Yet, other risks exist for the payer that should lead to lower negotiated prices than in the patient-based program. If the treatment works less well than expected, there is little recourse for the payer through renegotiation. If a more effective treatment is introduced, the payer may stick with the existing treatment because of its much lower continuation price. Finally, it requires the payer to have access to a large amount of financing up front, although this may be mitigated by the pharmaceutical company agreeing to delayed payment.



Relationship with Other Pricing Programs

Pricing strategies other than fee-per-dose have been suggested and tried. Two of these, capitation pricing and value-based pricing are interesting sub-cases of two-price programs. However, the more general two-price formulation has several advantages.

Capitation pricing, also known as a patient-level drug license, ascribes a single price to treatment of a patient over a period of time, no matter how many doses are used. [30] This is a patient-level program with a single initial payment due on the first dose, and a continuation price of zero. The patient-based program improves on this, for many drugs, by delaying the start of the initial payment, and spreading it out over time. This reduces costs if a patient discontinues treatment due to non-response or death. Additionally, the low (rather than zero) continuation price covers the pharmaceutical company's costs if treatment is prolonged or intensive. For example, in some cases, Sovaldi needs to be administered for 24 weeks, but its contract with AIFA requires Gilead to provide the treatment for free after 12 weeks, leaving Gilead with financial risk. [31, 32]

Value-based pricing is a treatment-based program where the initial price is set according to the drug's real-world effectiveness, and there is no limit to the number of doses on which the initial price is paid. [11, 33] Performance-based pricing generally has a lag before the initial price is paid to allow for the assessment of effectiveness, which is also occurs in the patient-based program. The addition of a continuation price in the treatment-based program has several advantages. First, once the continuation price is reached, patient access can expand rapidly at very little cost to the payer. Second, this lower price would now form the basis for pricing of future drugs treating the same condition(s), likely leading to lower drug prices over the long term. [34]

These, and other creative reimbursement schemes, are often called Managed Entry Agreements (MEAs). Italy is a leader in using many types of MEAs, but these are all constrained by the information known at the time of the agreement. Costs and profits may vary substantially based on how far off projections are from realized outcomes. [24, 33, 35, 36, 37] Two-price programs, by contrast, are much better insulated from uncertainties and flaws in usage predictions.

Considerations when Choosing a Two-Price Reimbursement Program

If the key uncertainty is the number of doses-per-patient, a patient-based program should generally be chosen. If the key uncertainty is the number of patients, then a treatment-based program is better. However, patient-based programs can expose payers to more substantial financial liabilities, and are easier to implement. Treatment-based programs offer more insurance to both pharmaceutical companies and payers, but are trickier. As both payers and pharmaceutical companies familiarize themselves with these new programs, the more robust patient-based contracts seem like the right first step.

Negotiated terms will depend on too many factors to list and discuss here. Yet, some general principals are useful in designing two-price programs. The main considerations—and tools for dealing with them—are listed in the table.

Consideration / Concern	**Design Solution**
Quality of Treatment	-Higher continuation price
Cost of production of treatment	-Lower continuation price
Over-prescription and over-treatment	-Lower continuation price -Later initial payment in patient-based program -Fewer and higher initial payments in treatment-based payments
Large uncertainty about effectiveness of related compounds and / or for related conditions	-Patient-based program -Treatment-based program with quantity threshold proportional to treated population
Large uncertainty about effectiveness of treatment	-Delayed high-cost repayments contingent on measured performance

For both programs, setting the lower continuation price involves a trade-off. If that price is set too low, it may cause underinvestment in production and possible shortages. If that price is set too high, there is little incentive for the pharmaceutical company to take common-sense cost-cutting measures. Additionally, high continuation prices may create incentives for pharmaceutical companies to treat patients unlikely to benefit by encouraging off-label use. The latter risk is

particularly acute in the patient-based program, but can be mitigated through a longer delay before high reimbursement costs apply, or through evaluation of treatment effects with monitoring.

Other concerns are program-specific. Patient-based programs may expose the payer to significant financial uncertainty when there is little clarity about upcoming changes to the treatment landscape for a given condition. The patient-based program may end up being quite costly if the current treatment has a long effective life because replacement treatments do not come to fruition. In this case, a treatment-based program may be preferred by the payer.

In treatment-based programs, there is an incentive for the pharmaceutical company to incrementally change treatments to benefit from renewed high initial payments. For example, the drug Kalydeco was initially approved only for use on patients with cystic fibrosis caused by a specific genetic mutation, and later approved for an additional eight mutations. [38, 39] Had a treatment-based program been negotiated for the first indication, it would not account for the additional indications, and a second program would need to be negotiated. However, this can, and should, be anticipated and addressed, perhaps by the contract covering payments for any future (albeit likely unspecified) new indications for the treatment. If the pharmaceutical company refuses such a proposal, then it's a sign that they are in fact planning to seek such approval.

Treatment-based programs also may increase renegotiation by pharmaceutical companies, and limit the scope for renegotiation by payers. Once treatment is delivered at the low continuation price, pharmaceutical companies can renegotiate by claiming higher-than-anticipated costs of manufacturing. Conversely, payers cannot renegotiate for lower prices if effectiveness is lower than anticipated as they have paid most of the expected total amount.

While these concerns could potentially be mitigated, they would require payers to have different tools. One way to address potential renegotiation by pharmaceutical companies would be to include a contractual provision granting payers a license to produce (with the low price playing the role of a royalty) treatment in the event that the pharmaceutical company is not able to deliver at the agreed-upon price. Payments indexed on realized effectiveness, including potential clawbacks, could be included in the program. AIFA's monitoring infrastructure (AIFA registries) and success in clawing back reimbursements when treatments are less effective than anticipated shows this is feasible. [22, 24, 35, 37] However, if these concerns cannot be addressed, payers should prefer patient-based programs to treatment-based programs.

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Appendix 1: A Basic Calibration

This appendix tries to provide some basic guidance on how to negotiate a two-price program given some ideas about what a traditional (single-price) program might look like. That is, we assume that you know the expected number of patients, and the expected number of doses per patient (even if both are uncertain); and also have some idea about the single price per dose that is likely to be obtained through bargaining with a pharmaceutical company. Given these, how should one think about choosing a patient-based or treatment-based reimbursement program? Once the program is chosen, how should one negotiate the multiple prices in the program?

Step 1: What is the Central Uncertainty?

Before beginning, it is useful to note that the total cost of a drug using a single-price program is given by:

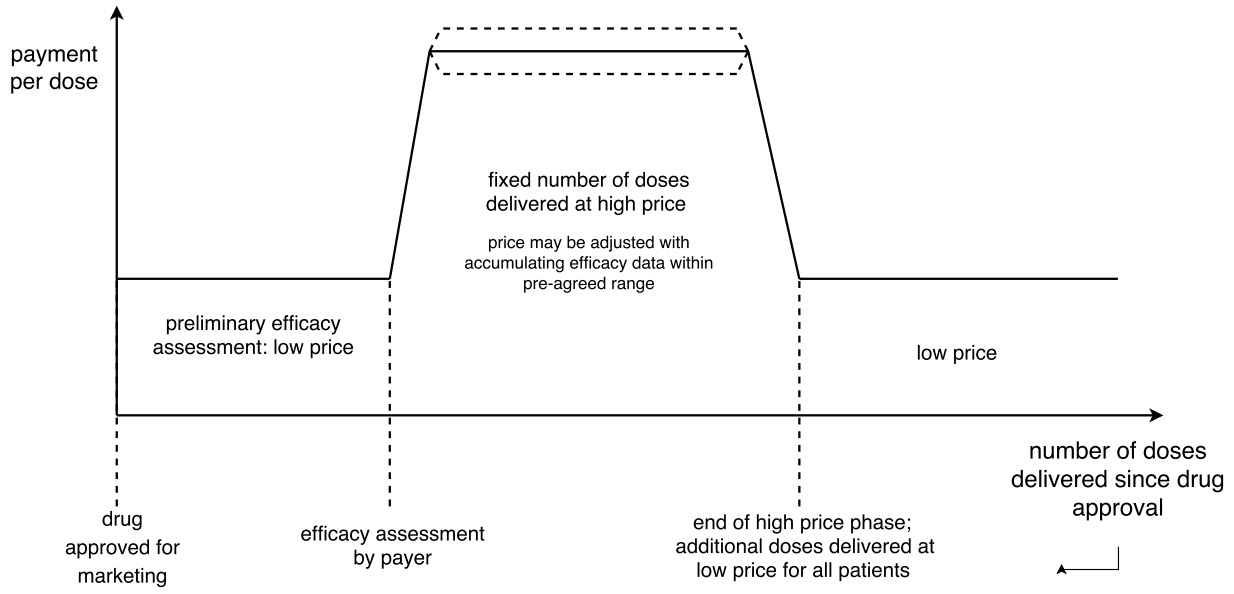
Total Cost = [Number of Patients x Number of Doses per Patient] x Price per Dose.

Note that we have already assumed you have expected values for all of these quantities. The two different types of programs are meant to deal with uncertainty in the first two quantities: if the most important source of uncertainty is the number of patients, choose the treatment-based program. If the most important source of uncertainty is the number of doses per patient, choose the patient-based program.

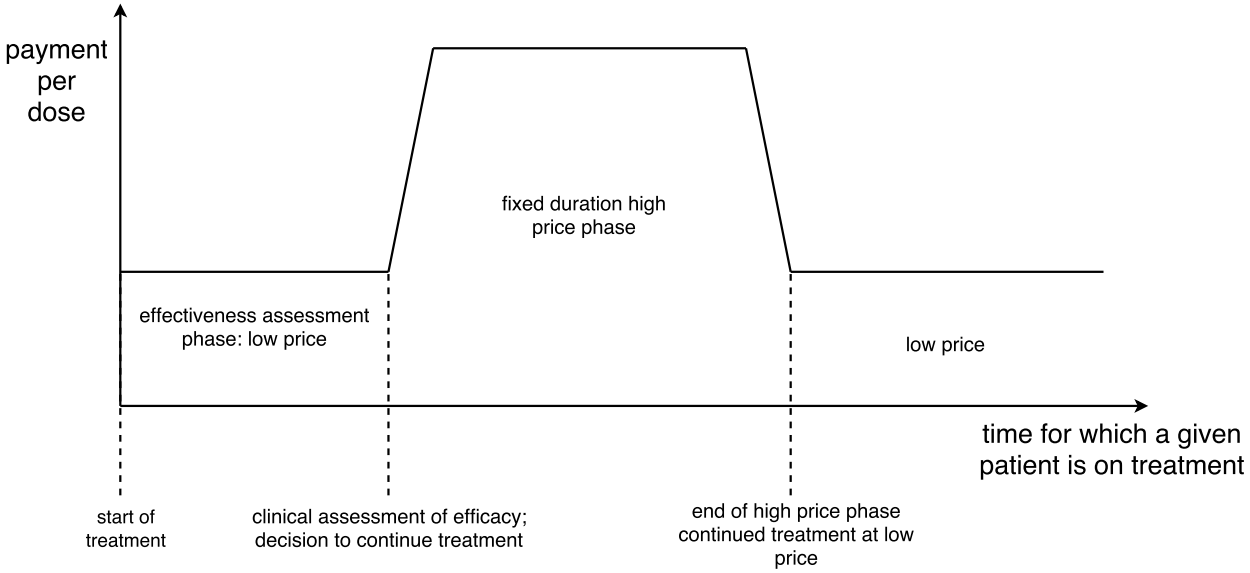
Step 2: Determine the Timing of the Program

Although the basic ideas are the same between the treatment-based and patient-based program, we illustrate them separately.

Treatment-based: The structure of the treatment-based program is shown below. The beginning of the high-price phase and the (second) low-price phase can be fixed based on the information available before approval. For example, in many cases, the initial low-price may not be necessary if the drug has proven efficacy in similar populations. The switch to the (second) low-price phase should be chosen so that under expected conditions the phase will end before the effective lifetime of the drug. Note that moving either of the "phase transitions" closer to the present is favorable to the pharmaceutical company, and may perhaps be translated into pricing benefits.



Patient-based: The structure of payments in the patient-based program is illustrated below. Note the general resemblance to the treatment-based program, with the big shift being that the x-axis is the number of doses to a single patient, rather than to the entire population.



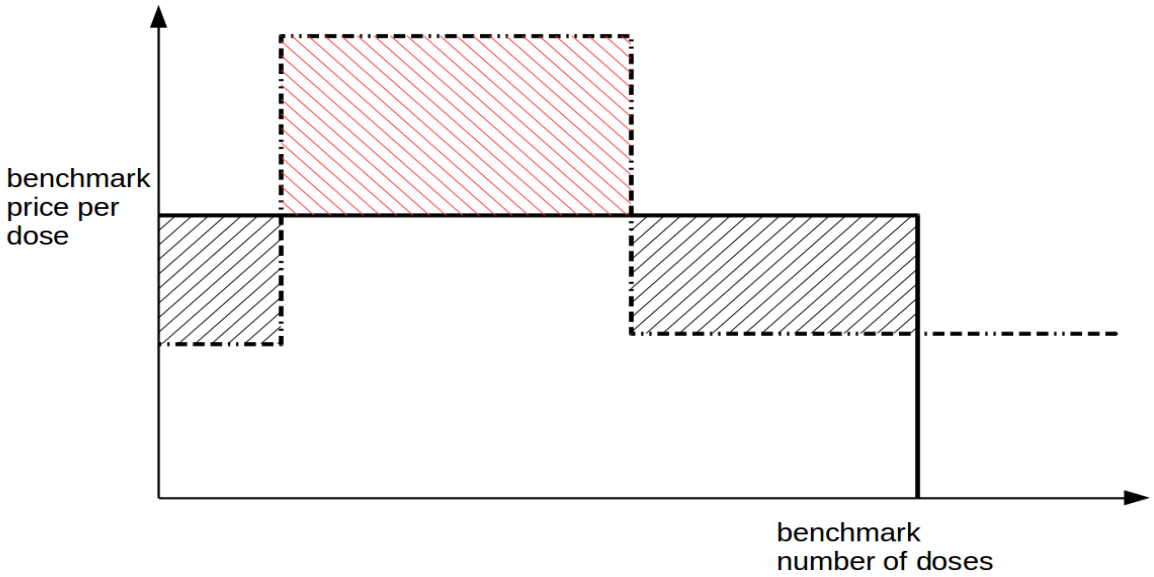
It is likely unwise to drop the initial low-price phase in the patient-based program, unlike in the treatment-based program. This is because there is considerable heterogeneity in individual patient responses (both in main effects and side effects), and for most medications there is little indication of how well a specific payment will respond to treatment. Moreover, it may be less

complicated to set this initial payment to zero for simplicity of administration—and there is no need for the first and second low price to be the same (despite the illustration!)

Step 3: Set Price Expectations

Once again, the basic ideas are the same for the treatment-based and patient-based program. Both involve having benchmark quantities (either the expected number of patients, or the expected number of doses per patient, respectively), and the benchmark price that the negotiator would expect from a single-priced program.

Treatment-based: The amount that would be spent in a single-price contract would be the expected number doses delivered (possibly discounted to a net present value) to patients (that is, the benchmark number of patients times the benchmark number of doses per patient) times the benchmark price per dose, as in the large rectangle below.

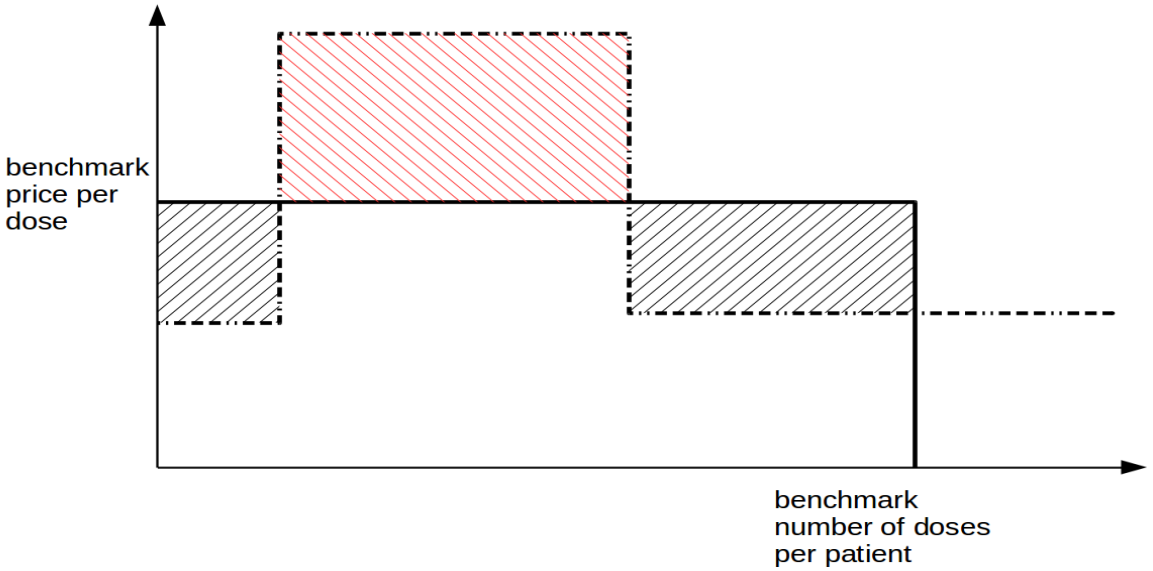


Overlaying the treatment-based program on this rectangle, one can see that there are two periods when payments in the treatment-based program are less than they would be in the single-price program, shown in the black-hatched rectangles. There is also one period when payments are higher, shown in the red-hatched rectangle. When the area of the two black-hatched rectangles equals that of the red-hatched rectangle, the expected payments under the treatment-based program is the same as the expected payments in the benchmark single-price program.

Note that there is a continuum of high-price and low-price pairs that will produce an equal spend under the treatment-based and single-price programs. Which one of these should be

chosen? The rule of thumb here is to set the low prices based on the amount of uncertainty there is. If there is great uncertainty about the population efficacy, the first low price should be set as low as possible, even as low as zero. For the second low price, the greater the uncertainty about the number of patients, the lower that price should be set, as this is the price that will be paid if there is an unexpected surge in patient numbers. However, for reasons explored in the paper, this price should never be set too low.

Patient-based: The diagram for the patient-based program is similar, and shown below.



The preceding discussion for the treatment-based program applies more or less as written, although the final paragraph requires some elaboration. In particular, because the uncertainty about patient-level efficacy will (almost) always be very high, this motivates the suggested zero initial price mentioned in the previous Step. However, following the same logic described in this Step in the treatment-based program above, the more uncertainty there is about the number of doses per patient, the lower the second low price, but it is still inadvisable to drive this price all the way towards zero.

Step 4: Negotiate

In addition to the considerations listed in the paper, it is important to keep in mind that the two-price program reduces uncertainty for the pharmaceutical company as well (especially in the case of the treatment-based program!) As such, it should be possible to negotiate prices so your expected spend is lower (perhaps considerably) under a two-price program.

Appendix 2: Details of Simulations

In order to focus on the issues addressed by two-price programs, we have made a number of assumptions. The purpose of this section is to spell out the assumptions made, and to discuss why changing those assumptions would not materially affect the results. The Excel spreadsheets used to produce these simulations are available from the authors upon request, and will allow the interested reader to change parameters to see the results for themselves.

In general, we have used real data from the Italian experience and published sources wherever possible. The assumptions that are made are done so to increase transparency of the mechanisms at work in our proposed payment programs.

Fee-per-dose Benchmark

As should be clear from the text the fee-per-dose benchmark we simulate assumes a single price for each dose purchased by a payer. The most common way this assumption is violated in practice is through the negotiation of price-volume discounts. However, if the price-volume discounts are based on the amount purchased in a particular time frame, for example, a year, in most cases this would perform just like a fee-per-dose program as we have modeled it, but the cost per dose would be replaced by the average cost per dose over the year. On the other hand, if the price-volume discount calculated those discounts over the entire length of time that the drug was being purchased by the payer, this would be very similar to a treatment-based program, except that the continuation price would be going down over time. Such price-volume discounts are, in our experience, exceedingly rare.

Patient-based Program

The simulated patient-based program is based on the treatment of metastatic melanoma with nivolumab + imipilumab. The pricing in the fee-per-dose program is based on the monthly list price of these two compounds of 20,000 €.

The number of patients is determined using very simple survival dynamics. Without treatment, patients die at a constant rate over quarters, so that all patients diagnosed at a given point in time are all dead by a specific point in time in the future. Thus, the survival dynamics depend only on a single parameter. For the purposes of this simulation, 50% of patients are

assumed to die each quarter so that the median survival time after diagnosis / progression is 3 months, and all patients have died in two quarters. More complicated survival dynamics would increase the number of parameters in the simulation, and introduce uncertainty associated with each of them, without materially affecting the results.

Survival once on the immunotherapy nivolumab + imipilumab is also modeled simply. Essentially, for most patients, the treatment is assumed to make no difference in the length of their survival after diagnosis / progression. However, for some minority of patients, the treatment is assumed to drastically increase their life expectancy—in the case of the simulation, all patients who respond in this way are assumed to survive until the end of the simulation. The major difference between the two scenarios considered in the simulation is that in one case the number that respond extremely positively to treatment is 10 and 20%.

The number of patients, and the percent of those patients that survive a very long time are based on the number of patients in the Italian system, and preliminary evidence from clinical studies, which last at most a year. The assumptions here would need to be drastically changed in response to two focal possible changes. The first would be new indications for the treatment, such as other cancers, or earlier stage cancers of the same type. The second would be bio-markers that predict more accurately which patients will respond extremely positively to treatment. The former would unambiguously increase the total number of patients. While this would drastically increase the cost of either the fee-per-dose or treatment-based program, it would keep the relative costs of the two programs the same. More accurate bio-markers would decrease the cost of the fee-per-dose program towards the cost of the patient-based program. Perfectly predictive biomarkers would make these two programs essentially the same (for properly calibrated prices).

As noted in the text, prices in the patient-based program are calibrated so that the total cost to the payer in the fifth year is approximately the same. This is done using an initial waiting period before initial payment in the patient-based program of 3 months (so that 50% of the patients that do not respond to treatment do not cost the payer anything), and an initial payment of 240,000 € (four times the list price of one-quarter of treatment), followed by a continuation payment of 2,000 €.

Treatment-based Program

The simulated treatment-based program is based on the Hepatitis C treatment Sovaldi (Sofosbuvir). We have focused only on the list price of taking this compound for 12 weeks, ignoring the fact that this drug is often combined with others, and the length of treatment is often as much as 24 weeks. As such, the fee-per-dose we use here is 135,000 € (per patient, per 12 weeks of treatment). Accurately assessing the treatment mix in a particular population would change the estimate of the fee-per-dose (per patient) price, but unless the pricing of these additional compounds were negotiated under the same treatment-based program as Sovaldi this would not change the cost savings (or additional costs over the short term) of our simulated treatment-based program. On the other hand, the fact that many patients are treated up to 24 weeks means that the potential savings of the treatment-based program may be significantly understated.

As described in the text, the prices in the treatment-based program are calibrated to deliver increased costs to the payer in the short term, and the same total cost by around year five. These numbers are thus implied by all the other numbers in our simulation. So if the price per patient is too high in the fee-per-dose formulation is too low or too high, so too will be the initial price in this simulation. For reference, the initial price of 270,000 € (double the list price used in the fee-per-dose program) to be paid on the first 100,000 patients. As such, using a more accurate mixture of treatment lengths would just require re-calibrating the prices in the treatment-based program by doubling the (more accurate, based on mix of length-of-treatment, and standard discounts) price per patient in the fee-per-dose program. The assumed continuation price of 1,000 € may be negotiated to be much lower based on the fact that Sovaldi is a small-molecule drug, and likely not all that costly to produce.

The baseline number of patients in the simulation are based on the Italian experience, with a number of assumptions about future patient trends. The first full year the treatment with Sovaldi was available was 2015. In the first half of 2016 the number of new patients grew by about 10%. We assume that this growth is constant across quarters, and will continue for 5 years, followed by a gradual decline in new patients due to reduced transmission and other factors. In order to give the range of possible costs in the simulation we modify this baseline number by both adding and subtracting 10% in each quarter. This allows us a reasonable range of mis-estimation of 20% of the patient population. Making this range wider would have two effects:

first the gap in total cost between the two scenarios in the fee-per-dose program would be widened; and second, the amount of time it would take for the treatment-based program to get to the very flat portion of the total cost curve would be widened.