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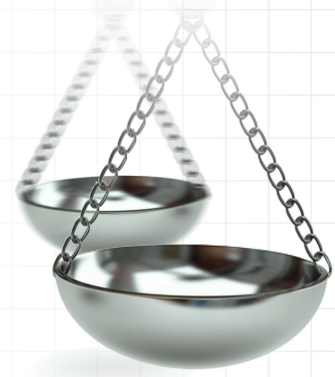

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The next generation of rare disease drug policy: ensuring both innovation and affordability

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Scientific advancements, new US FDA approval pathways and limited competition have contributed to rapid growth in the number of approved rare disease treatments in recent years. While the rising numbers of orphan drug approvals are a sign of success, the rapid growth in approved rare disease treatments has created concerns about the pricing of orphan drugs and their cumulative affordability to the health system. To support efforts to build a policy and practice infrastructure that drives innovation within a platform that is affordable to patients and the health system, this paper provides an analysis of potential risks as well as advantages of reform options related to drug development, pricing and coverage.

Tweetable abstract: New Institute for Clinical and Economic Review policy analysis evaluates potential risks and advantages of reforms of current policies related to orphan drug development, pricing and coverage.

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The USA defines a rare disease as a condition affecting fewer than 200,000 people in the country or one in which "*there is no reasonable expectation*" of recovering research and development costs. In recent decades, hundreds of new drugs – so-called orphan drugs – have been approved to treat these diseases, but there remains a substantial unmet need for new treatments for an estimated 7000 rare diseases affecting millions of Americans and people worldwide [1].

Given concerns about the inherent risk associated with drug development and the very small patient populations across which rare disease treatments can derive revenue, a variety of incentives have been introduced through the years to encourage manufacturers to develop drugs for rare diseases. The Orphan Drug Act of 1983 (ODA) heralded the dawn of these efforts by providing longer market exclusivity and tax credits for expenditures incurred in conducting clinical trials for orphan drugs [2]. Other policies and programs introduced later also support orphan drug development by offering fee waivers and research grants for orphan drug development [3,4].

There is little disagreement that the ODA and these additional benefits have contributed to boosting the number of products approved to treat rare diseases, with over 800 orphan drug indications approved between 1983 and 2019 [5]. This progress has also been spurred by advances in cell and gene therapies, among other scientific discoveries, which have revolutionized care for many rare conditions [6]. The patient community has contributed to this success and has demonstrated its ability to spur investment, inform research and influence policymakers at all levels. Today, many new biotech companies launch with a singular focus on developing treatments for patients with orphan conditions, a market landscape that would have been unimaginable to the sponsors of the ODA nearly 40 years ago.

This success should not obscure the fact of the substantial unmet need represented by the great majority of rare diseases for which there is still no licensed treatment available [7,8]. But the hope that more orphan drugs will be developed to address that need is now shadowed by a growing problem of affordability. In 2019, the average

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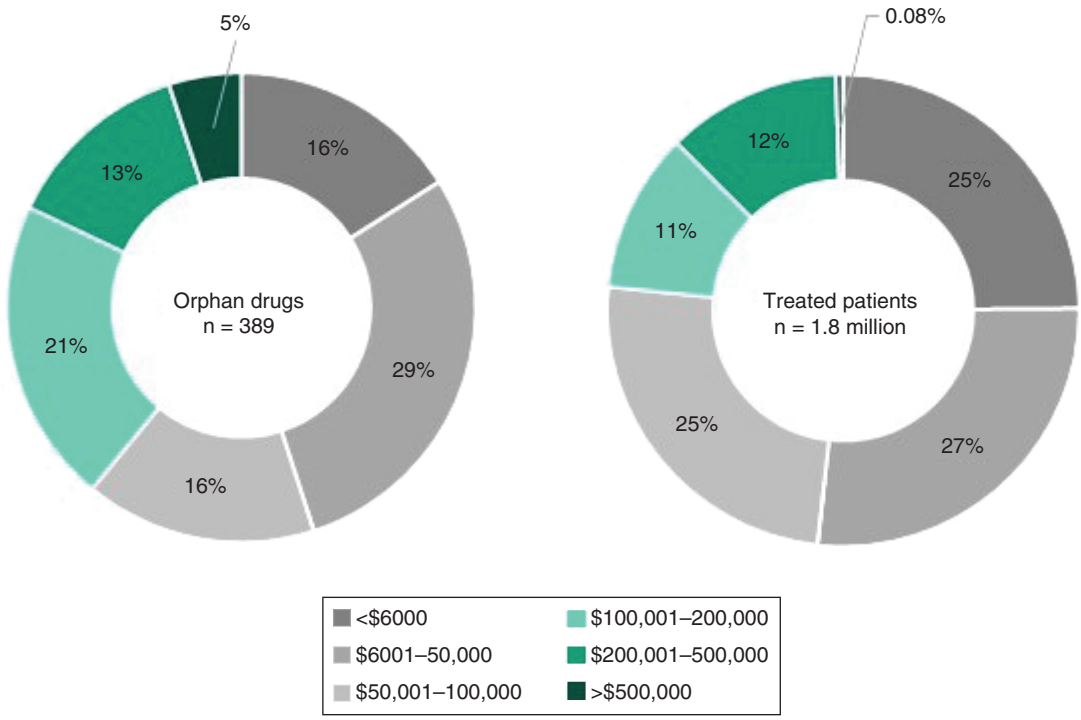

Figure 1. Orphan drugs and patients treated by drugs with an orphan indication in 2019 by annual drug cost bands. Data taken from [5].

annual cost of an orphan treatment per treated patient was US$32,000, with treatments ranging from US$6000 to $500,000 per year (Figure 1). Most orphan drugs have high list prices, with 39% of orphan drugs costing more than US$100,000 annually [5] and gene and cell therapies costing hundreds of thousands of dollars or more [9]. For a drug priced at US$100,000 per year, a treated patient population of only 10,000 individuals produces revenues of US$1 billion per year – an orphan 'blockbuster'.

Therefore, today, as the proportion of new US FDA approvals gaining orphan drug designation crests above 50% each year, some people no longer see the primary challenge related to orphan drugs as that of creating a viable business model [10]. They see a growing challenge in absorbing the cost of a growing wave of high-priced orphan drugs that may threaten sustainable insurance premium levels and throw up greater barriers to access for individual patients [11]. This affordability challenge is magnified by concerns regarding the quality of the evidence being generated to support FDA approval of orphan drugs. While high drug prices are a concern across the entire spectrum of therapies, orphan products are commonly approved with more limited evidence on relative safety and effectiveness due to their reliance on nonrandomized trials using short-term surrogate outcomes [12,13].

Premium pricing for orphan drugs has persisted despite other tailwinds that have helped facilitate orphan drug development, including scientific advances, new FDA approval pathways and limited competition. Scientific advances allow for more precise targeting of treatments to underlying disease mechanisms, producing higher success rates for orphan drug applications, lowering the risk to life science companies and investors [14]. Second, the creation of the accelerated approval pathway at the FDA has simplified evidence requirements for many rare disease products that qualify for this approval pathway. Finally, insufficient potential profits and anticipated market size may not attract generic competitors to enter the market [15]. Whether premium pricing at current levels is still required as an incentive to drive orphan drug development is hotly contested, but the data on orphan drug approvals suggest that the combination of scientific advances, regulatory flexibility, market conditions and premium pricing power has made rare disease treatments an attractive market for investors and life science companies.

And so, the landscape for orphan drugs includes signals that innovation is flourishing but not yet near the level to meet the unmet need; that the infrastructure of incentives created by the ODA has been critical in advancing innovation but now may be overshadowed by other factors driving investment and innovation toward rare diseases; and that the welcome success of a growing wave of orphan drugs has not led to lower prices and therefore is creating

financial strain that threatens to undermine access to these treatments and the affordability of health insurance for all patients. All participants in the healthcare system, including patients, innovators and payers, would agree that the goal should be to build a policy and practice infrastructure that drives innovation within a platform that is affordable to patients and the health system. Do we have the right balance in policies and practice to achieve this goal?

The purpose of this paper is to examine potential reforms to current policies and practices related to orphan drug development, pricing and coverage. As suggested above, any reform to these policies and practices carries the risk of tilting the ecosystem too far in one direction. This paper will explore potential risks as well as advantages of reform options. The goal is to provide policymakers and others with a deeper understanding of the options to ensure innovation's future ability to successfully address the needs of patients and families with rare diseases. That success will require new insights and new action to make innovation and affordability inseparable outcomes of our health system.

Methods

To inform this work, the authors performed a literature review focusing on the US policy landscape surrounding rare and ultra-rare disease drugs. They conducted 13 expert interviews with representatives from patient community organizations, large and small pharmaceutical manufacturers, investors, health plans and pharmacy benefit managers.

From this background work, the authors developed a set of potential policy reforms reflecting different themes and challenges discovered throughout their research. These potential policy reforms were the basis of a formal discussion during a 2-day policy summit in December 2021 with representatives from 29 payers, life science companies and patient groups. These stakeholders provided feedback on the policy options, which informed the final report.

Analysis of potential policy reforms

When considering policy proposals that address rare disease products, there are trade-offs between measures taken to improve affordability and innovators' incentives for new drug development. Therefore, in presenting an analysis of potential policy reforms, this paper seeks to convey that any potential policy reform carries both potential benefits and potential risks. Given the current stresses in the system and the concerns of many stakeholders about the potential for even greater problems in the future, the authors believe that policymakers should consider reforms aimed at striking a more sustainable balance between the incentives and structures that favor orphan drugs and the need of the health system for sustainable affordability.

Encouraging ultra-rare drug development

While the ODA and other factors have resulted in tremendous growth in rare disease products [10], payers, manufacturers and investors alike believe that new incentives and business models may still be needed to support the development of treatments for ultra-rare diseases. Many experts believe that very small disease areas may never be commercially viable targets for private pharmaceutical companies without new, significant incentives or development pathways [16].

Policy option: establish a definition of ultra-rare disorders

To target research, development and commercialization of drugs to treat ultra-rare conditions requires agreement on a definition distinguishing ultra-rare disorders from other rare diseases. One reasonable threshold, following European approaches, would be to identify as ultra-rare those conditions with fewer than 10,000 patients in the USA. Most stakeholders agree that even with high prices, products for patient populations this small are very hard to commercialize [17]. Some observers have argued that population standards should consider not just the USA but the global patient population in order not to overapply special incentives where they are not needed.

This research found that patient advocates for rare conditions have not favored the idea of separately identifying a narrower ultra-rare group. They argue that even if ultra-rare conditions receive a boost to support innovation, such a separation over time would give policymakers too much leeway to decrease incentives that are still vital for future innovation across the broader range of orphan conditions. If such a distinction is to be drawn, however, advocates underscore the importance of considering not only absolute patient numbers but also patient-level quality-of-life indicators, such as disease severity, level of disability and premature mortality. They argue that these factors should

also be considered if a subset of orphan conditions is to be carved out and given special incentives. Policymakers, however, would need to weigh the potential advantages of including additional, less objective criteria, with a subjective algorithm for designating which conditions should be eligible for additional incentives.

Policy option: increase incentives to develop treatments for ultra-rare disorders

Unless development of ultra-rare treatments is taken over by government-directed programs, enhanced financial incentives would be needed to stimulate more research and development of these treatments. One option is to increase ODA tax credits or other subsidies specifically for products treating ultra-rare disorders. Such a change would explicitly prioritize ultra-rare diseases as requiring more incentives than products for other rare conditions, though some stakeholders worry this could create too strong an incentive to move resources toward conditions that impact fewer people. Regardless, changes to the tax credits may be insufficient to overcome the market challenges faced by ultra-orphan drugs and enhancements to the tax credit may not be immediately useful for early-stage companies because of the structure of a tax credit.

Another, more direct approach to supporting the development of ultra-rare drugs would be to expand direct federal funding for and involvement in ultra-rare drug research and development. One option would be to establish a new federal authority to conduct critical research and development for ultra-rare conditions, akin to what the Defense Advanced Research Projects Agency does for technology and military innovation. The Defense Advanced Research Projects Agency does not have its own laboratories or research facilities, instead directing promising research pathways through grant making and partnerships with scientists. In a similar model, the Bespoke Gene Therapy Consortium is an example of a public-private partnership among the NIH, FDA, industry and nonprofit partners that seeks to foster development of gene therapies by developing tools to streamline the development process [18]. Operation Warp Speed, which accelerated the COVID-19 vaccine development, is another potential model. In that example, the federal government directly subsidized research and development costs, contracted to support manufacturing capacity, purchased necessary ingredients and supplies and provided advance-purchase commitments to underwrite market risk [19]. The federal government could also encourage ultra-rare drug development through increasing NIH funding for basic research in ultra-rare conditions, creating a loan or other system to offset manufacturing expenses, establishing subsidies to underwrite commercialization costs and guaranteeing market access via pre-established coverage and reimbursement expectations in Medicare and Medicaid.

Looking abroad, another option for creating special arrangements for ultra-orphan drugs has been to create special assessment pathways and reimbursement mechanisms at the national level. For example, NICE in the UK has a separate pathway for assessment of 'Highly Specialized Technologies' that in principle is willing to accept much higher cost–effectiveness thresholds for treatments for ultra-rare conditions [20]. Congress could consider creating a similar national coverage structure for ultra-rare treatments through the Centers for Medicare & Medicaid Services that would leverage the existing coverage with evidence development mechanism to accelerate access to these treatments with a corresponding evidence development requirement. This mechanism could also be linked with a requirement for value-based pricing (see below), at least during the evidence generation phase of coverage. If this approach, with or without a pricing component, were limited expressly to treatments for ultra-rare conditions, the resulting improvement in access might spur additional interest in developing these treatments while creating manageable increases in spending.

Policy option: use value-based pricing & reimbursement for ultra-rare disorders

Once a product to treat an ultra-rare condition is brought to market, whether developed by industry or government, its price determines its cost–effectiveness. If the product is developed by government, pricing can be done by administrative fiat. If it is developed or codeveloped by industry, the product's price, shaped as described above, underpins the economic incentives for innovation. As such, prices paid by payers for products that treat ultra-rare conditions, especially those with the lowest prevalence, may need to exceed typical thresholds used in cost–effectiveness assessments.

Instead of relying on traditional cost–effectiveness assessments, prices for ultra-rare products could be developed based on a different pricing paradigm, according to which the rates of return for investments in developing orphan drugs should not be greater than the industry average [21]. In this approach, a calculation would be done of the maximum allowable price that society should be willing to pay. Such a change would represent a major departure from current US reimbursement models in which the government does not set prices. A downside of this approach is that it could reward inefficient research and development programs while under incentivizing the kinds of risk

taking needed on early assets that promise substantial clinical gains. Nonetheless, a rate-of-return approach could be twinned with cost–effectiveness, with the greater price calculated through either paradigm the one that would be accepted by payers. Ultimately, by managing the balance between innovation and affordability more explicitly and consistently, a reasonable rate-of-return methodology could generate pricing recommendations that would do a better job of balancing the need for greater incentives for ultra-rare treatments within a more predictable and affordable framework.

Limiting incentives for partial orphans

Many orphan products also secure FDA approval for nonorphan indications, products sometimes referred to as 'partial orphans'. As of 2018, 23% of approved orphan drugs also had non-orphan indications [22]. While ODA exclusivity benefits apply only to orphan indications, once a product receives approval for an expanded indication, manufacturers almost always maintain the initial high 'orphan-level' pricing while expanding their product sales and revenue [23]. Thus, it is perhaps not surprising that partial orphans are particularly common among drugs with the highest overall revenue. In 2018, five of the six top-selling drugs in the USA were partial orphan drugs, and a recent Office of Inspector General report found that a majority of the highest-expenditure drugs in Medicare have been granted at least one orphan designation [24,25]. As one extreme example, pegfilgrastim (Neulasta®) had the fourth highest spend among partial orphan drugs currently on the market, but only 0.6% of this amount was for its orphan indication of acute radiation syndrome [24].

There are clear benefits for manufacturers in testing the viability of promising pharmaceutical agents first within narrowly targeted patient populations and if found successful, to expand development more broadly to additional indications. As such, it is neither surprising nor problematic that some products launch as an orphan drug before gaining nonorphan indications. However, the evident commercial success of partial orphans, in part derived from their sustained 'orphan pricing' as patient populations expand, suggests that ongoing federal research and development tax credits and waived user fees may not be necessary or appropriate. Specific policy options for modulating orphan drug benefits for partial orphans are described below.

Policy option: establish a maximum revenue threshold to be eligible for ODA incentives

One potential policy reform is to limit or remove orphan drug incentives once a product is approved for nonorphan indications or once it exceeds a given threshold of revenue (e.g., US$200 million). Such a change would tend to focus orphan drug incentives on products that need it most – those treating very small patient populations and/or those for which competition has limited their market share. The potential risk in this approach is that a reduction in ODA benefits tied to revenue might discourage companies from taking the risk of conducting additional clinical trials to assess the effectiveness of a product for a broader population, thus limiting the ultimate clinical benefit to the broader population of some treatments that start out as orphan drugs.

Policy option: assess FDA standards for defining distinct diseases

Another option to rebalance incentives for partial orphan drugs would be to reassess and sharpen the FDA's definition of distinct diseases. Increased use of new molecular biomarkers to diagnose and treat conditions is resulting in narrower definitions of distinct diseases and thus some heterogeneous conditions that did not qualify as rare are now being subdivided into multiple 'new' rare diseases. As this trend continues, the FDA could change its approach to defining distinct diseases to favor the preservation of broader indications. A broader definition would reduce the incentive for manufacturers to start their development program targeting a very narrow population, potentially blunting the trend of leveraging early orphan pricing into larger populations over time. As with any narrowing or reduction of ODA benefits, however, this policy option might increase uncertainty regarding the scientific and commercial success of some emerging treatments, producing less investment and innovation in new treatments for rare diseases.

Policy option: eliminate 340B exclusions for partial orphans

Policymakers could restrict the 340B exemption for Affordable Care Act-expanded covered entities to apply to only the utilization of an orphan indication, rather than all indications the partial orphan is designated for, which would dramatically reduce the financial incentives for partial orphan products [24]. This change would likely require legislation to surmount the US District Court decision that struck down the Health Resources and Services Administration's interpretive rule. However, as with all potential reductions in ODA benefits, this policy change

harbors some risk of driving investment and innovation away from certain rare disease areas and it would be challenging to implement, as it would require participating providers to document, monitor and report their 340B drug utilization by indication. While such reporting is conceptually possible in the context of well-integrated electronic medical records and data systems, in practice it could create a significant operational burden on 340B entities.

Strengthen evidence generation

There are many ways in which orphan drugs face distinctive challenges in generating the same type of body of evidence as drugs for more common conditions. Orphan drugs often lack regulatory precedent, have small trial populations [13] and/or suffer from limited understanding of the natural history associated with the disease. These factors can combine to create special challenges in developing feasible clinical trial end points that capture outcomes that matter to patients.

Policy option: fund patient registry development

Federal investment is needed to spur the development of more robust systems for capturing and analyzing observational data to meet the needs of patients, clinicians and payers. These data systems should be developed so that they can capture patient-reported outcomes reflecting broader patient and family effects of treatment. Federal funding, along with help from disease and patient groups, can accelerate efforts to improve evidence generation by sponsoring rare condition registries. Broadening rules on data ownership and using federally funded program claims data (e.g., Medicare and Medicaid) to augment registry data that could further enhance these resources. The federal government should consider additional strategies to expand registry development for rare conditions, including supporting their development by patient and disease groups and by requiring registry participation by entities delivering services to Medicare or Medicaid patients with the associated rare condition.

Reducing prices for rare disease products

Increased spending on orphan drugs has paralleled the growth in orphan drug development. Spending for orphan indications increased from 2% of invoice spending on drugs in 1992 to 11% in 2019 [5]. An additional 16% of drug spending was on non-orphan indications of drugs that also had orphan indications [5]. Such spending increases are driven by increases in the volume of orphan drugs and because these products have higher prices. In 2017, the average annual cost of orphan drugs at launch was 25-times higher than the annual cost of treatment for nonorphan drugs [26]. Another analysis found that among the top 100 drugs by US sales, the average cost of treatment for orphan drugs was 4.5-times that of nonorphan drugs (US$150,854 vs $33,654 per year), a difference of US$117,200 on average [27].

In the absence of effective and affordable mechanisms to manage spending for extremely high-cost, low-utilization products, some plan sponsors have resorted to the extreme of stripping out cell and gene therapies entirely from their health benefits [28]. Health plan and pharmacy benefit manager executives interviewed for this report indicated that they experience regular and growing pressure from self-insured employers to exclude coverage for these products and anticipate that this trend will only increase as the numbers of these treatments add to the actuarial impact of pharmaceutical coverage.

Policy option: expand outcomes-based contracts

Outcomes-based contracts make some or all of the payment for a treatment contingent on the degree of patient benefit [29]. Such a model could take several forms, with sliding scale bonuses or refunds depending on outcomes [30]. These contracts require manufacturers and payers to agree on a set of measurable outcomes and to track those outcomes to adjudicate the contract. Experience has proven that this effort to track and adjudicate outcomes can be administratively burdensome and expensive to negotiate and implement. Nonetheless, payers are attracted by the general principle of modulating payment (and, indirectly, pricing) by linking it to outcomes achieved in real-world use. This approach has the benefit of appearing to address the interlocked concerns about the pricing of orphan drugs with those regarding the uncertainty of the evidence on their effectiveness.

One potential policy reform option to leverage outcomes-cased contracts would be to require this kind of contract to be applied for orphan drugs (particularly those approved through the accelerated approval pathway) in exchange for insurance coverage. Many gene and cell therapies are already launching with outcomes-based contracts negotiated with certain private payers [31]. However, many payers are skeptical that they have the negotiating leverage

to get manufacturers to agree to outcomes-based contracts yielding meaningful financial savings, especially after considering the high administrative costs of negotiating and adjudicating these contracts. Historically, Medicaid best-price rules have limited the magnitude of price concessions in commercial outcomes-based contracts, since contracts that offered outcomes-based prices lower than Medicaid best price would trigger higher rebates across all Medicaid utilization. Recent regulations modified the best-price rules to allow more outcomes-based contracts across payers, but the impact of these changes remains uncertain [32].

Manufacturers and payers alike agree that outcomes-based contracts, as currently designed, are unlikely to dramatically reduce overall spending or increase affordability for orphan drugs [32]. However, one option for policymakers is to create a new process through which contracts can be negotiated at a national scale. Specifically, Medicare could create a demonstration program in which coverage for certain orphan products, such as cell and gene therapies, could be conditioned on negotiation of an outcomes-based contract. This program could include a formal pricing function in which Medicare could set a value-based price and, in conjunction with the manufacturer and other stakeholders, select end points and the timing and mechanism of linking rebates from the manufacturer back to the Centers for Medicare & Medicaid Services when the drug does not perform up to expectations. This program could also serve as a model for private payers. Some manufacturers might welcome the opportunity to negotiate a standard outcomes-based contract applied consistently across all payers. This approach might solve many of the barriers to the rapid uptake of cell and gene therapies that have plagued the launch of the first generation of these treatments. However, many manufacturers and stakeholders are likely to view any centralized process that includes some regulation of price as a slippery slope to broader application of federal price controls that would cast a pall over investment and innovation.

Policy option: adopt volume-based contracts

Volume-based contracts are another approach that could support rare product commercialization by guaranteeing coverage, promoting patient and provider education, assuring equitable access and utilization and simplifying contracting [33]. While volume-based contracts have historically been used by the government to purchase large volumes of drugs (e.g., vaccines), a similar model could be employed in the orphan drug space. Achieving the necessary product volumes for rare conditions at an affordable price requires a single-purchaser model. Under this model, the federal government or a consortium of private payers could directly negotiate to purchase enough orphan product volume to cover all eligible patients with a given rare condition. The contract would enable the government or private consortium to set a price unique to the orphan indication, distinct from the (lower) price for the product for nonorphan indications. Manufacturers would benefit from a single contract, improved patient access and predictable utilization.

Volume-based contracts could also be structured to ensure that product prices fall as utilization expands. For instance, the volume-based contract could establish a graduated pricing arrangement tied to the total amount of product utilization. When products launch for small patient populations, they are guaranteed a premium price. As utilization expands (due to uptake, off-label use or label expansions), rebates would increase and the net price of the drug would fall. Such a proposal would likely appeal to payers and could have the support of patient groups, if it encouraged broader access and utilization. However, manufacturers would likely be concerned about granting power to another entity or agency to set long-term prices, and they would want to ensure long-term profit growth even as prices decline.

Policy option: consider indication-based pricing

High prices for drugs that are first approved with an orphan indication usually stay high, even after additional, broader indications are approved [24]. If indication-based pricing could be effectively implemented, it would enable payers to negotiate higher prices for rare indications and lower prices for broader indications or those for which the product demonstrates less clinical value [34]. Independent value assessment entities could help establish a value-based price for a given rare condition and indication, based on the clinical benefit and strength of the evidence by disease area. While indication-based pricing would help expand access, one potential risk is that this pricing flexibility would allow manufacturers to increase prices for high-value indications, which could increase cost sharing for rare disease patients [35].

Unfortunately, operationalizing indication-based pricing has been extremely challenging for payers in the USA, given the current pharmaceutical supply chain and rebate model [36]. Some experts have even warned that indication-

based pricing could lead to unintended consequences such as higher prices for patients with rare diseases, higher overall spending and higher manufacturer profits [35].

Pursue value-based pricing

As noted earlier in regard to several policy options, value-based price regulation could be a complement to other policies seeking to realign incentives and improve affordability. There are numerous mechanisms available, including the use of international reference pricing, or pricing based on cost–effectiveness thresholds and algorithms suggested by value assessment by groups such as the Institute for Clinical and Economic Review (ICER) [37]. One benefit of this approach is that the value-based price-setting methodology might shift over time as additional evidence is generated. Further, value-based price setting creates incentives for investment in evidence development to demonstrate the clinical benefits of emerging treatments and provides handsome market rewards for products bringing significant added benefits to patients while scaling those rewards down for drugs that do little to improve patient outcomes.

In adopting a value-based price-setting mechanism for orphan products, policymakers must consider whether products that treat rare and ultra-rare conditions should be afforded different standards for cost–effectiveness. ICER addressed this question as part of its consideration of adapted assessment methods for treatments for ultra-rare disorders [17]. While the custom of accepting higher prices for ultra-rare disease products suggests a societal willingness to pay more for these products, ICER concluded that the logic and ethics of opportunity costs suggested that cost–effectiveness thresholds should not shift systematically solely on the basis of rarity and that such shifts threaten the goals of health equity. However, absent a comprehensive approach to encourage affordable pricing for rare diseases while encouraging investment in ultra-rare treatments, ICER could consider adjusting its cost–effectiveness thresholds (or granting higher weights to health gains for patients with ultra-rare disorders) to achieve the policy aim.

As with any policy that would lead to lower prices for some orphan products, value-based pricing mechanisms may result in pushing prices too low to incentivize investment in areas in which success is less certain, or in which the clinical gains from treatment would be relatively small. Some would argue that progress in the treatment of orphan diseases often seems to come in small steps and that prices generated by value-based mechanisms would not be adequate to keep the field moving forward. The contrasting argument is that patient populations between 10,000 and 200,000 appear large enough to generate sufficient revenue to keep investments and risk taking at robust levels. For example, a product that treated only 10,000 patients at a price of US$100,000 per year (22% of treated patients today receive an orphan drug that costs US$100,000 or more [5]) would generate an annual revenue stream of US$1 billion for the manufacturer. Nonetheless, judging the impact of value-based prices on the broad range of orphan drug development remains a hypothetical exercise, with the potential benefits and negative consequences frequently debated.

Create a national treatment benefit for rare conditions

Insurance structures depend on the presence of shared risk pools large enough that diseases are distributed relatively evenly across the risk pools. For common conditions, with reasonably modest costs, risk pools can be small, down to the level of the individual self-insured employer and its employees. But for rare and ultra-rare conditions with extremely high costs, risk pools need to be very large – otherwise, the individual employer or small group of plan sponsors might not be able to absorb the unexpected cost shock of an unanticipated number of patients with rare and expensive conditions.

Many national health plans are now trying to create insurance products to manage the extreme risk of unanticipated high-cost orphan drug treatments. Some federal policymakers have supported this approach [38]. One example of these efforts is Embarc Benefit Protection, offered by Cigna. The program carves out coverage for cell and gene therapies into a set per-member, per-month premium for employers and other plan sponsors who join the network. This premium structure protects the individual employer from the financial burden of an unanticipated high-cost therapy while allowing individual patients to access therapies without any out-of-pocket payment [39].

Although the commercial experience with these carve-out programs is limited, policymakers may wish to consider launching one at even larger scale at the national level. A new national benefit for cell and gene therapies for orphan diseases would create a single national risk pool for all identified rare conditions. Such a program would carve out payment for orphan products generally, or cell and gene therapies specifically, from other public or private coverage. Carve-outs and national risk pools have been proposed in several forms by some policymaking bodies, including

the Medicaid and CHIP Payment and Access Commission [40]. Others have proposed carving these products out of Medicare's hospital payment system to ensure adequate reimbursement [41].

A carve-out could include a single program (e.g., Medicaid) or could aggregate multiple public or private purchasers via optional or mandatory participation. In its most expansive form, a carve-out program would constitute a new federal entitlement for all Americans. While more limited carve-outs would be more politically feasible in the near term, fragmenting a diffuse risk pool could create unintended consequences that result in some payers seeking to deny coverage for these products in order to drive coverage into the carve-out.

A standardized national benefit for rare disease products generally, or cell and gene therapies specifically, could create uniform coverage and risk-pooling arrangements across the patient population, giving payers the opportunity to compete on providing patients with fair and equitable access to products and appropriate care and home support services. Pricing could be based on an outcomes-based contract or a value-based pricing arrangement, as described above. Such a proposal would be a significant change to current insurance coverage that would have widespread effects on stakeholders.

Conclusion

Since its passage, the ODA and accompanying scientific advancements have been successful at increasing the number of treatments available for patients with rare diseases, but tremendous unmet need remains. As a society, we must prioritize ongoing innovation and drug development for rare diseases – particularly those with no available treatments today. Treatments for ultra-rare conditions have been particularly elusive, as current market dynamics make it challenging for manufacturers to bring these products to market. Progress will require new incentives and partnership approaches to stimulate investment in drug development for ultra-rare conditions.

At the same time, there are widespread concerns about perceived weakening of evidence standards for orphan drug regulatory approval and the long-term sustainability of orphan drug pricing as the number of orphan drugs continues to increase. Orphan products launch at persistently high prices that are neither scaled to clinical benefit at launch nor decreased when additional indications are obtained. To ensure that patients enjoy broad access to future innovation, policymakers and healthcare industry leaders must consider solutions to focus incentives for innovation and improve the affordability of rare disease treatments.

This paper presents an analysis of the potential benefits and risks of a range of policy reforms that would improve evidence generation, target increased incentives to drugs for ultra-rare conditions and regulate orphan drug pricing directly or indirectly in a way that would improve affordability without undermining future investment and innovation. For those stakeholders and policymakers who see the current market ecosystem as functioning perfectly, no policy reform is likely to appear desirable. But for policymakers more broadly, the authors have presented an analysis of potential policy reforms that would create a new landscape for orphan drug development, coverage, pricing and payment. Policymakers and stakeholders will need to consider carefully whether these policy reforms would be able to retain the special incentives needed to ensure continued investment in orphan drugs while creating a better balance between the joint goals of broad innovation and affordability. Views will differ; however, one thing is certain: continued innovation will only prove sustainable and helpful to patients if the costs of the overall effort of innovation can be better managed, both for individual patients and for health systems and society.

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Executive summary

- The USA defines a rare disease as a condition affecting fewer than 200,000 people in the country or one in which "*there is no reasonable expectation*" of recovering research and development costs. In recent decades, scientific advancements, new US FDA approval pathways and limited competition have contributed to a rapid growth in the number of approved rare disease treatments but there remains a substantial unmet need for new treatments for an estimated 7000 rare diseases affecting millions of people worldwide.
- While the rising numbers of orphan drug approvals are a sign of success, high orphan drug prices and their cumulative impact on health budgets have created concern about the long-term sustainability of the current model of orphan drug development and pricing.
- All participants in the healthcare system, including patients, innovators and payers, would agree that the goal should be to build a policy and practice infrastructure that drives innovation within a platform that is affordable to patients and the health system. Do we have the right balance in policies and practice to achieve this goal?
- This paper examines the risks and advantages of a menu of potential reforms to current policies and practices related to orphan drug development, pricing and coverage.
- These potential policy reforms include establishing a narrower definition of ultra-rare disorders and targeting incentives to develop treatments for these disorders; using value-based pricing and reimbursement for orphan drugs; establishing a maximum revenue threshold to be eligible for orphan drug tax incentives; assessing FDA standards for defining distinct diseases to reduce unnecessary subdivisions into smaller populations; eliminating 340B exclusions for drugs with mixed orphan and nonorphan indications; funding patient registry development to support strengthened evidence standards; expanding the use of outcomes-based contracts; adopting volume-based contracts; considering indication-based pricing; and creating a separate national treatment benefit for rare conditions.
- For those stakeholders and policymakers who see the current market ecosystem as functioning perfectly, no policy reform is likely to appear desirable. But for policymakers more broadly, this paper presents an analysis of potential policy reforms that would create a new landscape for orphan drug development, coverage, pricing and payment.
- Views will differ; however, one thing is certain: continued innovation will only prove sustainable and helpful to patients if the costs of the overall effort of innovation can be better managed, both for individual patients and for health systems and society.

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