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PERSPECTIVE

The economics of moonshots: Value in rare disease drug development

The authors review the literature surrounding the economics of rare disease drug development and access before advancing the case for novel approaches to funding treatments. To fund the next stage of rare disease drugs, which will likely center on gene therapies and molecular medicine, they discuss value frameworks as well as patient-led models of finance, and how these may fit into the existing frameworks in the US to incentivize rare disease drug development and access.

INTRODUCTION

"Rare Diseases", sometimes called "Orphan Diseases", are those with low prevalence; a systematic review comparing definitions of Rare Disease found the prevalence definition averages around one case per 1700 people, although a common US definition often cites fewer than 200,000 people must be affected by a disease for it to be considered rare.[1] Despite low prevalence of each disease fitting this definition, about 1 in 10 Americans, or 30 million, are thought to have been diagnosed with a rare disease, compared to the overall prevalence of much more common diagnoses such as diabetes which affects 10.5% of the US population. Striking in contrast, though, is the consideration that within the "rare disease" population exist 7000 or more distinct diagnoses.

From a drug development perspective, the primary challenge to this market remains the balance of funding R&D while market opportunities on the commercialization end remain constrained by small patient populations (i.e., small market sizes). Financial incentives for rare drug development in the US were codified in the 1983 Orphan Drug Act (ODA), which includes tax credits, waives Food and Drug Administration (FDA) user fees, and increases marketing exclusivity for rare indications. A mosaic of programs now exists in the US to de-risk and incentivize rare disease drug development, including voucher programs (e.g., for rare pediatric diseases), grant programs (e.g., enabled under the Rare Disease Act of 2002), Small Business Innovation grants/contracts, targeted research efforts (e.g., Rare Cancer Moonshot) and others mentioned below, and regulatory pathways (e.g., Accelerated Approval). Outside of the US, incentives for development, as well as patient access to resulting treatments, vary widely by country and region.

To explore economics and value in rare disease drug development, the authors consider the historical context, current trends, present-day landscape, including insurance coverage and reimbursement trends and "value frameworks" as well as patient-led models of finance, and examine novel methods for rare disease funding and access as well as the "patient–economist" perspective given that both authors are economists and rare disease patients.

HISTORICAL CONTEXT: RARE DISEASE DRUG DEVELOPMENT AND MARKET ACCESS FROM THE 1980S TO TODAY

The current trend of patient-led activism in rare disease financing and discovery is not new, and continues the work led by the National Organization for Rare Disorders (NORD) in the 1980s that resulted in passage of the ODA in 1983. Key ODA provisions include 7-year market exclusivity for orphan drugs, tax credits, development grants, fast-track approval, and waivers of PDUFA fees (a category of FDA user fees for drug developers).

Some debate exists regarding whether increased development and discovery in rare disease over the past several decades, particularly with regards to repurposed molecules, is due chiefly to the ODA or to other market and landscape forces. While some researchers have argued that the ODA has not significantly impacted market exclusivity for drugs that would have patent protection regardless of the legislation, others have shown the increase of rare disease approvals as an indicator of the ODA's relative success.[2,3] Meanwhile, as the rise of "precision medicine" based on molecular diagnostics and next-generation

sequencing technologies influences clinical decision-making and patient population definition, potentially more and more diseases, including subindications of more prevalent conditions, can be categorized as "orphan"; as an example, nearly half of requested orphan designations are for rare cancers.[4]

Rare disease products are comparably more available to US patients than to patients in other countries (primarily due to broad FDA labeling), yet US patients still face a number of barriers, financial and otherwise, as detailed in a 2020 report commissioned by NORD. Given the rising volume of rare disease designations of drug candidates, with 753 in 2020, pressure for market and patient access to rare disease drugs is likely to accelerate in the coming years, along with significant debate as to what constitutes "value" in a rare disease drug.

CURRENT TRENDS FOR INVESTMENT IN RARE DISEASE DRUG DEVELOPMENT

Haendel et al. state that there are approximately 7000 rare diseases according to common classification procedures, but the authors estimate the actual number is closer to 10,000.[5] The sheer number of rare diseases, not to mention the paucity of research available on many of these illnesses, creates enormous challenges in drug development. Since much pharmacological research is undertaken by for-profit entities, a large number of rare diseases are never investigated for treatment simply because they afflict so few people. Investing millions of dollars into research to target a disorder affecting 50 people across the globe is unlikely to provide the return on investment sought by the biopharmaceutical industry. Shareholders of public biopharma firms represent another hurdle to pursuing rare disease drug development as such investors are often focused solely on financial returns.

Much rare disease drug development resides within smaller biotechnology companies. These firms, often privately held, face fewer demands for immediate earnings and have lower overhead costs than global pharmaceutical companies. After developing a promising drug candidate, such a biotech may be acquired or choose to go public to access the resources necessary to complete clinical trials. Typically, though, we see rare disease treatments marketed by major pharmaceutical companies only after the acquisition of an original developer. This process is certainly unique and frequently suboptimal overall.

PATIENT-LED MODELS FOR RARE DISEASE DRUG DEVELOPMENT

A recent trend is in patient groups, or in some cases individual patient advocates, seeking to create their own collaborations, funds, and research networks to address rare diseases. In some cases, these patient-led models are blending "traditional" venture-backed biotech approaches with philanthropic funding, cooperatives, and other models to create new and innovative means to accelerate discovery and approval, simultaneously seeking to prioritize the patient perspective. The Rare As One Network, for example, funded by the Chan Zuckerberg Science Initiative, backs 30 grantee patient organizations that are taking on activities usually left to venture-backed biotech, such as pharma partnership development, launching and maintaining clinical registries, building biobanks and tissue repositories, and starting clinical trials. Often, these novel approaches to early-stage development financing are paired with innovations in the development pathway, including "decentralized" or "just in time" clinical trials that allow trials to be opened on a one-off basis across a network of satellite sites so that patients can be accrued without having to travel to a central location, which previously limited trial access and accrual to large research hospitals. Other patient-led innovations include networks for data sharing and analysis, including RARE-X, NORD IAMRARE, and Genetic Alliance PEER, that enable patients to share personal health data with researchers and industry.

INSURANCE COVERAGE AND REIMBURSEMENT TRENDS IN RARE DISEASE

Few academic publications have thoroughly addressed US insurance coverage and reimbursement trends for rare disease, although the topic is a frequent area of focus for private-sector research and publication. A 2020 study from University of Michigan found that while spending on rare disease therapies increased from 2013 to 2018, patient out-of-pocket costs did as well, nearly doubling from $486 to $866 per year.[6] However, coverage across plans is highly variable, with restriction frequency for orphan drugs ranging from 11% to 65% in a 2019 study.[7] An earlier study found that 93% of orphan drug approvals are covered by payers, but formulary management and utilization management may lead to restrictions, high cost shares, and similar mechanisms that impact access to such products.[8]

CURRENT "VALUE FRAMEWORKS" AND INSUFFICIENCIES AS APPLIED TO RARE DISEASE

Assessing the "value" of rare disease treatments presents numerous challenges and is a topic of debate not only in the US but in countries with more formalized Health Technology Assessment (HTA) programs that determine insurance coverage or approval for new therapies. Small population sizes in clinical trials, limited experience with the best outcomes or endpoints to measure in such trials, the lack of existing treatments for many rare diseases, limited validated quality-of-life measurement instruments for rare disease populations, and challenges to project forward how new treatments will impact health utilization and other costs make HTA particularly difficult. The rare disease community has been vocal in criticizing use of measures such as cost-per-QALY (quality-adjusted life year), a perspective that has been supported by research demonstrating the insufficiency of such metrics in rare disease and the risk that applying them will lead to unjust policies for rare disease patients.[9] Health economists have encouraged the use of broader elements beyond those typically included in cost-per-QALY assessments when evaluating the value of rare disease therapeutics.

NOVEL METHODS FOR FUNDING RARE DISEASE DRUG DEVELOPMENT AND ENSURING PATIENT ACCESS

Alongside innovation coming from patient-led research and development groups, a number of academic and nongovernmental organizations have proposed or pioneered innovative funding models for rare disease drug development as well as business models that reduce risk and channel financing more efficiently. As a real-world case study, academics and venture capitalists alike have pointed to BridgeBio, a rare disease drug company with a portfolio model that reduces risk of developing only one molecule as traditional biotech companies often do. Other novel methods include crowdfunding, "venture philanthropy" that blends venture capital's search for returns with a philanthropic and social-impact mindset, incentive prizes, disease-specific venture funds, and social impact bonds (SIBs). From the pricing perspective, researchers have proposed a number of mechanisms to allow for risk sharing, including value-based or outcomes-based contracts or cost-based yardstick pricing.[10]

THE PATIENT–ECONOMIST PERSPECTIVE: WHAT VALUES AND PRIORITIES SHOULD GUIDE US?

While the high price of rare disease therapies can create "sticker shock" among the public and politicians, the authors believe it is important to consider the relevant context, emphasizing previous health economic research that has cautioned against applying an overly utilitarian view to rare disease drug development and patient access. The long-term economics and value of rare disease treatments are particularly critical to understand as they evolve over time and not be measurable (although they are possible to model) at the time of drug approval.

For example, the cost of a single dose of Zolgensma (onasemnogene abeparvovec-xioi) is over $2.1 million. The uproar following the approval of this drug was immediate, ferocious, and focused singularly on the price. A more comprehensive analysis, however, reveals important details about the economics of the treatment. While onasemnogene abeparvovec-xioi is a one-time treatment, the alternatives require continued doses for life. Evrysdi (risdiplam) costs $3.4 million for one decade of treatment, and Spinraza (nusinersen) costs over $4.1 million for 10 years of therapy, plus the cost of spinal injections. The full scope and cost of all available drugs to treat a disease, as well as the secondary costs and benefits such as avoiding additional hospital stays or reducing other therapies, should be fully assessed before declaring a treatment "unaffordable" in the court of public opinion.

Ultimately, the authors would agree to prioritize the development of rare disease drugs that cure or significantly alter the trajectory for the most serious and debilitating conditions affecting humanity, regardless of the size of population affected. We should always value patients by putting them at the center of development, approval, and treatment decisions. On a macro level, drugs that dramatically reduce the lifetime cost of treating rare diseases are also worthwhile to pursue, as doing so could free up capital for investment in other areas of drug discovery and improve sustainability of treating rare diseases in global markets. A two-tiered system whereby some people have access to rare disease drugs and others suffer without treatment is not ethical, but the solution is not to shortsightedly restrict development/approval of expensive medications. Instead, we should focus on economic solutions and innovative outcome-based frameworks that enhance access for all while maintaining strong incentives for research, development, and commercialization of products that can have positive life-altering and life-saving impact.

DISCUSSION

While investment in rare disease therapies has increased over the past four decades, both the number of new drug candidates for and the total number of investment dollars in rare disease—whether coming from "traditional" venture capital and private equity sources, or from new philanthropic, patient-led, and social-impact based backers—are likely to continue an upward trajectory. Alongside funding and development emphasis, rare disease patients and their families, with the present authors as an example, are increasingly taking roles in drug research, policy advocacy, biopharmaceutical business, market access, and financing innovation in ways that meaningfully advance the market for rare disease research, drug development, and drug commercialization. While numerous rare diseases remain without current treatment, the past decade has seen advancement for a number of conditions that were previously thought to be "untreatable"; these "moonshots"—ambitious efforts to treat rare diseases—have paved the way for more economically viable models. There is also a growing consensus that rare disease treatments bring significant value to society, despite the applicability of any one molecule to a relatively small population. With advances in financial innovation and patient-led research, these authors are optimistic that the market for rare disease drugs will continue to attract outside investment, although they acknowledge that market access innovations will increasingly be needed to meet patient demand for global access to the drugs that result from such investment.

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