Tackling the Barriers to Rare Disease Treatments

▶ Efforts to address the approximately 7,000 rare diseases worldwide have intensified as life-sciences companies increasingly turn their attention to these conditions.

According to some analysts reports, orphan drugs could account for one-fifth of global prescription sales by 2024. This increase in market share is being bolstered by life-sciences companies of all sizes leaning into the rare disease space.

On the diagnostics side, there has been increased emphasis on understanding genetic variation in clinical testing and disease and to develop better diagnostic tests for rare diseases, which will also help clinicians make the best decisions on the therapies. According to a report, the rare diseases diagnostic market is expected to reach $26.7 billion by 2024.

Nevertheless, many barriers remain, and the vast majority of rare diseases have no treatment options, with only 5% of rare diseases having treatments.

For patients struggling with rare diseases, the challenge typically starts with getting a diagnosis. In recognition of the difficulties patients and their families face, the National Organization for Rare Disorders launched the Undiagnosed Rare Disease Registry. Drug development is also more challenging in rare diseases. Experts note that in preclinical research, modeling can be difficult because simple genetic mutation models are typically inadequate for replicating the conditions in people with rare diseases. And once a product goes to clinical trials, the challenge is recruiting and retaining enough patients, given the tiny pool of people with most rare conditions.

The Year of Living Dangerously

Over the past year, one of the biggest barriers has been the same challenge faced by everyone: COVID-19. With so much research focused on finding vaccines and treatments for COVID-19, the impact on other diseases was inevitable. The COVID-19 pandemic has disrupted lives worldwide. It has delayed or halted clinical trials and changed the way patients interact with their doctors.

For patients with rare diseases, these disruptions have been hugely problematic. A study carried out in Hong Kong and published in September 2020 that looked at the impact of the pandemic on 272 patients with 89 distinct rare diseases found the health status of 46% of patients was adversely impacted by the reduced services provision, while 79% of patients said their mental health was impacted, particularly among those patients who are either severely or totally dependent.

According to a BMJ article, advice to U.K. patients with rare disease was also contradictory. The authors cite by way of example patients with Wolf-Hirschhorn syndrome (WHS), which is characterized by a deletion on the 4p chromosome. While the condition leaves patients extremely vulnerable because they have a chronic neurological condition, caregivers of those with WHS in the U.K. were given conflicting advice about whether patients should be classed as vulnerable and eligible for additional support.

And according to a survey from NORD, the pandemic has added to the emotional and financial strain that patients with rare diseases face. The data from the survey found that 32% of patients struggle with accessing medical care

The State of Rare Disease, Diagnosis, and Treatment

The National Organization for Rare Disorders (NORD) has published a report — Barriers to Rare Disease Diagnosis, Care, and Treatment in the US: A 30-year Comparative Analysis — that looks at survey data from 1989 to 2019. As part of an ongoing mission to generate evidence and data to advance a collective understanding of the rare disease patient experience, NORD conducted two studies aimed at identifying trends in rare disease diagnosis, care, and treatment in the United States.

NORD examined how barriers and facilitators have changed within the U.S. healthcare system, particularly in relation to the diagnostic odyssey, access to therapies, financial impacts, and engagement with research and clinical trials. Findings include:

- 88% of people today would consider using an investigational drug or treatment, compared to 62% in 1989
- 16% of individuals today reported that they had already participated in a clinical trial for their rare disease, compared to 12% in 1989
- 17% of individuals today have already relocated or are considering relocating to access care for their rare disease, versus 8% in 1989
- 2% of respondents today reported that they did not have healthcare insurance, versus 9% in 1989

The first survey, conducted by NORD, was published in 1989 on behalf of the National Commission on Orphan Diseases. The findings reflected information collected from 801 rare disease patients, family members, and caregivers. Thirty years later, a follow-up study gathered voluntary responses from 1,108 individuals via a Web-based survey from October 2019 through March 2020. The results from the report will be used to inform future research, advocacy, and engagement with stakeholders in the rare disease community.

Source: NORD, rarediseases.org

and treatment, 14% struggle to access medical supplies and devices, 14% have struggled to access the medication they need for their rare disease, 37% of households with a rare disease patient have had a loss of income, and 27% of households have experienced a job loss.

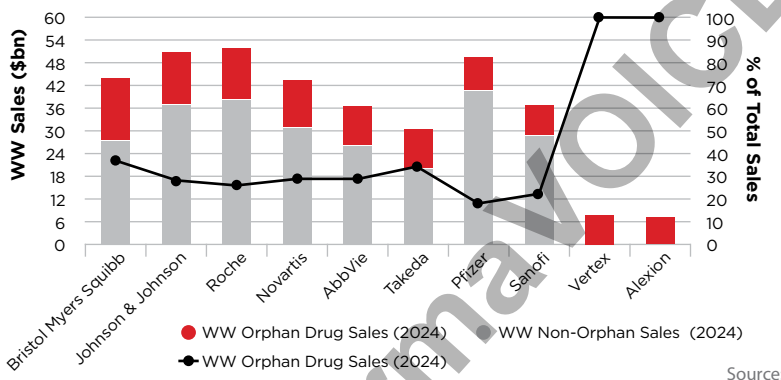
Hope on the Horizon

While the pandemic has created hardship for many patients with rare diseases, there have been some important developments. Investors are increasingly showing an appetite for gene therapies to treat rare diseases, buoyed by the success of Spark Therapeutics's Luxturna for RPE65 mutation-associated retinal dystrophy and Zolgensma, developed by Novartis to treat spinal muscular atrophy (SMA).

In addition, large pharma companies have been looking to expand their reach in rare diseases. Pfizer has been focused on two main areas of rare disease: hematologic disease, such as hemophilia and sickle cell disease, and neuromuscular disease, such as Duchenne mus-

Top Orphan Companies & Portfolio Percentage

Ranked on 2024 WW Sales



Source: Evaluate

EXECUTIVE VIEWPOINTS

Ryan Mason
Chief Strategy Officer
closerlook, inc.

Addressing Real-Life Needs

Often, the most debilitating and insidious aspects of a rare disease are the ways it can threaten not just patients' sense of identity, but also affect the community and people around them. Biopharma brands are in a unique position to support wraparound services by creating content and experiences that address the real-life, everyday needs of patients and the community they live in. As sponsors and publishers, biopharma can produce content that is rich, meaningful, and sustainable.

Taking a Content-Centric Approach

The COVID-19 pandemic has forced biopharma to shift en mass marketing to a more content-centric approach. The change is profound. This means we are now able to give customers uniquely relevant content when they want it and how they want to receive it. We can deliver hyper-relevant content that helps them live their lives as unique individuals while also bringing greater awareness and empathy to the communities. To improve engagement, we foresee content-centric marketing to alter the landscape.

Roshawn Blunt
Managing Director
1798, a Fingerpaint company

Ensuring Access to Lifesaving Therapies

Once a provider determines an appropriate therapy, the prescription process should be as seamless as possible. The manufacturer must design a comprehensive provider support program, payer value story, patient financial program, and distribution plan that minimize the prescriber's administrative burden; provide evidence and/or discounts that limit payer utilization controls; ensure out-of-pocket costs do not prevent a patient's ability to receive lifesaving therapy; and select a distribution approach matching the needs of the patients, providers, and payers.

Dan Schoen, Ph.D.
Head
Photo 51, a Fingerpaint company

Entry of More Affordable Gene Sequencing

Next-generation, whole-genome sequencing (WGS), rapid whole-exome sequencing (rWES), transcriptome sequencing (RNAseq), and combinations thereof facilitate the rate, coverage, precision, sensitivity, and efficiency of R&D for rare genetic diseases. While myriad factors comprise total sequencing costs, increases in affordability, along with collaborative genomic data sharing, are helping to transition sequencing to the clinic as first-tier diagnostic tests to uncover relevant variants. Ensuing, data-backed treatment modification, surgery reduction, and shorter hospitalizations further improve net healthcare savings.

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Nina Wachsman
CEO and Co-founder
Know Rare

Information is Everything

In a survey of 100 people with rare diseases, we asked why they wanted to know about clinical trials. The majority answered, "it would have been reassuring at diagnosis to know about clinical trials for my condition." For most people with a rare condition, there are no approved therapies. Knowing the industry is committed to the discovery of new treatments can be reassuring.

Telehealth to the Rescue

The COVID pandemic forced many doctors, hospitals, and people of all ages to use video platforms like Zoom for work, school, and healthcare visits, on desktops, iPads, and mobile phones. In fact, ZocDoc, the leading online doctor directory and visit scheduling portal, reports that 30% of visits scheduled are telehealth, with the percentage more than 50% in some specialties, such as neurology and endocrinology. This innovation can possibly enable better access for study centers to initially screen potential participants, who may be hesitant to travel or afraid to miss a day of work.

Amy Graham
Client Engagement Officer
Ogilvy Health

Making Gene Sequencing Affordable

More affordable and accessible gene sequencing can positively impact R&D efforts by helping to accelerate the identification of patients with specific gene-related diseases, thereby making available more individuals who might be able to participate in clinical trials, including potential subtypes of rare diseases. This would allow for better trial design and timing, but more importantly, it should decrease the time for patients to achieve a correct diagnosis and earlier access to treatment.

Tracking a Robust Rare Disease Pipeline

I am excited by the robust drug pipeline. The clinical pipeline for rare diseases is the most active it's ever been, with different therapeutic modalities that potentially allow for broad coverage of targets and mechanisms. This opens up possibilities to control disease and alleviate symptoms and side effects, as well as potentially getting to "cure" with gene therapies. Many of these targets may be monotherapies, but we might also combine modalities for better disease control.

Jeremy Edwards
CEO
Raremark

Working Together to Unlock Potential

Rare disease patients and caregivers have a strong willingness to participate in research to improve their lives and the lives of others in the same position. When industry works alongside rare disease communities, they will unlock better protocols and study designs, shorter timelines and ultimately bring treatments to market faster. Engaging the community will also give unprecedented access to organically collected real-world data to support post-approval initiatives.

Alex Garner
Chief Operating Officer
Raremark

DCTs and Rare Disease

A key trend we're adapting to are decentralized and hybrid trial models. Removing barriers around travel and site visits will increase patient access to studies and in turn speed up therapy development. COVID-19 has revitalized interest and innovation in decentralized trials, and this year we expect to see more sponsors running feasibility studies with patients to assess costs, study design, and how best to engage participants in this new virtual model.

Raymond Huml
VP, Medical and Scientific Strategy and Head, Rare Disease Consortium
Syneos Health

Understanding the Rare Disease Patient Journey

It is critical to start by understanding the rare disease patient journey. For example, looking at Duchenne muscular dystrophy (DMD) — children with DMD move from an ambulatory to non-ambulatory status. As their disease worsens their caregiver team expands exponentially, ultimately including neurologists, cardiologists, orthopedic specialists, physical therapists, occupational therapists, and nutritionists, to name a few. Understanding this evolution informs how we can bring forward feasible, practical, and ethical solutions to ease patient and caregiver burden. We need to be thoughtful about the stakeholders involved in the

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development and commercialization process. For example, incorporating the patient voice is essential across all stages. Patients provide the "data" that identifies and ranks clinical symptoms for therapies that are not a cure, but disease-modifying. Additionally, sponsors must consider how to build a value story — with clinical trial data or RWE — to share with payers and insurers before, during, and after approval to ensure access.

Pete Robinson
VP, Medical and Scientific Strategy and Head, Cell & Gene Therapy Consortium
Syneos Health

Opening the Door For Multi-Genic Diseases

As most rare diseases have a genetic basis, more affordable gene sequencing could significantly lead to earlier and more accurate diagnoses. It could address the high prevalence rate of misdiagnosis in rare populations and elucidate a spectrum within a disease group. The ability to determine and ultimately sequence solutions for the causative segments of genetic code faster and more comprehensively opens the door to create gene therapies for larger segments of code and multi-genic diseases.

Bradley Galer, M.D.
Executive VP and Chief Medical Officer
Zogenix

Advancing Rare Disease R&D

Accessible and affordable gene sequencing can advance rare disease R&D by providing deeper understanding of disease biology and sub-types, which in turn informs development of more effective or even potentially disease-modifying therapies. And enabling faster, more accurate diagnosis for patients and families can also improve the clinical trial recruitment timelines that are often challenging in rare and ultra-rare diseases — especially if more than one company is active in a particular indication.

Investing Beyond Development and Commercialization

We believe that for patients to truly benefit from new medications, the industry — even small companies like ours — must invest beyond development and commercialization to areas like managed access, financial assistance, and other programs to ensure access for all patients. Also key is educating the full range of stakeholders — from physicians and clinical staff to payers, policymakers, and health systems — about unmet needs and evidence-based clinical, quality-of-life, and economic benefits of new therapies.

cular dystrophy. To extend its capabilities in gene therapy research, Pfizer acquired Bamboo Therapeutics, providing a clinical and preclinical portfolio in neuromuscular and central nervous system rare diseases.

As important, stakeholders are paying greater attention to the patient voice, including regulators who are more and more willing to accept flexible trial designs that make it easier for the patient.

Nevertheless, correcting rare diseases through gene therapy has been hit and miss. BioMarin's hemophilia A gene therapy valoctocogene roxaparvovec failed to win approval after data showed levels of factor VIII fell 12 to 18 months after treatment. Other companies are adopting different methodologies to address similar issues. Generation, which is developing therapies to treat rare blood disorders, is using a technology that avoids setting off an immune response, which would prevent a second round of treatment. In so doing, it would be possible to re-dose the patient in the future. Other methodologies are being assessed. For example, BioMarin is working with Swiss startup Dinaqor on gene therapies for rare heart diseases.

Other companies are exploring different technologies and ways to improve how gene therapies target and correct the gene in question. Whatever the challenges, interest in rare diseases and gene therapies remains high. For example, in December 2020 AstraZeneca announced plans to acquire Alexion Pharmaceuticals, which developed the antibody therapy eculizumab (Soliris), initially approved for a rare and life-threatening blood disorder called paroxysmal nocturnal hemoglobinuri and later approved for another rare disease.

Extending Rare Learning

One area that has gained greater traction in recent years is the use of artificial intelligence to gain deeper insight into rare diseases. Using AI or natural language processing (NLP) tools can make it easier to sift through multiple data sources to give clinicians relevant insights and help them diagnose patients. This will ensure diagnosis is sped up and patients receive the medicines or support they need to manage or treat their rare diseases sooner. In a paper published in June 2020, researchers carried out a scoping review to investigate how machine learning is used in rare diseases. After exploring more than 200 studies over a 10-year period, the review found that machine learning can significantly improve diagnosis, treatment, and prognosis for patients with rare diseases.

As an example, researchers and clinicians at the University of Iowa Stead Family Children's Hospital used NLP to more quickly and accurately identify clinical phenotypes in infants.

Several companies are working to further advance these objectives, either through internal developments or partnerships and acquisitions. Illumina, which develops tools for analysis of genetic variation and function, entered into a partnership with AI company Emedgene to integrate automated interpretation of rare genetic disease into Illumina's TruSight software suite. The objective is to provide researchers with data that will help them make new discoveries. PV