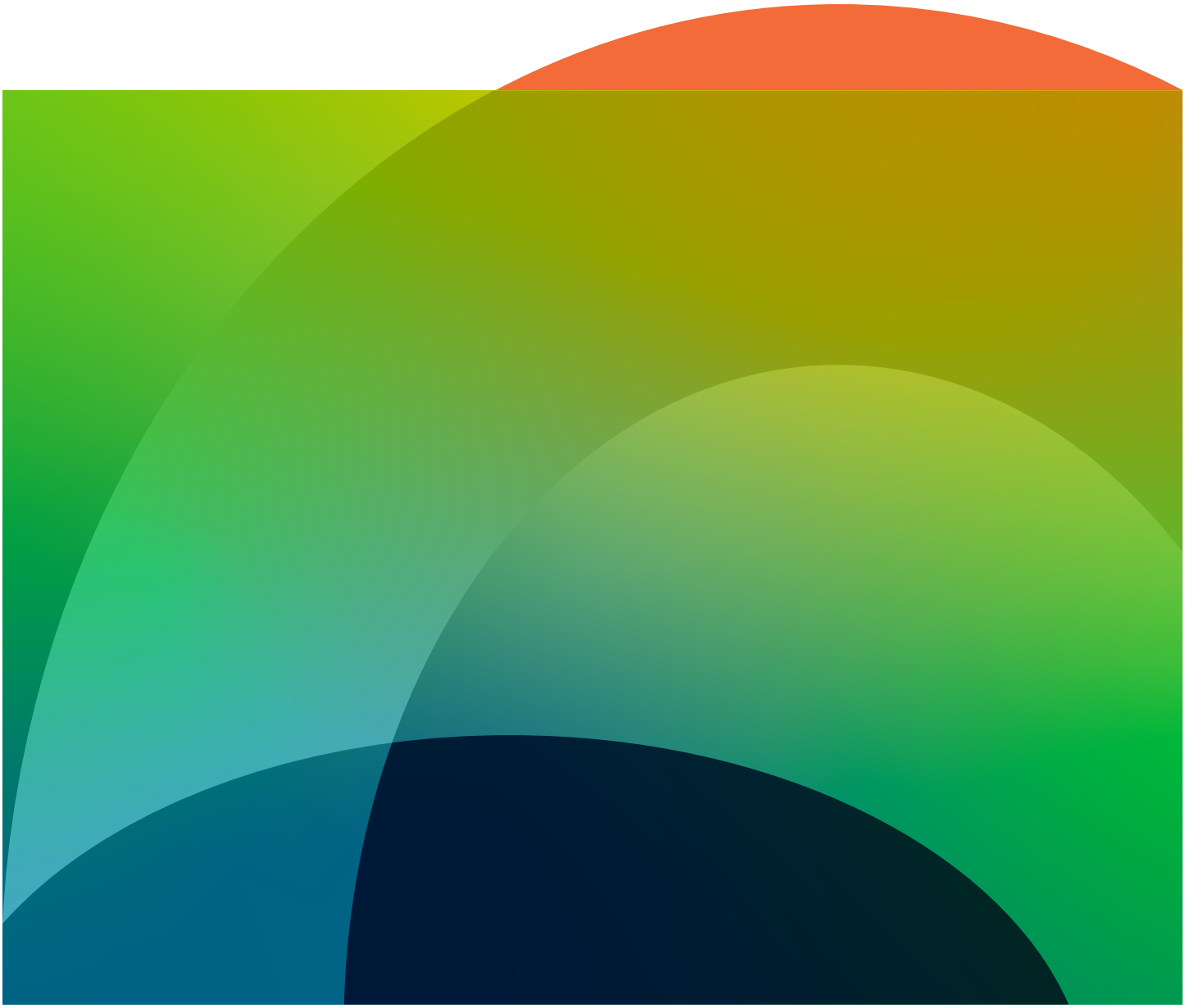
Avalere eBook

Rare Disease Biotech Landscape

Authored by Avalere and Avalere Health Experts



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Introduction

To learn more about how Avalere can help you with clinical development planning, value, and access strategies for rare and ultra-rare disease assets, **connect with us**.

Rare diseases are not so rare. This is a commonly used phrase in the rare disease community. There are more than 10,000 known rare conditions that affect more than 30 million Americans and more than 400 million people worldwide. This diverse and complex disease area poses challenges not only to patients but their caregivers, regulators, pharmaceutical manufacturers, policymakers, and other stakeholders. Considering that less than 10% of these conditions have any treatment options available, there is a significant unmet need in this space.

In this eBook, Avalere and Avalere Health* experts discuss issues and considerations associated with rare-disease drug development, the economic burden associated with these conditions, regulatory considerations, novel approaches to shortening the diagnostic odyssey, and clinical trial design.

*Avalere is part of **Avalere Health**. We partner with its Global team across markets and regions to help clients navigate complex healthcare ecosystems and make better health happen.

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Manufacturer Considerations for Rare-Disease Drug Development

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The development and launch of rare disease therapies require tailored strategies that account for unique patient journeys and the broader evolving landscape.

Drug manufacturers bringing therapies to market for rare diseases face challenges typically unseen with therapies for more prevalent conditions. These challenges span multiple stages—from clinical development through commercialization—and require coordinated efforts from medical affairs, health economics and outcomes research, policy, advocacy, and market access functions to execute successful evidence planning, stakeholder engagement, and patient access strategy.

Evidence Strategy: Defining Value and Identifying Appropriate Research Design

Defining value through a patient-centered lens is critical for all conditions but is especially important for rare disease treatment, as patients encounter disease impacts that don't routinely occur in non-rare populations. For example, adults with rare diseases are more likely to travel or relocate to be near specialists, incurring direct costs such as transportation and temporary lodging and indirect costs such as lost workdays or lost career opportunities. Spouses, other family members, or parents of children with a rare condition may have to change or prematurely end their careers to become full-time caregivers, resulting in major financial implications for the entire family. Limited research exists on these impacts and how to quantify them, which is needed to support more holistic value assessments.

Conducting research in the rare-disease space necessitates creative approaches to study design and recruitment to accommodate the small participant pools. Comparative effectiveness studies can be challenging with small patient populations, so innovative approaches, such as studies looking at total disease burden and the effect of therapies on patient- and caregiver-centered disease impacts can provide important context and

Patient Populations	• Thousands of rare diseases fragmented into small patient populations make it more onerous to understand the clinical manifestations and patient impacts of each rare disease. • Small patient populations also pose challenges for clinical trial recruitment, where issues around equity, access to care, and representation may be exacerbated due to lacking availability of trial sites.
Diagnostic Journey	• The diagnostic journey for patients with rare diseases is long compared to more common diseases, with a high likelihood of initial misdiagnosis. • Patients and their caregivers may face additional cost burdens associated with testing and treatment options. • Delayed diagnosis can result in diagnosis at a later stage, with greater impacts on the patient; this is especially relevant for conditions that have cumulative, non-recoverable, degenerative impact.
Care Navigation	• The lack of approved treatments for most rare diseases poses ethical challenges with placebo arms in randomized control trials, requiring innovative approaches to control groups and use of real-world data. • Patients may face delays in receiving care as they navigate insurance coverage and support programs for high-cost drugs with small target patient populations.
Treatment Options	• Specialists who have the experience and knowledge to diagnose and treat a rare condition are usually only located at major academic medical centers. • A lack of expertise at local providers and healthcare systems may result in delayed diagnosis, disruptions in treatment, or inappropriate care. • Rare diseases have disproportionate and severe impacts on children and require significant time and resources from caregivers.

perspective for payers. Further, manufacturers can capture longitudinal data to assess real-world safety and efficacy for new modalities of drug delivery and mechanisms of action that take place at the cellular and genetic level using patient registries and patient-reported outcomes. Endpoints in clinical trials can be designed in anticipation of potentially innovative contracting strategies and the outcomes that will need to be tracked from real-world data. For providers and health plans, few quality measures specific to rare disease and suited to this purpose are available. Because of the small populations, the impact of any one rare disease on the general population's quality outcomes is minimal. Patients with rare conditions share similar challenges that, when considered in aggregate, affect quality outcomes such as

readmissions, adverse events, and the total cost of care, and can have a major impact on a provider's or plan's performance in quality-driven payment programs.

Market Access Considerations

Developers of rare disease treatments must navigate a complex regulatory and commercialization landscape. Manufacturers often take on higher research and development (R&D) costs due to small clinical trial population size and difficulties in identifying and validating endpoints, especially in heterogeneous rare diseases, which poses additional barriers to manufacturers who already must navigate the changing policy environment (e.g., Inflation Reduction Act implementation). The Food and Drug Administration (FDA) recognizes these challenges and continues to invest in various programs focused on rare diseases that could help advance endpoint development and validation, promote innovative study designs, and enhance patient identification.

Patient access to available treatments may be a more significant challenge in the rare disease space given the diagnostic odyssey patients experience before receiving a correct diagnosis. For pediatric patient populations, newborn screening is available, but not all conditions are included, and due to budgetary constraints not all states screen for diseases on the Recommended Uniform Screening Panel (RUSP) or additional diseases outside the RUSP. Conditions not detected by newborn screening or those manifesting in adolescence and adulthood may be detected by novel testing approaches, such as whole genome or exome sequencing, but utilization management requirements may restrict patient access to these diagnostic tools, further delaying access to treatment.

Patient support resources needed in the rare disease space require a more tailored approach to address the unique challenges faced by patients and caregivers. Manufacturers may need to develop more patient-support education and resources about specific rare diseases. Demand for care coordination and case management support services may be even higher for rare diseases compared to non-rare diseases. Additionally, caregiver support resources and programs that mitigate breaks in care and disruption in therapy—such as bridge programs and site-of-care locators—are also important to consider for access. Once patients begin treatment, resources that enable tracking adherence and persistence also become critical as part of a robust suite of patient support offerings.

In addition, price sensitivities, driven by the need to balance R&D efforts with the associated return on investment, differ in the rare-disease space as compared to more common diseases. Downstream impacts include more restrictive utilization management by payers, who often replicate clinical trial inclusion/exclusion criteria in their formulary designs. Payers may also want to see the total cost of care when evaluating a product, but total cost of care may not be

widely studied or is poorly understood for many rare diseases. To address some of these issues, manufacturers may need to develop strategies early in the clinical development process for engaging payers, providers, and other key stakeholders.

Federal and State Policy Opportunities

Federal and state policies shape the rare disease landscape, influencing patient access and the broader R&D environment. Given the unique care journey and high-cost burden that patients with rare diseases and their families often face, policies may provide flexibilities and enable novel approaches to support access to treatments and drug development, or create specific policy exemptions for rare disease treatments in instances where patients could be adversely affected.

Federal and state policymakers are increasingly pursuing efforts to reduce cost exposure and improve patient access across the unique rare disease care journey (e.g., patient support and reimbursement for ancillary costs associated with **traveling to treatment centers**, limiting use of **copay accumulator** and maximizer programs). Meanwhile, **Medicare drug price negotiation** aims to reduce costs for high-spending drugs but could have adverse implications for rare-disease drug development due to the **orphan drug exclusion's** limitation that only enables a drug to qualify with a single rare-disease designation.

Approximately half of states have created rare-disease advisory councils. As novel treatments continue to emerge, opportunities exist to bolster and expedite efforts that shorten the diagnostic and treatment journey for patients, such as through newborn screening. Meanwhile, several states have been active in implementing **prescription-drug affordability review boards** aimed at reducing state costs for a subset of high-cost drugs, many of which could impact rare disease treatments if not otherwise carved out of the policy. Looking ahead, federal flexibilities for novel financing arrangements through the **value-based purchasing rule**, combined with efforts from the Centers for Medicare & Medicaid Services Innovation Center and state-driven initiatives, signal growing opportunity for stakeholders to engage in innovative models aimed at improving access and outcomes for patients.

The Impact of EU Policy and Advocacy on Progress in Rare Disease

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→ Economic Burden

→ Diagnostic Odyssey

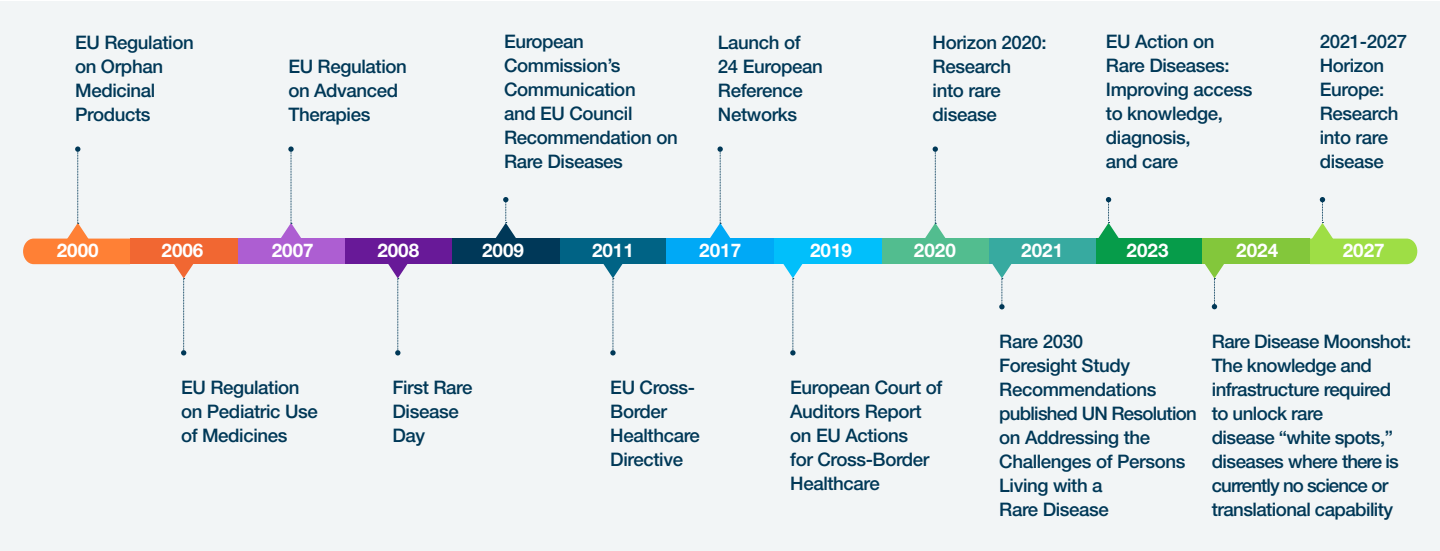
Up to 36 million people across Europe and more than 400 million globally are living with a rare disease.

It is widely understood that patients and their families face a number of challenges in accessing diagnosis and appropriate, timely treatment. Healthcare professionals are also faced with challenges with the availability of care for their patients, appropriate treatment, and access to suitable guidelines. Finally, investigators and researchers face challenges with research and development (R&D) in the rare disease space due to the small patient pool and limited funding for research.

EU policy and advocacy play a key role in overcoming these challenges; over the past two decades, policy changes and the introduction of awareness campaigns have increased the availability of treatment for patients with a rare disease. For example, in 2000, the implementation of the Orphan Medicinal Products Regulation, which provides incentives for pharmaceutical companies to invest in rare disease treatments, led to the approval of more than 170 orphan drugs in the EU. Since 2000, a number of policies and initiatives have helped increase awareness and stimulate investment to encourage the development of innovative treatments in the rare disease space. The following timeline highlights the key policies, awareness initiatives, and funding programs implemented to help elevate the standard of care for rare diseases.

Funding for research is an essential driver of innovation in the treatment of rare diseases. The availability of funding has been facilitated in part by the EU's research and innovation framework programs, such as Horizon 2020 and Horizon 2021-2027, which emphasize developing treatment and diagnostics via innovative collaborative research. The European Reference Networks (ERNs)—virtual networks of healthcare providers across Europe—have also played a key role in elevating the rare disease agenda. The first 24 ERNs were launched in 2017, with more than 900 specialized healthcare units from over 300 hospitals across 26 member states. The ERNs work via virtual advisory boards,

Policies, Awareness Initiatives, and Funding Programs Across the EU Since 2000



collaborating to review patient cases, diagnosis, and treatment and to share knowledge and experience with colleagues and patient groups. They also work on research projects, setting up disease registries, and developing clinical guidelines. As of 2022, the number of ERN members has grown to 1,500.

In 2023, the EU published its action plan for rare diseases, which aims to improve the diagnosis, care, and treatment of patients with rare diseases through the pooling of resources and collaboration.

The Rare Disease Moonshot program is another example of the coordination of policymakers, advocacy groups, and public and private partnerships in shaping the environment to promote advances in rare diseases. The program was established to foster collaboration between public and private organizations to support research in disease areas where there are no treatment options and where no R&D is currently taking place. The program has identified three key areas where public-private collaboration was thought to add most value:

- Optimizing the translational research ecosystem to accelerate translation
- Modernizing clinical trials (design, conduct, and regulatory sciences) to make them more suitable for very small populations
- Supporting infrastructure to shorten the path to diagnosis and treatment

The Rare Disease Moonshot program is uniquely positioned to leverage public-private collaborations to help amplify the patient voice. The program aims to achieve this by building partnerships with patient groups and helping build communities to collect vital data. However, in order for this collaboration to be

successful, stakeholders from patient groups, healthcare professionals, academics, drug and technology manufacturers, and regulators must work in collaboration to ensure that the correct data are collected and the program is truly multidisciplinary.

Patients and patient advocacy groups have also played a vital role in raising the profile of rare diseases. The first Rare Disease Day was marked in 2008, with patients, charities, and public and private organizations celebrating innovation or highlighting gaps in research and access to care. As a key stakeholder, patients add a unique perspective to research and market access endeavors. Between 2006 and 2016, the number of clinical trials focused on rare disease increased by 88%.

Despite the increase in awareness, drug development, and regulatory improvement, the rare disease market continues to face issues such as patient access and affordability. Navigating policies and engaging various stakeholders can be difficult. In recent years, with the introduction of gene therapies, which are potentially curative for rare diseases but come with a premium price, companies are faced with complex market access challenges.

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Assessing the Total Economic Burden of Rare Disease

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→ Diagnostic Odyssey

→ FDA Diversity Requirement

Innovative research methods can be used to measure the total burden of rare disease, including direct medical costs, indirect costs, and overall life impacts.

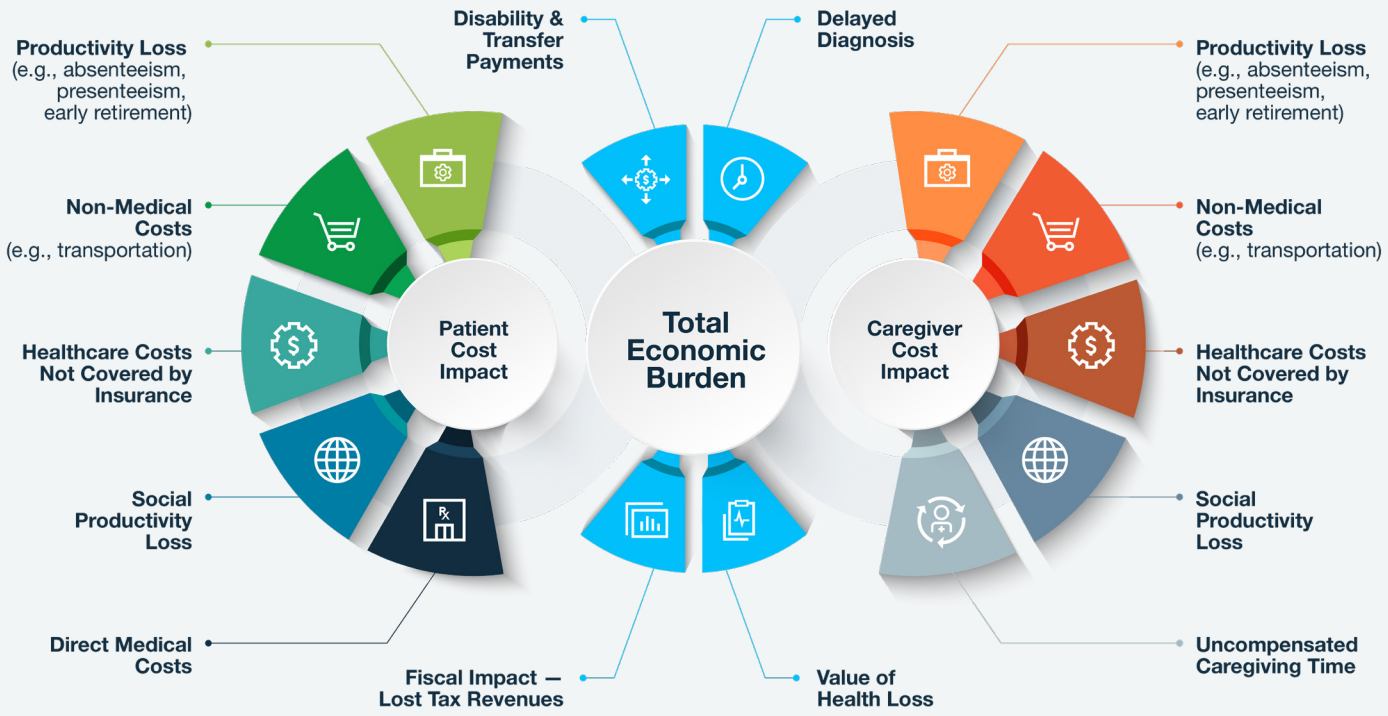
Despite the challenges of calculating the total burden of disease (especially for heterogeneous populations), robust and well-designed research can offer useful insights and context for patients, caregivers, payers, health technology assessment bodies, healthcare providers, policymakers, manufacturers, researchers, and society.

Avalere developed a whitepaper describing the opportunity and importance of measuring the total economic impact of diseases, particularly for rare diseases. First, experts present a case for considering the total economic burden of rare disease, then explore the current state of evidence on the burden of rare diseases, concluding with real-world application of total economic impact research. The proposed hybrid study approach builds upon a prior assessment by the EveryLife Foundation on the economic burden of 379 rare diseases, which can be used as a springboard for studying the disease-specific social and economic burden of a single rare disease. The team selected generalized myasthenia gravis (gMG) as a case study to measure direct and indirect non-medical costs based on Avalere's foundational research on patient- and caregiver-centered life impacts. A previous mixed-methods analysis found that financial and occupational impacts ranked highly among the eight impacts studied—emotional, financial, occupational, physical, planning & autonomy, safety, sleep, and social—elevating the importance of economic impacts.

The figure on the next page details potential components of total economic burden to be studied to better understand the true cost of these conditions, such as the significant out-of-pocket costs, labor and productivity impacts, and broader societal impacts. Understanding the true burden of rare diseases can help policymakers and the public better recognize the extent of the individual, family, and social impacts and allocate resources accordingly.

Access the whitepaper here.

Potential Components of a Total Economic Burden Study for Rare Diseases



Shortening the Diagnostic Odyssey: Benefits, Barriers, and Solutions

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A diagnostic odyssey is defined as the time between when a symptom or feature of a genetic or rare disease is noted to the time when a final diagnosis is made.

The average time to receive an accurate diagnosis for patients with rare and ultra-rare diseases is about 4.8 years, and patients may require more than seven specialists to receive a correct diagnosis. During this time, the condition may deteriorate, leading to low quality of life, disability, and, sometimes, premature death. Reducing the time between symptom onset and receiving a diagnosis provides numerous benefits to patients, caregivers, communities, and society.

Certain barriers stand in the way of shortening the diagnostic odyssey, including low disease awareness, access and coverage barriers, specialist shortages, and geographic barriers. Current solutions, such as newborn screening, genetic testing, and genome sequencing, may help in diagnosis and, potentially, treatment of rare diseases. Innovative approaches are also getting started—remaining on a research basis—that may become more widely available to patients.

Below, we outline the benefits to shortening the diagnostic odyssey, barriers that patients face, current solutions, and proposed innovative approaches.

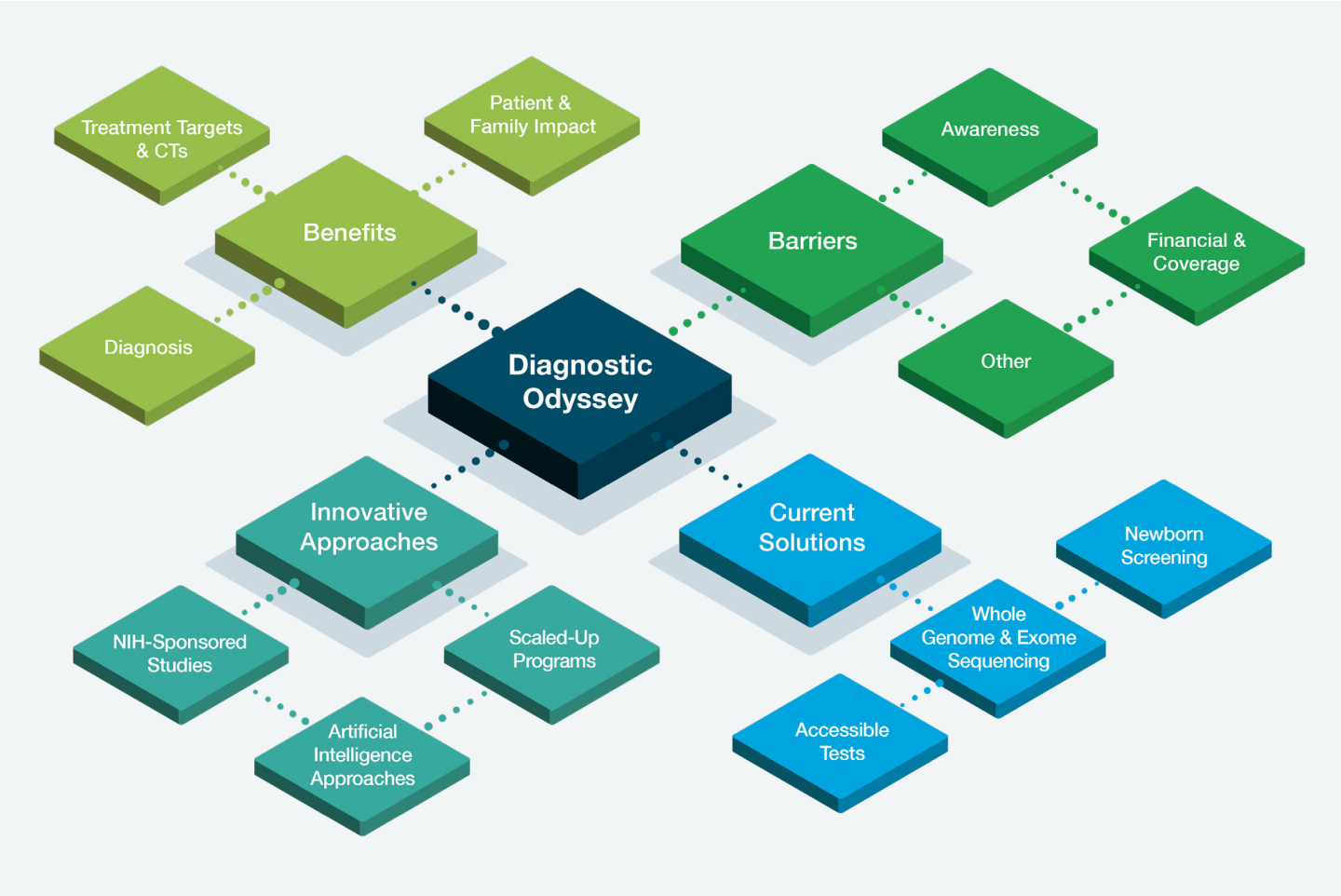
Benefits /

Patient & Family Impact

- Accurate diagnosis helps in understanding disease progression and life expectancy.
- Accurate diagnosis also assists in identification of risks for other health concerns and with family planning.
- Identifying a disease provides opportunities to connect with other families and advocacy groups.

Treatment Targets & Clinical Trials (CTs)

- Positive and negative results can inform treatments that target disease etiology, change clinical management, and improve outcomes.
- Identification of the underlying cause may lead to an increase in opportunities to participate in clinical studies based on genetic diagnoses.



Diagnosis

- Accurate diagnosis determines genetic cause or risk factor.
- Accurate diagnoses also provide diagnostic information that eliminates the need for other invasive, unnecessary, or expensive diagnostic tests.

Barriers /

Awareness

- Patients and caregivers may not have enough knowledge to request genetic testing.
- Physicians may not be aware of what tests to order for patients.
- Providers may have limited knowledge of alternative access opportunities (e.g., institutional, sponsored testing).

Financial and Coverage

- Some insurance plans may not cover advanced genetic tests or coverage may be limited.
- Patients who do not meet prior authorization criteria may face high out-of-pocket costs.
- National resources for families whose insurance does not cover genetic testing are lacking.

Other

- Providers face large workloads due to a shortage of geneticists, bioinformaticians, and genetic counselors.
- Patients and caregivers may be hesitant to participate in research or lack access to do so.
- Patients may have geographic barriers such as distance to tertiary care, centers of excellence, or genetic testing centers.

Current Solutions /

Newborn Screening

- Newborn screening helps identify conditions early and prevents long-term disability or premature death.
- Screenings include a limited list of conditions that vary on a state-by-state basis.
- Adding a condition to the list requires a joint initiative (e.g., patient advocacy groups, manufacturers, providers).

Accessible Tests

- Single gene testing, chromosome microarray, and gene panels are examples of targeted tests that identify structural changes in genes.
- These tests help identify the underlying causal gene mutation(s) leading to a correct diagnosis and potential access to treatments.
- Gene testing detects changes in genes that are not identified by sequencing (e.g., Huntington's disease, Friedreich's ataxia).

Whole Genome & Exome Sequencing

- Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES) help identify genetic variations or provide incidental findings (identify genetic disorder that has not been diagnosed).
- WGS has strict prior authorization requirements and WES is still on a research basis, limiting patient access.
- WGS and WES need both parents to rule out normal variations.

Innovative Approaches /

Large-Scale Programs

- Global Commission to End the Diagnostic Odyssey is a multidisciplinary initiative to develop roadmaps and pilot programs aiming to end the diagnostic odyssey.
- US BabySeq Project is designed to measure the utility of providing genomic sequencing to newborns.
- UK Newborn Genome Program aims to sequence and analyze genomes of newborns with the goal of ensuring timely diagnosis and improving health outcomes.

Artificial Intelligence (AI) Approaches

- AI-based facial phenotype analysis enables collaboration between clinicians and researchers to determine the correlation between facial features and rare diseases.
- AI-based motion capture system for diseases that affect movement helps predict a molecular biomarker, improve diagnosis accuracy, and evaluate treatment efficacy.
- Self-supervised image search for histology allows for expedited, accurate, and scalable search of histology images to assist in diagnosis of rare diseases.

National Institutes of Health (NIH)-Sponsored Studies

- Electronic health records (EHR) phenotyping algorithms seek to shorten the diagnostic odyssey through EHR identification of children and adults eligible for genetic testing.
- Primary care electronic medical records (EMR)-based machine-assisted referral decision support tool (machine-learning) aims to help identify patients at risk of neurodevelopmental disorders to ensure early specialist referrals.
- Virtual platforms for genetics evaluation of marginalized communities aim to improve genetic health through timely evaluation and genomic sequencing.

FDA Diversity Requirement: Impact on Rare Disease Drug Manufacturers

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→ Decentralized Clinical Trials

→ Case Studies

Increasing clinical trial diversity presents unique challenges for rare disease treatments due to population size, disease heterogeneity, and low awareness.

Many clinical trials underrepresent the diversity of the real-world population that may benefit from the product once marketed. Historically, factors such as race, ethnicity, age, gender, socioeconomic status, disability, and others have been passive data points captured as a result of a clinical trial, and have not been used to align the enrollment to the intended real-world patient population. This has led to gaps in understanding of treatment safety, efficacy, and long-term outcomes in specific patient populations, and in part has motivated statutory interest to increase diversity of clinical trial programs and ensure representative enrollment in trials. The Food & Drug Administration (FDA) now has increased authority to monitor the diversity of late-stage clinical trials, which introduces new sponsor trial design and enrollment planning decisions that have unique impacts on stakeholders in the rare disease community.

Demographics of Clinical Trial Participation

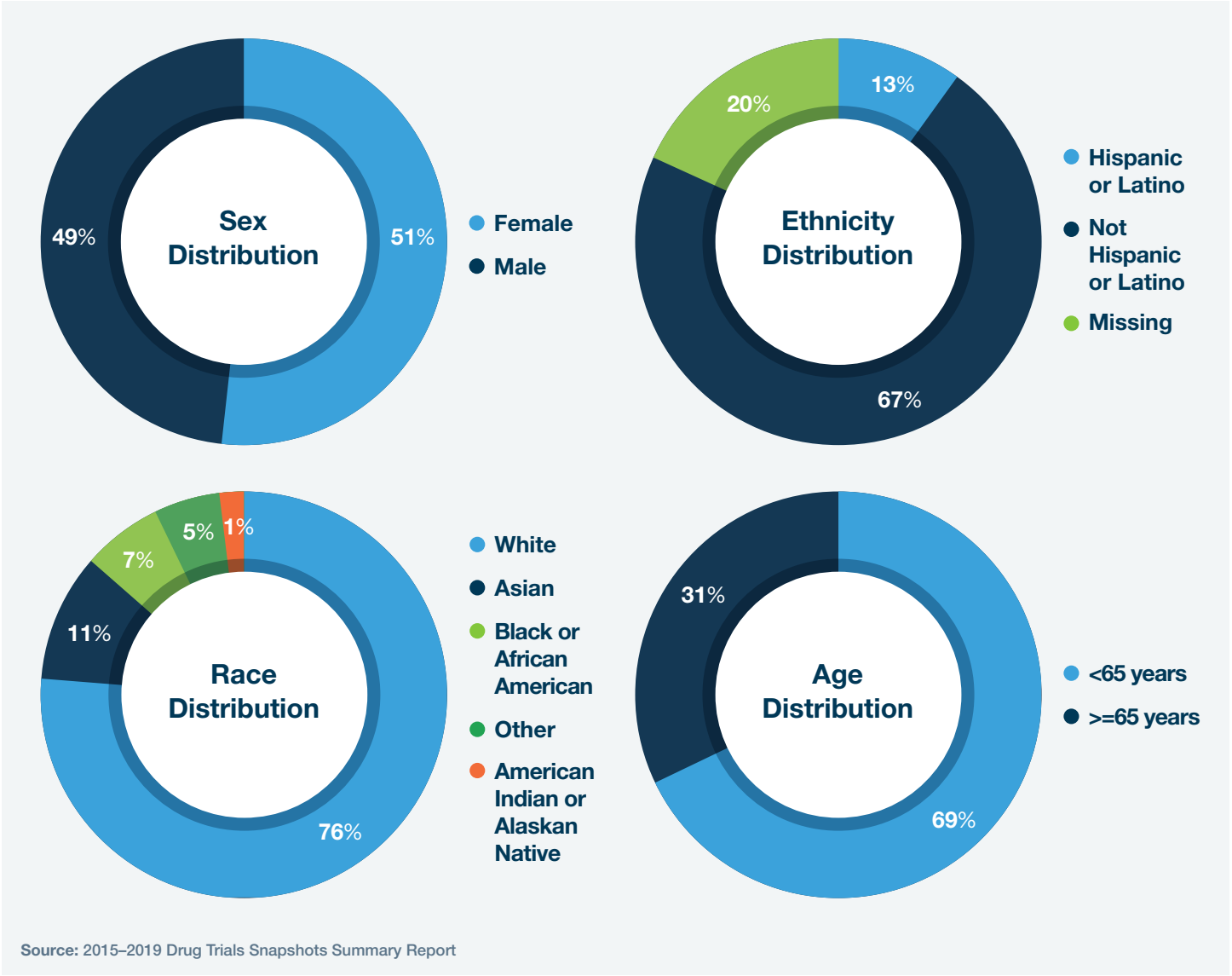
In response to mandates from the 2012 FDA Safety and Innovation Act, the FDA's Center for Drug Evaluation and Research has been reporting clinical demographic data for new drugs and biologics. The 2015–2019 Drug Trials Snapshots Summary Report provides aggregated data on trial participation across demographic groups.

The 2020 Report highlighted that clinical trial participants were mostly white, non-Hispanic females under the age of 65, and the 2022 Report indicated that even though some improvements have been made, broad enrollment of diverse cohorts remains a challenge.

FDA Initiatives Designed to Increase Diversity

The FDA has focused on increasing clinical trial diversity over the past few years, but authority has been maintained via regulatory rather than statutory changes. In April 2022, the agency issued draft guidance for sponsors developing medical products outlining how to enroll adequate numbers of trial participants from various racial and ethnic groups. This guidance

Demographics of Trial Participation



Source: 2015–2019 Drug Trials Snapshots Summary Report

aligned with language on Diversity Action Plan (DAP) requirements in the Prescription Drug User Fee Act VII commitment letter. The DAP policy became a law as part of the 2023 Consolidated Appropriations Act.

The included diversity provision applies to sponsors of a new drug or device and must include enrollment goals, rationale for those goals, and an explanation of how a sponsor will achieve them. This plan must be submitted to the FDA by the beginning of a phase 3 or pivotal study. Relevant information could include prevalence and incidence of the disease, current pharmacokinetic and pharmacogenomic data, or patient demographics.

However, the Health and Human Services Secretary can waive the DAP requirement for instances such as difficulty identifying patients

due to the small size of the testable population, multifactorial diagnosis that complicates eligibility, or the potential for a disease to affect a specific subset of the general population. Sponsors requesting a DAP waiver must have it granted by the FDA, whereas submitting a DAP does not require acceptance or rejection. DAP information will become part of a new mandate that will begin by 2025, whereby updated demographic information will be aggregated to demonstrate whether applicants met their DAP-established enrollment goals. This information will be made available in annual reports published by the FDA.

Impact on Stakeholders in the Rare Disease Community

The DAP provision impacts rare disease community stakeholders in unique ways.

Manufacturers

- Requires data collection and education to regulators on disease epidemiology (e.g., assessment of real-world evidence and claims data)
- Poses operational burden, including potential changes to clinical study protocols, enrollment practices, and retention resources to operationalize DAP
- Exposes existing tracking deficiencies that rare diseases experience (e.g., no diagnostic code available), which may require alternative approaches to determining prevalence and incidence numbers

Patients

- Allows historically underrepresented patients a stronger opportunity to have investigational access to treatments
- Requires safety and effectiveness data in real-world target population be on hand during drug review, providing more clarity on accurate product outcomes
- Requires accounting for logistical aspects of conducting a study with underrepresented groups (e.g., travel and monitoring)

Payers

While payers may not be directly affected by the policy, they will need to have a broader understanding of rare disease life-long patient journey and members' needs when transitioning between care systems (e.g., pediatrics to adults). Plans may also need to identify diverse data points from clinical trials that could be helpful in creating a patient-centric framework that would lead to cost reduction.

Decentralized Clinical Trials for Rare Disease Treatments

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Decentralized clinical trials offer the potential to democratize rare disease research, advancing drug development and improving patient experiences.

In rare disease research, traditional site-bound trials face unique challenges, including restricted patient populations, participant identification difficulties, and a lack of understanding of the natural history of the disease. However, the emergence of decentralized clinical trials (DCTs) presents a transformative avenue for trials. The increase of DCTs facilitated through remote technologies has been amplified by the COVID-19 pandemic. These trials have the potential to advance the research landscape by enabling patients to engage in their own environments and reducing the need for frequent site visits.

The shift toward decentralized trials extends beyond trial logistics; it has the potential to reshape the entire approach to clinical trials, evidence generation, and data communication. This transition aligns with the pharmaceutical pipeline's increasing focus on rare diseases, spanning gene and cell therapies, mutation-specific oncology, and RNA-interfering technologies. The modernization of clinical trials and rare disease research provides unique opportunities for stakeholders, including patients and manufacturers. However, several key factors must be considered.

Enhanced Patient Access and Participation

The dispersed nature of rare diseases can make decentralized trials a logical approach for certain manufacturers. Global research, advanced digital tools, and access to real-world data can potentially allow for more discoveries and provide effective treatments. This method leverages expertise from researchers and healthcare institutions worldwide, which allows for geographical barriers to be overcome and enables patient participation from homes or local healthcare facilities. By removing the barriers of physical distances, DCTs can bring diverse populations into the research fold, offering more understanding of disease impacts across ethnicities and regions.

Integrating digital health technologies like monitoring devices and electronic patient-reported outcomes supports patient engagement through this research. In turn, this engagement can support increased study retention and generate real-time data. Manufacturers can support this through user-friendly apps and remote monitoring devices, which can foster continuous communication with researchers and promote adherence to treatment protocols.

Accelerating Market Access

Meeting regulatory expectations requires robust clinical evidence across various domains. For rare disease therapies, the complexity of the payer landscape with its emphasis on cost effectiveness and real-world evidence (RWE) adds an additional challenge. DCT implementation can help address these challenges.

Streamlining data compilation from DCTs can facilitate **RWE collection**, potentially supplementing or diminishing the need for traditional clinical trial data. RWE can provide payers with comprehensive insights into treatment outcomes and real-world scenarios, potentially enabling informed, data-driven decisions during negotiations. RWE showcases real-world cost data, potentially strengthening the treatment's case and expediting market access negotiations by supplying evidence such as reductions in hospitalizations or emergency room visits. Moreover, robust data reinforces treatment efficacy and safety, potentially expediting regulatory approvals. Furthermore, the embrace of RWE by the Food & Drug Administration (FDA), exemplified by the **Pre-Approval Information Exchange Act**, signifies a shift toward evidence-based evaluations. This act enables payers to assess clinical trials and RWE before FDA approval, ensuring a parallel evaluation process.

Regulatory Recognition and Integration

Regulators are collaborating with patient advocacy groups and stakeholders to gauge the practicality and implementation of DCTs, heralding new regulatory guidelines. The FDA has outlined regulatory expectations for implementing DCTs in its draft guidance published in May 2023. The **draft guidance** paves the way for greater involvement and clarity in decentralized trials, addressing persistent challenges in rare disease research, such as recruitment hurdles.

The integration of streamlined data collection, compelling RWE, and alignment with regulatory and payer interests mark a paradigm shift in rare disease research and treatment access.

Video Series

Watch Now

How to Think About Rare Diseases in the US and Globally

Video Series

Watch Now

Avalere's Insights on Rare Disease

Explore examples of our collaboration with rare disease stakeholders to develop practical solutions and achieve meaningful outcomes for patients. ⟶

Case Studies

See More

Case Study

Payer and Contracting Strategy

Avalere developed VBA construct pilots, simulated pilots in data, and designed implementation playbook

Challenge

A gene therapy manufacturer was interested in assessing VBA opportunities for its pipeline rare disease gene therapy, in simulating VBA pilots in data, and thinking through key implementation considerations.

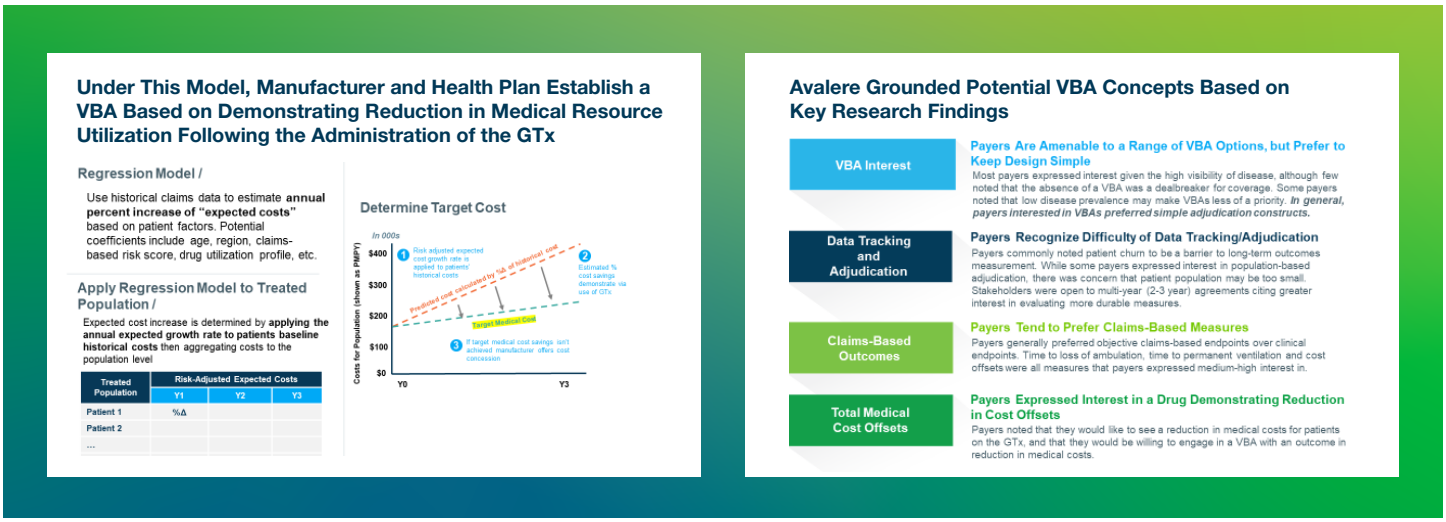
Solution

- We developed 5 separate claims-based and/or clinical-based VBA construct pilots (including a TCOC model) to help assess potential challenges, opportunities, limiting factors, and gaps in knowledge of each construct.
- We developed a regression-based model to assist in understanding the historical as well as predicted costs of patients.
- Then, we assisted client in prioritizing constructs and outlining steps for implementation.

Results

The findings provided the client with a roadmap for VBA constructs and allowed the client to understand the potential risk exposure and opportunities associated with the constructs.

TCOC: Total Cost of Care;
VBA: Value-Based Arrangement



Case Study

Scientific Advice to Inform Value Proposition

Avalere conducted reimbursement landscape assessment followed by US and ex-US advisory boards

Challenge

A client sought scientific advice on clinical development plan for the asset indicated for an ultra-rare neurodevelopmental disorder. The client also sought to understand what activities they could undertake to ensure successful product launch in the US and ex-US markets.

Solution

We conducted analog assessment to better understand reimbursement challenges for URD-indicated drugs. Findings from the secondary research informed the facilitation of US and ex-US (United Kingdom, Germany, France, Spain, Italy, Canada) advisory boards and IDIs with payers from Japan and Australia.

Results

We helped the client to identify reimbursement and access challenges and refine its pricing strategy. This engagement also deepened client's understanding of how regulators, payers, and HTA bodies assess different clinical trial endpoints, which will enable more refined future clinical trial designs that maximize the value propositions and reimbursement potential for its products.

HTA: Health Technology Assessment;
IDI: In-Depth Interview;
URD: Ultra-Rare Disease



Case Study

Clinical Development Program Validation and Value Proposition Assessment

Avalere conducted primary research across US and ex-US markets to validate clinical development program

CDP: Clinical Development Program;
FFS: Fee-for-Service;
HTA: Health Technology Assessment

Challenge

A client wanted to explore nuances of coverage and reimbursement of a novel treatment for an ultra-rare heterogeneous disorder affecting brain white matter and to validate coverage and utilization management decision-making processes. The client also sought to gauge theoretical product coverage, as well as attempt to gauge reimbursement levels across a representative mix of payers.

Solution

- We conducted in-depth interviews with experts from a range of health plans that cover multiple books of business (commercial, Managed Medicaid, Medicaid FFS) across different payer sizes and regions.
- We also conducted in-depth interviews with HTA advisors from each of the other nations of interest: Germany, Spain, United Kingdom, Japan.

Results

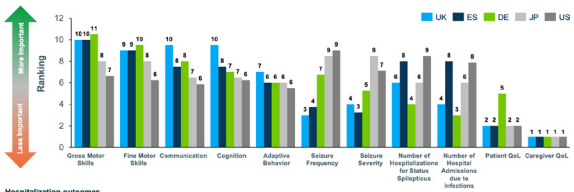
The client incorporated the outputs of the secondary and primary research and final recommendations into the refined product value proposition. Our recommendations informed client's access and reimbursement considerations and pre-launch activities across studied markets.

Improvements in 2-3 Neurodevelopmental Outcomes Drove Higher PMA Potential for Ideal/Full Approval Profiles

	Estimated price range[1]	Ideal TPP		Minimum TPP		Accelerated/conditional approval scenario[2]		Full approval scenario[3]	
		Payer /HTA outcome	Change in pricing	Payer /HTA outcome	Change in pricing	Payer /HTA outcome	Change in pricing	Payer /HTA outcome	Change in pricing
US	$200,000 - $700,000	●	—	●	—	●	—	●	—
UK	$13,000 - $276,000	●	—	●	▼	●	▼ $126K	●	—
ES	$13,000 - $274,000	●	—	●	▼	R	No pricing comments	●	▼ NS seizures (pre-epileptic population)
DE	$13,000 - $274,000	●	—	●	▼	●	No pricing comments	●	No pricing comments
JP	$13,000 - $754,000	●	—	●	No pricing comments	●	No pricing comments	●	No pricing comments

Likelihood of favorable reimbursement/HTA outcome: ● Low ● Medium ● High
R Restricted to a pediatric population ▼ Decrease in stated average price — No change in stated average price

Average Ranking* of Outcomes in Coverage and Reimbursement Context
with 11 Being Most Important and 1 Least Important



Hospitalization outcomes

- **US:** hospitalization outcomes related to seizures and infections were considered the most important outcomes. US payers stated clear preference for outcomes that demonstrate cost savings and improved survival of patients with MOS
- **Ex-US:** generally, functional and developmental outcomes were valued more highly than hospitalization and QoL outcomes

"From a plan point of view, it would be those things that cost you money, which is the hospitalizations. The rest of it is immaterial to a healthcare plan. QoL doesn't matter. Cognition doesn't get you in the hospital. The two main ones [seizures and infections] are the ones in the middle with hospitalizations." – US2
"QoL does not matter in Spain for pricing and reimbursement." – ES1
"I would generally put patient QoL first [in terms of ranking outcomes pricing and reimbursement decisions]. But in terms of the specifics, I pick out cognition and communication as the main, then motor, then adaptive behavior." – UK1

Case Study

Payer Mix Analysis

Avalere analyzed the payer mix to determine patient populations of a rare neuromuscular disease and rare chronic inflammatory disease

ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; **ACS:** American Community Survey; **CMS:** Centers for Medicare & Medicaid Services; **MMC:** Medicare Managed Care Manual; **H-CUP NIS:** Healthcare Cost and Utilization Project National Inpatient Sample; **QE MBFS:** Qualified Entity Master Beneficiary Summary Files; **MORE:** Medical Outcomes Research for Effectiveness and Economics Registry®; **FFS:** Fee-for-Service

Challenge

A client had a drug in clinical trials to treat a rare neuromuscular disease and a rare chronic inflammatory disease that cause organ damage. The client was seeking to identify respective patient populations before applying for a new ICD-10-CM code.

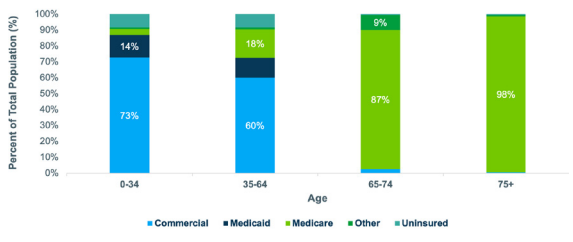
Solution

- We gathered data from ACS, CMS MMC, H-CUP NIS, and CMS QE MBSF.
- We utilized the Inovalon MORE 2® Registry private claims data and 100% Medicare FFS claims data to define selection criteria for the two patient populations.
- We used selection criteria and data to calculate, model, and identify the disease populations within Medicaid, Medicare, commercially insured, and uninsured patients.

Results

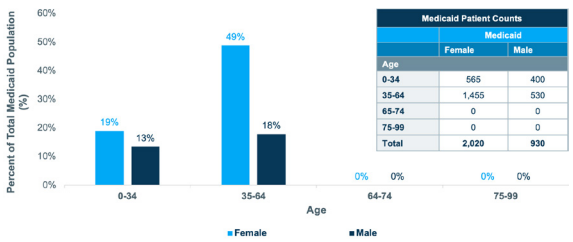
We detailed the payer mix of the neuromuscular and inflammatory disease patients for the client. The analysis allowed the client to understand the target patient populations and develop channel-specific strategies for its drug.

Age by Insurance Type, 2-Year Average



Almost 20% of patients ages 34 to 64 have Medicare coverage, indicating that these patients likely have a disability or other condition qualifying them for coverage before the age of 65

Medicaid Insurance by Age and Gender, 2-Year Average



Medicaid Patient Counts		
	Medicaid	
	Female	Male
Age		
0-34	565	400
35-64	1,455	530
65-74	0	0
75-99	0	0
Total	2,020	930

Medicaid patients comprise 9% of the total payer mix. Of the patients with Medicaid coverage, 68% are female and 32% are male

Case Study

Quantification of Rare Disease Burden

Avalere holistically quantified the total burden of disease for a rare neuromuscular disease

Challenge

A client was interested in quantifying the total disease burden for a rare autoimmune neuromuscular disease in a holistic way that considered the implications for patients, caregivers, and society at large.

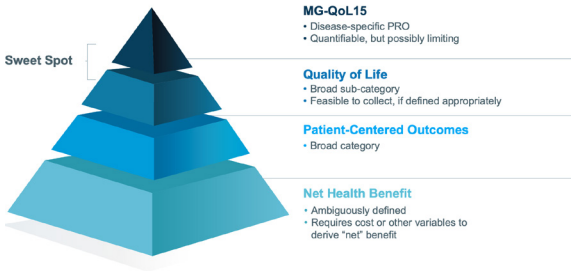
Solution

- We established a novel approach for incorporating patient perspectives into economic and value assessments.
- We identified key patient and caregiver "impact elements" to develop a model that more accurately quantified total disease burden.

Results

We provided insights into innovative methods for evaluating the cumulative disease impact. The client will use the novel approach when communicating the disease burden to stakeholders.

Illustrative Example: Value Framework Elements Vary in Their Level of Specificity



Avalere will aim to synthesize the patient-reported impact elements into inputs for the gMG algorithm that are measurable, feasible to collect, yet sufficiently broad

Best Practices for Incorporating PP in Economic and Value Assessments

Barriers[1]	Strategies[2]
Time constraints, complexity and heaviness of the approach in the HTA context (e.g., ethical review board)	Focus on specific questions: well-targeted consultation objectives and specific dimensions to be analyzed
Lack of financial and human resources in HTA units with limited hospital budget	Collaborations between HTA agencies on common projects and sharing of tools Find complementary funding opportunities
Perception of lack of rigor sometimes associated with qualitative studies	Adopt rigorous qualitative research approaches Use staff trained in social research
Difficult to recruit patients	Recruit patients through clinicians, users committees or patient associations
Integration of information coming from patients in the HTA report	Clearly define at the beginning of the process the objectives of patient consultation
Complexity of the exercise in multicultural contexts	

Case Study

Mapping Orphan Drug Policies and Pathways Across 12 Markets

Highlighting challenges and opportunities for the pipeline and strengthening the global value dossier

Challenge

A large biopharmaceutical client with a pipeline of drugs in development for rare diseases wanted to comprehensively map the P&R policy environment and understand potential market access pathways for orphan drugs in 12 countries globally.

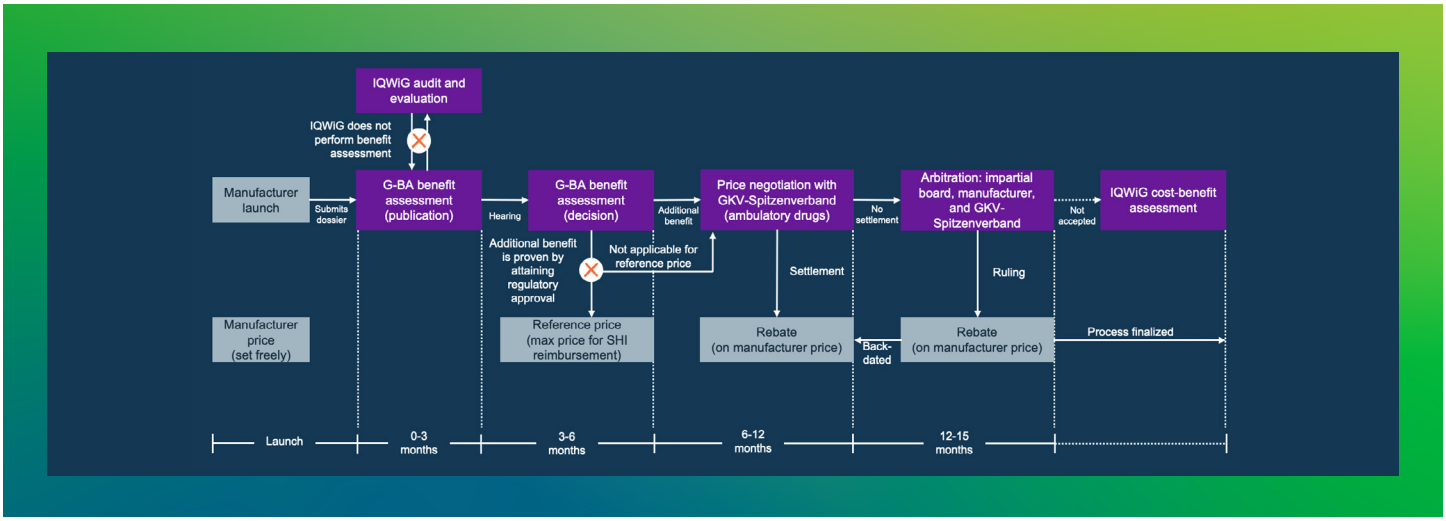
Solution

To understand the HTA and P&R of orphan drugs in the 12 countries, we conducted a literature review on the policy landscape, access and funding pathways, and payer evidence requirements. In addition, we reviewed HTAs of specific orphan drugs to gain additional insights into the evaluation process for this drug type. Semi-structured interviews were conducted with one or two payers in each scope country to validate findings and answer any remaining questions that arose during secondary research.

Results

- We comprehensively mapped the current and emerging policy landscape and access pathways for orphan drugs.
- We highlighted insights into the opportunities and challenges for orphan drugs in the client's pipeline.
- The final report provided content that could be included in global value dossiers as environmental context.

HTA: Health Technology Assessment;
P&R: Pricing and Reimbursement



Case Study

Payer Value Propositions Across 21 Markets

Global post-launch market access strategy to improve and extend in-market patient access

Challenge

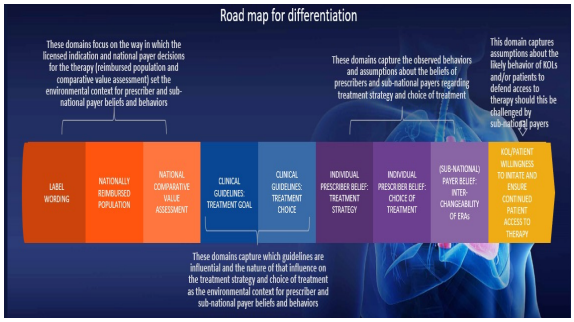
A competitor's loss of exclusivity posed a risk to the client's value proposition across the portfolio of rare disease therapies, potentially triggering sub-national payer re-evaluation. The client sought a partner to support a collaborative evaluation of the risks and action planning across 21 markets.

Solution

We facilitated a collaborative deep dive into each market to better understand the market access landscape. We identified a set of barriers and levers and created a common language framework for sharing learnings across the diverse markets. An interactive playbook captured cross-functional action plans for global and regional teams so that markets could network and to help the client's senior leadership team understand the situation and plan.

Results

Our structured methodology to challenge, capture, and theme individual market situations enabled the client to be fully engaged in the brainstorming and problem solving. The client was able to leverage learning to re-state the portfolio payer value proposition and maintain best achievable patient access jointly across the in-market cross-functional teams.





Case Study

Early Cost-Effectiveness Modeling for an Innovative Gene Therapy for a Rare Visual Disorder

Pragmatically informing strategies on pricing, trial design, and research prioritization to support commercialization decision making

Challenge

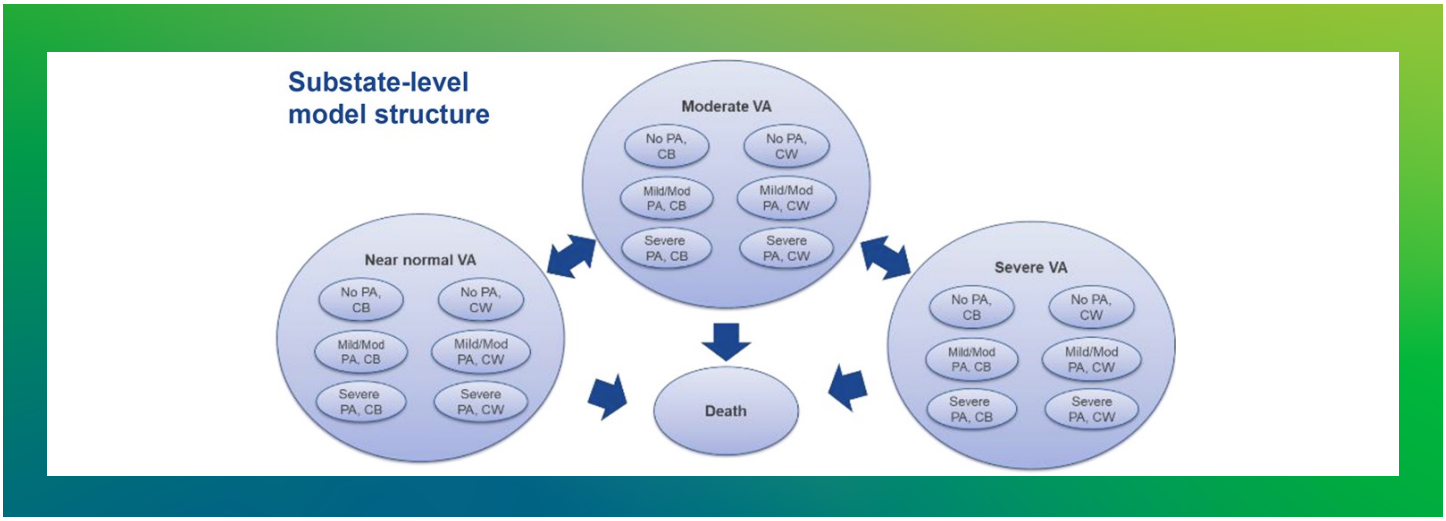
The client wanted to develop an early economic model for a gene therapy indicated for a rare visual disorder. Consideration was given to the treatment pathway, key cost drivers, and areas of uncertainty. Potential cost offsets and evidence gaps were identified.

Solution

We reviewed relevant literature in achromatopsia and X-linked retinitis pigmentosa to identify economic data and past models to inform the technical approach, which we validated with the client during a workshop. We conducted primary research with clinical experts to validate assumptions and develop a clinically representative model structure. The final model incorporated validated outputs and was tested by internal health economists. We facilitated a workshop to discuss the impact of the results on commercialization and recommended evidence generation plans.

Results

This project allowed the client to rely upon robust and pragmatic health economic modeling techniques to inform strategies on pricing, research prioritization, Phase 3 trial design, and mitigation challenges. This exercise helped the client make informed decisions about commercialization of its gene therapy being trialed for achromatopsia.



Case Study

Market Access Roadmap for a Novel Gene Therapy in Development: Hemophilia B

Gaining a clear understanding payer evidence requirements in major European markets

HEOR: Health Economics and Outcomes Research;
HTA: Health Technology Assessment;
P&R: Pricing and Reimbursement;
TPP: Target Product Profile

Challenge

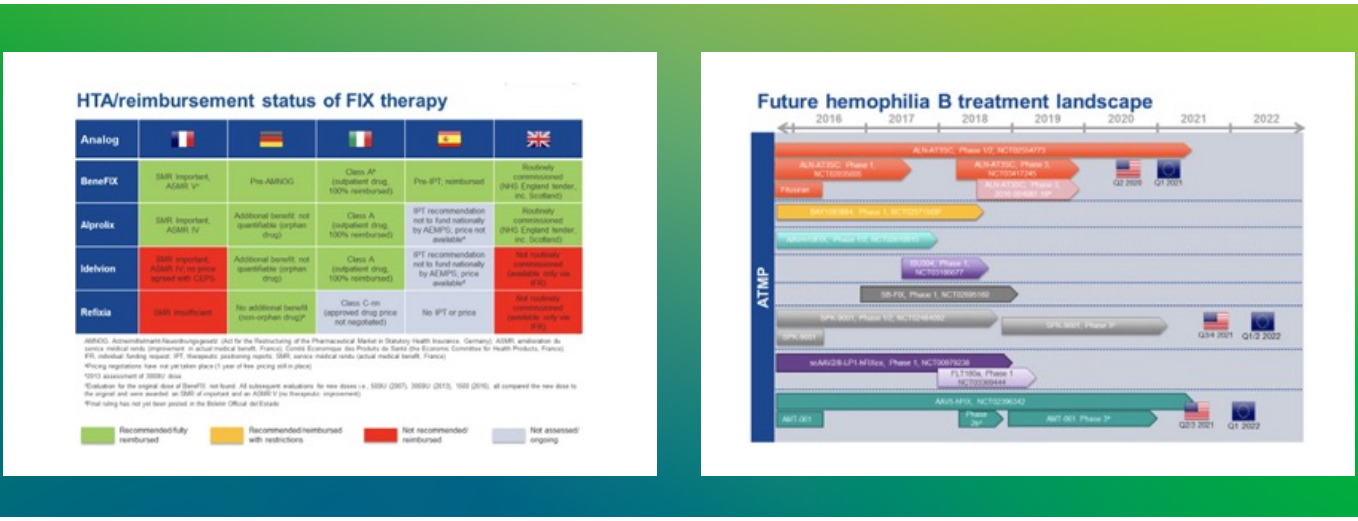
A small biotech company specializing in gene therapies was developing a novel, potentially curative treatment for hemophilia B and wanted to understand the market access opportunities and challenges and develop a market access roadmap for the gene therapy in Europe.

Solution

We conducted an HTA/P&R review of current and pipeline Factor IX (FIX) therapies to better understand competitive landscape. A critical review of the clinical trial and TPP versus payer requirements allowed to identify critical success factors and key vulnerabilities, which we used to develop evidence generation and mitigation strategies. A final roadmap detailed timelines, sequence of activities, objectives, methodology, risks, budget, and financial forecast breakdown.

Results

The executive team gained a clear understanding of HTA/P&R processes, payer evidence requirements, current and future FIX therapy landscape in major European markets. Based on the report, the company invested in a market access/HEOR team to implement the recommendations for evidence generation priorities and supporting activities as they prepare for launch of novel gene therapy.



We Know Healthcare.

Trusted Partnership.

Avalere, a US-based consulting firm, and **Avalere Health**, a global commercialization partner, offer deep expertise in rare disease treatment development and commercialization.

Experience that Matters.

Our subject matter experts advise throughout the lifecycle of a rare disease product, from clinical development planning to evidence generation, regulatory strategy development, and market access approaches.

Strategy Realized.

We also provide in-depth perspectives on the diagnostic odyssey, application of digital health technologies in the rare disease space, and domestic and ex-US policy developments in order to maximize access and benefit for patients.

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About Us

A healthcare consulting firm for more than 20 years, Avalere partners with leading life sciences companies, health plans, providers, and investors to bring innovative, data-driven solutions to today's most complex healthcare challenges.

Avalere is part of **Avalere Health**. We partner with its Global team across markets and regions to help clients navigate complex healthcare ecosystems and make better health happen.

For more information, please contact **info@avalere.com**. You can also visit us at **avalere.com**.

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