Avalere Health™

Volume 3 / 2026

Rare disease biotech landscape

February 2026

EVERY PATIENT POSSIBLE

Contents

Meet Avalere Health's Advisory experts

Avalere Health's Advisory team serves clients across the healthcare ecosystem, building actionable strategies and data-driven solutions that anticipate and adapt to the latest industry trends, so we can reach EVERY PATIENT POSSIBLE—now and in the future.

Partnering with our global Medical and Marketing experts at Avalere Health, we are uniquely positioned to understand every angle of life, health, and the human condition. Together, we are building a world where healthcare is not a barrier. And no patient is left behind. Discover our full service offering across the product lifecycle.

Introduction

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 also to their caregivers, regulators, pharmaceutical manufacturers, policymakers, and other stakeholders. Given that fewer than 10% of these conditions have any available treatment options, there is a significant unmet need in this space.

In this edition of the eBook, Avalere Health's Advisory experts describe their first-hand experience with the rare disease sector, identify regulatory avenues and mechanisms for manufacturers to pursue when developing treatments for rare disease, provide an overview of evidence generation strategies to fill data gaps that are inherent to small patient population numbers, and dive into niche topics, such as gene therapy stewardship across healthcare systems and multistakeholder collaboration to drive access in Asia-Pacific.

The journey to be heard

Mariia Salova, Senior Research Scientist

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Protecting the future of rare disease care

Recently, the Department of Health and Human Services (HHS) terminated the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). Since 2003, the ACHDNC's role has been to advise the HHS Secretary in recommending states to include specific disorders in their newborn screening panels, along with technologies, policies, and guidelines.

When the news about the ACHDNC termination came out, it raised significant concern in the rare disease community. Eliminating the ACHDNC means that states are left with no clear, evidence-based guidance, increasing the risk that children with rare but treatable conditions will go undiagnosed. This action by the HHS will exacerbate our lack of knowledge about rare diseases. It reminded me of my own feeling of helplessness when I encountered my first patient with a rare disease.

During my medical student years, I studied multiple common conditions.

However, rare diseases were never brought up in the classrooms. It's not uncommon for medical students around the world to not have any information or interactions with patients who have one of more than 10,000 possible rare diagnoses.

I was a medical student at the Okhmatdyt Children's Hospital in Ukraine—which was bombed during the Russia-Ukraine war on July 8, 2024— when I met a young boy with a rare neuromuscular disorder. At only eight years of age, he had already spent most of his life in multiple hospitals. Without an accurate diagnosis or effective treatment, we could only offer him supportive care while witnessing his diminishing quality of life. During my residency, I spent a significant amount of time at an oncology center in Kyiv. While I had rare disease patient encounters, accurate diagnoses were sparse, and most of our patients were referred out to specialized centers or abroad.

When I moved to the US, I knew that I would not be able to practice medicine because the healthcare system here has an entirely different patient care structure. After graduating from Johns Hopkins University, Market Access presented a unique opportunity for me. I can apply my clinical background, passion for medicine, and desire to help patients while also helping life sciences companies develop and execute product launch strategies and lifecycle management.

Ensuring that patient needs are conveyed through advocacy, congressional representatives, and other stakeholders will protect the progress made to date and prevent stalled efforts or lost achievements.

> **While significant strides in scientific discoveries have been made and we have a deeper understanding of rare diseases, this administration is now creating barriers to continuing these advancements. The recent HHS cuts, the tariffs' impact on health systems and pharma investments, and even pricing reforms could push our focus on rare diseases backwards. With the termination of the ACHDNC, which gave patients the voice they needed to be heard, it is up to the rare disease community to take on that role.**

The life sciences industry must work with patient advocacy groups to make certain that patient voices are translated into clinically meaningful therapeutic advancements. We must continue to work hard and persevere.

FDA programs offer advantages for manufacturers in rare disease space

Megan Hall, FDA Fellow; Rosalie Hoyle, Research Scientist I;
Mariia Salova, Senior Research Scientist

Manufacturers can accelerate innovation and improve rare and ultra-rare disease therapy access by leveraging new and established regulatory pathways.

Introduction

Rare disease drug developers face specific challenges not encountered by developers of drugs for common diseases, such as geographically dispersed and small patient populations, prolonged trial recruitment periods, and a lack of approved biomarkers, among others. Several programs at the Food and Drug Administration (FDA) incentivize the development of drugs for rare diseases and help fill the treatment gap for patients with these conditions. Herein, we discuss regulatory pathways and designations that manufacturers in the rare disease space can utilize.

Overview of established and novel FDA programs

While the FDA has several long-established pathways, designations, and voucher programs to accelerate drug development and approval timelines, only one is specific to rare disease drug development: the Orphan Drug Designation (ODD). Irrespective of rare disease focus, many drugs in development for rare diseases will also meet the eligibility requirements for Accelerated Approval and/or Fast Track or Breakthrough designations. Table 1 details eligibility requirements and benefits associated with the various FDA programs.

Table 1. Overview of rare disease-specific FDA programs

Program/initiative	Eligibility criteria	Potential benefits
Orphan drug designation	• Drug is for a disease or condition that affects fewer than 200,000 people in the US; OR • Drug is for a disease or condition that affects more than 200,000 people, but for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the US	• Tax credits for clinical trial expenses • Exemption from user fees • Study design assistance • Eligibility for Orphan Products Grants Program • Two additional years of market exclusivity
Rare disease endpoint advancement pilot	Drug for rare diseases with novel efficacy endpoints	Additional FDA assistance and meetings
Rare disease evidence principles	Drugs that treat genetic causes of ultra-rare diseases with unmet need	FDA approval based on a single clinical trial with confirmatory evidence

Recently, the FDA has demonstrated its growing support of the rare disease community and associated challenges with drug development in this space. In July 2024, the FDA introduced the Rare Disease Innovation Hub, which leads several new initiatives and programs that specifically address rare disease drug development hurdles and provide certain benefits or incentives for manufacturers to leverage (i.e., the Rare Disease Endpoint Advancement Pilot and the Rare Disease Evidence Principles).

The Hub also coordinates rare disease efforts across the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, and engages with the rare disease community through its Rare Disease Innovation, Science, and Exploration workshop series.

The FDA's newest initiative related to rare diseases is the proposed Plausible Mechanism Pathway for personalized therapies with known specific biological causes. While program details are still in development, this pathway may be useful for antisense oligonucleotides and gene-editing treatments for ultra-rare diseases, as it may lead to market approval following successful clinical "n of 1" studies.

Additionally, the Commissioner's National Priority Voucher Program—which is not limited to rare diseases—has been awarded to 18 drug products across various diseases with unmet needs and stages of development since the pilot program launched in June 2025. Recipients in the rare disease space include drugs in development for multiple myeloma, sickle cell disease, drug-resistant tuberculosis, and porphyria.

Recent policy developments

In early February, Congress reauthorized the Rare Pediatric Disease Designation and Priority Review Voucher (RPD Designation and PRV) program through the Consolidated Appropriations Act of 2026. Created in 2012, this program incentivizes the development of treatments for rare pediatric diseases by granting RPD approvals with a voucher that expedites review timelines to six months.

The FDA's newest initiative related to rare diseases is the Plausible Mechanism Framework for personalized therapies with known specific biological causes. In late February, the FDA published a draft guidance providing new details on the framework's safety and evidentiary standards, including the potential use of master protocols, hybrid study designs, external control arms,

and New Approach Methodologies. This pathway may be useful for antisense oligonucleotides and gene-editing treatments for ultra-rare diseases, as it may lead to market approval following successful clinical “n of few” studies.

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Dive deeper

There are several regulatory assistance programs available to help manufacturers in the rare disease space which reduce development burdens and may enhance the market viability of their products. Importantly, a single product may qualify for and participate in multiple programs simultaneously. By strategically leveraging these regulatory pathways, manufacturers can accelerate innovation and improve access to much-needed therapies for patients with rare and ultra-rare conditions.

Avalere Health applies expertise in FDA regulatory strategy and evidence generation planning to access strategies for rare disease treatments, helping rare disease drug developers and patient advocacy groups meet their objectives.

Can RWD and RWE influence decision-making in orphan drugs?

Shelby Harrington, Managing Director;
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***Disclaimer:** This article was originally published by Med Ad News/PharmaLive.*

In recent years, within the United States and Europe, we have witnessed the growing utilization of real-world evidence (RWE) in drug approval submissions at both the regulatory and payer levels incorporated in awareness campaigns, disease education, and even in policymaking in some markets. For rare and ultra-rare diseases specifically, the use of real-world data (RWD) and RWE by life sciences companies can help address the unique challenges during the patient-focused drug development process, conceptualize and supplement traditional randomized controlled trials (RCTs), and inform regulatory and/or payer decision making.

Although the practical applications of RWD/RWE differ between the United States and Europe, and the use of such evidence in the rare and ultra-rare disease category has methodological shortcomings, different approaches can be utilized to overcome these limitations and successfully optimize the robustness of outputs and relevance for key decision-makers in those regions.

Randomized controlled trials (RCTs) remain the gold standard for assessing treatment efficacy and safety, serving as the foundation for drug approval in

most diseases. However, RCTs are expensive, time-consuming, and often are either placebo-controlled or use active comparators that do not reflect clinical practice. In rare and especially ultra-rare diseases, conducting RCTs may be either unethical due to control arm requirements or not feasible because of tiny patient populations that are geographically dispersed across the globe.

Recognizing these limitations, regulators and payers are increasingly more receptive to incorporating RWE into their decision-making processes. This creates opportunities for lifesciences companies to collaborate with patient advocacy groups on generating RWD/RWE and utilizing it in awareness campaigns, disease education, and in advocating for policy changes that could promote not only earlier product commercialization but also patient access.

U.S. regulatory considerations

The FDA defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." These sources include electronic health records (EHRs), medical claims, disease or drug registries, and data collected from digital health technologies. The FDA defines RWE as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."

Although the FDA has a long history of using RWD/RWE for post-marketing drug safety monitoring, it was only in 2018 that the FDA created a framework for evaluating the potential use of RWE to help support drug approval or satisfy drug post-approval safety requirements. The framework builds on the 21st Century Cures Act enacted on December 13, 2016, intending to expand the application of RWE.

Additionally, the FDA continues to issue rare disease-specific guidance documents that provide recommendations to the industry on rare disease drug development approaches, including the use of RWE. For instance, the FDA guidance on the use of EHRs and medical claims data highlights not only the agency's openness to integrate RWE into regulatory decision making but also opportunities for the industry to reduce R&D costs when developing drugs for rare diseases.

The FDA has several guidance documents outlining patient-focused drug development (PFDD). These documents emphasize the importance of a systematic approach to help ensure that patient experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug

development and evaluation. Furthermore, the agency's perspectives outlined in PFDD documents can inform and guide more efficient drug development and longitudinally support activities beyond drug approval.

Another critical guidance for manufacturers in the rare and ultra-rare disease space is the use of natural history studies (NHSs) in the drug development process. NHSs present a unique opportunity for manufacturers to not only leverage data to better understand the natural disease progression, but also to evaluate the impact of treatments on the disease; use NHS as an external control arm (ECA) for regulatory purposes; and educate payers through value communication approaches. Although the use of NHSs and other RWD as an ECA has limitations (e.g., differences in baseline patient characteristics, imprecise population matching techniques, subjectivity in defining study endpoints, selection bias, etc.), the FDA has provided positive feedback on manufacturer applications containing ECA and incorporated these data into the drug labels.

Regulatory and payer considerations in Europe

The role of RWE in decision making is an increasing priority for both the European Medicines Agency (EMA), national regulators, and health technology assessment (HTA) bodies. This is reflected by the proliferation of guidance and perspectives on RWE/RWD from relevant agencies published in recent years, although the tangible impact on decision-making is yet to be fully realized.

Currently, the most common use cases for RWE in regulatory and HTA submissions are characterizing disease epidemiology and treatment landscapes; demonstrating unmet need; and providing supplementary evidence to clinical trial data or post-marketing surveillance efforts. In some markets, RWE is an increasingly common requirement to support reassessments and/or satisfy requirements of conditional approvals. Regulators and payers have also recognized the potential value of RWE to support comparative effectiveness claims and better reflect real-world clinical practice via, for example, "pragmatic" RCTs.

Despite broad recognition of the potential value of RWE in drug approvals, in practice, the impact and acceptability of RWE on marketing authorization and national pricing and reimbursement decisions remain limited. While key

stakeholders across markets and organizations agree that RWE has a role to play in supporting evidence to complement clinical trial outcomes and mitigate uncertainty, the widespread preference for RCTs and real/perceived limitations of RWE continue to be a barrier to its use as a primary source of clinical effectiveness evidence for initial drug approvals. Furthermore, a lack of consensus between regulators and payers across markets on how and when to leverage RWE in decision making impedes widespread acceptability and influence. This also poses challenges for manufacturers when designing RWE generation strategies to satisfy the needs of a range of stakeholders across markets.

In rare and ultra rare diseases, specific approval pathways exist for drugs with orphan designation in some markets (e.g., UK, Germany) with a goal of mitigating some of the challenges (e.g., cost-effectiveness thresholds, process timelines, etc.) traditional approval pathways pose for disease areas with such small patient populations and limited (if any) alternative treatment options. However, the evidentiary standards typically remain consistent with those of non-orphan drugs, posing unique challenges for disease areas with small, dispersed patient populations where RCTs are often not feasible or — where no alternative treatment exists — unethical to conduct.

For patients, the culmination of these challenges can lead to suboptimal access to treatment. Not all technologies that receive marketing authorization from the EMA secure national reimbursement when assessed by HTA bodies. Similarly, while conditional approvals often require RWE collection to remove restrictions, it can take a long time to capture sufficient data to meet evidentiary standards. In turn, this creates health disparities in accessing orphan drugs across Europe.

“For patients, the culmination of these challenges can lead to suboptimal access to treatment. Not all technologies that receive marketing authorization from the EMA secure national reimbursement when assessed by HTA bodies. Similarly, while conditional approvals often require RWE collection to remove restrictions, it can take a long time to capture sufficient data to meet evidentiary standards. In turn, this creates health disparities in accessing orphan drugs across Europe.”

It is well recognized that to optimize patient access, there is a continued need for future policy evolution to enhance the acceptability of RWE in regulatory and national payer decision-making.

Translating stakeholder needs into evidence generation strategy

For life sciences companies, these sometimes conflicting and yet-to-be-codified signals on the use of real data for regulatory and payer decision making can be frustrating and cause hesitancy to invest in robust RWE generation strategies. But the fact remains that as health care has become more complex, the demand for data from a widened circle of stakeholders has risen exponentially.

In an earlier era, the needs of regulatory/national HTA bodies and prescribers were prioritized and consequently met through data from clinical trials curated with those stakeholders' informational needs in mind (and centered around development of therapies for more common conditions). In contrast, today's healthcare decision makers include subnational payers, population health leaders, quality leaders, and patients themselves. Even prescribing providers are asking for evidence that goes beyond clinical efficacy since they are practicing in a world where patients are engaged in shared decision-making that reflect their personal preferences, priorities, and goals for treatment. RWE is a critical tool to meet these more diverse needs for understanding how a new treatment changes the status quo; how it impacts patients in real-world settings; and how to quantify long-term impacts.

> **Professionals developing evidence generation strategies must consider that to accurately demonstrate the benefits of a therapy, there must be an established evidence base clearly describing the experience of disease and (if applicable) the experience of the current standard of care against which to compare a new therapy. RWD has the advantage of being able to elucidate both the effects of a treatment as well as the unmet need in a condition's current therapeutic landscape.**

One of the shortcomings of clinical trial data is that it rarely captures the impact of the disease prior to the study, nor the longitudinal experience

and impacts over long time periods. Traditional RWD sources like claims and EHR can address this shortcoming by looking at the clinical, utilization, and cost impacts of the disease prior to the initiation of treatment and/or for years after a treatment began. These are critical contextual information for payers determining cost-effectiveness of new therapies and for providers considering the holistic risks and benefits for their patients. These real-world patient experiences can further be explored using non-traditional sources of data like disease-specific clinical registries, wearable devices, and patient-reported data from surveys, interviews, focus groups, or online communities. The latter can be especially insightful in rare disease when gathered and analyzed by experts in qualitative research, given the lack of concentrated populations of patients within specific geographies or clinical sites.

Strategic considerations in selecting RWD sources should be a primary criterion of the evidence generation plan, considering the key questions that each stakeholder needs addressed in the resulting evidence. For example, can the data source illuminate the experience of patients being cared for in non-academic, non-clinical trial settings? How does the journey compare to those who receive care at centers of excellence or academic medical centers? Payers will be asking through the lens of total cost of care over time, while patients will be considering whether they can receive effective care in their own communities. These considerations on data sources and data collection methods are even more important in rare disease, where each disease's unique presentation and affected population can have implications for where to find appropriate data or how to generate it.

Despite the current obstacles, the promise of RWE and its potential to revolutionize how therapies are approved, how care is delivered, and how it is covered merits a strong focus and a dedicated strategy to optimize generation of evidence that meets all stakeholder needs.

Disease registries offer solutions in rare disease

Shelby Harrington, Managing Director;
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Disease registries can provide high-quality data and may serve as an additional resource when developing medical interventions for rare and ultra-rare diseases.

Components and considerations for disease registries

Disease registries are tools to collect, store, retrieve, analyze, and disseminate clinical and outcomes data for a predefined patient population. Registries can be sponsored by professional medical societies, patient advocacy organizations, government agencies, non-profit organizations, private companies, or healthcare facilities. While there is no centralized source that lists all registries available in the United States, the National Institutes of Health and National Organization for Rare Disorders have a comprehensive list of registries for both prevalent and rare diseases. Over forty of them were designed specifically for rare and ultra-rare diseases.

Establishing a disease registry is a multi-step process that requires a clear purpose and scope, assembly of a multidisciplinary team, a thoughtfully designed data collection, establishing governance and oversight plan,

and analysis and dissemination of findings. The patient population to be enrolled in the registry must be clearly defined before enrollment begins. Participants may enter a registry during a normal course of care such as through newborn screening programs, through recruitment into a research study, or through voluntarily participation in a self-identified registry.

Disease registries serve many purposes and have the potential to support researchers and manufacturers with drug development programs, inform the design of interventional and observational studies, enhance understanding of the natural history of a disease, and support the selection of appropriate endpoints and biomarkers that are associated with clinically meaningful outcomes. Furthermore, registries provide additional insights into an intervention (e.g., drug, device) and its efficacy and safety in populations underrepresented in clinical trials.

Multiple stakeholders can be involved in establishing disease registries, including regulatory agencies, patient advocacy groups, clinicians, key opinion leaders, scientists, payers, patients, and their caregivers. Collaboration between these stakeholders can drive not only research and development of new treatments but also lead to public policy changes and promote access to treatments. Various organizations around the world, including the National Organization for Rare Disorders in the United States recognize the challenges associated with data collection and clinical trial recruitment for rare and ultra-rare diseases, and have thus become advisors and supporters of rare disease registries.

Registries for rare and ultra-rare disease

While drug developers in the rare and ultra-rare disease space face many unique challenges, registries can help address some of them (Table 1).

Table 1. Registry benefits for rare and ultra-rare diseases

Program/initiative	Eligibility criteria
Disease heterogeneity	Rare diseases, even within the same category (e.g., leukodystrophies, mitochondrial disorders), vary greatly in their clinical presentation, severity, progression, prior exposure to different treatments, etc. Registries can help aggregate data on genotypically similar but phenotypically different conditions.
Disease natural history	Registries provide consistent updates on the patient's status throughout a predefined schedule that offers consistent, high-quality data on the natural progression of the disease. In addition, as more treatments extending the life span of patients with rare diseases become available, registries provide opportunities to learn more about the disease trajectory.
Establish the patient base for small, geographically dispersed populations	Data is typically collected in multiple institutions and geographic regions, providing comprehensive information on patients with rare and ultra-rare diseases who are dispersed throughout the country. Registries also support the shaping of the patient base for evaluating treatments, devices, and other medical interventions for clinical trial development programs.
Support development of biomarkers and clinically meaningful endpoints	Registries may involve the collection and storage of biospecimens that can be further studied as potential biomarkers for the establishment of clinically meaningful endpoints. Considering the lack of knowledge about many rare and ultra-rare conditions coupled with the lack of established and approved biomarkers, registries can help manufacturers overcome some of the barriers associated with limited data availability and limited knowledge.

Although registries provide significant opportunities, they do face headwinds:

- Disease registries lack the randomization factor, which has the potential to produce a skewed sample and biased data.
- Many registries exist in silos and there may be duplicate registries for the same condition, meaning that there is no centralized repository for the already small patient populations' data.
- There is significant variability in the depth and consistency of patient participation in registries.

Coordination of efforts among all stakeholders involved in registries, proper data management, standardized data collection methods, participant education, and confidentiality assurances are among the most important areas when planning and implementing disease registries. Before establishing a registry or leveraging an existing registry, drug manufacturers and diagnostics companies should have a comprehensive plan in place to ensure the data is of the highest quality and that the registry's approach aligns with their clinical development program goals.

Dive deeper

At Avalere Health, we apply our expertise in evidence generation planning and market access strategies to help stakeholders meet their business objectives through effective commercialization. We help clients address unmet needs in rare and ultra-rare diseases and develop comprehensive clinical development programs and evidence generation strategies.

Gene therapy in rare disease: From breakthrough to stewardship

Maria Katsarou, Associate Principal; Mariia Salova, Senior Research Scientist

As gene therapies for rare diseases scale, system readiness and long-term stewardship–not science alone–will determine access, impact, and sustainability.

Gene therapies for rare diseases are moving from isolated, one-off interventions to an established treatment modality with significant implications for healthcare delivery and system design.

By the end of 2025, the US Food and Drug Administration (FDA) had approved 26 gene therapies across in vivo, ex vivo, and cell-based platforms. After early, sporadic introductions, the period from 2022 to 2023 marked a clear inflection point, with multiple modalities simultaneously entering clinical practice. While activity appeared to slow in 2024, this reflects regulatory timing rather than a contraction in development momentum; 2025 signaled renewed activity across platforms and indications.

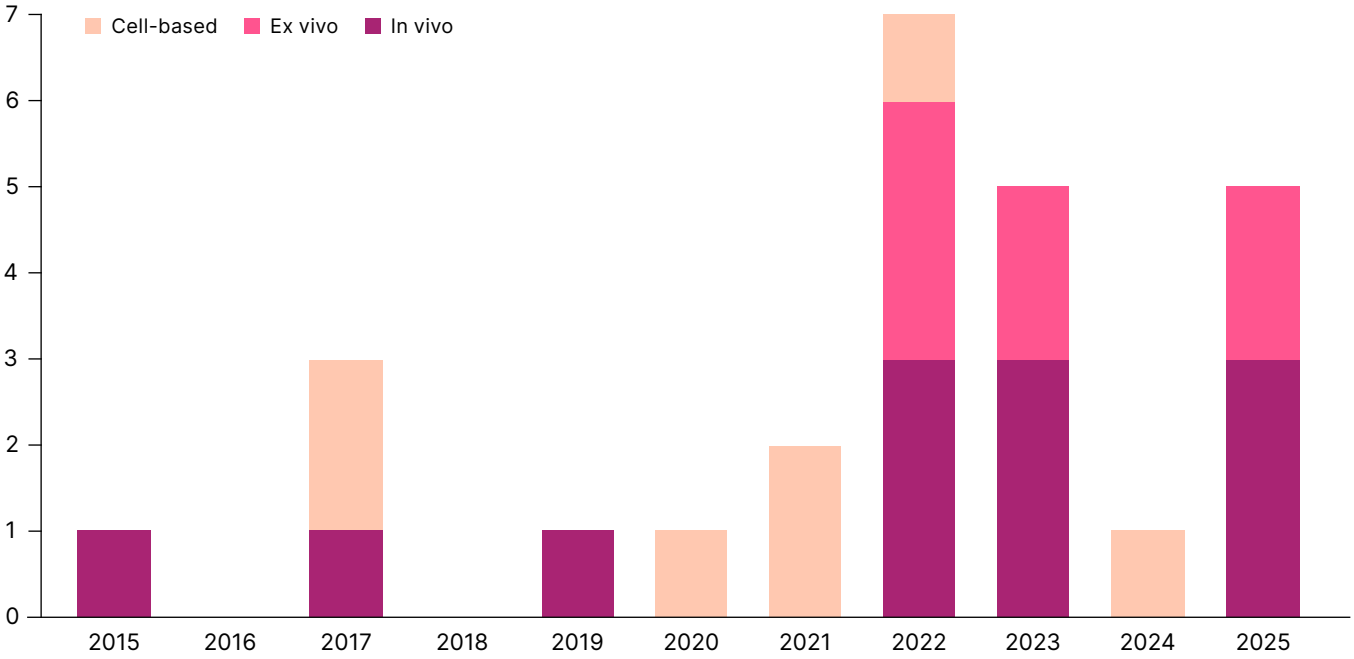
The majority of these gene therapies address rare or ultra-rare conditions, with each modality bringing distinct requirements for manufacturing, delivery, monitoring, and follow-up, thus increasing operational complexity as portfolios expand. This raises a core question for the rare disease sector: Can infrastructures built for scarcity sustain delivery, evidence generation, and oversight at scale?

Importantly, these therapies do not enter a neutral landscape. Rare diseases already carry substantial societal and economic burden. In the United States alone, the aggregate economic burden of rare diseases has been estimated at nearly $1 trillion annually when accounting for direct medical costs and indirect productivity losses across just 379 analysed diseases. Despite recent advances, fewer than 5% of rare diseases have an approved therapy, leaving the vast majority of conditions without effective treatment options.

Temporal mismatch: annual systems, multi-decade obligations

Gene therapies are typically administered once, yet their benefits, risks, and evidentiary obligations unfold over many years. By contrast, healthcare systems operate on annual budgets, short coverage horizons, and near-term evidence expectations.

Figure 1. FDA-approved gene therapies by modality and year (2015–2025)



Note: Excludes non–gene-modified cell therapies.

In the rare disease space, this misalignment is particularly acute. Prolonged diagnostic odyssey, narrow referral pathways, and concentrated specialist expertise already strain delivery. One-time interventions therefore collide with systems built for chronic management, creating pressure for redesigned care pathways, sustained monitoring infrastructure, and continuity of evidence over time.

This persistence is not discretionary. For many gene therapies, regulators require structured, long-term follow-up extending up to 15 years to monitor delayed safety signals and durability of effect. Delivery thus initiates an extended regulatory and operational commitment that sits uneasily alongside short-term funding cycles and fragmented accountability. The result is not simply a pricing challenge, but a structural tension between how gene therapies function and how systems are financed and governed.

Ownership mismatch: fragmented accountability over time

Responsibility for long-term outcomes is fragmented. Manufacturers may scale back involvement once post-approval commitments are met. Payers change as patients move across plans or geographies. Providers deliver a one-time intervention but are expected to monitor outcomes for years. Patients themselves bear potentially irreversible biological and financial risk. No single stakeholder experiences the full spectrum of benefits, costs, and accountability.

Rare disease ecosystems further complicate this picture by relying on non-commercial actors. Patient organizations, advocacy groups, and philanthropic entities have long been the driving force behind rare disease research prioritization, trial recruitment, and data generation. As gene therapies scale, these actors are increasingly drawn into post-market evidence generation and access discussions, often without clear governance structures, defined ownership, or sustained resourcing. Patients, caregivers, and patient advocacy groups should be involved in clinical development programs, regulatory conversations, commercialization phases, and post-marketing approval. Early and often engagement of these stakeholders at each phase of the drug development program increases chances of success.

Portfolio effect: when exceptions accumulate

Health systems can accommodate isolated exceptional therapies, but struggle when exceptions accumulate.

As developers build gene therapy portfolios, system impact becomes cumulative rather than product-specific. Infrastructure designed for scarcity, such as specialist expertise concentrated in centers of excellence, must now support multiple therapies in parallel. Requirements for delivery, monitoring, and long-term follow-up therefore stack across assets, rather than resetting after each launch.

Rare diseases have long functioned as proving grounds for innovation, driving advances in platform technologies, regulatory flexibility, and patient engagement models that later diffuse into broader medicine. As portfolios expand, however, gene therapy developers' role increasingly shifts from scientific experimentation to operational orchestration: coordinating shared infrastructure, aligning follow-up expectations, and sequencing launches to avoid system overload.

Without deliberate, portfolio-level planning, these cumulative demands risk constraining uptake, slowing access, and ultimately limiting the scalability of gene therapy innovation in the rare disease ecosystem.

Strategic implications for gene therapy developers in rare diseases

The shift from breakthrough interventions to enduring commitments carries clear implications for developers operating in the rare disease space:

Stewardship must be designed, not assumed: Long-term evidence generation, follow-up models, and data governance increasingly shape access and system confidence and must be considered and embedded early.

- **Portfolio strategy is now a system strategy:** As post-treatment delivery obligations accumulate across assets, launch sequencing, shared infrastructure, and capacity planning become central to sustainable growth.
- **Access strategy must account for ill-defined ownership:** Payer churn and diffuse accountability weaken incentives for improved access to these treatments unless addressed through aligned evidence and strong partnership models.
- **Trust is becoming a differentiator:** In the rare disease sector, where communities are tight-knit, and histories of unmet needs are long, sustained credibility with patients, regulators, and providers increasingly depends on developers' ability to plan for and support ongoing system responsibility.

Avalere Health supports a spectrum of stakeholders across the highly complex rare disease ecosystem in assessing system in assessing system readiness, quantifying long-term stewardship obligations, and designing access and evidence strategies aligned with the evolving realities of gene therapy portfolios.

Data supporting Figure 1

Year	Product	Indication	Modality	Delivery
2015	**IMLYGIC**	Melanoma	In vivo gene therapy	HSV-1
2017	**LUXTURNA**	Inherited retinal dystrophy	In vivo gene therapy	AAV2
2017	**KYMRIAH**	B-cell ALL / DLBCL	Cell-based gene therapy	CAR-T (LV)
2017	**YESCARTA**	Large B-cell lymphoma	Cell-based gene therapy	CAR-T (RV)
2019	**ZOLGENSMA**	Spinal muscular atrophy	In vivo gene therapy	AAV9
2020	**TECARTUS**	Mantle cell lymphoma / ALL	Cell-based gene therapy	CAR-T
2021	**ABECMA**	Multiple myeloma	Cell-based gene therapy	CAR-T
2021	**BREYANZI**	Large B-cell lymphoma	Cell-based gene therapy	CAR-T
2022	**SKYSONA**	Cerebral adrenoleukodystrophy	Ex vivo gene therapy	Lentiviral
2022	**ZYNTEGLO**	β-thalassemia	Ex vivo gene therapy	Lentiviral
2022	**LENMELDY**	Metachromatic leukodystrophy	Ex vivo gene therapy	Lentiviral
2022	**ROCTAVIAN**	Hemophilia A	In vivo gene therapy	AAV5
2022	**HEMGENIX**	Hemophilia B	In vivo gene therapy	AAV5
2022	**ADSTILADRIN**	NMIBC (bladder cancer)	In vivo gene therapy	Adenovirus
2022	**CARVYKTI**	Multiple myeloma	Cell-based gene therapy	CAR-T
2023	**CASGEVY**	Sickle cell disease	Ex vivo gene therapy	CRISPR-edited
2023	**LYFGENIA**	Sickle cell disease	Ex vivo gene therapy	Lentiviral
2023	**ELEVIDYS**	Duchenne muscular dystrophy	In vivo gene therapy	AAV
2023	**KEBILIDI**	AADC deficiency	In vivo gene therapy	AAV
2023	**VYJUVEK**	Dystrophic epidermolysis bullosa	In vivo gene therapy	HSV-1
2024	**AUCATZYL**	B-cell ALL	Cell-based gene therapy	CAR-T
2025	**ENCELTO**	Macular telangiectasia type 2	In vivo gene therapy	AAV
2025	**ZEVASKYN**	Dystrophic epidermolysis bullosa	Ex vivo gene therapy	Lentiviral
2025	**PAPZIMEOS**	Rare genetic disease	In vivo gene therapy	AAV
2025	**ITVISMA**	Spinal muscular atrophy	In vivo gene therapy	AAV
2025	**WASKYRA**	Rare immunodeficiency	Ex vivo gene therapy	Lentiviral

Source: FDA, https://pmc.ncbi.nlm.nih.gov/articles/PMC10609992/#sec4-pharmaceuticals-16-01416

Driving rare disease access in APAC through multi-stakeholder collaboration

Carol Kao, Associate Director; Rui Min Fung, Senior Consultant

Asia-Pacific (APAC) is home to more than 258 million persons living with a rare disease, yet only one-third receive the best available evidence-based care.

While each condition affects a small population, rare diseases collectively impose a substantial health burden across the region. Fragmentation across stakeholders remains one of the greatest barriers to patient access. For patients, these misalignments translate into delayed diagnoses, restricted eligibility, uneven geographic access, or no access at all. Unlocking sustainable access, therefore, requires a shift from siloed thinking to deliberate collaboration across the stakeholders in the rare disease ecosystem.

In 2025, Avalere Health's APAC team undertook a pro-bono initiative to (1) map the evolving roles of key stakeholders (including patient groups, payers, healthcare providers, and manufacturers) across emerging and established health technology assessment (HTA) markets in APAC, (2) identify critical barriers to interconnectedness, and (3) highlight case studies of successful collaboration that are positively reshaping the access landscape and fueling the rare-disease momentum in the region. This article summarizes the key insights from the initiative.

Patient groups as indispensable partners within the rare disease ecosystem

Patient groups sit at the center of the complex rare disease ecosystem, operating at the intersection of patients, clinicians, policymakers, payers, and manufacturers. By connecting stakeholders with differing priorities, they play a critical role in building disease awareness, amplifying patient voice, and supporting effective advocacy.

Beyond awareness and advocacy, patient groups in APAC play a key role in humanizing healthcare decision-making and pushing for patients' voices to be heard in supporting reimbursement decisions. While advanced HTA-implementing countries like Australia, Singapore, and Taiwan have formal patient input channels, in many emerging countries where formal processes are still lacking, patient groups are collaborating with other stakeholders, including manufacturers, and proactively ensuring their voices influence decision-making.

While these developments mark clear progress in collaboration with patient groups, resource constraints, rigid and complex evidence frameworks, and changing policy priorities remain barriers to impactful collaboration. One way in which inter-patient group collaboration is solving some of these challenges is by strengthening their collective voice. When patient organizations unite under one umbrella, rare diseases are no longer truly rare – strengthening advocacy and amplifying influence in decision making. Umbrella organizations and coordinated advocacy help to identify and connect unrepresented patients, support emerging rare disease communities to organize effectively, and strengthen patient–physician engagement by aligning clinical and lived-experience insights.

Case study: Hereditary angioedema in China

China's experience in hereditary angioedema (HAE) illustrates how patient groups are amplifying patients' influence in decision-making. With low awareness, frequent misdiagnosis, and no dedicated advocacy group, patients were previously largely unorganized. To address this, the Chinese Organization for Rare Disorders (CORD) helped identify patients, build a unified community, and strengthen engagement with clinicians; it also partnered with manufacturers to support access efforts. When the first HAE therapy received regulatory approval, this groundwork enabled more effective policy advocacy, contributing to inclusion in the basic medical insurance scheme and subsequent listing on the National Reimbursement Drug List.

Shaping the payer reality: Elevating the patient voice to drive reimbursement

Strong advocacy does not guarantee access, as reimbursement systems in APAC are not designed to incorporate patient experience into reimbursement decisions. Even in advanced HTA markets with established feedback channels, patient input has largely been limited to informing and consulting rather than influencing final outcomes. Recognizing this, payers are increasingly involving patients as active participants in the decision-making process.

However, patient involvement in reimbursement decision-making is only whalf the battle won. The experiences of people living with rare diseases and their caregivers can be excluded or insufficiently included within existing HTA evidence frameworks. When patient input is not structured in ways that fit appraisal needs, or when frameworks cannot incorporate that input, decisions tend to default to traditional metrics and models. This leads to delays, inconsistent decisions, and missed opportunities to align funding with real-world needs. To amplify the impact of lived experience in reimbursement decision-making, it is essential for stakeholders in the rare disease ecosystem to collaboratively address the following systemic barriers:

- Rigid evidence frameworks that struggle to incorporate patient-generated insights.
- Capacity constraints that limit the development of structured, credible inputs by patient groups.
- Unclear expectations about what types of patient input are useful, how they will be assessed, and how they affect decisions.

While significant gaps remain, especially in emerging markets, advanced HTA markets are making efforts to address these systemic barriers.

Case study: Patient involvement in Taiwan's Pharmaceutical Benefit and Reimbursement Scheme (PBRS)

A recent review of Taiwan's PBRS Committee meeting records and the Online Patient Opinion Platform revealed that patient involvement in HTA remained limited in practice. This gap was a central theme of a white paper published by the Taiwan Foundation for Rare Disorders in 2023, which called for strengthening patient participation, improving the integration of patient insights, and developing clearer guidelines for collecting and using patient input in decision-making. The white paper ultimately enabled patients to share their perspectives during PBRS committee discussions, rather than simply attending as observers.

A clear message from all stakeholders—that systems must make participation easy and purposeful, and patient groups must be supported to engage in informed, structured dialogue—is driving change.

Manufacturers have an important complementary role to play here by providing technical, evidentiary, and capacity-building support where appropriate, and helping to strengthen the quality and sustainability of patient engagement within established frameworks. For example, supporting digital and decentralized approaches to collecting patient input—such as mobile-based surveys, virtual consultation platforms, or social media channels—can help patient groups build broader patient participation and standardize the collection of patient input that meets rigid and complex evidence frameworks mandated by payers.

The need to go beyond reimbursement and address system-level challenges

Reimbursement alone does not determine access; access depends on whether the care pathway can deliver outcomes such as diagnosis, referral patterns, specialist capacity, and services. Many countries have established centers of excellence to concentrate expertise, coordinate care, and contribute to research, but their capacity and geographical reach vary widely, and implementation gaps exist even when needs are recognized.

Addressing this requires collaboration that moves beyond policy intent toward shared problem definition, with stakeholders jointly documenting pathway failures, quantifying diagnostic and referral delays, and aligning clinicians, patient groups, and policymakers around targeted service redesign priorities that translate identified access gaps into actionable system-level improvements.

Case study: Operationalizing low-burden patient input in Singapore

Singapore's Agency for Care Effectiveness (ACE) demonstrates how to operationalize patient input through low-burden, standardized tools such as structured surveys and patient journey forms. These are open to patients, carers, and groups, with templates in English and Mandarin to improve accessibility. ACE worked with local patient groups to co-develop a living patient involvement process guide, accompanying Plain English Summaries (PES), targeted training materials, and a patient glossary. Success quickly followed: Between 2022 and 2024, ACE gathered input from more than 700 patients and carers across 40 patient groups, and more than 80% of ACE's HTAs included lived experiences, which informed funding recommendations for drugs, gene therapies, and medical devices. This enabled consistent patient evidence that complements traditional quantitative data, accommodating different levels of health literacy and capacity.

Manufacturers can also play a catalytic role by working with patient groups and clinical associations to surface structural gaps in care pathways. When coordinated through industry organizations, such efforts can provide a neutral convening platform to translate shared gaps into system-level reforms that strengthen system-level change, rather than product-specific advocacy.

The way forward: Strategic imperatives for industry stakeholders

Across APAC, the rare disease access landscape is gradually being reshaped by a more mature understanding of the problem: Access fails when stakeholders act independently, but it improves when they align around shared “system readiness.” This is resulting in a shift from lower levels of Across APAC, the rare disease access landscape is gradually being reshaped by a more mature understanding of the problem: Access fails when stakeholders act independently, but it improves when they align around shared “system readiness.” This is resulting in a shift from lower levels of engagement (e.g., inform, consulting) to higher levels of engagement (e.g., co-design, co-refine). While many of these advances have been led by countries with established HTA frameworks, emerging HTA systems are doing more than simply adopting existing approaches. By leveraging shared knowledge and experience from the outset, they are co-developing solutions to shape rare disease policy in ways tailored to their own contexts.

Case study: Malaysia’s implementation gap

Malaysia’s genetic counselling landscape illustrates the implementation gap. Genetic counsellors are recognized in principle, but formal public sector positions do not exist. The downstream effects are material: non-specialists manage complex patients independently, referrals are fragmented, and diagnoses are delayed. Over time, this results in suboptimal care and long-term disease management.

Looking ahead, the APAC rare disease ecosystem is expected to see the following developments:

- Evolving payer frameworks to recognize nuance in the rare disease landscape and incorporate patient voice in decision making;
- Increasing stakeholder willingness to co-design innovative access solutions; and
- Growing need for investment in diagnostic infrastructure, specialist capacity, and allied health roles so that funded therapies can translate into outcomes.

Together, these collaborative efforts—still uneven but clearly advancing—will shape the rare disease momentum across the region and present a growing opportunity for manufacturers to engage in innovative models aimed at improving access and outcomes for patients. Realizing this potential will require manufacturers to move beyond asset-specific priorities toward aligning on common priorities across stakeholder groups, actively contributing to co-design efforts spanning both policy and implementation, and mobilizing cross-functional collaboration to support system readiness for the future of rare disease care.

Case study: Investment in early stakeholder engagement and co-development of solutions in Malaysia

Malaysia's multicriteria decision analysis (MCDA) framework demonstrates how co-development of solutions can work. Developed through multi-stakeholder working groups that included clinicians, health professionals, patient representatives, and industry, the MCDA defined prioritization criteria in plain language before assigning weights. This approach aligned expectations, built trust, and enabled consensus despite differing priorities. The framework was embedded into Malaysia's rare diseases technology assessment process under the 2025 National Policy for Rare Diseases.

Case studies

Trusted partnership

Avalere Health, a global strategic partner, offers 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 and evidence generation to regulatory strategy development and market access.

Strategy realized

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

Policy, regulatory, and market access trends impacting rare nervous system disorder

Challenge

The client sought to better understand key policy and market access developments, dynamics, and trends in preparation for the launch of its asset indicated for the treatment of a rare neurodegenerative disorder.

Solution

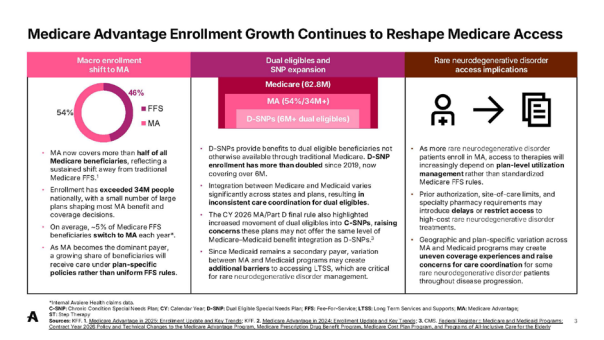
Avalere Health team assessed policy and market access landscapes across identified priority areas:

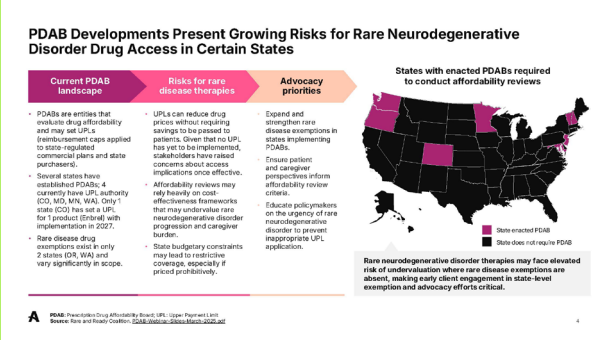
- Drug pricing pressures and reforms
- FDA guidance and policies for rare disease drug development
- Payer coverage and access dynamics
- Advocacy and stakeholder environment
- Other market trends affecting uptake

Value

Client was provided with a deliverable for internal educational purposes, to conduct further discussions with partners, and to build on the findings presented to them to assess gaps and build strategic frameworks.

FDA: Food and Drug Administration





Payer strategy for a next-generation rare disease therapy

Challenge

The client sought to understand how payers would evaluate a new treatment for a rare long-term brain condition amid existing and emerging competitive landscape, considering its broader indication and superior efficacy, and identify which endpoints would support preferential coverage.

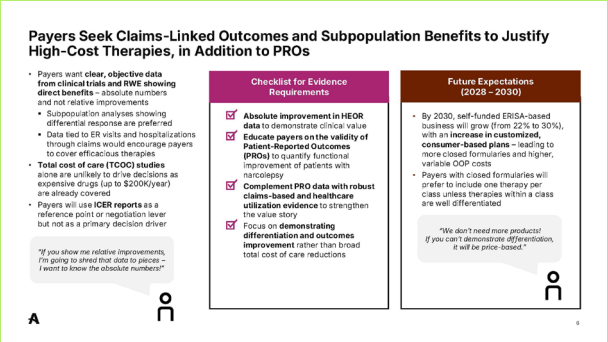
Solution

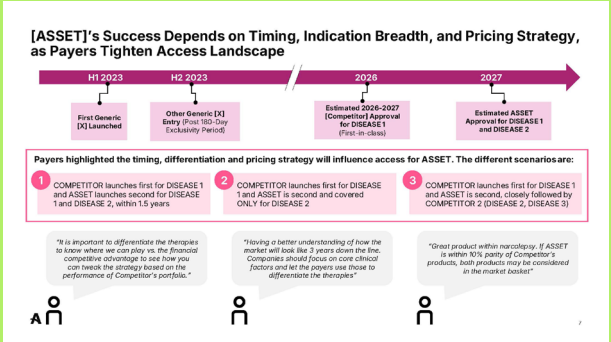
Avalere Health designed and executed an in-person advisory board with 10 expert payers representing diverse plans. This included developing a tailored presentation to guide discussions on unmet needs, clinical evidence requirements, and potential endpoints to support preferential coverage. Following the ad board, Avalere Health synthesized and delivered a comprehensive summary of key insights to inform Phase 3 trial design and a targeted pricing and coverage strategy.

Value

Avalere Health provided actionable guidance on endpoints for Phase 3 trials and a clear roadmap for pricing and coverage activities, enabling the client to strategically position the therapy for preferential coverage.

CMS: Centers for Medicare & Medicaid Services; **MAC:** Medicare Administrative Contractor





ICD-10 environment assessment to inform coding strategy

Challenge

Client identified a gap in the existing ICD-10-CM codes for a newly recognized medical condition, looking to initiate the process of obtaining a new ICD-10-CM code to accurately document and report.

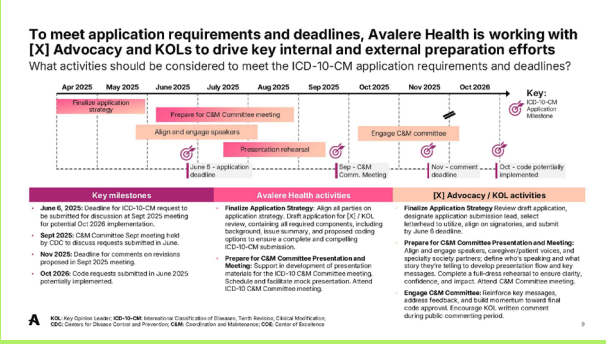
Solution

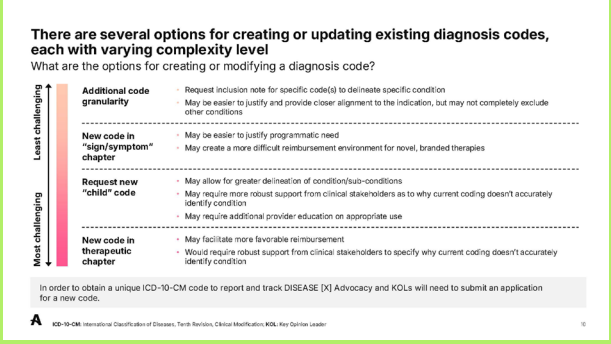
Avalere Health formulated an optimal strategy for developing and submitting a request for new coding and drafted comprehensive guidance for the new ICD-10-CM code, and included detailed clinical information, rationale for the new code, and potential impact on healthcare reporting and research.

Value

Avalere Health was able to clearly articulate the clinical and system benefits to the healthcare community by delivering a CDC-ready code request backed by comprehensive evaluation of the coding, coverage, and site-of-care payment implications for the newly recognized medical condition.

CDC: Centers for Medicare & Medicaid Services; **ICD-10-CM:** International Classification of Diseases, 10th Revision, Clinical Modification





Building a consensus framework to manage rare liver disease

Challenge

The client sought to bridge the gap in current guidelines by reaching practical consensus recommendations for a clinical audience on the comprehensive assessment and management of a rare liver disease (i.e., considering both liver function and symptoms).

Solution

Avalere Health conducted targeted background research supplemented by the scientific steering committee's input to shape a consensus framework, which was followed by the online survey. Insights from the survey aimed at understanding current clinical practice in the management of the disease across prioritized markets. *Lastly, a real-time Delphi panel explored the topics identified in the online survey, aiming to achieve consensus on recommendations to allow for a more holistic approach to management of the scoped rare liver disease.

Value

Avalere Health's insights provided the client with a comprehensive understanding of current clinical practice and disease management issues across prioritized countries. The outcomes of the online survey and Delphi panel were intended to be presented at conference(s) and published in an academic journal to disseminate the consensus recommendations to clinical audiences and support in standardization of assessment and management of patients.

*Canada, China, France, Germany, Italy, Spain, United Kingdom, USA

Early scientific advice support for a rare CV disease asset

Challenge

A client sought a partner to support the obtainment ofearly scientific advice from key HTA agencies (CADTH, G-BA, and NICE) for its pipeline asset that was being submitted for fast-track approval for the rare cardiovascular disease.

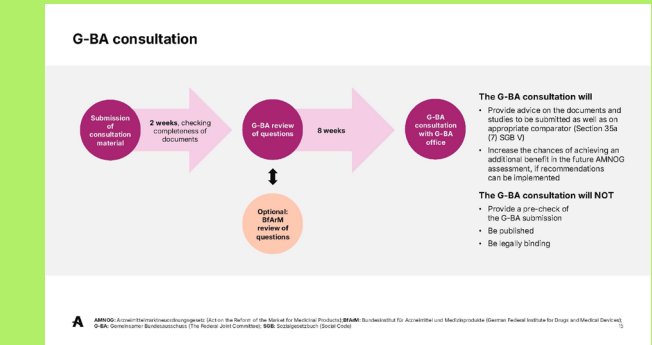
Solution

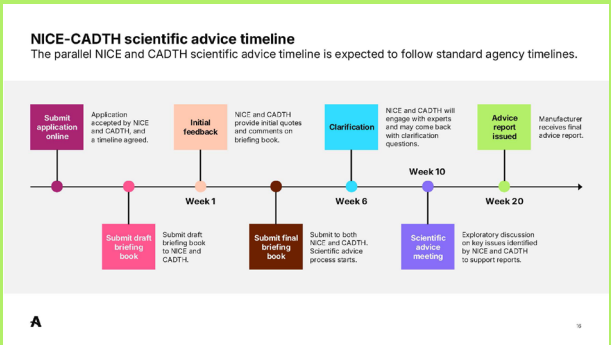
Avalere Health prepared ESA briefing books for a G-BA consultation meeting and a NICE-CADTH joint scientific advice meeting. Specifically, Avalere Health developed and workshopped with the client a list of themes and questions to be addressed with the HTA agencies, which were included in the draft briefing book along with the rationale and supporting evidence. Materials were shared with expert advisors from Canada, Germany, and the UK for input. Mock ESA meetings involving the client and the advisors were then held to prepare for the final meetings. The ESA meetings were attended by members of the Avalere Health team, and a report with recommendations was developed based on the feedback obtained.

Solution

Upon receiving feedback from the HTA agencies on the target population and subpopulations, appropriate comparators, endpoints, and proposed approach to economic modeling, the client incorporated it into evidence generation plans and the market access strategy.

CADTH: Canadian Agency for Drugs and Technologies in Health; **CV:** Cardiovascular; **ESA:** Early Scientific Advice; **G-BA:** Gemeinsamer Bundesausschuss (The Federal Joint Committee; **HTA:** Health Technology Assessment; NICE: National Institute for Health and Care Excellence





Evidence review and strategic CDP insights

Challenge

The client needed to understand the evidence base for its asset in a rare autoimmune inflammatory condition to inform decisions about proceeding to Phase 3 trials.

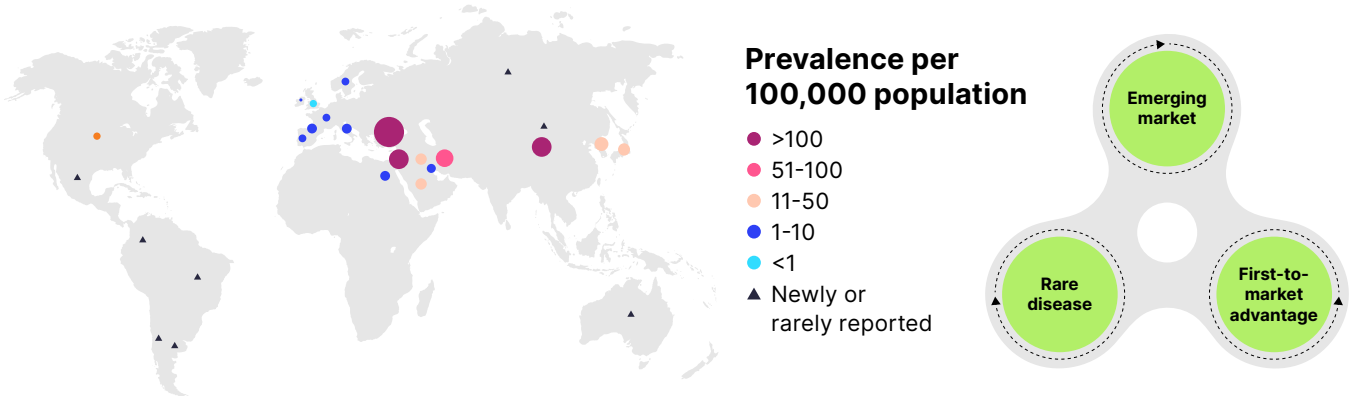
Solution

Avalere Health conducted a targeted literature review focused on disease epidemiology, competitive landscape, patient-reported outcomes, costs, and HTA landscape to identify key evidence gaps and challenges the client would need to address in clinical development and pricing and reimbursement preparations for its asset. Findings were summarized in a comprehensive evidence package and supplemented with an early-value one-page story ("leave-behind" document).

Value

The report served as a comprehensive source of key evidence for internal reference that could be updated throughout the clinical program. Strategic insights, evidence gaps, and recommendations aided in internal planning for Phase 3 decision-making and trial design. The client implemented the tailored advice into the value story for its first-to-market opportunity in the rare disease space across emerging markets.

CDP: Clinical Development Program



Curating curiosity through a museum-like medical education experience

Challenge

Autoimmune diseases have a complicated pathophysiology; our clients wanted to create novel, engaging and effective educational materials for HCPs, providing clarity of the complex interplay occurring at a cellular level.

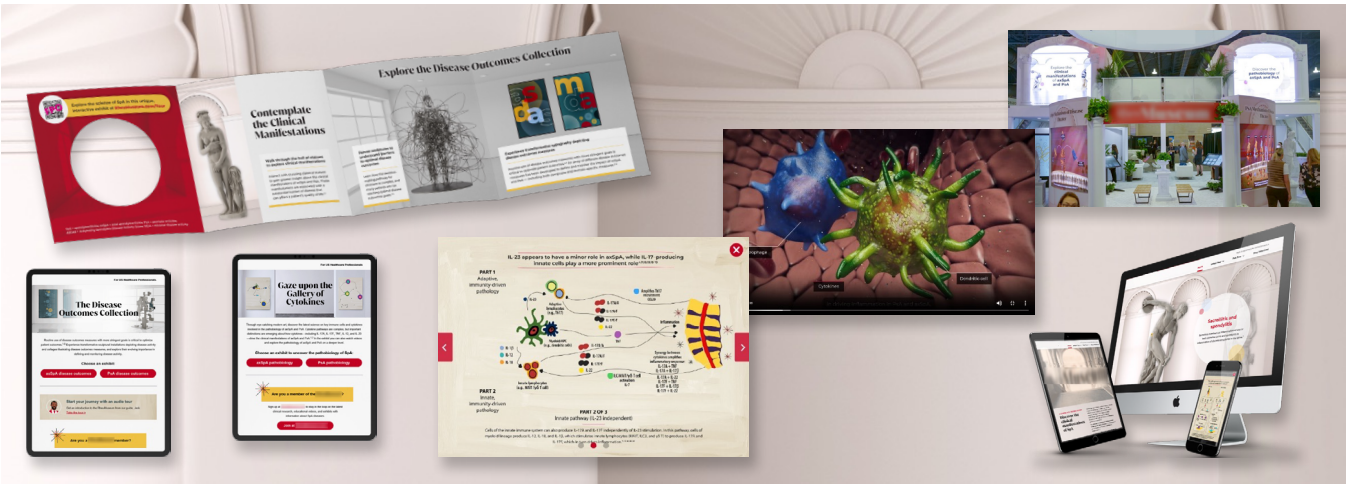
Solution

Our in-house team created an immersive, experiential museum-themed educational website with modern art-themed infographics along with 3D mechanism of disease videos to illustrate disease progression in axSpA and PsA.

- **Mimics a museum experience,** using various art mediums to illustrate clinical manifestations, pathobiology and outcomes measures
- **Tour guide,** interactive statues, 2D- and 3D-animated MOD video theatres
- **Media plan to drive traffic to website:** banner ads, paid search, videos, pre-roll video ads, rheumatology journal ads, email campaign
- **Rolling updates and content additions** including additional indications, KOL-led content and downloadable materials

Results

Based on our key educational objective and outcome, we believe that our program increased HCP awareness and belief from 15% in 2022 to 42% by the end of 2024, based on data from our custom-built proforma model and SERMO.



Optimizing launch sequencing and readiness

Challenge

A global pharmaceutical company sought to optimize the P&R strategy for a first-in-class targeted therapy for a rare mutation in AML across key APAC markets. The client needed a framework grounded in market realities that synchronized launch sequencing with global evidence development timelines, local clinical practices and payer expectations in an increasingly crowded rare space.

Solution

Avalere Health evaluated market-specific risks, benefits, and opportunities across clinical, economic, and policy dimensions using guideline reviews, analogue assessment, and local P&R analysis, validated with clinical and payer experts. Next, Avalere Health prioritized key risks and evidence gaps with the client for each indication by reviewing the clinical development plans and access and pricing assumptions. A prioritization framework, evaluating the impact of the prioritized risks and evidence gaps on the feasibility and attractiveness of launch across indications, was applied to define the base-case launch sequence.

Value

The client gained a deep understanding of the launch opportunity and key trade-offs to consider across scope markets. The client also received clear guidance on evidence requirements and market-shaping activities needed to maximize the overall recognition of value and commercial potential of their novel targeted therapy.

AML: Acute Myeloid Leukemia; **APAC:** Asia Pacific; **P&R:** Pricing and Reimbursement

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