

A man with a beard and a woman with glasses and a brown turtleneck sweater are looking thoughtfully to the side. The man is in the background, and the woman is in the foreground, resting her chin on her hand.

2022 Alnylam Rare Disease Trend Report

PERSPECTIVES FROM HEALTHCARE PAYERS

THIRD EDITION

alnylam.com

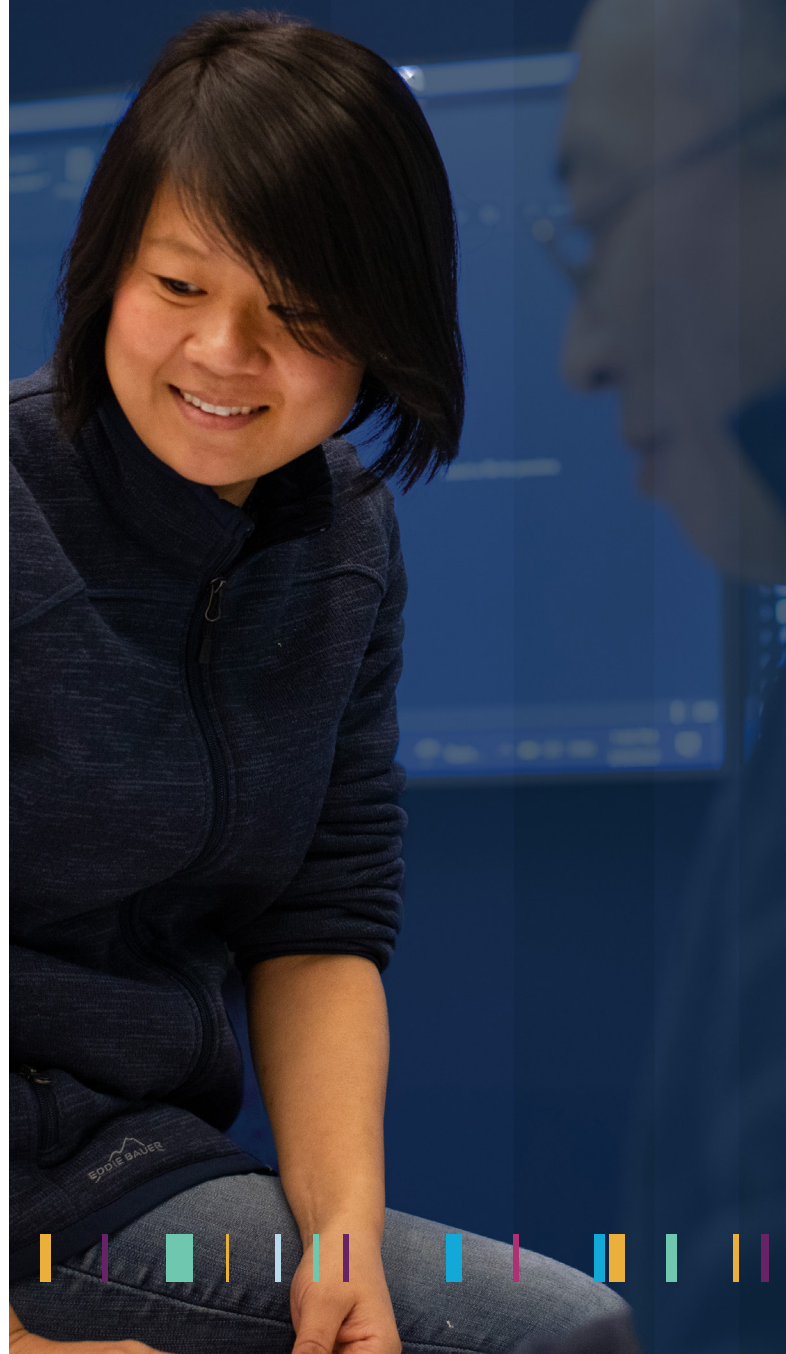


Foreword

Since the global COVID-19 pandemic hit, the healthcare industry has increasingly struggled to at-once serve the needs of patients, support staff, and make ends meet without jeopardizing long-term economic sustainability. Many questioned where and how the management of rare diseases would fit within the ever-evolving and suddenly chaotic healthcare environment, and how payers may react. However, despite the immediate pressures of the pandemic, payers stayed the course with their commitment to finding prudent ways to connect patients to the unique high-cost, innovative therapy options for rare and orphan diseases.

Now, in the wake of the pandemic, the 2022 Alnylam Rare Disease Trend Report offers crucial insights from U.S. payers on the potential longer-term consequences of the extraordinary global circumstances and prior market challenges. The latest report explores the effect of budget pressures on the desire for innovative, aggressive approaches to management vs. the investment and practicality of implementation.

Payers aim to resourcefully manage and future-proof their budgets to ensure funds are available for next and new generations of innovative rare disease therapies. Areas of much discussion and interest include shifting medical management via specialty pharmacy mandates, managing risk through innovative contracting, as well as how to balance the management of product improvements and enhancements (e.g., additional documentation and clinical measures within prior authorizations) with operational challenges for implementation. Published to inspire open dialogue among payers, providers, manufacturers, patient advocacy groups, and patients, this report serves to provide all stakeholders with a deeper understanding of the urgent and emerging access barriers that must be overcome to improve patient outcomes. Possible solutions for future consideration might include, but are not limited to, data considerations, collaborations among differing stakeholders, outcomes, assurances, or new opportunities within the rare disease space.



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Introduction

This report is intended to increase transparency across the payer community on prevailing trends in the management of rare disease products and the potential impact of market dynamics on payer priorities. Included among these are the impacts of the COVID-19 pandemic aftermath, the continuing emergence of novel therapies, systemic issues affecting manufacturers and payers, policy and pricing reform, outcomes-based contracting and payment models, and distribution models. Several central questions answered within this report include:

- How have payer priorities shifted since the first two editions of this report? (2020 and 2021)
- What management and reimbursement tools are payers using or planning to use for rare disease products?
- How do payers perceive innovative reimbursement models in the market, and what do they envision for future models?
- What trends will most influence payer decision-making and engagement?

By sharing critical insights and perspectives on current and future management considerations, the authors of this report aim to elevate the discussion around rare disease products. With a clearer understanding of how payers perceive, evaluate, and prioritize the unique challenges of rare disease and orphan drug management, the healthcare industry as a whole can more effectively and expeditiously work toward mutually beneficial and sustainable treatment and care solutions.

This report was sponsored and developed by Alnylam Pharmaceuticals, Inc. Alnylam is a biopharmaceutical company leading the translation of RNA interference (RNAi) into a new class of medicines for patients who have limited or inadequate treatment options.



Key Findings

- **Increased focus on rare disease management**
 - While most payer organizations do not use differential management for rare and ultra-rare disease, there is an increased focus on products within this space. As the pipeline for high-cost rare products continues to expand, payers will be forced to adapt their management approach directly affecting areas such as benefit management, contracting models, and distribution.
- **Uncertainty regarding recent federal legislation**
 - Recent legislation such as the Inflation Reduction Act and the AMP cap removal will have broad implications to the pharmaceutical space and will, therefore, have an impact on rare disease products. The IRA, specially, defines several changes that are specific to orphan drugs, including exemptions from Medicare price negotiations for therapies that fall into this orphan category. Payers are still unsure how such legislation will drive changes to their internal organizational policies, however, these policy changes will likely be necessary as payers look to properly react to these impending changes to the rare disease space.
- **Innovative contracting remains a challenging area for payers**
 - While a select number of payers are currently participating in innovative reimbursement structures, these types of agreements are still infrequent, specifically for rare disease products. This hesitancy is caused by several challenges such as difficulty measuring outcomes and endpoints, challenges with data collection, and lack of clear metrics that define value. Most payers do agree, however, that innovative contracts will become more frequent in the near future, insinuating there is an expectation for effective solutions to the above challenges for rare disease drugs.

Methodology

Alnylam Pharmaceuticals, Inc., sponsored and developed this publication in partnership with their vendor, Guidehouse. Alnylam is a biopharmaceutical company focused on the discovery, development, and commercialization of RNA interference (RNAi) therapeutics. The Commercial Health Group at Guidehouse, a leading global consultancy that specializes in life sciences across both the commercial and public sectors, provided research services.

Survey Development

A survey was developed to capture payer sentiment on the quantitative management of rare diseases. The survey was designed to assess current practices and perspectives, as well as to gather information on anticipated changes over the next five years and beyond. Taking 2022 as the current health plan year, the survey specifically delves into anticipated changes within the next plan year (2023), the next 3–5 plan years (2024–2028), and beyond (2028+).

The survey focused on the same payer-resonant themes used to inform the report structure, namely, benefit assignment and utilization management, price reform and policy changes, innovative contracting, distribution, and patient

costs. No specific products were assessed, although some may have been discussed in interviews as examples to illustrate themes or trends.

Potential respondents were screened for participation (see “Participant Selection and Demographics” below), and a total of 30 U.S.-based medical and pharmacy directors meeting the predefined eligibility criteria were recruited to complete the survey and provided with the online link. Guidehouse engaged a commercial vendor on Alnylam’s behalf to recruit participants and transfer the survey to an online format.

Recruitment & Fielding

Respondents were selected for relevant expertise and involvement in rare disease product evaluation. The agency informed respondents that data and insights would be aggregated, and respondent identities would remain anonymous. The authors then selected participants to ensure a mix of both medical and pharmacy directors from a variety of health plan types (e.g., commercial or managed Medicaid affiliate), as well as a mix of stakeholders with national and regional purviews.

All participants completed the survey from September 12 to October 13, 2022. While survey respondents may choose to participate in the annual updates to the research, each sample of respondents will be considered an independent sample.

Participant Selection & Demographics

Research participants were required to meet specific qualifying criteria to ensure integrity of responses across topics. Specific prequalification criteria for payers included:

- Current medical or pharmacy director employed by a commercial or managed Medicaid payer, or a pharmacy benefit manager;
- Past experience and current active involvement in policy development within the organization, including experience in medical and utilization management of policy development for rare disease products at their organization; and
- Willingness and ability to discuss management approach for rare disease products, such as new product evaluations, pharmacy and therapeutics (P&T) committee processes, innovative reimbursement model composition and implementation, and distribution network determinations.



Follow-Up Interviews

Participants were interviewed in tandem with the survey over a 16-day period from September 14 to September 30, 2022. Fifteen respondents participated in a 60-minute follow-up interview to provide additional, qualitative insight. Guidehouse researchers conducted all interviews over the phone in a double-blinded manner, such that no respondent knew the company supporting the research and no Alnylam employee knew which payers were providing input. All interviewees provided consent for using their responses in the composition of this report.

Respondents who met all eligibility criteria and completed the survey and follow-up phone interview received honoraria according to Fair Market Value calculations.

Data Analysis, Reporting & Limitations

Guidehouse collected, analyzed, and reported survey and interview responses. Data was blinded and aggregated across the entire sample of respondents.

Researchers had no way of validating survey responses for accuracy regarding payer practices or internal processes and operations. All statements and opinions contained within the report reflect responses received by included payer participants and do not necessarily reflect those of Alnylam or other reviewers.



Participant Sample Profile

Stakeholders with a strong understanding of rare disease management, representing payers across the United States, were selected to participate in primary research.

Of the survey participants, 67% had more than six years of product evaluation experience directly reviewing rare disease products and indications (**Figure 1**). The remaining sample has 3–5 years of experience (**Figure 1**). Of payers sampled, 57% are medical directors and 43% are pharmacy directors (**Figure 2**).

National commercial payers comprise 39% of the sample, regional commercial payers, 43%, Medicaid managed care plans, 7%, and pharmacy benefit managers (PBMs), 11% (**Figure 4**). The majority of respondents (79%) indicated their plans have integrated specialty pharmacy capabilities, which is an important consideration when evaluating distribution and design trends (**Figure 3**).

Across the commercial, managed Medicare, and managed Medicaid plans sampled, the majority of spend is in medical benefit (57–60% of spend) compared to pharmacy benefit (40–43% of spend) (**Figure 5**).

FIGURE 1: Participant Years of Product Evaluation Experience

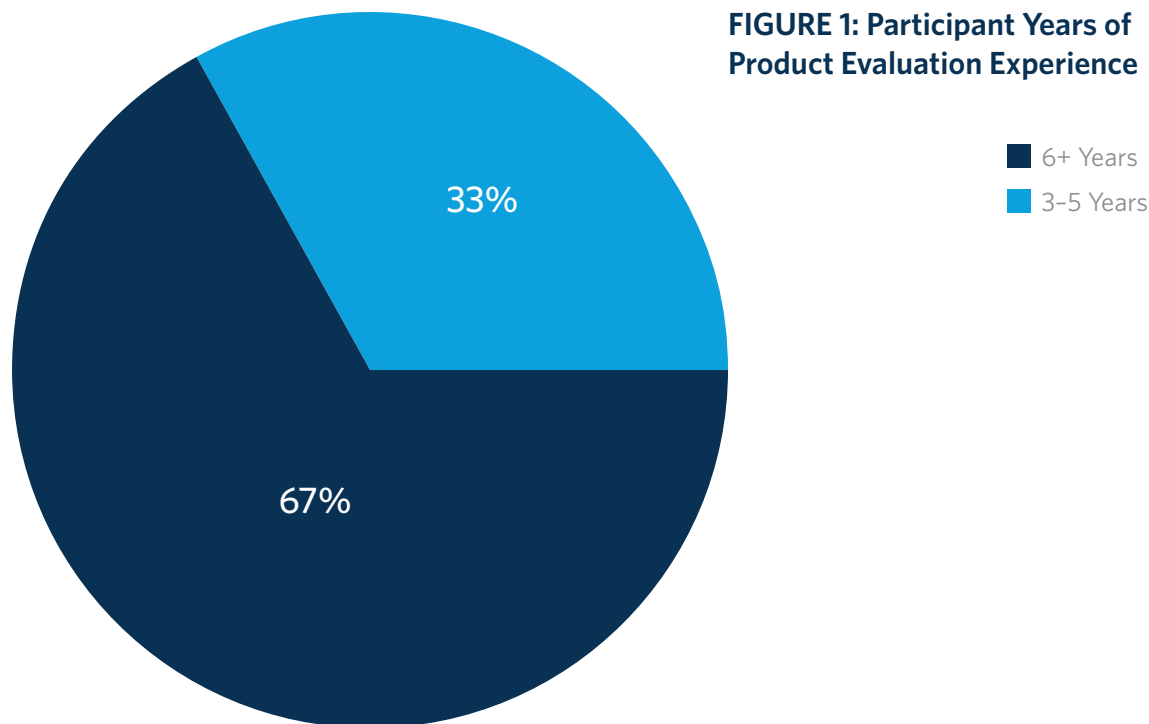


FIGURE 2: Participant Sample Titles



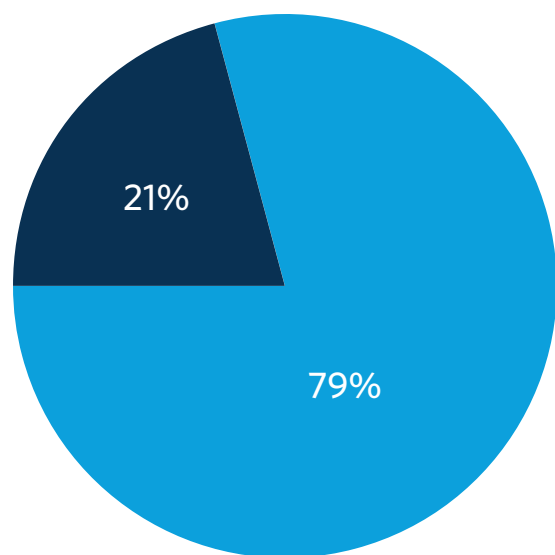


FIGURE 3: (left) Payer Sample Specialty Pharmacy (SP) Capabilities

Integrated SP
No Integrated SP
Low Priority

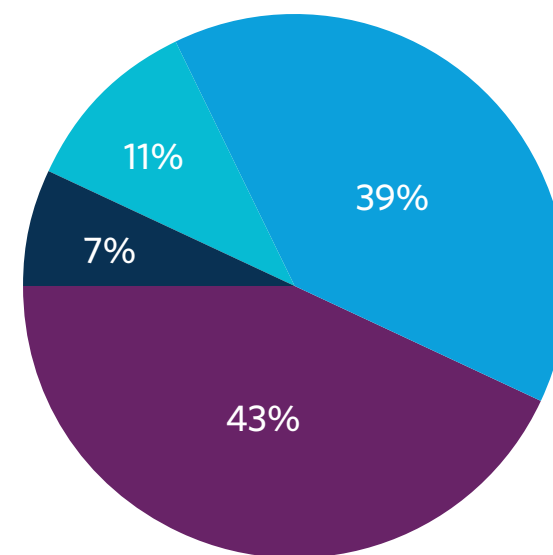


FIGURE 4: (right) Research Sample Mix

National Commercial Plan
Regional Commercial Plan
Medicaid Managed Care
Pharmacy Benefit Managers

FIGURE 5: Spending Allocation by Payer Mix



Rare Disease Landscape

Value Drivers to Rare Disease Products

As the pipeline for rare disease products continues to grow, so too does the pressure on stakeholders to find the precarious balance between the investment in time and resources required to develop safe, effective life-changing treatment options and the significant economic burden of providing access to them. Despite this tension, payers continue to prioritize addressing unmet needs in rare diseases and, for the third consecutive year of this report, the importance of acknowledging unmet needs increased in priority — moving from fourth-highest in 2020 to third-highest in 2021 to second-highest in 2022 (Figure 6). However, year over year, clinical efficacy remains the ultimate value driver, signaling to manufacturers a continued interest and willingness to support proven innovations for rare disease patient populations.

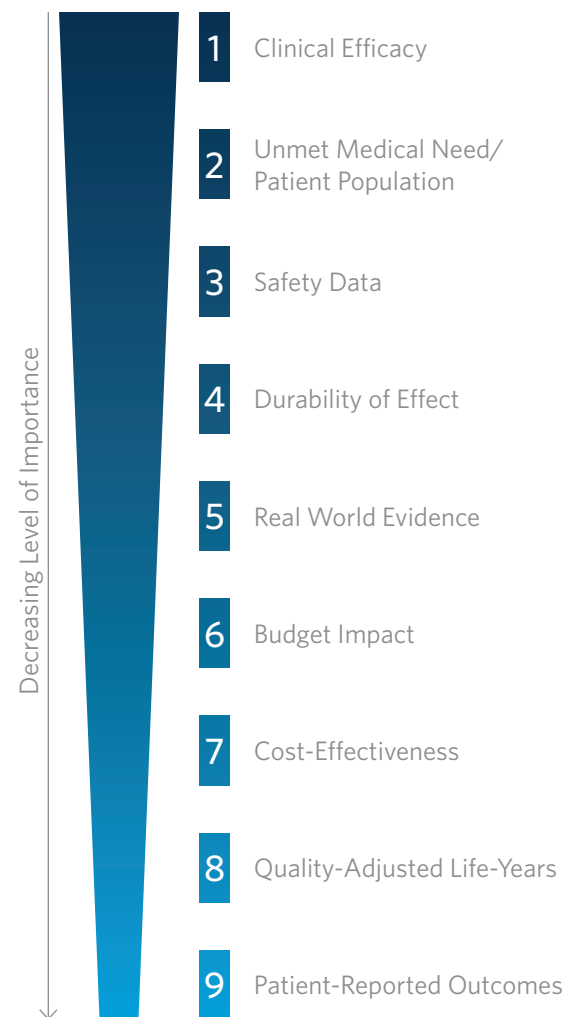
Currently, real-world evidence (RWE) factors little into coverage and reimbursement decisions, as it remains heavily dependent on availability, quality, and study design. Yet, interestingly, RWE increased significantly as a value driver, moving from seventh overall most important in the 2021 trend report to fifth in the 2022 trend report. This

reprioritization is consistent with the increased emphasis among stakeholders, including global regulatory bodies, on realizing the potential of RWE to expedite the development and delivery of innovative new therapies, while establishing the longer-term clinical efficacy and durability of effect of them. As the collection of RWE becomes more consistent and reliable, payers expect to leverage this data to accurately track and monitor patient health. It is likely that payers will see RWE as an additive piece to their current set of evaluation criteria. Widespread use of RWE among payers to inform coverage decisions is still quite limited and remains a challenging area for payers and manufacturers.

“RWE can have a significant influence. It is dependent upon whether an RWE study is available. It could play a greater role, given the study design and quality of the data itself.”

– Medical Director, National Payer

FIGURE 6: Most Significant Factors for Rare Disease Therapy P&T Review



Relative to non-rare diseases, payers consider cost-effectiveness (CE) models as less important for the evaluation of rare disease therapies. This is often due to a lack of perceived credibility in the CE evaluation if there is not a head-to-head comparison for the rare disease product. Typically, payers will use a value analysis or internal analysis, which focuses on the actual financial impact the product is expected to have. However, the payer's perspective on CE evaluations is evolving and will likely change as the volume of high-cost therapies grows over the coming years for rare indications. As more drugs enter the market, many payers expect more reliance on CE models for the evaluation of rare disease products. This expectation is even greater as the industry begins to see more situations with multiple therapies treating a single indication.

“I’m embracing CE models more and more. We expect cost-effectiveness models to have more impact over time for rare disease products. The totality of dollars and long-term cost offset to the system will greatly impact our use of these models moving forward.”

– Pharmacy Director, Regional Payer

Payers place less importance on manufacturer-developed CE models, noting there is an assumption of inherent bias. However, payers routinely look to model inputs to better inform or assess potential gaps with internal assessments.

Rare vs. Ultra-Rare Disease Management

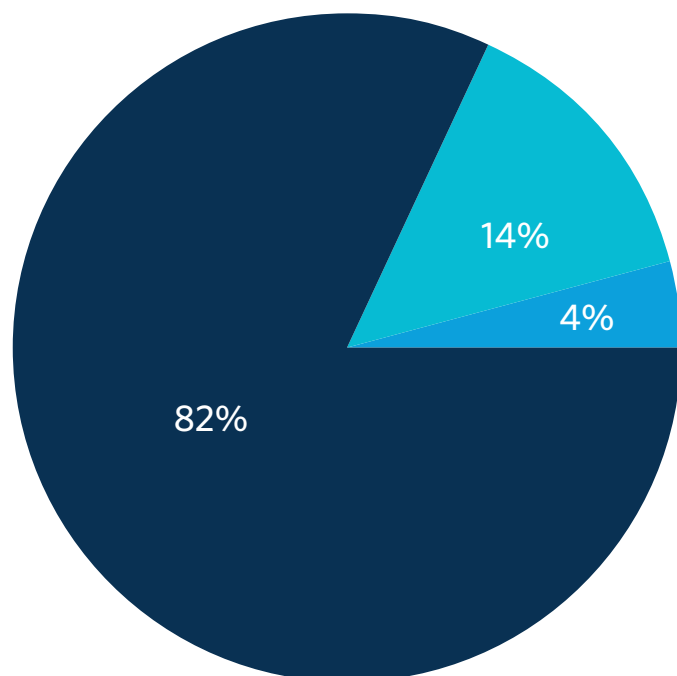
Similar to the 2021 rare disease trend report findings, the majority of payers either do not or minimally differentiate the management of rare vs. ultra-rare diseases. This is likely due to the low prevalence of patients in their plan receiving a rare disease therapy.

“From a management perspective related to policy, protocols, distribution strategy, and contracting and reimbursement, we do have a specialty tier reserved for rare-indicated products. However, for P&T review purposes, we do not differentiate between rare and ultra-rare diseases.”

– Pharmacy Director, National Pharmacy Benefit Manager

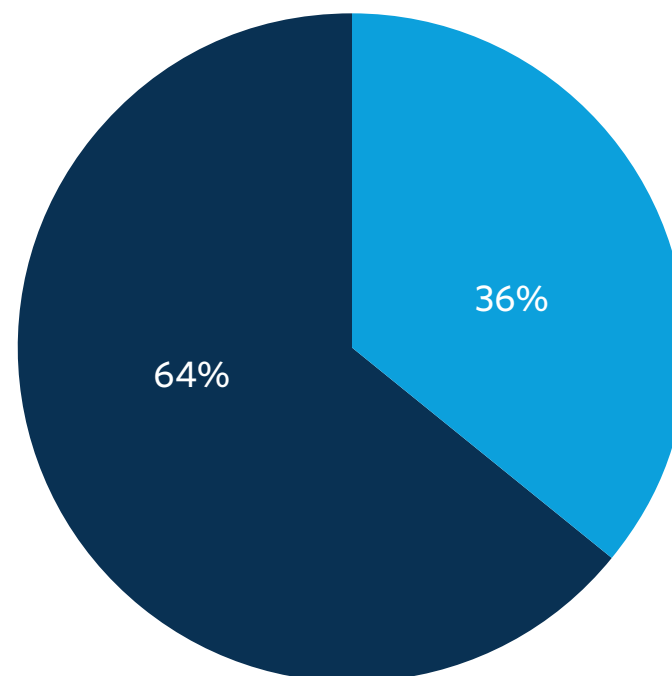
Additionally, 82% of payers are not evaluating these patient populations differently. Despite the defined differences in population thresholds, both categories are typically comprised of high-cost therapies with high unmet needs, requiring similar levels of rigor with P&T decisions and establishing management techniques. As a result, differentiating rare vs. ultra-rare vs. non-rare disease are not likely to lead to significant cost savings. While payers acknowledge the need for unique management of certain rare products, the difference in approach is made on a case-by-case basis, and is based on factors outside of a rare or ultra-rare distinction (Figure 7).

FIGURE 7: Please Indicate in Which Region(s) Your Organization Serves Members



- More Active Management of Rare Disease
- More Active Management of Ultra-Rare Diseases
- Rare & Ultra-Rare is Not Managed Differently

FIGURE 8: Management of Rare Diseases



- Increased Focus on Rare Disease Management
- Decreased Focus on Rare Disease Management
- No Change in Rare Disease Management

“We don’t make a distinction here from a P&T perspective”

– Medical Director, National Commercial Plan

“No differentiation here. Doesn’t mean a lot. The number of patients here do not impact our perception of an asset.”

– Medical Director, Regional Commercial Plan

Rare Disease Management Processes

The management of rare disease products continues to be a dynamic space within healthcare, often forcing payers and providers to shift their approach to the treatment of these complex conditions. The 2022 rare disease trend report revealed several significant changes in management approach compared to the 2021 trend report. In 2021, only 10% of payers reported an active management approach to rare disease products.² In sharp contrast, 64% of payers reported an increased focus on the management of rare, indicated products

in 2022 (Figure 8). Historically, payers viewed their management techniques as sufficient for both rare and non-rare indications. However, this dynamic is shifting as high costs, specialty requirements, and the need for specialty pharmacy distribution are increasing. This has led payers to adopt a more focused management approach for rare products to ensure coverage is appropriate and in line with inclusion and exclusion criteria as defined in a given clinical trial. Additionally, the limited use of rare disease products remains a challenge for payers, as they seek to cover products that address patient needs, while assisting patient access.

In 2020, 25% of survey respondents anticipated establishing subcommittees focused on rare management within the next five years, and, in 2021, 17% anticipated developing them in the next year, including citing the COVID-19 pandemic as a potential reason for delay. However, despite these year-over-year expectations, and the recession of the pandemic, the prevalence of rare disease subcommittees did not grow in 2021 or 2022. Further, results from the 2022 research shows most payers

express no expectation for this approach to change in the future. The increased focus on the management of rare disease products will not typically occur through a specialized committee, however, management of these products commonly occurs on a case-by-case basis.

The majority of payers do not implement differential management of rare and ultra-rare diseases. This is likely due to the low prevalence of patients receiving a rare disease therapy in their plan.

Moreover, payers see their current management techniques for non-rare products to be a sufficient starting point for rare products. Differences in management techniques are only implemented according to the unique challenges a particular orphan drug presents to the payer, such as high cost and small patient population size. In these unique situations, key opinion leaders and other informative resources in the P&T committee often inform the implementation of differing management techniques and bridge knowledge gaps regarding a rare disease product.

Benefit Design & Utilization Management

Benefit Assignment

Rare disease continues to be an important focus area for payers as they seek to navigate the rapidly growing space, with an expanding pipeline of specialized products situated within complex treatment landscapes for smaller patient populations. While payers recognize certain rare conditions affect a smaller number of patients more than others, they did not view rare and ultra-rare diseases differently from a management perspective. Ultimately, payers do not utilize differential management approaches for coverage and reimbursement decisions based on these classifications.

Similar to the 2021 trend report findings, the majority of payers are managing rare disease products under the medical benefit, specifically for gene-targeted therapies. Payers also expected to increase the use of medical benefit for rare disease products according to the 2021 report.² In 2022, 80% of payers reported managing gene-targeted therapies through the medical benefit, a 27% increase year over year (**Figure 9**). Traditionally, management via the medical benefit has allowed payers to address challenges for rare disease drugs, such as product complexity, administration, and patient population. However, in stark contrast

to the 2021 trend report findings, respondents to the 2022 survey noted an increasing shift to pharmacy benefit for the management of gene-targeted therapies.² The shift to the pharmacy benefit for rare disease products allows payers to better predict costs and more easily manage products through traditional utilization management techniques such as prior authorizations, step therapy, and detailed inclusion/exclusion criteria. Payers raised concern about differential charge rates among hospitals. As such, many plans are looking to implement a specialty pharmacy to solve for this cost uncertainty.

“In regard to medical vs. pharmacy benefit management, hospital care/administration tends to upcharge patient care. Therefore, many plans want to implement a specialty pharmacy so that the provider is not responsible for the drug. Hospital specialty pharmacies are not aligned to payer incentives. Pre-selected non provider specialty pharmacies are the future.”

– Medical Director, Regional Payer

FIGURE 9: Pharmacy vs. Medical Benefit Management of Orphan Drugs

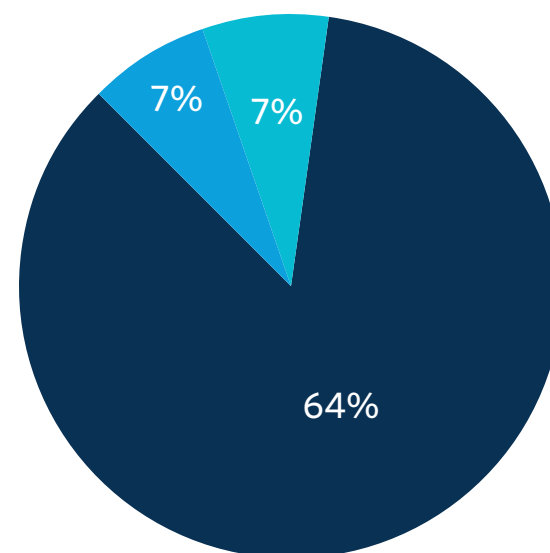
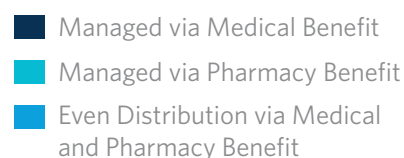


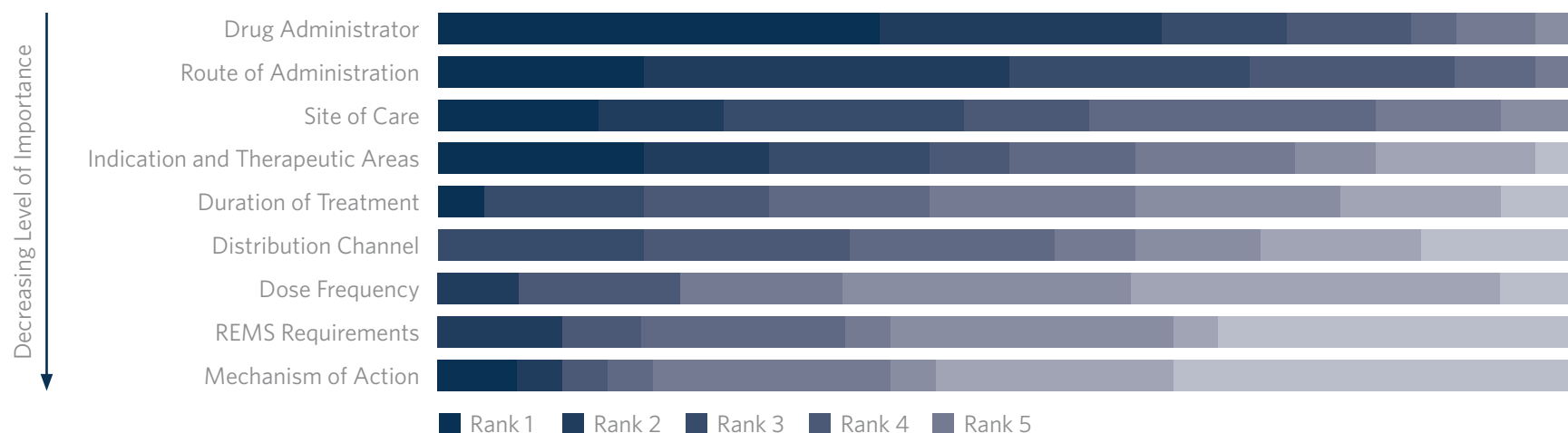
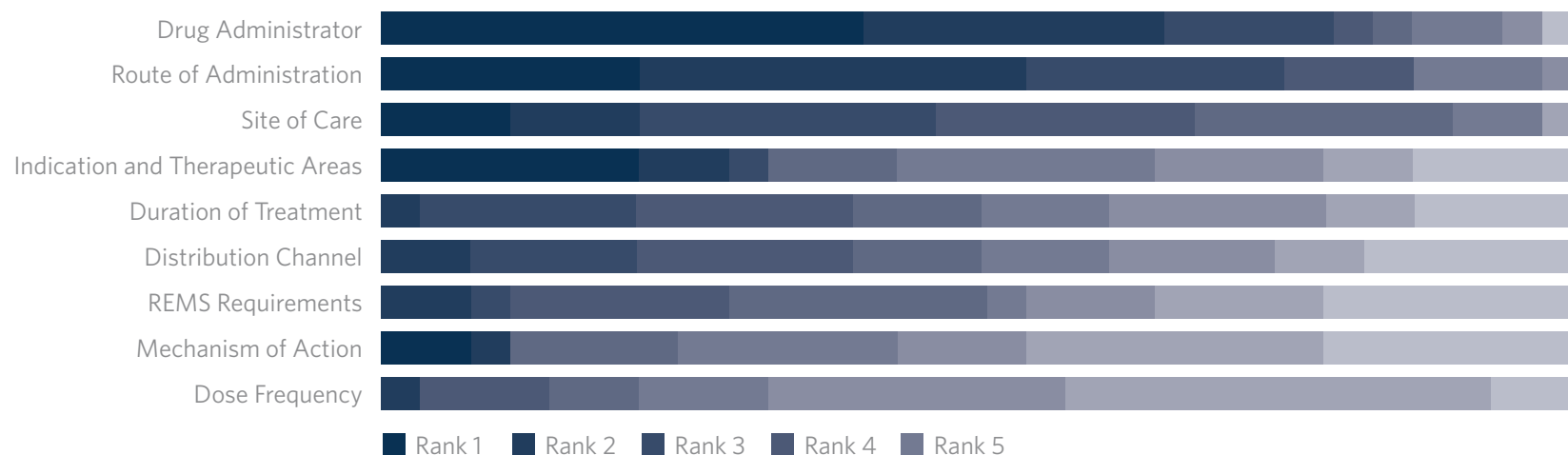
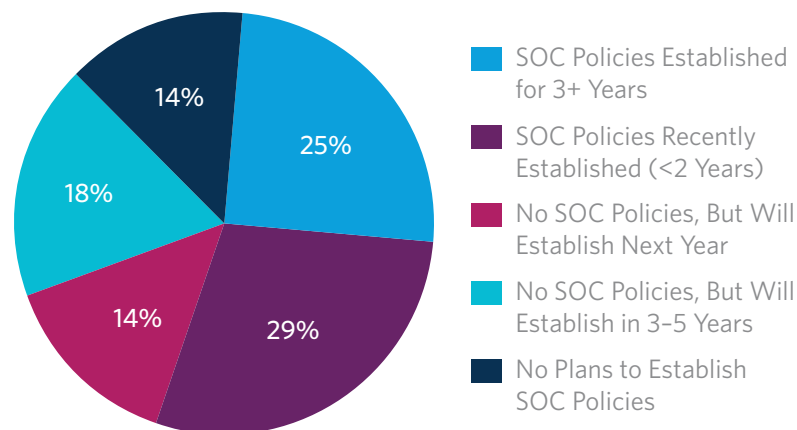
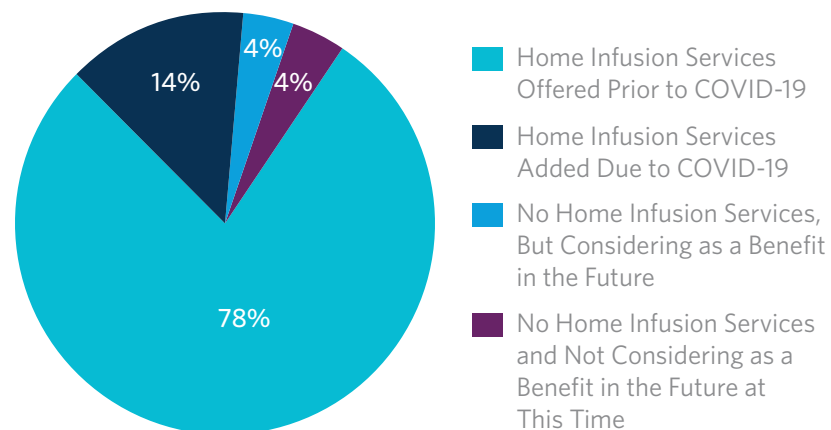
FIGURE 10: Determining Factors for Benefit Assignment (Future)**FIGURE 11: Determining Factors for Benefit Assignment (Future)**

FIGURE 12: Site of Care Policy Development for Orphan Drugs

Site of Care Policies

Site of care policies remain essential to access for many rare-indicated products. Utilizing less expensive sites of care to lower the cost of administration for specialty drugs has proven to be a valuable tool for providing effective and affordable treatment to patients in need. Similar to findings from the 2021 rare disease trend report, the use of site of care policies for the administration of specialty therapies is continuing to increase.² The use of these policies grew over the past 3–5 years, as the COVID-19 pandemic escalated their adoption among payers. Traditional settings of care, such as hospitals, oftentimes carry higher costs associated with the administration of rare disease products. Payers expressed a desire to reduce these costs through flexible site of care policies that

FIGURE 13: Coverage of Home Infusion Services

allow patients the ability to access specialty therapies in a convenient and affordable setting. An example of this would be coverage of home infusion services. The vast majority of payers (92%) surveyed currently offer home infusion services, while 4% of respondents are considering developing this service as a benefit in the future (**Figures 12 and 13**). Administration of specialty products outside the conventional hospital setting will likely increase the use of specialty pharmacies. This shift will impact the current buy-and-bill model, and result in the increased use of white bagging (the distribution of medications from a specialty pharmacy directly to a provider for administration), further lowering the financial risk for payers. As payers continue to navigate the post-COVID-19 healthcare landscape, changes to benefit design will be necessary to effectively manage rare disease products.

Utilization Management

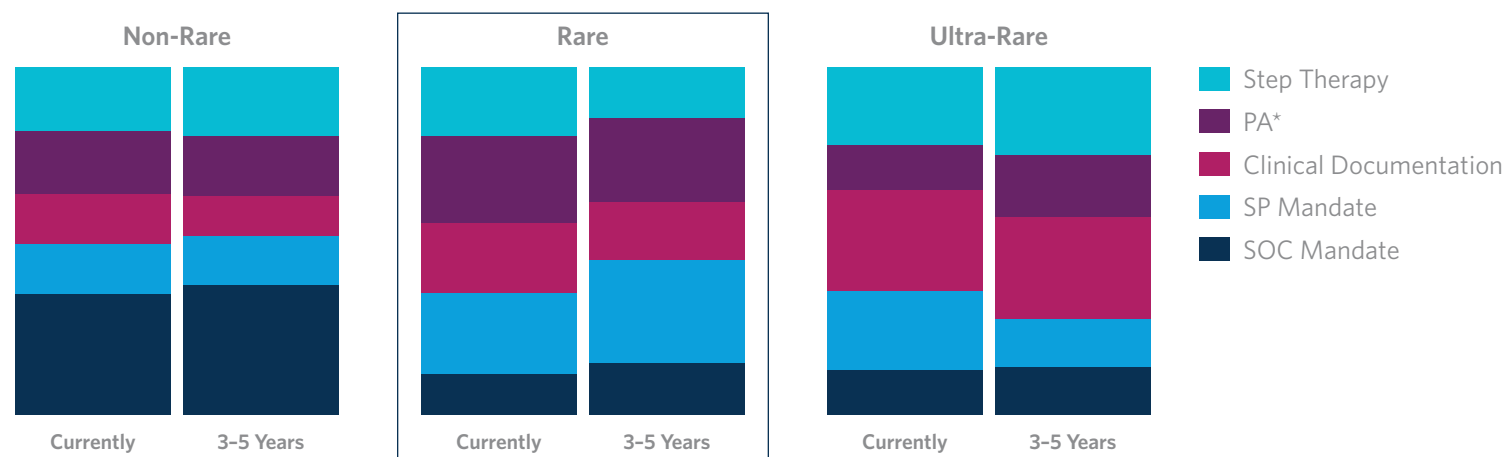
Despite the changing environment taking place in the rare disease space, payers continue to leverage similar utilization management techniques across rare and non-rare-indicated products. Given the increased attention from payers in this area (64% of payers report increased focus on rare disease management), certain management tools — i.e., step therapy, prior authorization, and clinical documentation — are seen as more impactful than others (Figure 14). Specifically, the use of specialty pharmacy mandates is expected to grow in the next 3–5 years, bypassing traditional buy-

and-bill models. This shift will allow payers to better control their distribution models. Several factors are likely to influence whether payers decide to mandate specialty pharmacy use for a given rare disease product, such as inpatient vs. outpatient administration. However, cost remains at the forefront of the minds of payers as health plans are beginning to push back on provider organizations, such as hospitals, due to the increased bill charges for specialty products. Increased specialty product mandates will allow payer organizations to ensure specialty pharmacy organizations, not the provider, hold a drug title, further controlling costs and helping provide higher value for plan members.

“Providers are going to see continued pushback from health plans regarding the administration of high-cost rare disease products. The contract of the specialty pharmacy holds the title. Often, our plan’s incentives are not aligned with a hospital-owned specialty pharmacy and billing charges can exceed past what is owed. We want a specialty pharmacy that is offering the highest possible value to our members.”

– Medical Director, Regional Payer

FIGURE 14: Current vs. Future Frequency of Utilization Management Tools



“The management of rare disease products is more active than non-rare indications. This is mainly due to the limited use for rare disease products.”

– Pharmacy Director, National Payer.

Impact of Health Technology Assessments (HTA)

Payers report moderate use of HTAs for rare disease products and expect little change with this approach in the coming years. Specifically, 64% of payers report a moderate influence of external HTA reports, and 57% report moderate influence in 3–5 years (Figures 15 and 16). This is likely due to the impact of published studies and internal analysis. Typically, small organizations utilize HTAs to make decisions, while large organizations use HTAs to inform or reinforce current policy or decision-making. Many payers currently use external HTAs as a confirmation of internal processes and conclusions surrounding a given therapy. Since the 2021 trend report, payer priorities impacting P&T processes remain largely unchanged aside from the higher ranking of importance listed for RWE. Additionally, payers noted that some U.S.-based organizations, such as Institute for the Clinical and Economic Review (ICER), may be more influential during the pricing and contracting phase.¹

Rare Disease Carve-Outs

In select, usually unique instances, such as a high-cost specialty drug administered in a hospital setting, stakeholders implement carve-out payments for rare disease products to reduce the potential cost burden

FIGURE 15: Impact of External HTAs to Rare Disease Management Decisions: Current

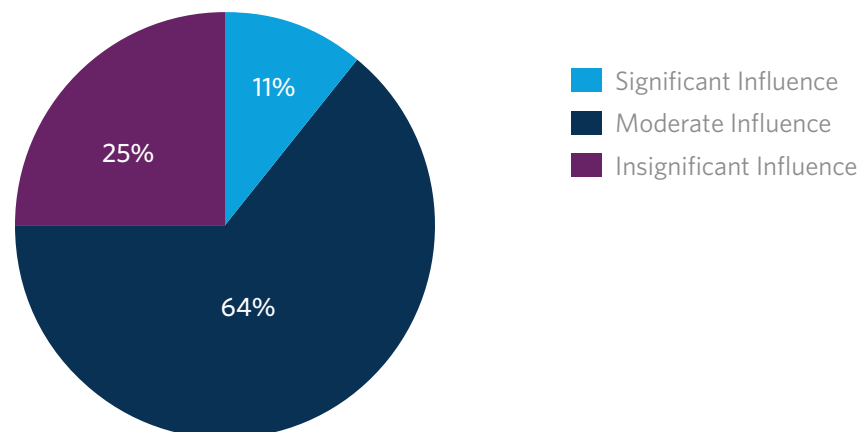


FIGURE 16: Impact of External HTAs to Rare Disease Management Decisions: 3–5 Years

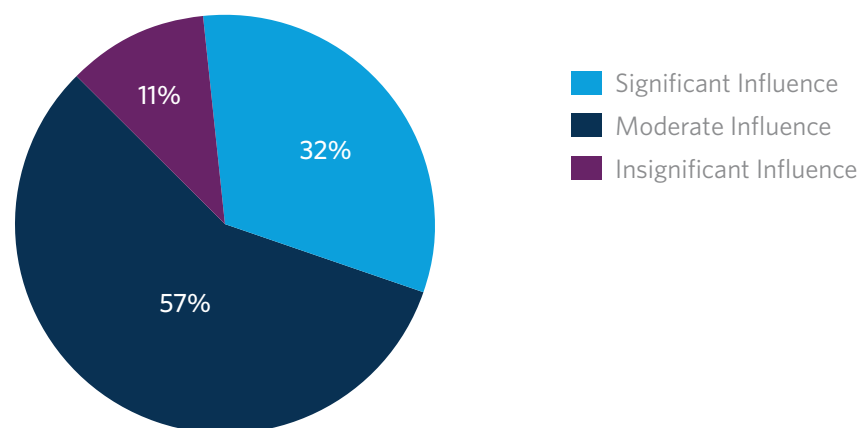
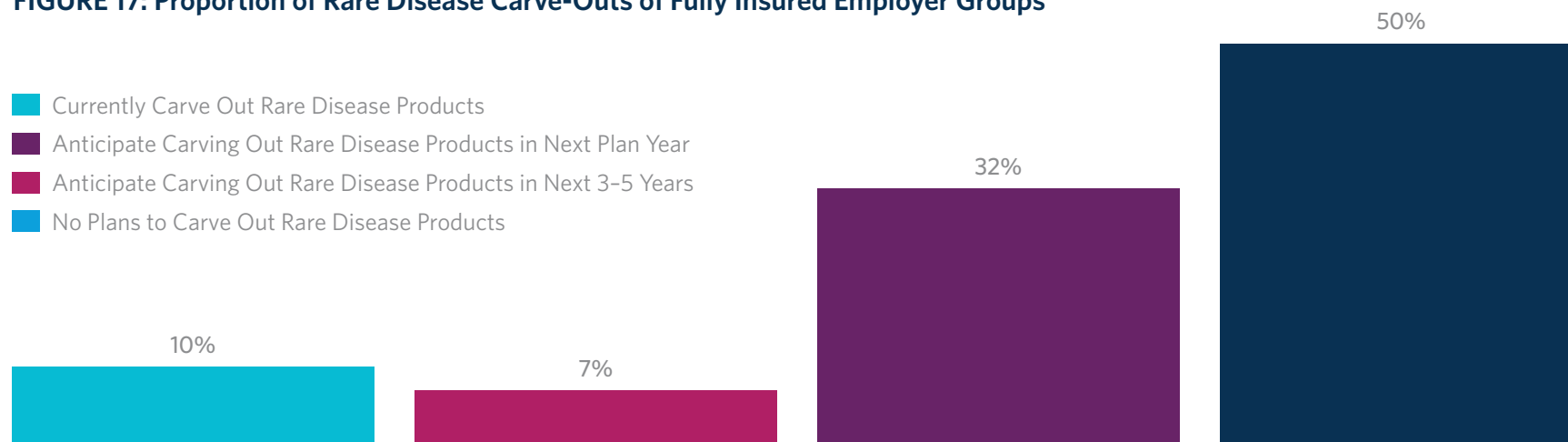


FIGURE 17: Proportion of Rare Disease Carve-Outs of Fully Insured Employer Groups

associated with these products. Overall, however, rare disease carve-outs from employer groups are uncommon today as rare products still represent a smaller portion of overall payer spend. With the pipeline for rare disease products rapidly growing, payers will be forced to evolve their approach. Half of the respondents (50%) stated they do not have plans to carve out rare disease products, while 32% responded they anticipate carving out rare disease products in the next 3–5 years (Figure 17). Additionally, 39% of organizations that do not carve out rare disease products today may use carve-outs in the future. Many small-to-mid-size payer organizations are particularly interested in using carve-outs as an effective cost-management tool.

“Yes, we anticipate carving out gene or gene-targeted therapies in the future due to affordability. The current spend is unsustainable and profoundly impacting overall budget.”

– Medical Director, Regional Payer

“If the employer group initiates a carve-out and assumes the risk, then that’s fine. Internally, we are hesitant to implement carve-outs due to patient membership. I do not anticipate this to change.”

– Medical Director, Regional Payer

FIGURE 18: Off-Label Access of Rare Disease Therapies by Therapeutic Area (Current)

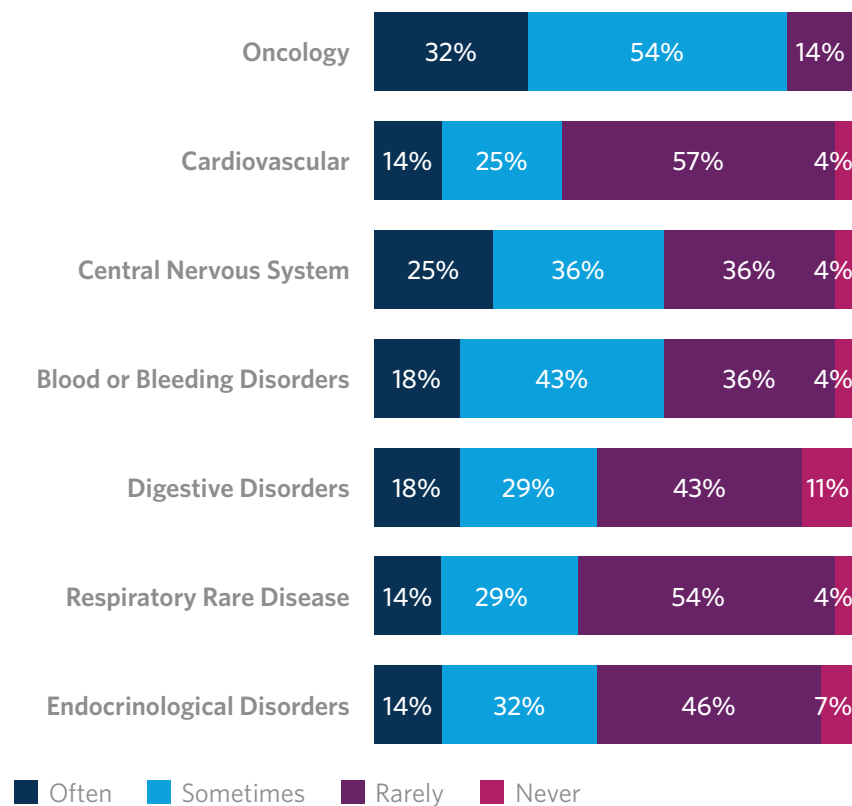
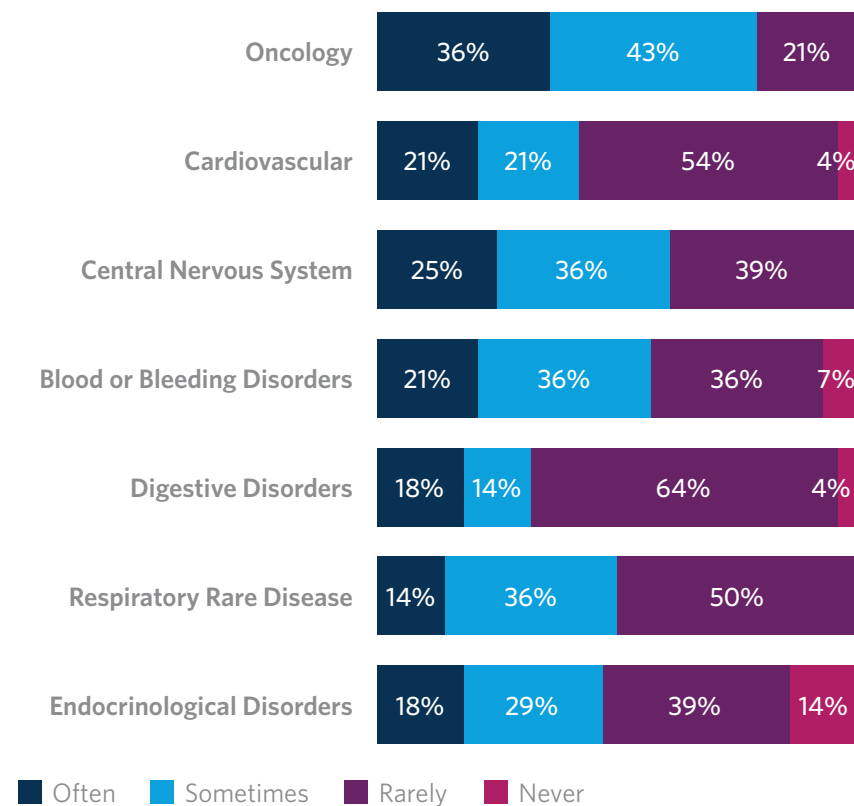


FIGURE 19: Off-Label Access of Rare Disease Therapies by Therapeutic Area (Future)



“We are still investigating how we will deal with gene therapies in the future.”

– Medical Director, National Payer

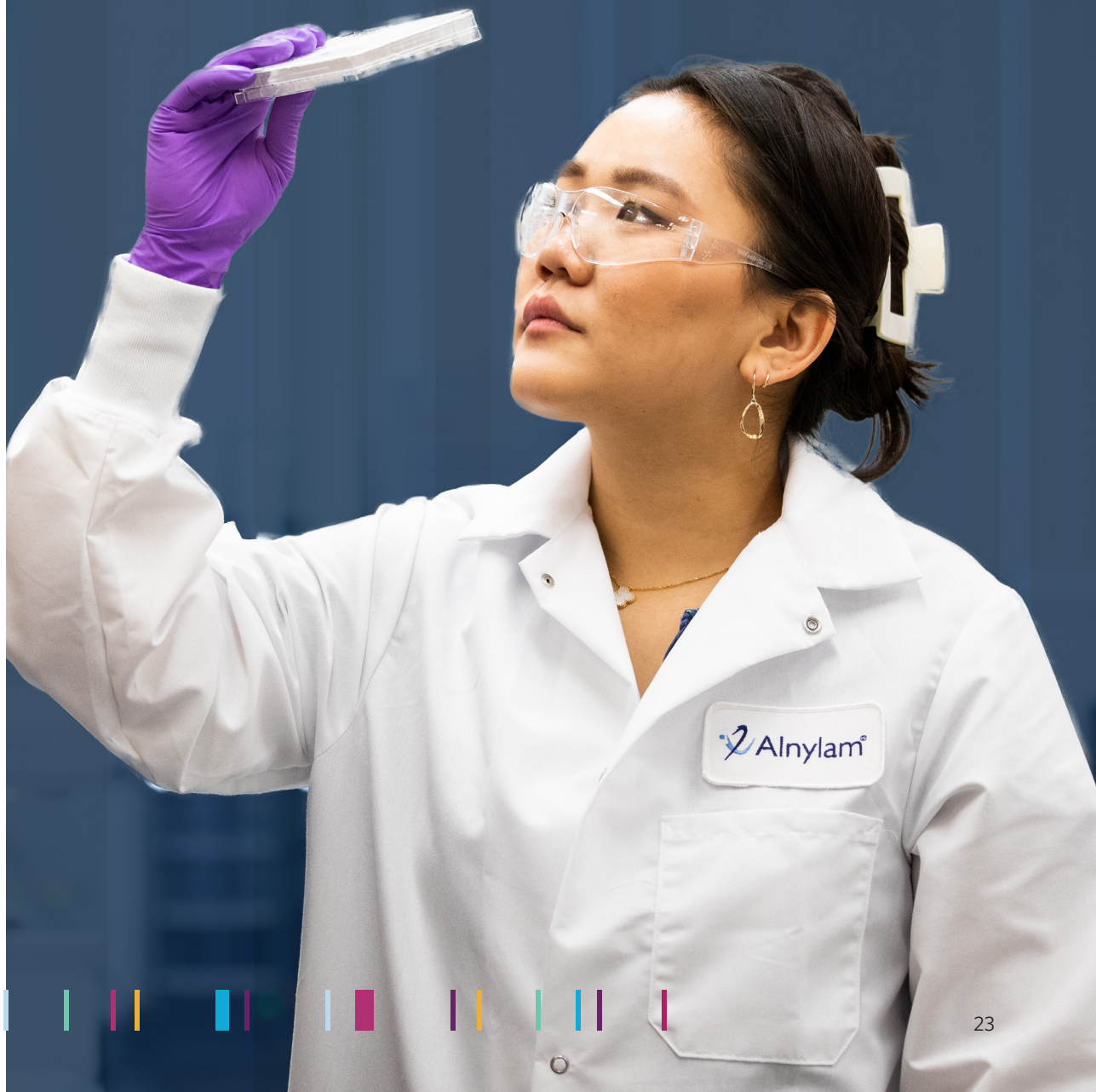
Off-Label Use

While off-label use for rare disease products remains uncommon, payers expect this to change in the coming years as complex treatment options continue to evolve for specialized patient populations.

Many payers noted that off-label use typically is considered when a practitioner petitions its use for a patient. Given the complex treatment landscape, off-label use is more common in certain therapeutic areas, particularly oncology, in which patient prognosis depends critically on the urgency of treatment timing. Because of this, leading cancer research organizations like the National Comprehensive Cancer Network (NCCN) often release guidelines allowing for off-label use in this therapeutic space (**Figures 18 and 19**).² However, many other therapeutic areas require two peer-reviewed publications, rendering off-label use less common. Still, many payers expressed an expectation for future off-label use of rare-disease products to increase in coming years given compendium support. This reliance on physician expertise and verifiable medical literature to guide payers' decision-making process will be critical.

“We allow for non-oncology off-label use based on compendium support.”

– Medical Director, National Payer



Payer-Driven Policy Change

Many legislative policy changes have broad implications to the pharmaceutical space and are not typically specific to rare disease. That said, larger policies without specific rare disease initiatives can cause a ripple effect on the rare disease space, such as legislative pieces with changes that would apply across all drug management and reimbursement. Generally, pharmacy and medical directors remain aware that approved policy changes often significantly alter or shape their operations, benefit designs, reimbursement structures, payment policies, and a host of other activities within their purview. As such, payers are generally focused on finalized legislation that directly affects their management of orphan drugs.

However, as policy proposals make their way through legislative committees and entities, they often undergo many iterations before they are finally approved or dropped. Understanding this conventional process, pharmacy and medical directors surveyed stated they invest little time in tracking the day-to-day developments of proposals within the rare disease space and noted little impact on coverage decisions or other changes prior to policy approval. Instead, they rely on internal public policy teams to monitor proposals and reactively address finalized policies as relevant and necessary.

“We do monitor current policy changes occurring within this space for rare and non-rare indications. However, we will typically look to larger payer organizations for guidance regarding best practices on how best to react to larger pieces of legislation rather than taking an active approach.”

– Medical Director, Regional Payer

As policy change proposals come to fruition and become finalized, payers place more focus on these pieces of legislation. In the 2022 trend report, survey respondents consistently discussed the potential impacts of two recently approved proposals: the average manufacturer price (AMP) Medicaid rebate cap removal,³ which goes into effect January 1, 2024, and the Inflation Reduction Act (IRA) of 2022,^{4,5} both passed by the U.S. Congress.

As designed, the AMP cap removal could significantly lower a drug manufacturer’s potential profitability, since it removes the cap on rebates manufacturers pay Medicaid when they raise the price of a drug at a rate that outpaces inflation. The rebate cap was previously set at 100% of the AMP. With the removal of this rebate

cap, some manufacturers paying inflationary penalties for price increases could be required to pay Medicaid rebates that exceed their AMP.

Respondents also expressed interest regarding how the new IRA legislation could have an impact on the rare disease space. This legislation will impact several areas of pharmaceutical payment and distribution, including Medicare price negotiations of certain drugs, mandatory rebates paid by manufacturers for price increases that outpace inflation, Part D benefit design, delays to the Trump administration’s rebate rule to the year 2032, and a temporary increase in biosimilar reimbursement. The IRA specifically outlines the definition of which drugs are exempt from Medicare price negotiations. These exemptions include orphan drugs with one orphan designation and one orphan indication associated with that designation. Rare disease drugs that do not fall within these parameters would remain subject to potential Medicare price negotiations. Payers were most focused on the Medicare price negotiations piece of the IRA legislation when considering impact to the rare disease space. However, payers were uncertain regarding the exact downstream implications the IRA will have on orphan drugs, aside from the specific language outlined in the act.



“The description of a wait-and-see approach is spot on. There are so many actual and potential changes currently being proposed that changes more specific to rare-indicated products are going under the radar. Many recent policy changes, such as the Inflation Reduction Act, were impactful. However, it is not clear how these policies directly affect the rare disease space”.

– Pharmacy Director, National Pharmacy Benefit Manager

Participation in



Innovative Contracting

Participation in Innovative Contracts

The strength of clinical outcomes and overall cost of a therapy continue to drive payer interest in innovative contracts. Innovative contracting for the purpose of this report can refer to a variety of agreements, including but not limited to outcomes-based agreements (OBAs) and value-based agreements (VBAs). Participants in the 2021 survey described OBAs as those that typically align rebating with measurable clinical endpoints, and VBAs as those that typically tie financial measures to nonclinical measures such as utilization and metrics used to inform payment schedules.² However, most participants in the 2022 report did not draw a distinction between the terms (Figure 20), noting that, whatever term is used, contract specifics depend on the organization and stakeholder type.

As seen in the 2021 trend report, payers saw innovative contracting as a means to mitigate the financial risk associated with high-cost rare disease therapies and enable patient access to them. Year over year, the number of payers who anticipated using innovative contracting models in the future more than doubled — from 20% in 2021 to 53% in 2022 (Figure 21).² The overall rise

in spend across specialty drugs and all rare disease categories is driving the continued shift toward further adoption of innovative contracting.

Despite the rising interest, payers and manufacturers will face the traditional implementation challenges associated with innovative contracting, including determining data measures, collection methods, and responsibility of data collection and analysis, among others. For example, a lack of agreeable measurable endpoints oftentimes can stymie an agreement that might seem attractive to both parties. The rate at which interest converts to action will be a key indicator as to when the value of risk mitigation outweighs the many implementation challenges within and outside of payers' management or control.

Innovative Contracting Value Detractors

Several adoption barriers for innovative contracting remain within this space (Figure 22). Determining how to measure clinical outcomes and determine which endpoints are most useful continues to be an obstacle for payers and manufacturers. Payers will require

FIGURE 20: Differentiation Between Outcomes-Based vs. Value-Based Contracts

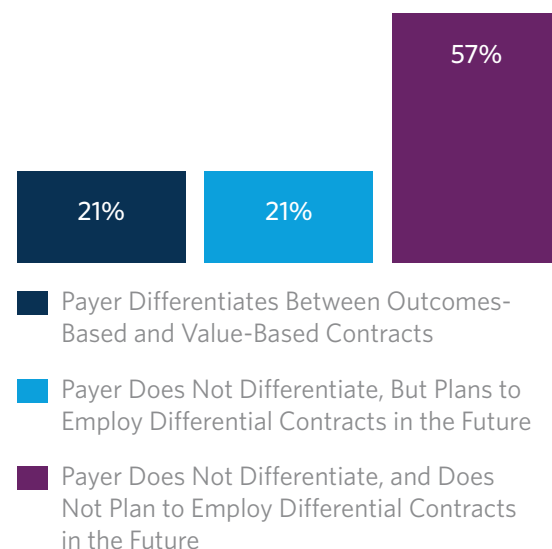


FIGURE 21: Anticipated Participation in Innovation Reimbursement Models

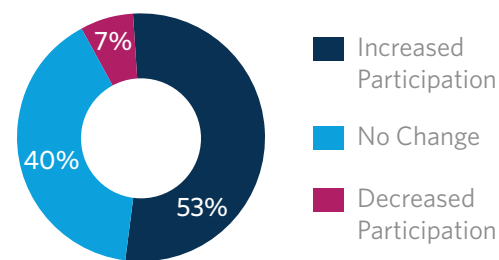


FIGURE 22: Barriers to Innovative Contracting in Rare Disease



a greater volume of clinical data to support decision-making along with the consensus among all stakeholders on the most valuable metrics. Additionally, the administrative burden associated with data collection and electronic health record (EHR) implementation may prevent many payers from pursuing innovative contracting, as the responsibility for each of these areas can be unclear and cumbersome for the assigned party. Manufacturers continue to seek the use of innovative contracts as a viable alternative to traditional buy-and-bill reimbursement models. However, in order for payers to adopt these types of contracts more broadly, the above challenges must be overcome.

“We don’t have an appetite for value-based agreements in the rare disease space. However, this decision is based on cost and achievable clinical endpoints. The only value-based agreements for rare diseases we have are within the cell and gene therapy space.”

– Pharmacy Director,
National Pharmacy Benefit Manager

“This is not a big focus for us. We have not been successful here yet in terms of identifying a value-based agreement that is actually worth it. This is true of rare and non-rare indications. The cost would be the number one driver here.”

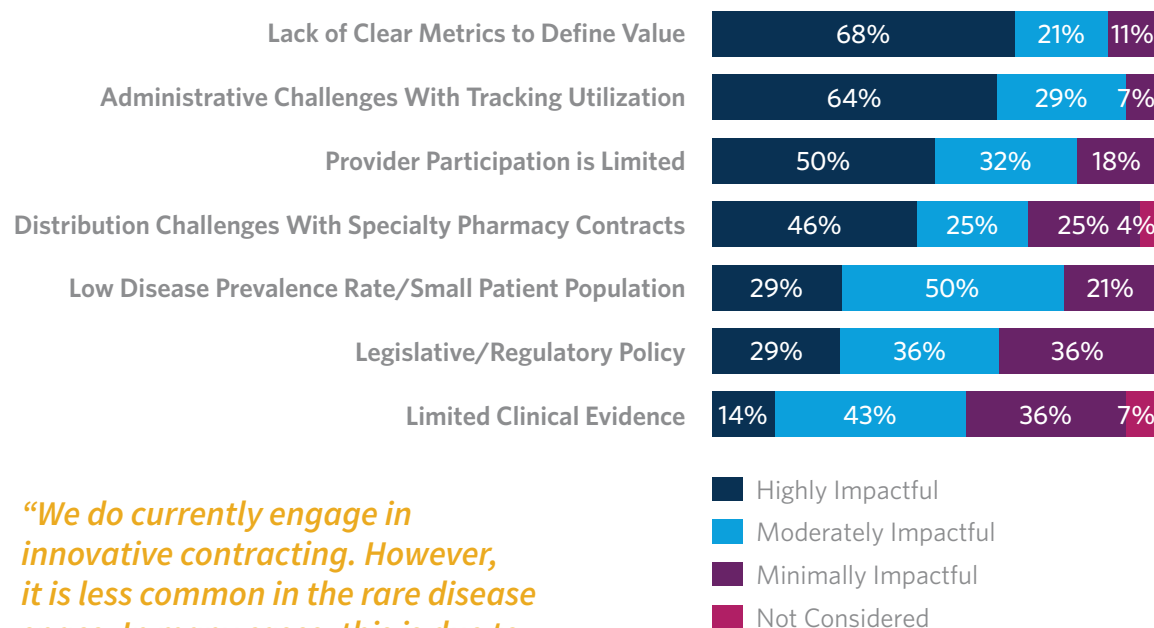
– Pharmacy Director,
Regional Managed Care Organization

Innovative Contracting Value Drivers

Currently, innovative contracting use is limited, and mainly used for high-cost, high-risk cell and gene therapies. Traditionally, the majority of innovative contracting agreements have applied to non-rare indications, leaving payers unsure of what success looks like for rare disease products. While progress has been made within the rare disease space, best practices for innovative contracting models have yet to be defined or mutually accepted among stakeholders. Still, payers are interested in them and foresee them becoming more common in the future.

Controlling costs remains the primary motivation among payers for pursuing innovative contracts (Figure 23). Historically, large national health plans have been most likely to work with manufacturers to align on innovative contracts for many higher-cost therapies, including cell and gene therapy, though these contracts have been less common within the rare disease space. However, innovative contracting agreements could offer a solution for smaller regional plans with less budgetary resources, giving them the ability to share cost risk and ultimately offer coverage to their members for higher-cost specialty therapies. Before payers will increasingly adopt innovative contracting agreements, survey participants noted it is critical for manufacturers and payers to align on successful models for determining, defining, measuring, and tracking clinical outcomes. Further, payers anticipate the administrative burden associated with long-term patient data monitoring for rare disease clinical outcomes will become more streamlined and less expensive as more innovative contracts are adopted.



FIGURE 23: Highest Impact Factors for Pursuing Innovative Reimbursement Contracts

“We do currently engage in innovative contracting. However, it is less common in the rare disease space. In many cases, this is due to the inability to collect long-term patient data. If this data were to be more readily available, agreeing on patient outcomes would be much easier, making it much more likely for us to pursue these types of agreements.”

– Pharmacy Director,
National Managed Care Organization

“We do have some interest in using value-based agreements specifically within the cell and gene therapy space due to the high upfront cost these drugs present to our organization.”

– Pharmacy Director,
Regional Managed Care Organization

Stakeholders Engaging in Innovative Contracting Discussions

Similar to findings in the 2021 report, manufacturers most often initiate conversations on innovative reimbursement structures, and employers and providers are least likely to initiate these conversations.² While payers will often engage in conversations regarding innovative contracting initiated by the manufacturer, they remain reluctant to proactively suggest innovative contracting due to administrative burdens. Payers are, however, showing an increased appetite for value-based agreements due to limitations associated with traditional cost-controlling methods. The ability to leverage multiple competitors against one another for lower net pricing is less likely within the rare disease space. Most orphan drugs do not have a true head-to-head comparator due to biomarker differences or subpopulations. These challenges could result in payers becoming more receptive to innovative contracting strategies as means to reducing cost.





Impact of CE Analysis, CE Policy, & Price Reform

Impact of CE Analysis & CE Policies

Payers do not consider CE analysis to be a core component of their rare disease therapy management process and do not use such assessments to inform medical policy. Generally, a CE assessment serves to confirm internal analysis or as ancillary evidence to help validate the overall P&T process. Smaller regional plans with tighter budget restrictions are more likely to consider CE assessments as an important piece of supplementary evidence that better informs P&T decision-making. National plans with larger budgets view these assessments as an added layer of validation to a completed analysis and place less emphasis on their overall importance to the P&T decision-making process when compared to smaller health plans.

Overall, CE assessments typically lack direct comparisons within the rare disease space due to the small number of treatment options. Without multiple comparators, payers noted it would be difficult for these CE assessments to drive decision-making. Payers also expressed skepticism regarding the accuracy, and therefore value, of CE models for negotiations and management decisions. This skepticism can

often be traced to model authorship. The majority of payers have a preference for, and place more trust in, third-party-generated models, such as those produced by ICER, over manufacturer-generated ones.³ However, most payers focus primarily on unmet need, efficacy, and safety for rare disease products, with demonstrated cost savings serving as a secondary value driver.

“In the end, our internal analysis will be most important regarding P&T decision-making. However, we do use CE assessments and reports generated from third-party organizations like ICER. Although, it’s important to point out that these reports do not directly inform medical policy decisions.”

– Medical Director, Regional Payer

Price Reform & Pricing Policy Change

Given frequent changes in Centers for Medicare and Medicaid Services (CMS) pricing and policy proposals, pharmacy and medical directors are generally less aware of externally driven proposed pricing reforms until they are approved. However, payers are proactively considering policy strategies that support cost savings, such as innovative contracting, and the advancement of ultra-rare drug development in the rare disease space. Nearly 61% of payer respondents are currently considering implementing innovative contracting for orphan drugs (**Figure 24**). While these pricing agreements carry a series of challenges, as discussed in the prior policy-driven policy section (see p. 10), payers view the future use of these agreements as highly likely.

Another area of interest to payers is strengthening the requirements for evidence generation. Sixty-one percent of payers reported the need to better clarify evidence expectations within the rare disease space (**Figure 29**). Currently, a gap exists between payers and manufacturers regarding best practices for evidence generation for highly complex rare disease products, such as orphan drugs. As guidelines regarding the collection and monitoring of evidence data becomes more consistent, endpoints such as patient-reported outcomes and quality-adjusted life years will become easier to measure and agree upon, and may lead to an increase in innovative contracting agreements.



In addition, payers reported several other policy implementation considerations aimed at reducing prices for rare disease products. These include case agreements, volume-based contracts, indication-based pricing, and the expansion of outcomes-based contracts (Figure 25). As the number of high-cost orphan drugs introduced into the market continues to rise in the next 3–5 years, price reform will continue to be integral to the rare disease space.

FIGURE 24: Policy Implementation Considerations — Encouraging Ultra Rare Drug Development

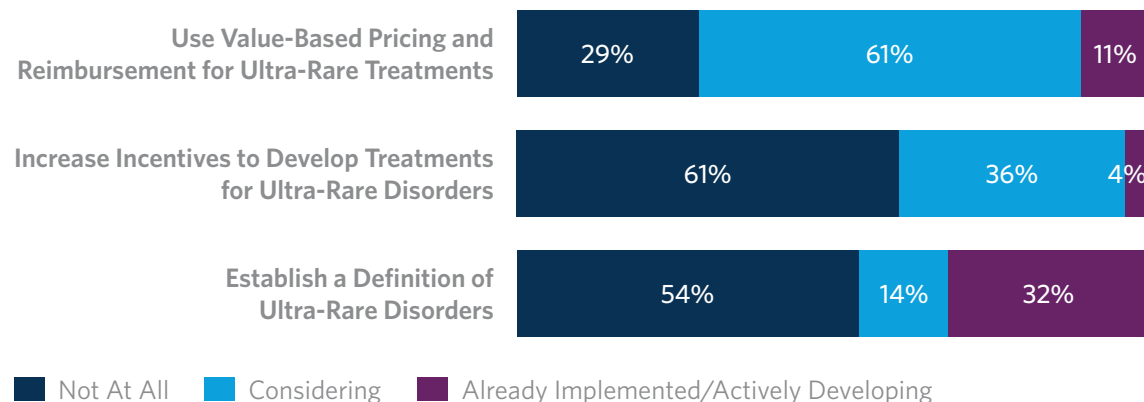
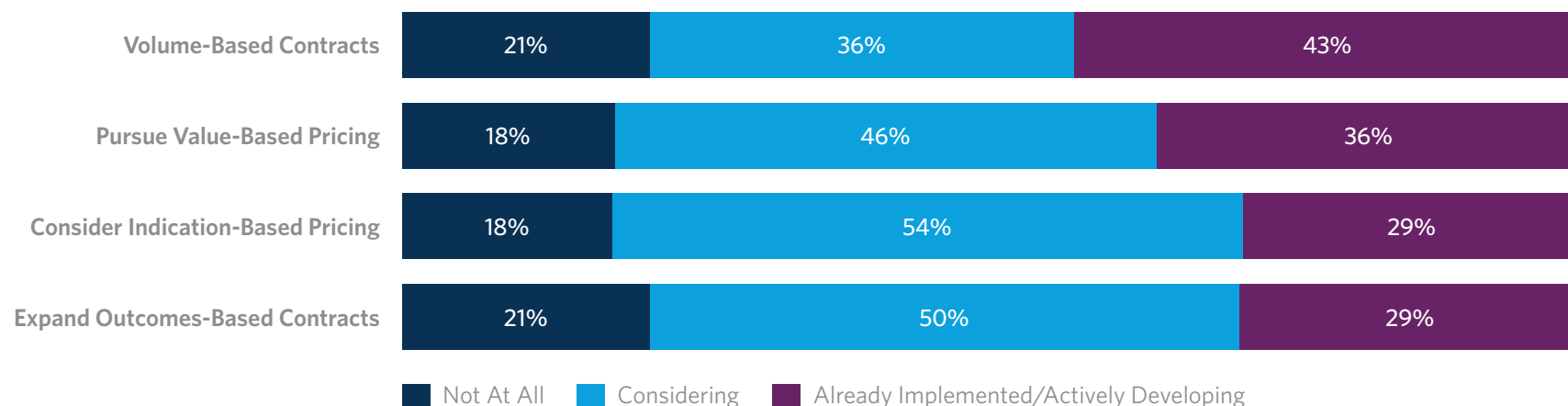


FIGURE 25: Policy Implementation Considerations — Reducing Prices for Rare Disease Products



Manufacturer-Payer Partnering on Systemic Issues

Manufacturers and other stakeholders in the healthcare industry point to the potential of payer-manufacturer partnerships as a possible solution for addressing systemic issues to access for rare disease therapies. For example, together, payers and manufacturers could leverage risk-based innovating contracting agreements to manage costs, coordinate education and outreach, implement administration and administrative processes to streamline and expedite diagnosis, treatment, and continuity of care, as well as initiate data-sharing mechanisms to collect and leverage RWE for safety and efficacy metrics and benchmarking analysis, among other opportunities.

While roughly half of sampled payer organizations engage in payer-manufacturer partnerships, these partnerships are typically not specific to rare disease (**Figure 26**). Of the payers currently involved in partnerships with manufacturers, the majority say the partnerships have had a positive or neutral impact within their organization. Additionally, many payers note a particular interest in partnerships targeting rare disease therapies, but add they currently are not typically focused on partnerships within the rare disease space (**Figures 27 and 28**). Only 7% of payers report having at least one rare-disease-focused payer-manufacturer partnership in place.

While the potential of such partnerships seems clear for the rare disease space, payers report that implementing them currently is no easy feat. For example, data-sharing and research partnerships aimed at better identifying patient outcomes and improving the overall cost of care requires mutually agreed upon areas of focus, which is highly selective and subjective to both parties' interests, as well as the infrastructure for data collection, management, and analysis, which largely does not exist. For reference, these systemic challenges are similar to those seen with innovative contracting (see "*Innovative Contracting*," p. 26).

Further, the perceived merit of and interest in such partnerships differs based on organization type. As they rarely see the value in them to their organization, national payers expressed strong resistance to these types of partnerships. While manufacturer-payer partnerships do exist among these larger national plans, most organizations viewed these partnerships with hesitancy, citing concerns with transparency among parties. Medical and pharmacy directors representing national plans noted they did not feel these partnerships typically benefited the payer. This viewpoint, however, was not true for other stakeholder types. Pharmacy benefit managers and smaller regional health plans, which generally have fewer resources than large plans, shared a more neutral and receptive position. Moving forward, small and regional payers will be most likely to evaluate the benefits of partnering with manufacturers to address systemic access-to-therapy barriers.

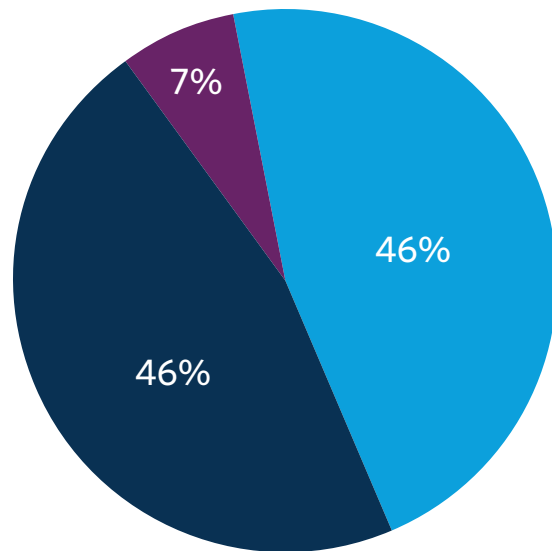
“A good partnership in this space would be focused on treatment algorithms, patient identification, projection of costs, and having a small team to pilot an approach, alongside continuity of care.”

– Pharmacy Director, Regional Managed Care Organization

“We are involved in data sharing (we have a hub that includes data for our specialty pharmacy, that is accessible to manufacturers). Data includes distribution and delivery information, patient adherence, etc.”

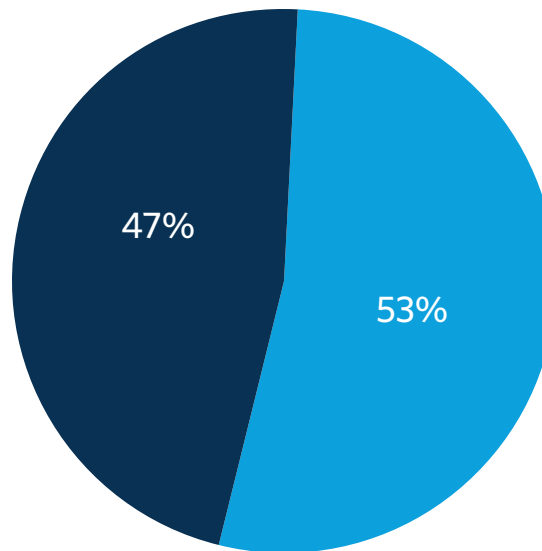
– Pharmacy Director, National Pharmacy Benefit Manager

FIGURE 26: Current Participation in Payer/Manufacturer Partnerships



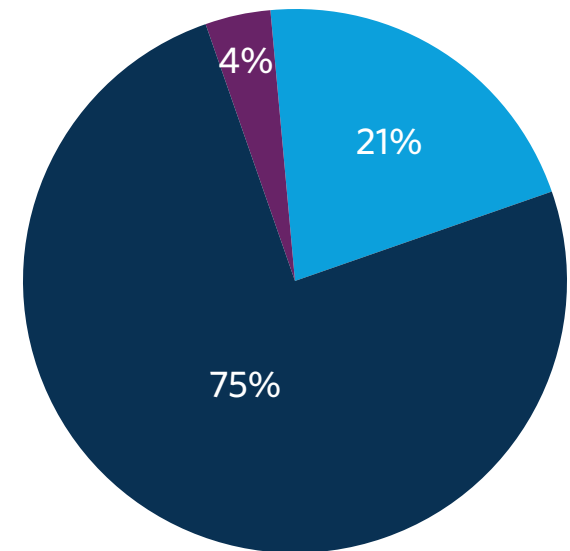
- Currently Does Not Utilize Payer/Manufacturer Partnerships
- Currently Utilizes Payer/Manufacturer Partnerships, But They Are Not Specific To Rare Disease
- Currently Has at Least 1 Payer/Manufacturer Partnership in Place With a Specific Focus on Rare Disease

FIGURE 27: Level of Impact These Partnerships Have Had Within Your Organization



- Positive Impact
- Neutral Impact
- Negative Impact

FIGURE 28: Current Interest in Manufacturer/Payer Partnerships That Are Exclusively Targeted Toward Systemic Issues Within Rare Disease

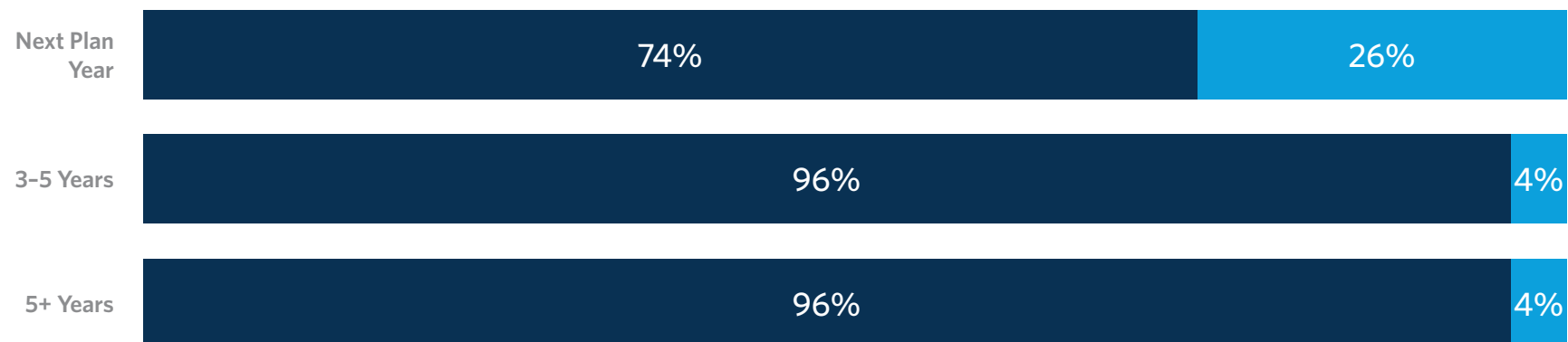


- No Interest At All
- Potential Interest
- High Levels of Interest

FIGURE 29: Current And Future Anticipated Use of Open Distribution Networks for Rare Disease Products



FIGURE 30: Future Anticipated Use of Closed Distribution Networks for Rare Disease Products



Distribution Models

When comparing preferences for open vs. limited distribution models, most payers agreed that open distribution for rare disease products is preferred. This is especially true of rare disease products that require the use of a specialty pharmacy. Limited distribution can introduce challenges with patient access, such as higher costs for drugs being provided to patients through non-covered out-of-network specialty pharmacies (Figure 29). Additionally, payers can often experience contracting challenges when working with out-of-network pharmacies. Potential delays in contract negotiations with these specialty pharmacies could result in complications to access, such as patients receiving their medications late. Due to these drawbacks associated with limited distribution networks, most payers prefer an open network for rare disease treatments.

This preference, however, is expected to shift, with over 60% of respondents anticipating an increased use of limited distribution networks for rare disease products in the future (Figure 30). This was primarily true of payers who have implemented or plan to implement specialty pharmacy mandates through an integrated specialty pharmacy.

The use of mandates through a limited network would allow payers to ensure that in-network pharmacies can provide needed medications to patients. This would help alleviate concerns surrounding patient access associated with open distribution models, while enabling payers to better manage expensive rare disease therapies. This trend has remained consistent over the past two years. Over 67% of payers in 2020 reported a likely shift to limited distribution networks for rare disease products and nearly 60% of payers in 2021.^{1,2} Nearly 80% of payers in 2022 surveyed have already implemented an integrated specialty pharmacy, further reinforcing the expectation that payers will prefer this distribution method for rare disease products in the future because it allows greater control over utilization management (Figure 31). While payers expressed the preference for distribution of orphan drugs through an integrated specialty pharmacy, payers noted this remains a difficult process to implement, since manufacturers and regulatory bodies can significantly impact the eventual distribution of a pharmaceutical product.

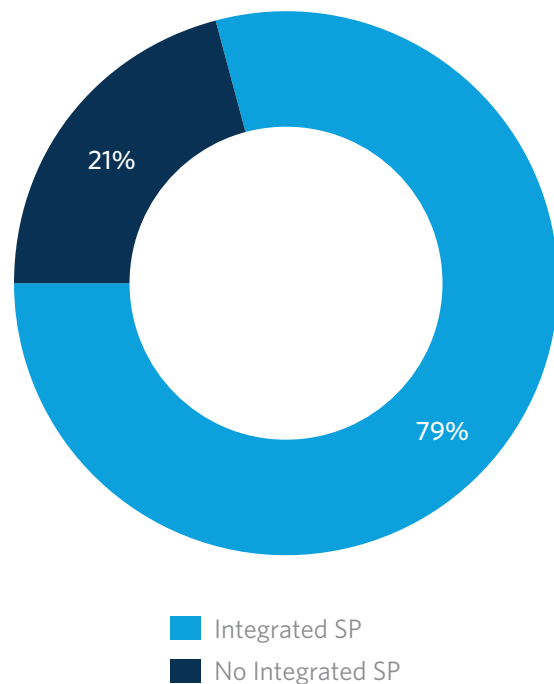
“We anticipate that integrated specialty pharmacies will be the preferred distribution method of rare disease drugs. Limited distribution networks seem to make the most sense for orphan and ultra-orphan products. The goal being to avoid ‘buy and bill’ for these high-priced treatments.”

– Medical Director, Regional Payer

“We prefer high-cost orphan drugs to be available through our specialty pharmacy. However, this doesn’t always happen. We do mandate specialty pharmacy for certain products, however, not very successfully. Outpatient use, self-administration, geographic factors, all impact whether or not we will successfully implement specialty pharmacy mandates for a rare disease drug.”

– Medical Director, Regional Payer

FIGURE 31: Current Integration of Specialty Pharmacy



Conclusions

The research for the third annual Alnylam Rare Disease Trend Report was conducted in September and October of 2022, during the aftermath of the COVID-19 pandemic. Similar to previous reports, payer survey findings show that key value drivers for evaluating rare disease therapies continue to include efficacy and safety, level of unmet need in the patient population, and durability of effect. However, while clinical efficacy and unmet need remained a driver for P&T review in both 2020 and 2021, real-world evidence in rare diseases elevated in importance. Additionally, payer survey data show that utilization management techniques do not typically differ between rare and non-rare indications. Instead, payers emphasize that management differs on a product-to-product basis. Most payers agree that innovative contracts will become more frequent in the next 3–5 years, insinuating there is an expectation for an effective solution in the pipeline for rare disease products. The Rare Disease Trend Report is designed to assist commercial payers in the U.S. in understanding key trends and by benchmarking rare disease drug management practices against industry peers. In the next issue, the report will continue to track the potential long-term implications of COVID-19 and other policy efforts that may be coming down the pipeline.

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This report did not ask any questions or anticipate any potential impact from the COVID-19 pandemic.



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