



2021 Alnylam Rare Disease Trend Report

PERSPECTIVES FROM HEALTHCARE PAYERS

SECOND ANNUAL EDITION

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Foreword

As the drug pipeline for rare and orphan conditions continues to grow, payers are diligently trying to determine how to connect individuals to treatment options, and manage the economic intricacies of these high-cost novel therapies. With the emergence of the global COVID-19 pandemic, it seemed this delicate balance would become even more precarious for payers, especially given the complexity of the rare disease patient population, growing number of drugs, and enhancements in biologic research. However, the findings of the second annual Alnylam Rare Disease Trend Report revealed payers' commitment to addressing the needs of patients suffering from rare and orphan diseases, despite the distressing global circumstances.

From the perspective of US payers, the 2021 Alnylam Rare Disease Trend Report offers readers a clear view of the latest trends and potential implications in rare disease and orphan drug management. The report is published to inspire open and transparent dialogue among payers, providers, manufacturers, patient advocacy groups, and patients, so stakeholders can work together to address access barriers and ultimately improve patient outcomes.



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Introduction

The COVID-19 global pandemic created significant challenges for the healthcare industry. The economic and humanistic impact of this tremendous event will likely be studied and analyzed for decades to come. While this global event has placed substantial financial strains on the healthcare community writ large, the focus of this report is on the potential impact of various market dynamics on commercial payer management of rare disease products.

This report is intended to discuss the potential impact of various market dynamics on evolving payer priorities and management of rare disease products. Included among these are the COVID-19 pandemic and the continued emergence of novel therapies intended to treat rare or orphan indications. Several key questions that are answered within this report include:

- How have payer priorities shifted since publication of the first edition of this report (2019)?
- To what extent has the global pandemic impacted payer management of rare disease therapies?
- How have evolving market dynamics (e.g., the emergence of novel rare disease therapies, national policy reforms, etc.) influenced payer management of rare and orphan drugs?
- Did payer perspectives on innovative structures evolve between 2019 and 2021?
- What are the potential long-term trends in payer management of rare disease products?

The authors of this report hope to increase transparency among the payer community and elevate the discussion around rare disease products by offering key insights and perspectives on current and future management considerations.

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.

Methodology

Alnylam Pharmaceuticals, Inc., sponsored and developed this publication in partnership with 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 2021 as the current health plan year, the survey specifically delves into anticipated changes within the next plan year (2022), the next 3–5 plan years (2024–2026), and beyond (2027+).

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 partnered with a commercial vendor to recruit participants and transfer the survey to an online format.

Recruitment & Fielding

Respondents were selected for appropriate 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 (i.e., commercial or managed Medicaid affiliate), as well as a mix of stakeholders with national and regional purviews.

All participants completed the survey over the course of three weeks, from June 25 to July 16, 2021. 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 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;
- Active involvement in policy development within the organization, including experience developing policies for rare disease and management; and
- Willingness and ability to discuss decision-making focused on 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

Each respondent 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 U.S., were selected to participate in primary research. All stakeholders are active members of their P&T committees and 93% of the sample has over 6 years of experience directly reviewing rare disease products and indications. The remaining sample has 3–5 years of experience (**Figure 1**). Of payers sampled, 43% are medical directors and 57% are pharmacy directors (**Figure 2**). Across the sample, 87% indicated their plans have integrated Specialty Pharmacy (SP) capabilities, which is an important consideration when evaluating distribution and benefit design trends. (**Figure 3**). National commercial payers comprise 21% of the sample, regional commercial payers, 52%, Medicaid managed care plans, 17%, and pharmacy benefit managers (PBMs), 10% (**Figure 4**).

Across the commercial, managed Medicare, and managed Medicaid plans sampled, the majority of spend is in medical benefit (58% of spend) compared to pharmacy benefit (42% of spend) (**Figure 5, 6**).

FIGURE 1:
Participant Years of Product
Evaluation Experience

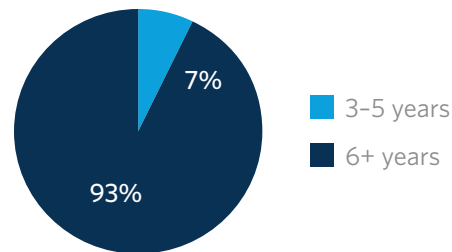


FIGURE 2:
Participant Sample Titles

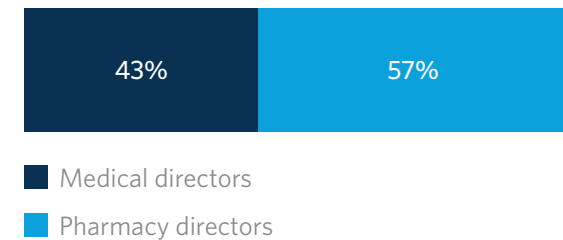


FIGURE 3:
Payer Sample Specialty
Pharmacy (SP) Capabilities

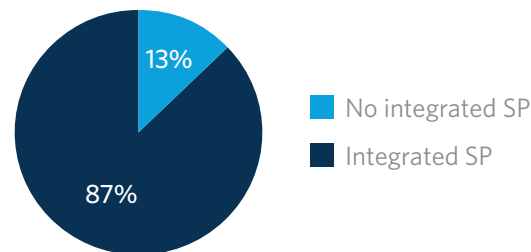


FIGURE 4:
Sample Payer Mix

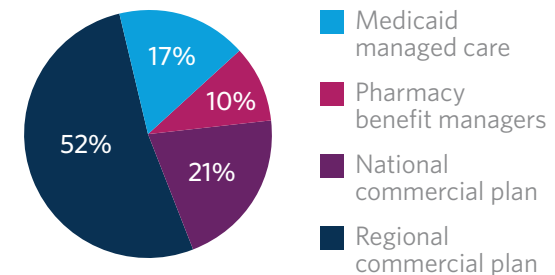


FIGURE 5:
Benefit Spend by Book of Business



Detailed Research Findings

Rare Disease Landscape

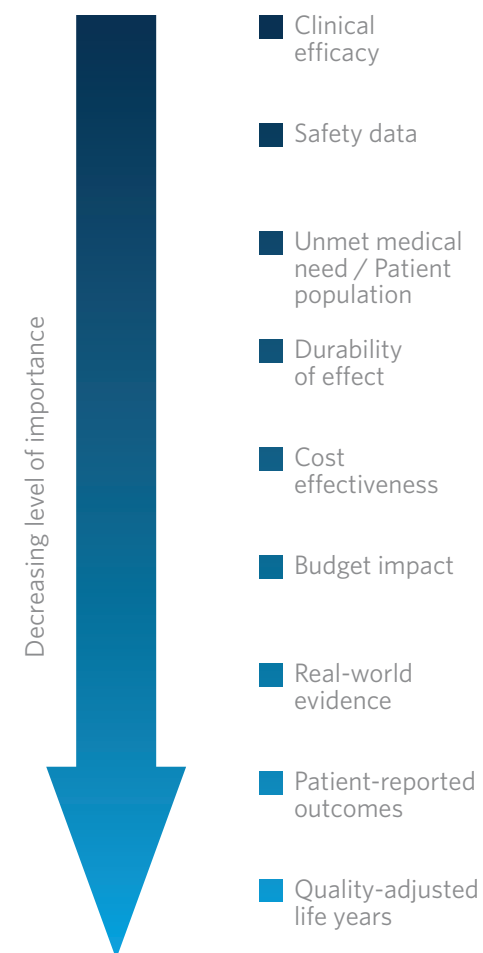
Value Drivers to Rare Disease Product Review

Key value drivers for rare disease therapy evaluation include efficacy and safety, level of unmet need in the patient population, and durability of effect (**Figure 6**). Payers recognize the added pressure of addressing the unmet need in rare disease and, compared to 2020, the importance of unmet need in rare disease product evaluations increased from the fourth-highest priority to the third-highest priority. This change may be credited to the growing awareness of the lack of treatment options available for rare disease patient populations. Driven primarily by the volume of orphan drug approvals in recent years and efforts from patient advocacy groups, this increase in awareness has potentially led to greater consideration for new products that address unmet needs. Especially as more gene therapies come to market at high price points, payers are more willing to pay a premium if products are curative or provide significant durability of effect. Conversely, payers are less likely to accommodate premium pricing and broad access for products that provide short-term benefits or require regular dosing for longer periods of time.

Relative to non-rare diseases, payers consider patient-reported outcomes (PROs) and quality-adjusted life years (QALYs) to be important metrics in the rare disease space. The severity and complexity of the condition coupled with the high cost of care can result in the need for payers to more accurately track and monitor patient health and overall disease management. As the collection of real-world evidence (RWE) in the rare disease space becomes more consistent, reliable, and extensive in the future, PROs and QALYs will be easier endpoints to measure, and these will hold more importance in orphan drug evaluation.

Most US payers associate RWE with post-marketing surveillance or Health Economics and Outcomes Research (HEOR), and are less familiar with the potential for RWE to answer questions related to the safety and efficacy of new drugs.¹ However, this use is expected to become more common in the future. Additional evidence, including cost-effectiveness models, may be factored into product evaluations and management decisions if available decisions, if available. While it is difficult to base

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



decision-making on cost-effectiveness unless multiple treatment options are available (which is uncommon for rare diseases), payers hope to be able to incorporate this into management decisions in the future as overall costs to the health plan continue to rise.

“Although difficult to measure, PROs and QALYs can be relevant endpoints for value and outcomes-based contracts in rare disease to protect from high-cost implications.”

– Pharmacy Director, PBM

Rare vs. Ultra-Rare Disease Management

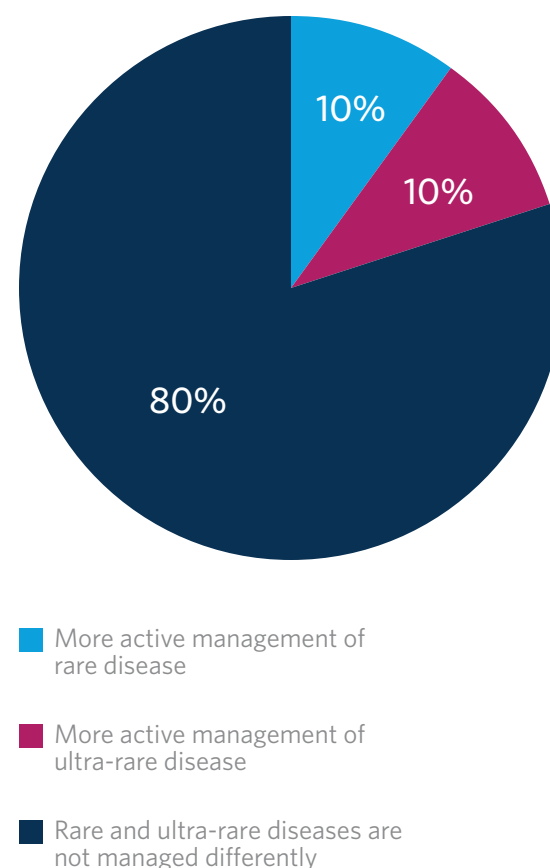
There is minimal differentiation in management of rare vs. ultra-rare therapies. Eighty percent of payers are not evaluating these patient populations differently, because either current management practices target rare diseases effectively or the frequency of rare and ultra-rare disease patients can be evaluated on a

case-by-case basis (Figure 7). Further, most organizations are following US Food and Drug Administration (FDA) guidelines for defining rare populations based on the threshold of patients, and payers indicate that strictly defining rare vs. ultra-rare vs. non-rare diseases will not lead to significant cost savings, and therefore to differential management techniques. However, payers note that rare disease evaluation and management likely will require greater education from key opinion leaders (KOLs,) specialized societies, and clinical experts in a therapeutic area in order to more effectively manage the complex patient populations and the associated budgetary burdens from high-cost, rare disease therapies.

“We define rare and ultra-rare diseases by patient population thresholds, but defining these terms will not impact policy decisions regarding these diseases.”

– Medical Director, National Commercial Payer

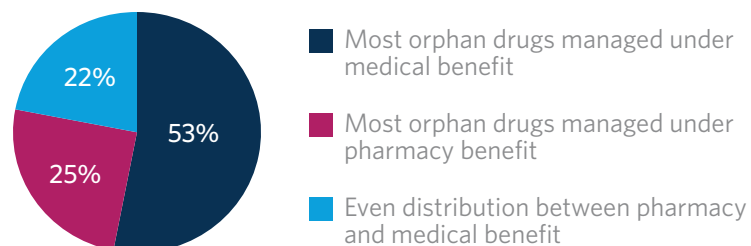
**FIGURE 7:
Management of Rare vs.
Ultra-Rare Disease**



Rare Disease Management Processes

In 2020, 40% of payers had designated subcommittees for rare disease therapy management and an additional 17% anticipated developing them in the next year. However, despite this expectation, prevalence of rare disease subcommittees has not grown in 2021. Most payers believe their current committee for the evaluation and management of therapeutics allows for the appropriate amount of focus and does not require creating a separate committee. Payers are likely to involve additional key opinion leaders (KOLs) and resources into the committee when evaluating a rare therapeutic. As more rare disease products come to market and pose a greater economic burden, payers recognize that separate rare disease committees will likely be established. Even though management of non-rare and rare disease do not differ, payers with dedicated subcommittees seek to ensure they have the appropriate expertise to review such complex therapies for rare patient populations. While rare disease subcommittees will become more common over time, current trends indicate they are not being developed as quickly as previously thought, likely due to shifting priorities amid the COVID-19 pandemic. Payers expect rare disease subcommittees to become more commonplace in the future as the global pandemic subsides.

FIGURE 8:
Pharmacy vs. Medical Benefit Management of Orphan Drugs



Utilization & Benefit Management

Benefit Assignment

Rare disease therapies are primarily managed through the medical benefit, given the complexity of product, administration, and patient population. When asked how often cell and gene therapies are managed under the medical vs. pharmacy benefit, 53% of payers responded that the majority are managed under medical benefit, while 25% indicate the majority are managed under the pharmacy benefit, and 22% indicate an even distribution (**Figure 8**). Whether the drug is physician- or self-administered, drug indication, route of administration, and site of care are the most influential factors when making a benefit determination (i.e., medical or pharmacy) for a drug both currently and in the future (**Figures 9, 10**). Therapeutic area will also play a significant role in determining assigned benefit because certain indications are more likely to require physician administration and therefore are more likely to be medical benefit therapies. Further, compared to pharmacy benefit, some payers believe medical benefit assignment allows payers to develop more detailed policies based on the clinical evidence to specify appropriate patient populations.

“The medical benefit side is more flexible, so we need to be more rigorous to put controls in place. But the medical benefit side allows for more creativity and direct contact with physicians which lends deeper insights into complex rare patient populations.”

– **Pharmacy Director, PBM**

FIGURE 9: Determining Factors for Benefit Assignment (Current)

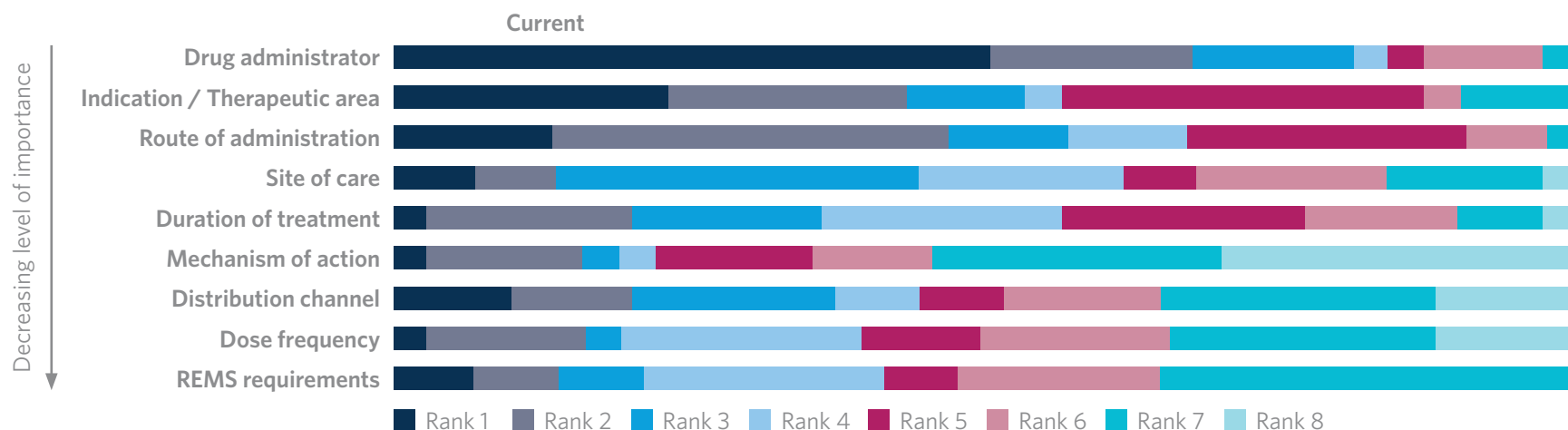
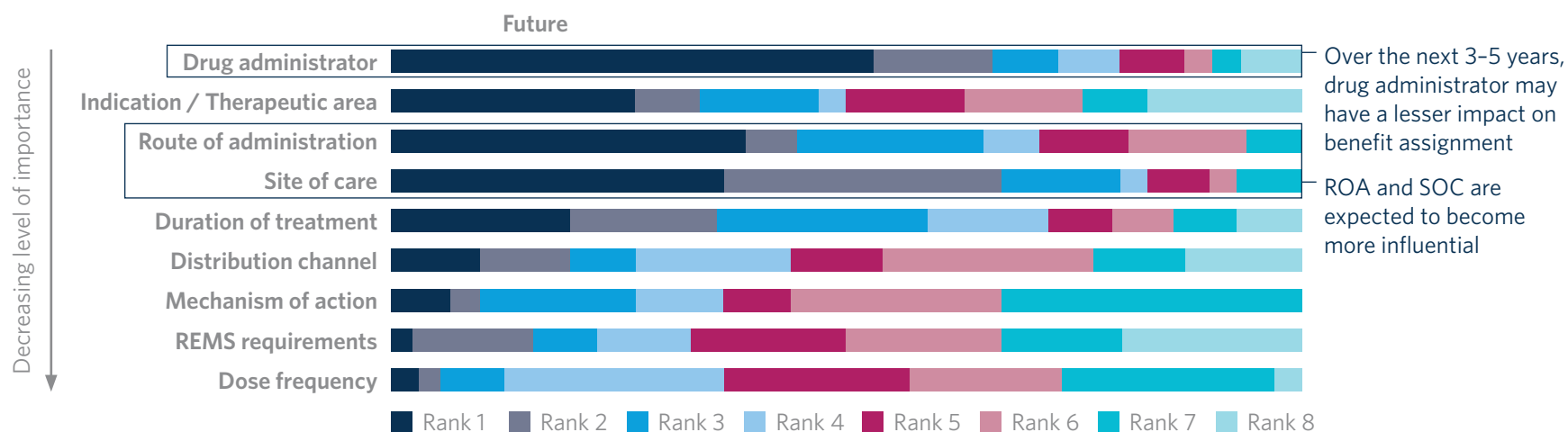


FIGURE 10: Determining Factors for Benefit Assignment (Future)



Site of Care Policies

Payers indicate, while COVID-19 was not the defining factor, the pandemic spurred an increase in site of care policies with an overall trend toward increased flexibility for patients to be treated closer to home (**Figure 11**). Use of site of care policies for orphan drug management has become more common in recent years because certain clinical settings are reimbursed at lower rates than others (**Figure 11**). For example, hospital outpatient departments typically demand higher reimbursement relative to infusion centers or home settings due to higher overhead costs. Further, 87% of payers stated their plan offers home infusion services, and 20% report these services were offered following the COVID-19 pandemic (**Figure 12**). As payers look to shift away from drug administration in the hospital setting and establish more flexible site of care policies, benefit assignment also will be impacted. Shifting to home administration creates an opportunity for white bagging, which may reduce buy-and-bill use. While these trends will impact rare disease management, they also apply across indications with opportunities for flexible administration. The pandemic was a catalyst for more flexible site of care policies, which, now established, are likely to remain.

FIGURE 11:
Site of Care Policy Development for Orphan Drugs

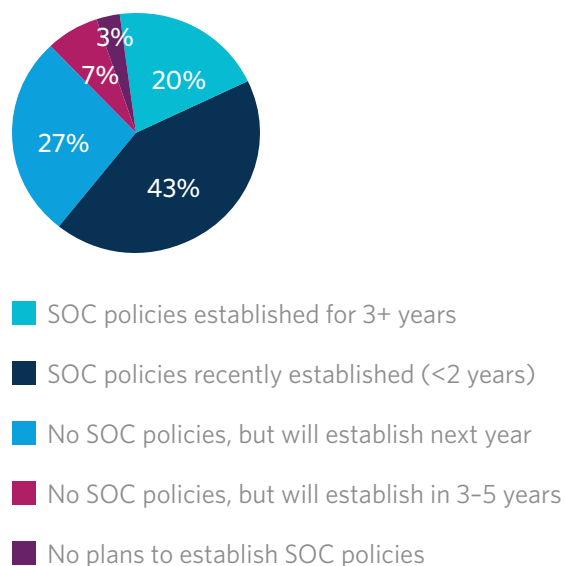
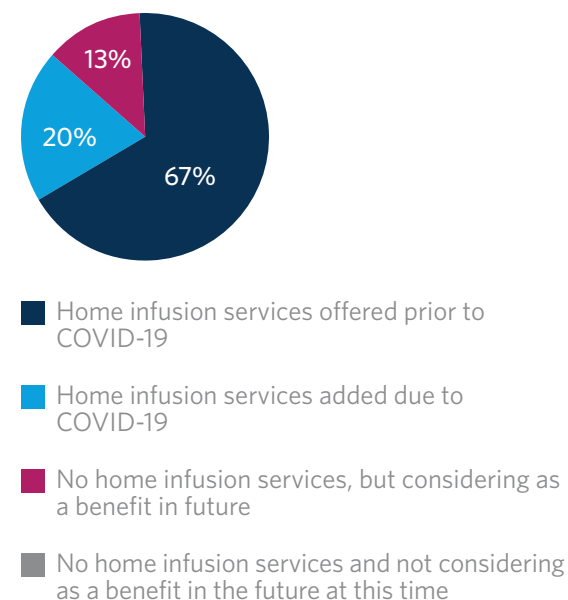


FIGURE 12:
Coverage of Home Infusion Services



Pharmacy Benefit Management and Specialty Pharmacy Mandates

When asked how benefit design of rare disease products may evolve in the future, 47% of payers stated they anticipate a shift toward pharmacy benefit management, in part driven by specialty pharmacy (SP) mandates (**Figure 13**). It is important to note that 87% of the payer sample has an integrated SP, which likely may be a biasing factor and reflect greater interest in mandating the SP (**Figure 3**). The financial implications of SP mandates and techniques such as white bagging incentivize payers to move products historically managed under the medical benefit to the pharmacy benefit. However, as noted above, the medical benefit allows payers to establish more tailored and specific policies and

medical necessity requirements. This flexibility is particularly pertinent to rare patient populations and may lead to a lesser shift toward pharmacy benefit management than currently anticipated.

There is a growing preference for integrated SP mandates, as payers seek greater insight into the patient journey to better manage care. SP mandates allow for more control over a given therapeutic area, yielding more accurate therapy distribution, dosage, and management (Figure 16). Among payers with an integrated SP, 63% expect to leverage specialty pharmacy distribution mandates via their integrated specialty pharmacies to provide higher quality patient management and to have greater control of high-cost therapies (Figure 14). Buy and bill is currently the primary channel at 33% of the payer sample, and only 7% of the sample expects this to remain the primary distribution channel in the next 3–5 years (Figure 15). As further evidence of the expected shift toward pharmacy, currently 40% of payers cite SPs as the primary distribution channel for orphan drugs, and 57% of the sample expects SPs to be the primary distribution channel in the future (Figure 15). While this aligns to trends seen widely across plans that look to more closely control rare disease spending, it is important to note that smaller plans lacking integrated SPs

will not have these same incentives, and are more likely to allow for buy and bill in the future, and not mandate SP use.

“We’ll mandate specialty pharmacy distribution for rare disease products because the quality of patients services is higher and it makes sense from a cost perspective vs. using a third-party specialty pharmacy.”

– Pharmacy Director, Regional Medicaid Managed Care

FIGURE 13:
Benefit Management Expected Distribution by Product Type Next Plan Year (2022)

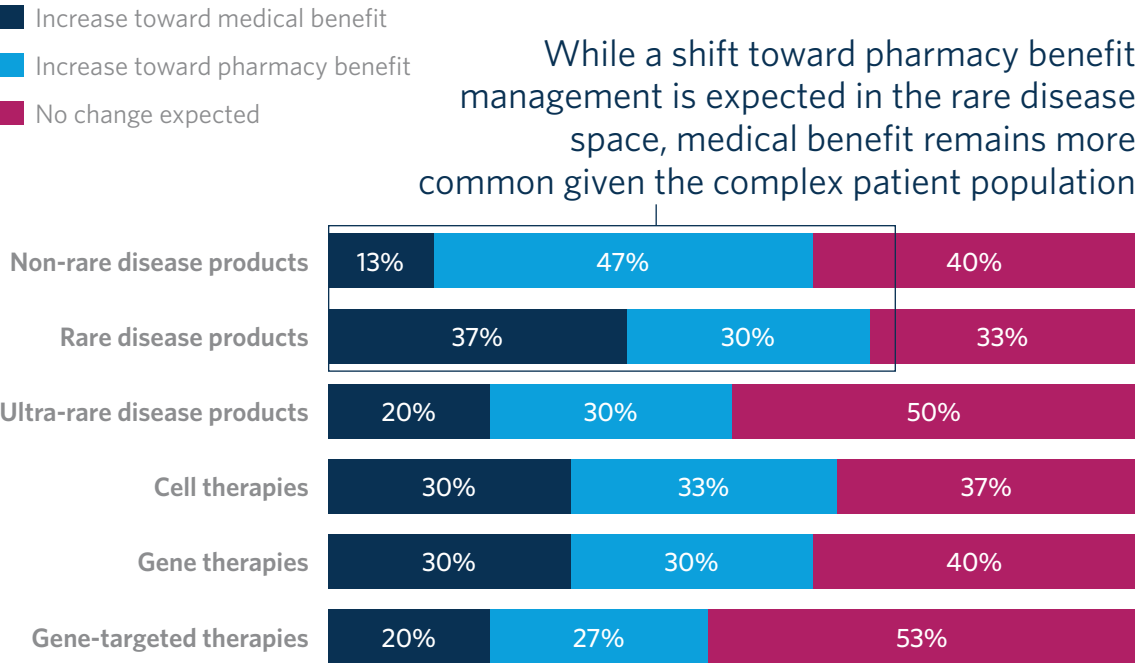


FIGURE 14: Anticipated Future SP Mandate Use

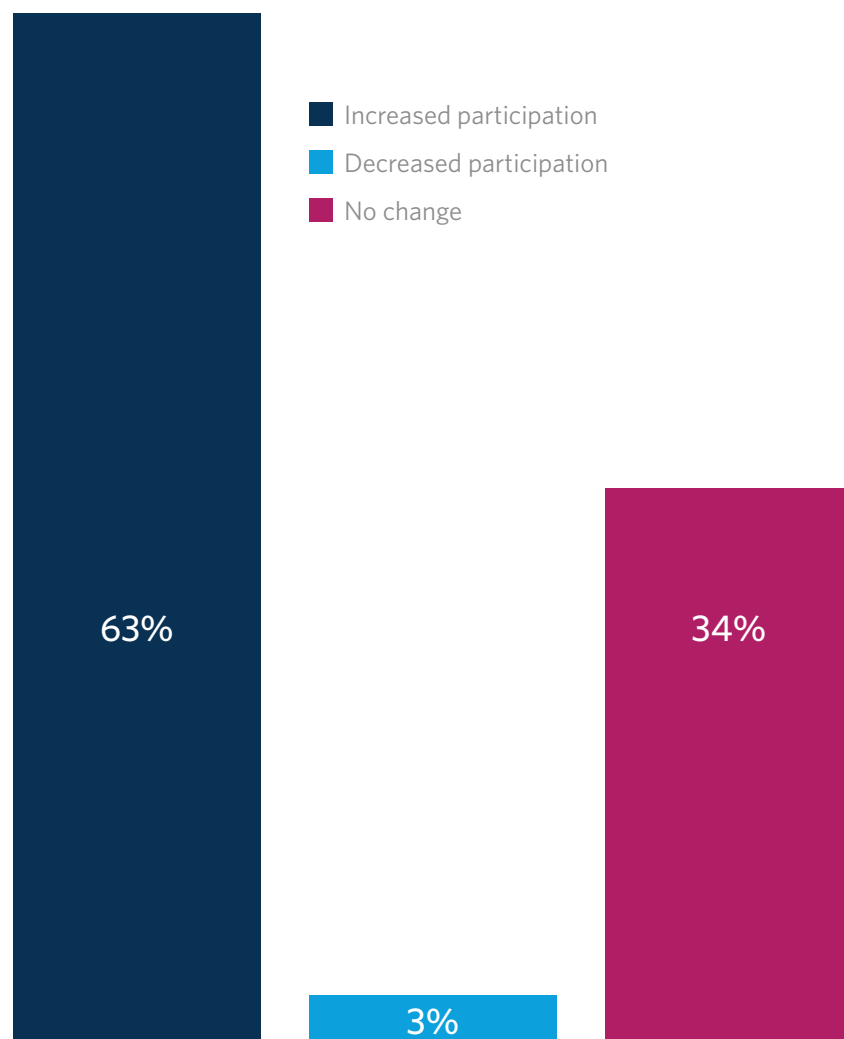


FIGURE 15: Orphan Drug Distribution Channels

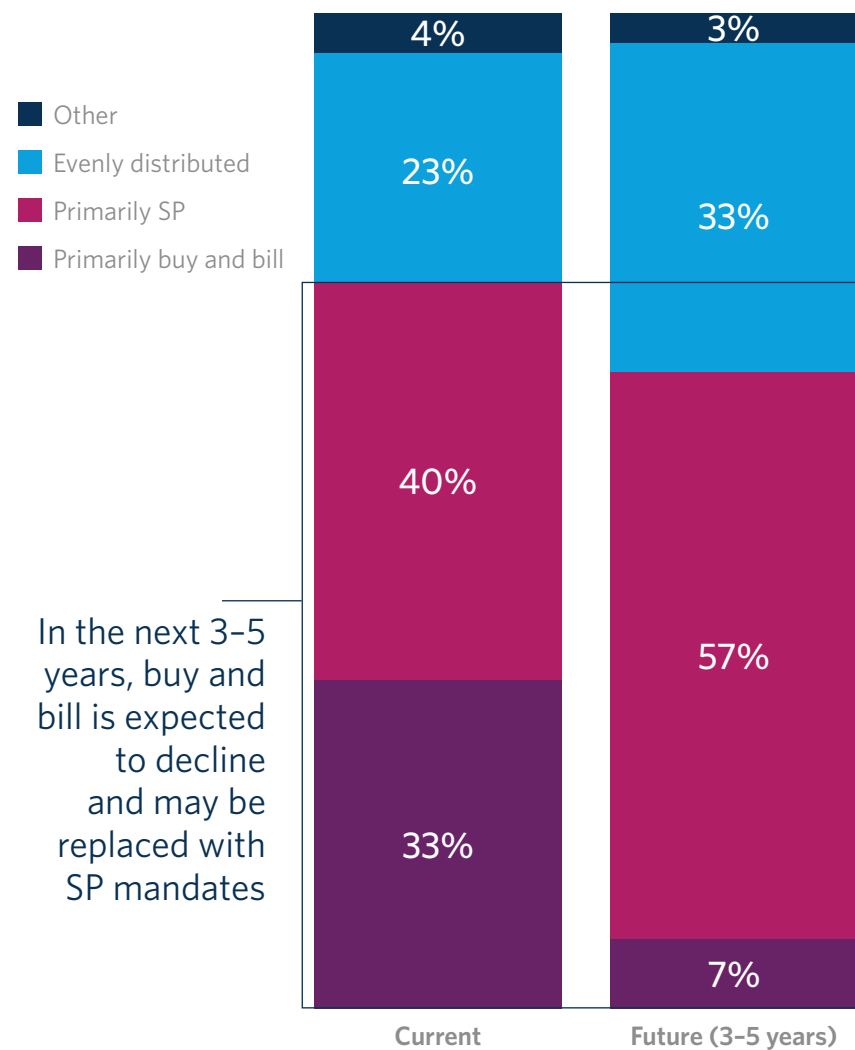
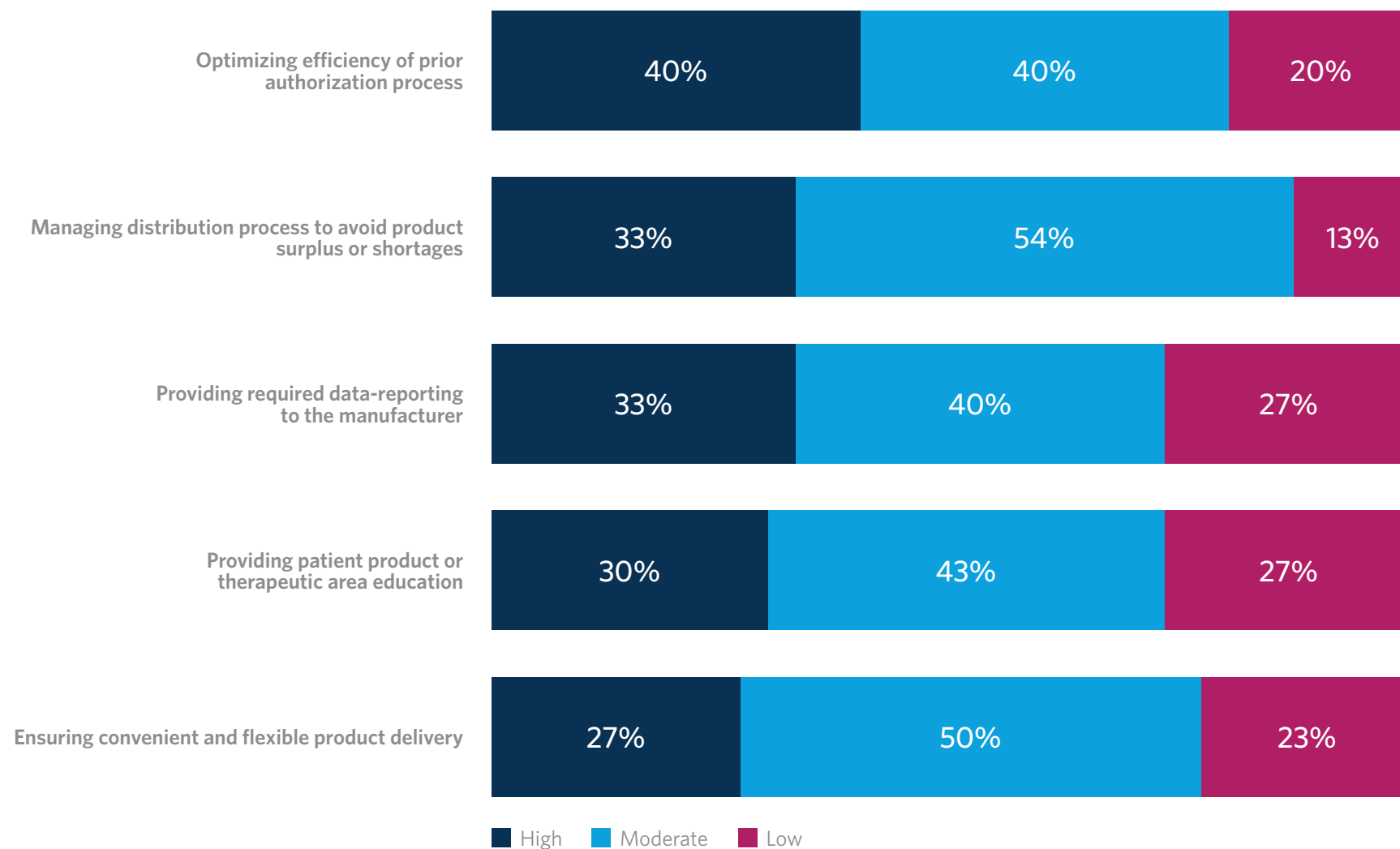


FIGURE 16: Drivers of SP Use for Orphan Drugs



Utilization Management

Although similar utilization management techniques are leveraged across non-rare and rare disease, utilization management is more common in rare disease and its application is expected to increase in the next 3–5 years (**Figure 17**). In 2020, 53% of payers cited more active utilization management of rare diseases compared to non-rare diseases, which is consistent with payer perception in the current

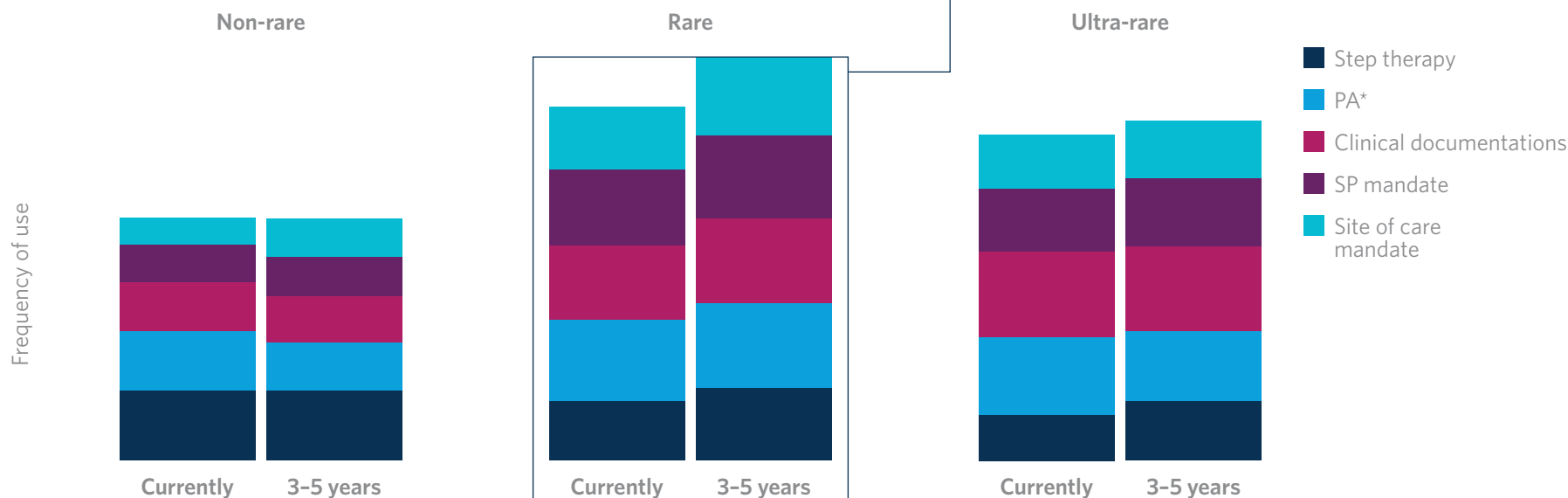
plan year. Tools, such as prior authorizations, clinical documentation, specialty pharmacy (SP) mandates, and site of care mandates, are used more frequently to manage the use of rare disease products, and are expected to become increasingly common. In addition, as more orphan drugs are approved and more rare-disease data are published, step therapy and site of care requirements are expected to increase in prevalence to help ensure patients receive the most appropriate treatment options.

“Although management looks the same, rare disease products are relatively managed more actively than non-rare disease products because it is a more complex area.”

– Pharmacy Director, National PBM

In 2020, 53% of payers reported more active management of rare disease vs. non-rare. In 2021, management has not changed and payers indicate more active utilization management of rare disease

FIGURE 17: Current vs. Future Frequency of Utilization Management Tools



Impact of Health Technology Assessments (HTA)

Historically, payers have relied more on internal HTAs for product evaluation than external HTA groups to support medical coverage policies. However, resource-constrained payers are more likely to base decisions on externally developed HTAs, while larger payers use these evaluations as further support for already-made management decisions. While the level of impact of HTAs varies across plans, in the next three to five years, 50% of payers anticipate HTAs, such as those produced by the Institute for Clinical and Economic Review (ICER), will have a greater impact on rare disease management and manufacturer negotiations (**Figure 18**). ICER and other HTA organizations do and will continue to allow payers to benchmark product costs to negotiate reimbursement rates. Given the high cost of therapies and the complexity of many rare disease indications, HTAs are especially pertinent to orphan drug management. Cost effectiveness models are the most impactful type of HTA and are increasing in the level of importance. In 2020, 23% of payers ranked cost-effectiveness and budget-impact models

as highly impactful to decision-making vs. 37% in 2021 (**Figures 19, 20**). HTAs and real-world evidence in the rare disease space provide more data and greater insights for product evaluations and the potential to provide relevant competitor benchmarking in lieu of head-to-head studies.

ICER’s cost-effectiveness analyses hold greater importance to payers for rare disease products compared to non-rare disease products due to the high cost of therapy, lack of alternative options and, at times, lack of treatment guidelines for rare disease populations. However, incorporating ICER evaluations into medical policies today is challenging, given the lack of comparator orphan therapies and high unmet need in the space. Additionally, payers are likely to be reluctant to base medical policy decisions entirely upon ICER evaluations, considering it is a singular organization and healthcare professionals have highly debated its methodology, particularly its rare disease evaluation framework.

FIGURE 18:
Impact of External HTAs to Rare Disease Management Decisions

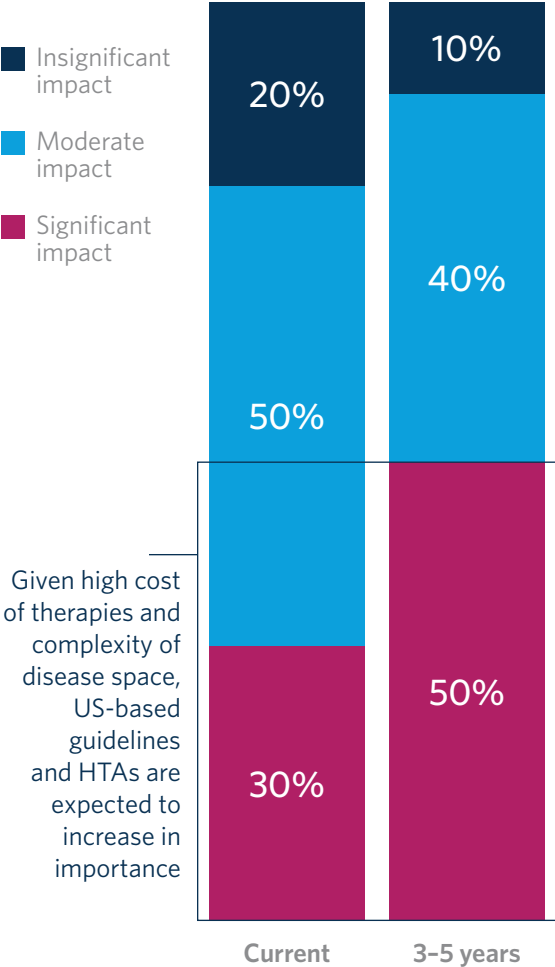


FIGURE 19: Impact of HEOR Assessments to Rare Disease Management Decisions (Current)

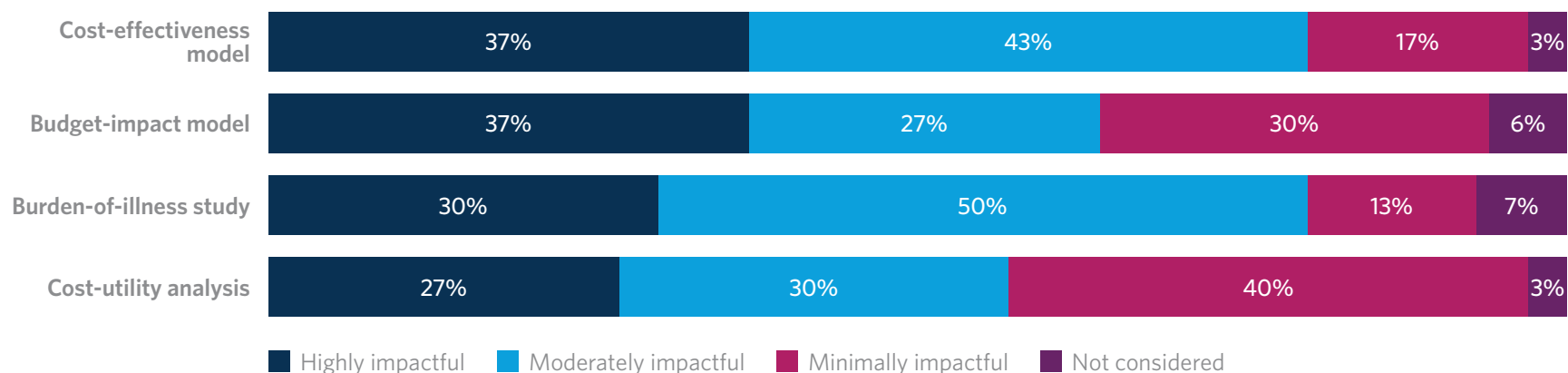
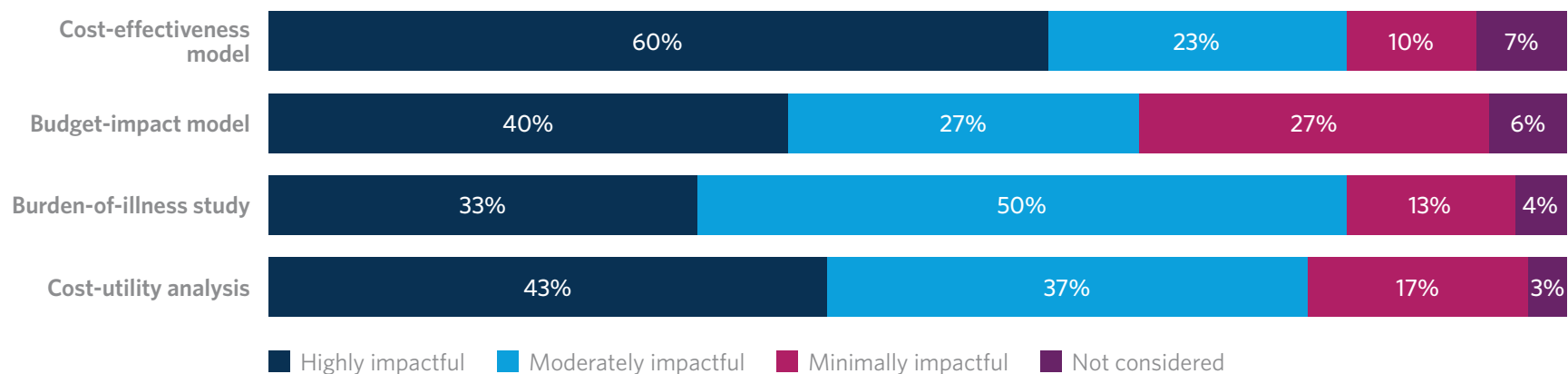


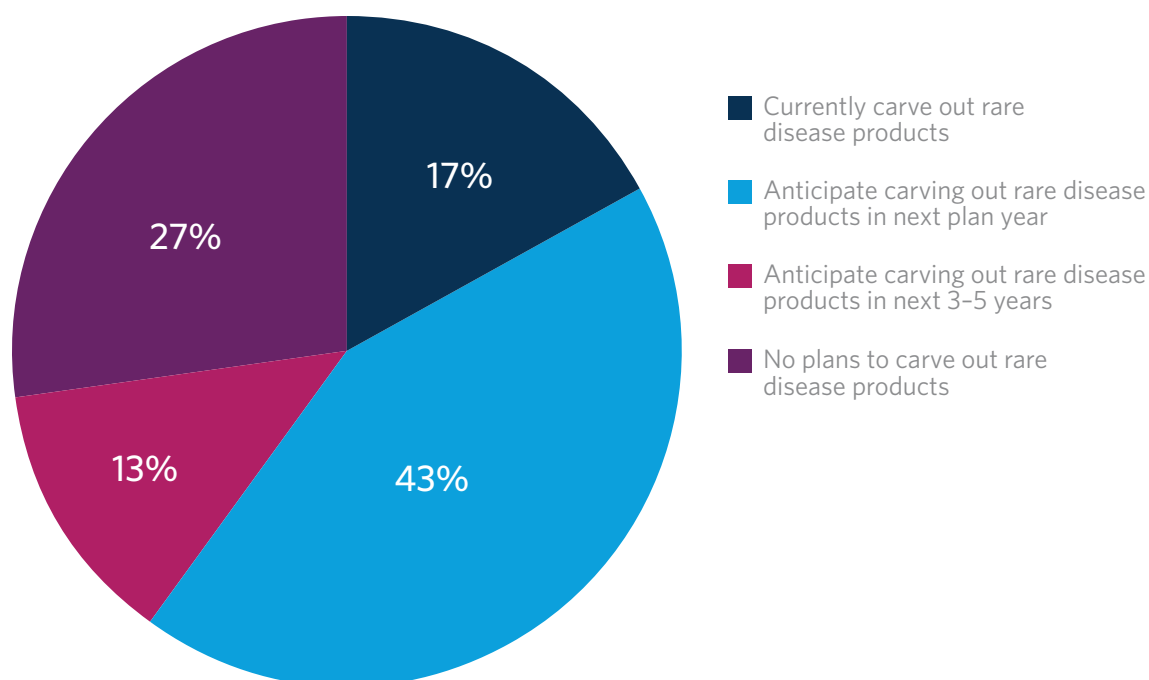
FIGURE 20: Impact of HEOR Assessments to Rare Disease Management Decisions (Future)



Rare Disease Carve Outs

While uncommon today among employer groups, the use of carve outs from health plan coverage for rare disease products is expected to increase in the next 3–5 years (**Figure 21**). However, a lack of clarity regarding the value and financial burden of carve outs for rare disease products stands as an adoption barrier for employers. Payers believe employers may be more interested in this approach as more high-cost therapies become available and continue to drive up costs. Carve outs typically enable employers to better manage health plan costs. Additionally, Medicaid carve outs are becoming more common. States may choose this approach for prescription drug benefits or specific drugs within their managed care contracts in order to more closely manage spending. Managed Medicaid plan sponsors note they must follow state Medicaid mandates regardless of their individual health plan's perspective on the relevant policies.

FIGURE 21: Proportion of Rare Disease Carve Outs of Fully Insured Employer Groups



“Self-funded employer groups have freedom to craft benefit plans as they desire and carve-outs may increase as cost and volume of therapies rise and safety nets can be leveraged.”

– Medical Director, Regional Commercial Payer

Off-Label Use of Rare Disease Therapies

Interestingly, while off-label use is currently less frequent within rare diseases, the limited treatment options available for these highly specialized populations may result in increased off-label utilization. Payers indicate off-label use currently occurs most commonly in oncology

in both rare and non-rare disease indications, where management is less restrictive given the unmet need and time sensitive nature of treatment (**Figure 22**). The National Comprehensive Cancer Network guidelines support for off-label therapies lead payers to approve off-label use, and drive off-label use in oncology. As more data become available

across therapeutic areas, payers expect to see more frequent off-label use in the rare disease space (**Figure 23**). Management for off-label use, however, is not expected to change, because policies mandating review and potential approval of off-label drug use are expected to remain in place, and payers will continue to review off-label use on a case-by-case basis.

FIGURE 22:
Off-label Access of Rare Disease Therapies by Therapeutic Area (Current)

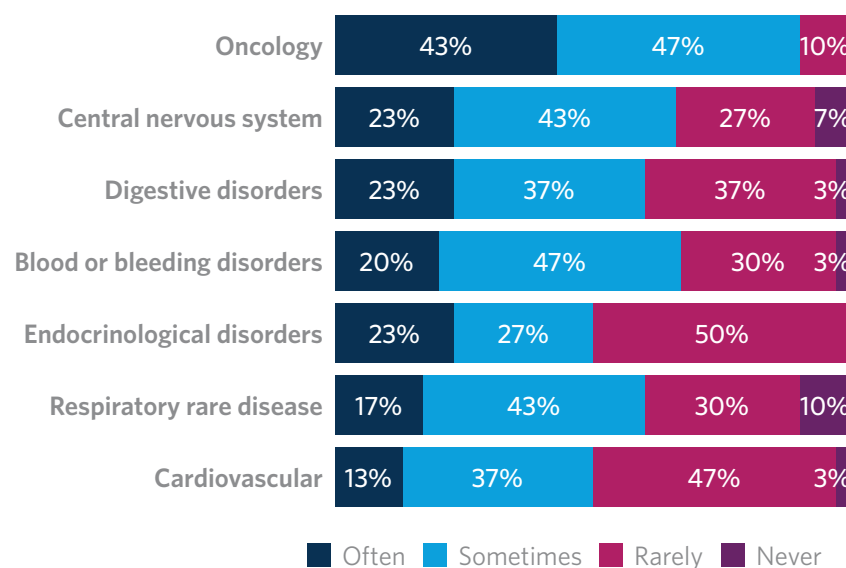
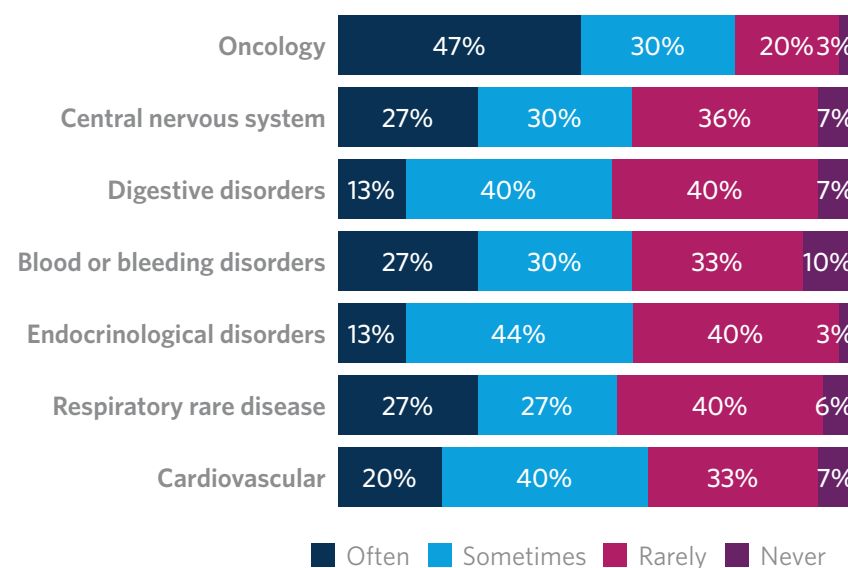


FIGURE 23:
Off-label Access of Rare Disease Therapies by Therapeutic Area (Future)



Price Reform & Policy Changes

While pharmacy and medical directors are generally aware of proposed legislative and regulatory reforms, they consider tracking them to be a low priority. Since the likelihood of passing or finalizing proposed policy changes can be difficult to predict, pharmacy and medical directors believe their time is better spent reactively addressing finalized policies, as relevant and necessary. Additionally, in larger payer organizations, they can rely on internal public policy teams to monitor the proposals on their behalf. Further, many of the proposed policy reforms by Congress or the Centers for Medicare & Medicaid Services (CMS) are viewed as having a greater potential financial impact to provider practices than payer organizations. Two recent examples cited were the International Price Indexing (IPI) Model and Most Favored Nations (MFN) rule, both of which aimed to lower drug costs and reduce out-of-pocket costs for patients. These proposals would have changed how provider practices and hospitals are reimbursed, leading to lower reimbursement for high-cost drugs by CMS. Not only would Medicare reimbursement have

changed, but commercial payers likely would have implemented similar changes, especially if financially advantageous to the plan. Similarly, the proposed transparency in coverage rule stands out as a broad policy reform that likely would have affected manufacturers more than payers. Under this rule, health plans would have faced a significant administrative barrier to publicly disclose the required information; however, manufacturers would have borne a greater burden, as further insight into negotiated rebates have driven smaller health plans to seek steeper discounts.

Meanwhile, payers look forward to CMS policies that help better define product value and influence coverage policy. The potential benefits of such policies are especially top of mind for payers given the recent approval of Aduhelm® (aducanumab). The US Food and Drug Administration (FDA) granted the monoclonal antibody indicated for the treatment of Alzheimer's disease accelerated approval in June 2021. The perceived uncertainty around the product's clinical efficacy, coupled with its high price point and accelerated decision, created controversy and scrutiny over the approval, including whether the FDA worked

too closely with the manufacturer during the review process. Payers referenced the Aduhelm case during interviews to help explain why they support CMS' policy proposals to factor in product value when evaluating high-cost therapies.

“We’re tracking the movement toward government negotiated drug prices. This would resonate through the commercial sector, but occur on a global scale not specific to rare disease.”

– Pharmacy Director, National PBM

Innovative Contracting

Participation in Innovative Contracts

The strength of a product's clinical outcomes and therapy cost drive interest in engaging in innovative contracts. Seventy-three percent of payers expect an increase in participation in innovative contracts over the next five years, especially in high-cost therapeutic areas, such as oncology and central nervous system

(Figure 24). Some payers interviewed consider an outcomes-based contract to be related to a specific clinical outcome, whereas they consider a value-based contract to be based on utilization data and metrics to inform payment schedules (Figure 25). Contract specifics depend on the organization and stakeholder type, and the terms they use to define outcomes-based vs. value-based. Regardless of nomenclature, innovative contracts seek to address the risks borne by the payer community and represent a step forward in tackling the inherent uncertainties of a newly approved drug.

FIGURE 24:
Anticipated Participation in Innovative Reimbursement Models

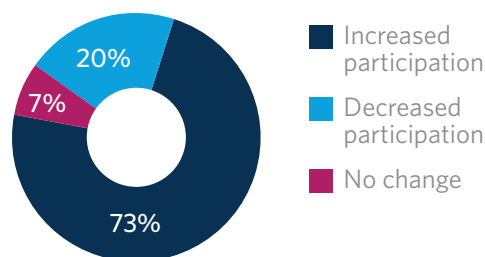
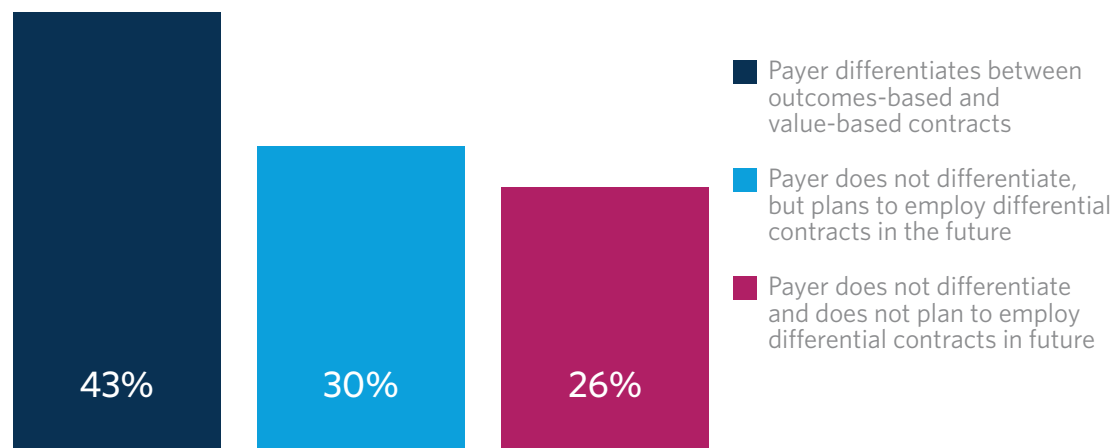


FIGURE 25: Differentiation between Outcomes-Based vs. Value-Based Contracts



Innovative Contracting Value Drivers

Overall, payers are interested in innovative contracting as a tool to help control the cost of care, especially as more rare disease therapies become commercially available and create larger financial liability for health plans. As noted in the 2020 Rare Disease Trend Report, payers indicate that product cost is a top driver of elevated participation in innovative contracting. With the unpredictability of patient volume, high cost of drugs, and limited clinical data, rare disease is a high-risk area for payers. As such, value-based contracts can provide a safety net for payers to better define and manage risk. The primary consideration for engaging in innovative contracting continues to be the level of improvement in clinical outcomes. Regardless of the budget impact concerns, payers continue to prioritize clinical improvements for the rare disease patient population. As more clinical data becomes available in the rare disease space and orphan drugs pose an increasingly larger burden on health plans, innovative contracts are expected to become more common, because they address some of the unique challenges related to patient population size, cost, and clinical data. Further, participation in innovative contracts demonstrates good faith efforts to address the rising cost of care and manage the small number of high-cost patients with rare diseases.

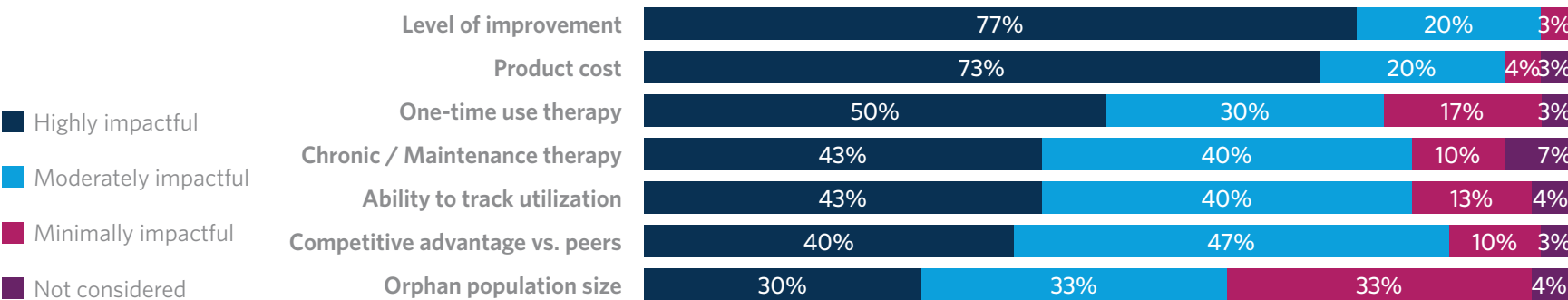
“We are very interested in pursuing annuity models, as the frequency and price tag of rare disease products continue to rise.”

– Pharmacy Director, Regional Commercial

“Product cost and patient efficacy will continue to drive the use of outcomes-based models and shared cost contracts in the rare disease space.”

– Pharmacy Director, PBM

FIGURE 26: Highest Impact Factors for Pursuing Innovative Reimbursement Contracts



Innovative Contracting Value Detractors

Despite interest in pursuing innovative contracts, payers indicate there are barriers to overcome, including the currently limited availability of clinical evidence to inform contracting and a lack of clear metrics to define a product's value (Figure 27). However, they expect these barriers can be overcome as more clinical data become available and consensus grows around the outcomes and metrics to inform innovative contracting terms. As innovative contracting is still in the early stages, payers describe two scenarios that could unfold. One, as payers and manufacturers gain more experience and are able to reduce the operational challenges of innovative contracting, the administrative burden and barriers of implementing innovative contracts will become lower and their value will increase. Or, two, innovative contracts will be viewed as low value, simply providing the same average discount as traditional contracts, but reshuffling the rebates and adding administrative burden. The perception that outcomes-based contracts do not shift sufficient risk to the manufacturer leads payers to hesitate to participate. Shifting greater risk to the manufacturer or reducing risk to payers, for example by allowing for payment over time, may make innovative contracting more attractive.

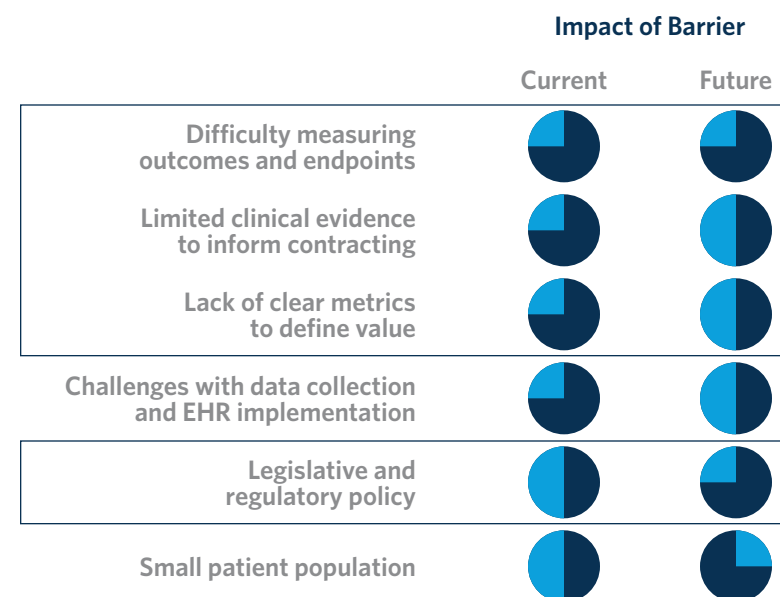
“Some outcomes are a little tricky to track and it’s not clear how some rare products would be tied to clinical endpoints, which makes these hard to use right now. A clear understanding of how trackable metrics tie to an orphan product’s clinical endpoints will make these models more impactful in the future.”

– Medical Director, National Commercial Payer

“We are not pursuing innovative reimbursement contracts. They are too complex and do not mitigate cost exposure or transfer risk.”

– Medical Director, Regional Medicaid Managed Care

FIGURE 27: Barriers to Innovative Contracting in Rare Disease



Stakeholders Engaging in Innovative Contracting Discussions

Manufacturers most often initiate conversations on potential innovative reimbursement structures, whereas employers and payers are less likely to initiate these conversations. In the 2020 Rare Disease Trend Report, 86% of payers indicated that the manufacturer or payer was most frequently initiating conversations on innovative contracting. This finding is consistent with our 2021 survey and highlights that the stakeholders interested in initiating innovative contracts have not changed significantly in the past year.

Distribution Models

Aligned with greater flexibility in contracting negotiations and lower administrative burden, 62% of payers today prefer open distribution channels for rare disease therapies (**Figure 28**). However, in the future, the sample (87% with an integrated specialty pharmacy (SP)) expects closed distribution networks to become more common for rare disease product distribution because it allows for closer management of high-cost therapies (**Figure 29**). As opposed to open distribution, over 60% of payers with an integrated SP expect to mandate the use of their specialty pharmacy within a closed network, which allows for enhanced patient management and data tracking, as well as stricter utilization management (**Figure 14**). In the 2020 Rare Disease Trend Report, 67% of payers anticipated an increase in closed networks across all rare products in three-plus years, which remains consistent with the 59% of payers that expect an increase in closed networks for rare disease therapy distribution currently.

Payers (13%) without an integrated SP at their organization also prefer open distribution networks to manage rare disease products, citing more flexible contracting options with manufacturers, easier access, and lower overall administrative burden. Similarly, these payers also prefer to manage high-cost rare disease therapies through the pharmacy benefit and to leverage SP mandates based on the manufacturer's distribution network. Regardless of payer preference, payers acknowledge that the manufacturer, along with the US Food and Drug Administration-approved label and safety profile, heavily influence the distribution of a product, and the evaluation process remains the same for either distribution model.

“Closed distribution networks allow for manufacturers to control appropriate use and they mitigate the risk of wasting high-cost therapies.”

– Pharmacy Director, Regional Commercial

“We prefer open distribution networks to have options to obtain the product at varying price points and reduced contracting complications.”

– Medical Director, National Commercial

FIGURE 28: Current Preferred Distribution Network in Rare Disease

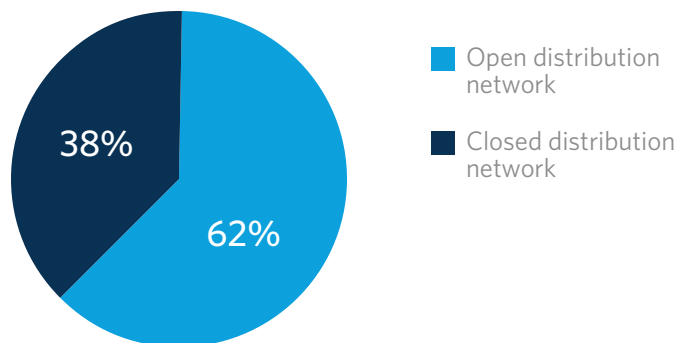
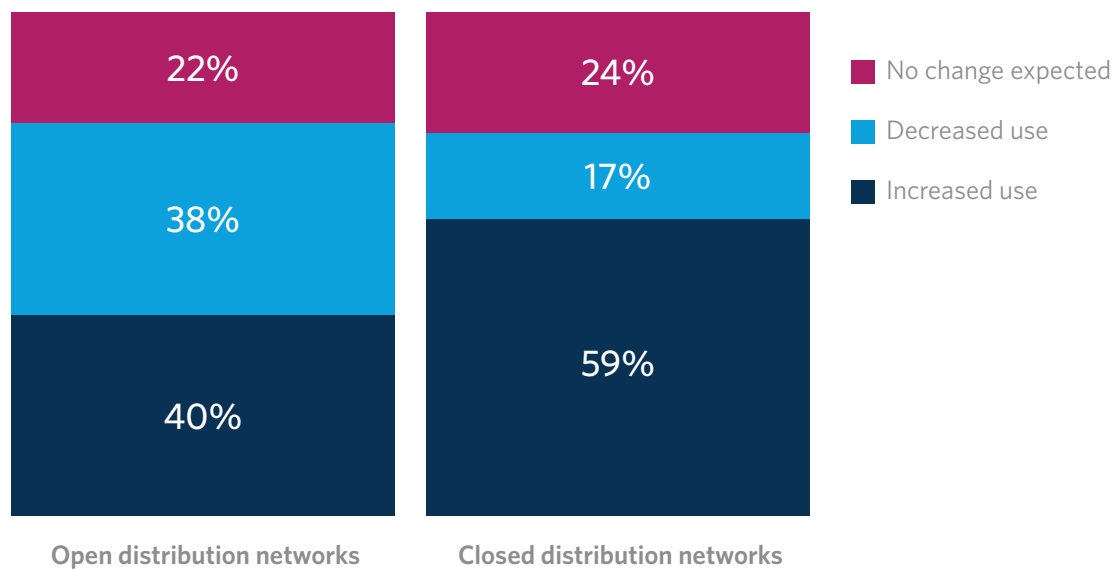


FIGURE 29: Future Anticipated Distribution Network Use in Rare Disease





Patient Cost-Share Implications

As new scientific breakthroughs enable more effective treatments for previously untreatable diseases, payers acknowledge that drug costs are rising, and patients face significant out-of-pocket (OOP) costs. Patient cost-sharing can create significant financial burden for patients. Plans with high deductibles and coinsurance are especially burdensome for patients with chronic rare diseases who require long-term specialized care and medication. Depending on insurance coverage, the average annual OOP cost for a patient with a chronic rare disease can range from hundreds of thousands to over a million dollars, especially for single-administration treatments (e.g., gene therapies).²

Acknowledging the significant financial burden, payers believe the increase in OOP burden is due to the overall rising cost of healthcare. Plan benefit design, including OOP maximums and copayments, coupled with manufacturer support can address patient OOP burden. Under commercial plans, OOP maximums are perceived to mitigate against high patient financial burden, particularly for rare disease patients who often quickly meet the OOP max, given their high cost of treatment. As a potential solution, payers are considering moving products traditionally managed under the medical benefit to the pharmacy benefit, where they believe benefit design may be more predictable and manufacturers may offer more easily accessible support. However, payers also acknowledge that cost sharing has not evolved in recent years to address rising OOP costs, including when the COVID-19 pandemic exacerbated financial stress for all stakeholders. Payers suggest manufacturers play a greater role in supporting patients who cannot afford OOP expenses.

To try to reign in their own costs and disincentivize use of high-cost therapies, payers are leveraging copay accumulator and maximizer programs to shift costs away from the plan, and toward patients and manufacturers. Payers are familiar with copay mitigation programs (i.e., programs that prevent copay assistance funds from being counted toward patient OOP costs), and implement them in a subset of their plans, primarily to address high orphan drug costs and the increasing prevalence of patient assistance programs. The majority of payers cite no or limited use of copay mitigation programs; however, a subset of payers describe widespread use of copay accumulator and maximizer programs (20% and 27% of payers respectively). Citing the influx of manufacturer patient assistance programs as well as the rising pharmaceutical costs and total cost of care, payers expect to continue offering this measure unless public pushback or legislative policy restricts them. Because manufacturer support programs are not offered to Medicare plans, commercial payers seek to standardize cost-sharing support. Another factor influencing the decision to implement copay mitigation programs is the high cost of gene therapy.

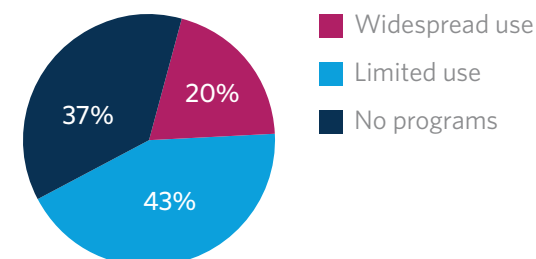
“Our plan does not engage with these copay mitigation programs and expects them to decrease in the future as the pushback against these programs grow and they create negative PR for PBMs.”

– Pharmacy Director, Regional Commercial

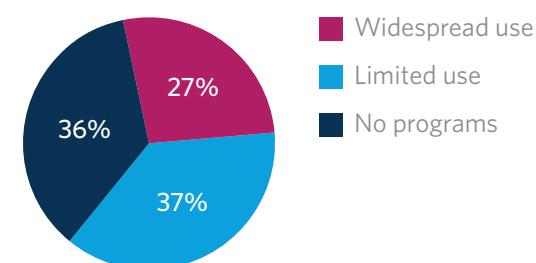
“Rare or other specialty diseases will be where the greatest impact of these copay mitigation programs is. I’d anticipate some changes and greater utilization of them, but they may eventually go away because there’s so much pushback against them.”

– Pharmacy Director, Medicaid Managed Care

**FIGURE 30:
Copay Accumulator Program Utilization**



**FIGURE 31:
Copay Maximizer Program Utilization**



Conclusion

The research for the second annual Alnylam Rare Disease Trend Report was conducted during the COVID-19 pandemic. Despite the strains of the pandemic and the evolving healthcare environment, payers remained steadfast and intentional with regard to managing rare diseases and recognizing the unique nature of products to treat them.

Compared to the inaugural report, payers acknowledged heightened pressure to address unmet needs in the rare disease space. Year over year, payers increased their focus on determining ways to more effectively manage products for rare diseases, including by considering alternative approaches and tools, such as innovative contracting, that could make these products more economically viable and accessible for patients. Payers also cited the efforts of other stakeholders in potentially helping advance this effort. These include employers who payers anticipate will increase the use of carve outs from health plan coverage for rare disease products to better manage costs. To meet rare disease patient needs, however, payers continued to believe manufacturers must play a greater role in helping mitigate risks and increase access.

The Rare Disease Trend Report is designed to assist commercial payers in the US 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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