



2020 Alnylam Rare Disease Trend Report

PERSPECTIVES FROM HEALTHCARE PAYERS

INAUGURAL EDITION

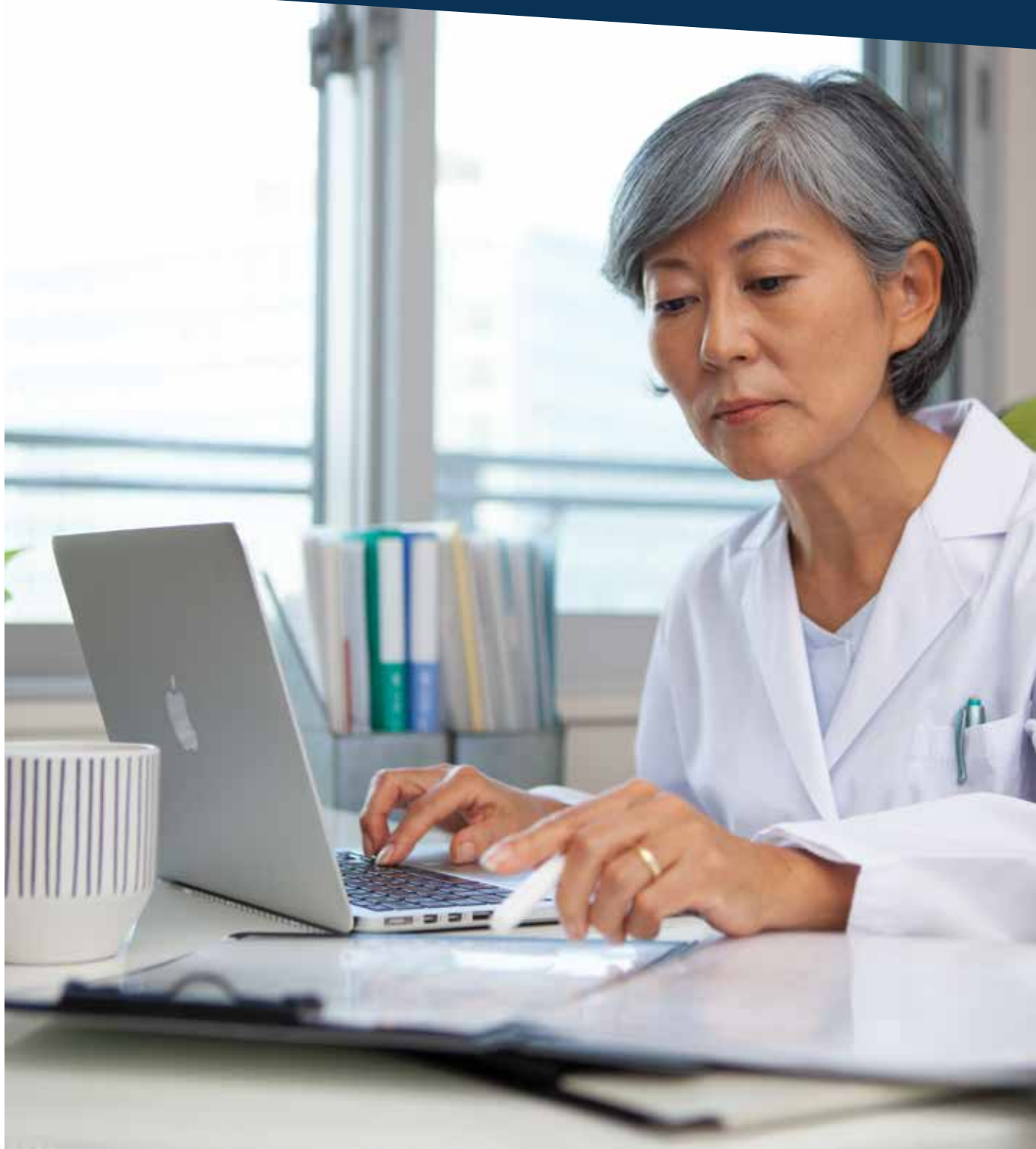
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Foreword

In the past decade, rare disease management has become an increased focus for payers. While unmet need and clinical burden of rare diseases have long been acknowledged, the lack of available treatment options has left patients living with these diseases despondent. Rare diseases, however, affect nearly 10% of the US population and transformative changes to research and development, as well as modernized regulatory pathways, have accelerated the entry of orphan drugs to the market. This uptick has necessitated transparent discussions on how best to manage these conditions to ensure the right therapy is provided to the right patient at the right time.

From the perspective of US payers, this inaugural Rare Disease Trend Report is a first step in creating an open and transparent dialogue on the challenges faced by insurers in a resource-constrained healthcare environment. By highlighting the key issues and opportunities, we hope that payers, providers, patients, and biopharmaceutical manufacturers will bridge the access gaps and ensure patients can receive medically necessary therapies to ultimately improve patient outcomes.



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A woman with dark hair pulled back, wearing black-rimmed glasses and a thick, textured purple turtleneck sweater. She is standing in front of a dark, textured wall, possibly made of stone or concrete. The lighting is soft, highlighting her face and the texture of her sweater. The overall mood is professional and thoughtful.

This inaugural issue of the Alnylam Rare Disease Trend Report aims to offer readers a view of the **latest trends in rare disease / orphan drug market access**, summarizing current payer perspectives, and offering insights and potential implications of these data on rare disease and orphan drug management. The report is designed to assist commercial payers in the U.S. in understanding key trends and benchmarking rare disease / orphan drug management against industry peers.

Introduction

Rare diseases are defined by the U.S. Food & Drug Administration (FDA) as those affecting under 200,000 patients in the U.S., in accordance with the Orphan Drug Act of 1983.¹ While individual rare diseases affect relatively small populations of patients, the category of rare disease therapeutics on the market is growing, garnering the attention of manufacturers, payers, providers, and patients. Estimates suggest that rare diseases affect around 30 million people (~10% of the population) living in the United States (U.S.)—over half of whom are children.² Many of these diseases negatively impact life expectancy and quality of life, and most remain untreatable. As many rare diseases are also genetic in nature, they may also lead to familial or regional pockets of prevalence. Due to the absence of therapeutic options for these rare conditions, these new medicines came to be known as orphan drugs. The significant unmet need to treat patients with rare diseases led Congress to pass legislation providing financial incentives to stimulate the development of new treatments for rare diseases. This legislation, the Orphan Drug Act, went into effect in 1983 when only 38 orphan drugs had been approved in the U.S.³

Today the growing pace of innovation made possible by emerging scientific breakthroughs and new understanding of diseases has led to the development of novel therapies. These include modalities that are directed toward genes and gene expression, allowing providers to address what were previously considered untreatable diseases. While 2018 saw the highest number of annual orphan drug approvals, 2020 is expected to surpass this record.² Still, despite the rise in the number of orphan drug approvals in recent years, only 5% of rare diseases are treated with commercially available therapeutics.²

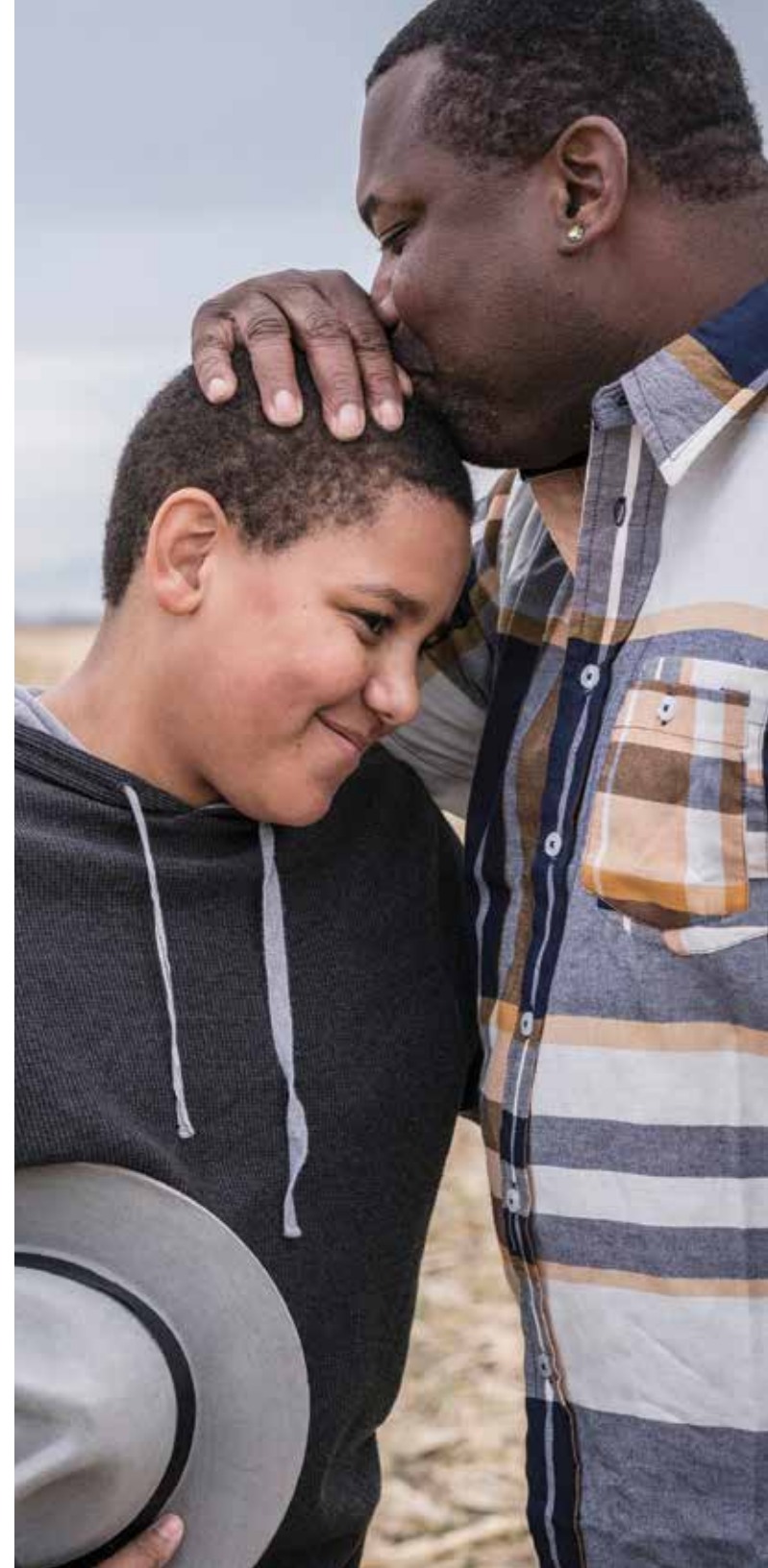
The global orphan drugs market is forecasted to reach \$242 billion by 2024, growing at a compound annual growth rate (CAGR) of 12.3% from 2019 to 2024.³ Improved detection and increased rates of diagnosis of rare diseases are likely to contribute to rising costs. While the humanitarian benefits of rare disease therapies are indisputable, concerns regarding high treatment costs play a meaningful role in how payers administer and manage healthcare benefits that ultimately dictate patient access to orphan drugs.

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 innovative medicines with the potential to transform the lives of patients who have limited or inadequate treatment options.

As our healthcare system faces the challenge of having to allocate limited financial resources to optimize both patient access and clinical outcomes, rapidly rising spending on drugs have encouraged discussion about potential novel approaches to manage spending. Several initiatives have been proposed or launched to address the rising costs of U.S. healthcare, such as the Most Favored Nation Pricing model, which uses foreign reference prices as a basis for Medicare drug price negotiations for high cost, high spend drugs. Along with implementing new utilization management techniques, payers are considering methods such as shifting management of a drug class from the medical to pharmacy benefit or mandating the use of specialty pharmacies to more effectively manage new market entrants. Another approach that various stakeholders have shown continued interest in is the potential to develop cost- or risk-sharing agreements between the payer and drug manufacturer (or some other counterparty). The goal of such arrangements is to distribute risk so that no one party is wholly responsible for the entire cost of care. Value-Based

Contracting (VBC) agreements have emerged as opportunities to tie clinical outcomes to payment and to adjust for the financial risks that payers assume; these are of particular interest in rare disease, where orphan therapies have been studied in limited populations and often entail high therapy costs.

The confidential nature by which each payer makes decisions (e.g., in policy development) bars widespread understanding of which tactics effectively manage rare diseases. As such, the intention of this report is to increase transparency across the payer community on trends in the management of rare diseases, with an in-depth assessment on the role of innovative reimbursement models within this space. Offering key insights and perspectives on current and future management considerations of rare disease products, as well as some of the perceived challenges that may unfold, will allow for benchmarking and could potentially lead to more innovative approaches and opportunities for rare disease and orphan drug management.



Key Findings

- **Rare Disease Spending as a Driver of Rising Healthcare Costs:** Rare disease therapies are having a greater budget impact as a proportion of total spend on payer budgets and this trend is projected to grow. There is widespread concern that the current system may be unsustainable in the long-run given the rate at which overall healthcare costs are exceeding the rate of inflation.
- **Uncertain Future for Role of Health Economic Evidence:** While the integral role of clinical efficacy and safety in the product evaluation process is not expected to change, health economic evidence is expected to play a greater role in the product evaluation process in the future, particularly in the rare disease and orphan drug market. Still, some payers are hesitant to incorporate such evidence until the results are made enforceable.
- **Continued Challenges with Innovative Payment Models:** Payers acknowledge several barriers in their ability to develop innovative reimbursement contracts that fairly distribute cost- or outcomes-related risks across relevant stakeholders. While some potential methods for overcoming these barriers have been proposed, limitations in data sharing and outcomes measurement continue to be challenging for payers, providers, and manufacturers alike.

Scope and Structure

This report focuses on rare diseases and orphan drug management from the U.S. commercial payer perspective. Rare diseases comprise

a group of distinct indications that vary by etiology, pathophysiology, and epidemiology. Naturally, the resulting disease characteristics such as prognoses, symptoms, and burdens of illness are similarly variable by specific indication. Additionally, there is little clarity on the distinction between the “rare/orphan” and “ultra-orphan” conditions. While the current accepted definition for a rare disease is that it affects a population of less than 200,000 patients, payer management of this population may differ substantially when compared with a condition affecting less than, for example, 10,000 patients. Drugs treating patients within this type of population are sometimes referred to as “ultra-orphan” therapies. Given the complexity of rare diseases, they are often managed by physician specialists, though the exact type of specialist required (e.g., rheumatologist, oncologist, etc.) varies according to the specific disease. Considering the broad and diverse set of diseases encompassed by the label “rare” and the goal of this report, the structure is aligned to five priority questions and topics of widespread interest for and relevance to rare diseases:

- What are the **priority therapeutic areas** for rare disease management?
- How do payers currently **manage rare disease products** and how are management techniques likely to evolve in the near future?

- To what extent do **distribution models** impact payer management decisions of rare disease products?
- How are **innovative contracting** structures considered in the management of rare disease products and what can we expect in the near future?
- What is the impact of **patient out-of-pocket costs** on payer management decisions for rare disease products?

Annual Updates and Other Follow-Up Publications

The payer landscape surrounding rare disease treatment and management has been changing rapidly in the U.S. and shows no signs of slowing in future years. As such, this inaugural report will be updated on an annual basis to capture the evolution of trends representative of the current environment.

The topics included in this report could each, independently, support an entire report. Given the amount of content and interest associated with the topics presented, there is the possibility that follow-up reports exploring the considerations, challenges, and opportunities in greater depth will be published.

Methodology

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

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 2019 as the current health plan year, the survey specifically dives into anticipated changes within the next plan year (2020), the next 3–5 plan years (2023–2025), and beyond (2026+).

The survey focused on the same payer-resonant themes used to inform report structure, namely: priority therapeutic areas, benefit assignment and utilization management, distribution, innovative contracting, and patient costs. No specific products were assessed.

The majority (n=31) of the 55 survey questions were multiple choice questions limited to one response. The remaining questions were: multiple choice questions allowing for multiple answers to be selected (n=4); forced relative rankings (n=4); forced scale-based ratings (n=4); categorical selections (n=2); respondent-designated 100% distribution (n=1); or specific indications of anticipated times-to-events (n=9).

Potential respondents were screened for participation (see ‘Prequalification Criteria’ below), and a total of thirty 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 translate the survey to an online format.

Recruitment and Fielding

Potential respondents were identified by the vendor using predefined screening criteria (see ‘Prequalification Criteria’ below). Guidehouse provided respondents with an assurance that only blinded, aggregated data would be made available to the broader public. 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.

The survey was completed by all participants over the course of four weeks, from August 23 to September 17, 2019. While the survey respondents may choose to participate in the annual updates to the research, each sample of respondents will be considered as an independent sample.

Participant Selection and Demographics

Research participants were required to meet qualifying criteria to ensure integrity of responses across the various 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



- 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 30-minute follow-up interview during which the respondent was probed to provide additional, qualitative insight. All interviews were conducted over the phone by Guidehouse researchers. The interviews were conducted in a double-blinded manner, such that no respondent knew the company supporting the research and no Alnylam employee knew which payer individuals were providing input. All interviewees provided consent for using their responses in the composition of this report.

Honoraria were paid to respondents who met all eligibility criteria and completed the survey and follow-up phone interview.

Data Analysis, Reporting and Limitations

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

Guidehouse had no way of validating survey responses for accuracy regarding payer practices or internal processes/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.

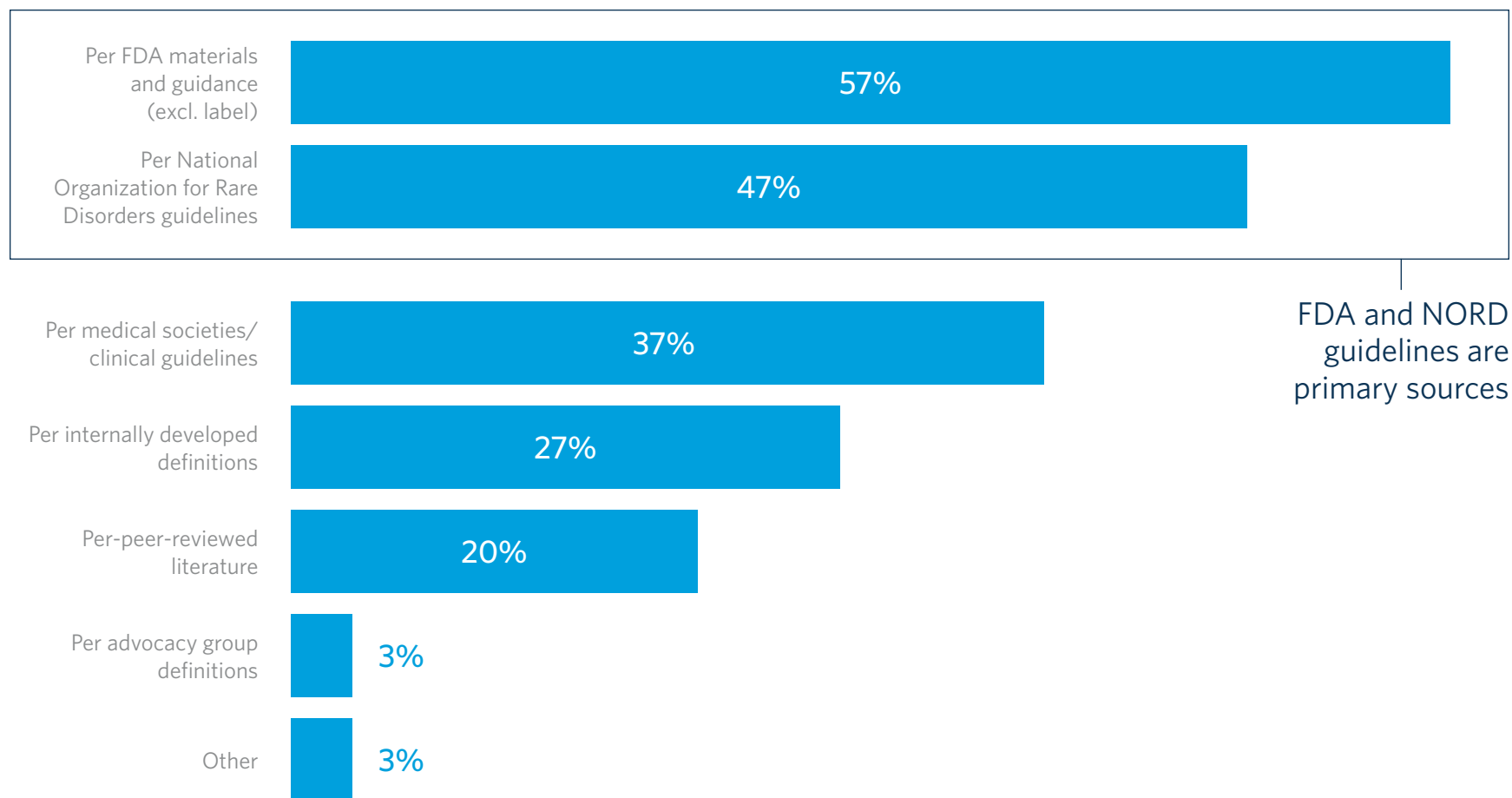
Payer Priorities: *How do payers identify priority therapeutic areas and products?*

Payer Definitions for Rare Diseases

The Orphan Drug Act of 1983 characterizes rare diseases by an absolute prevalence rate, however, the collective set of rare disease conditions are not universally defined in the U.S. Payer organizations, for example, utilize different definitions for the term, often reflecting the core beneficiary or patient base. Given this variability, respondents to the Guidehouse survey on rare disease management were asked to share how rare diseases are defined within their organizations for policy development purposes. Follow-up discussions with some of the payer respondents highlighted the need for a more concrete definition of “rare” such that all stakeholders are able to leverage common language.

The majority of respondents (77%) described relying on information from leading authorities including the Food & Drug Administration (FDA) and the National Organization for Rare Disorders (NORD). The consensus of these organizations is that rare diseases comprise those affecting less than 200,000 people nationally. While there is little consensus on the definition of ultra-rare diseases in the U.S., this subcategory has been defined in the European Union (EU) as a condition that affects fewer than five people per 10,000 of the population.⁴ This categorization is reflected in payer management strategies; only 3% of respondents noted employing differential management strategies for rare versus ultra-rare diseases.

FIGURE 1: Rare Disease Policy Definitions and Sources



Given the variability in language to describe the term ‘rare’, payer stakeholders discussed a need for standardization to empower more effective evaluation of emerging products. If NORD were to be used as the national reference, for example, its guidelines could be used to help inform payer review of innovative therapies and better identify medical necessity in appropriate patient populations.

The lack of standardized definitions for rare diseases is not the only issue, however.

Gene therapies are designed to introduce genetic material into cells to compensate for abnormal genes while **gene-targeted therapies aim to inhibit gene expression**.⁵

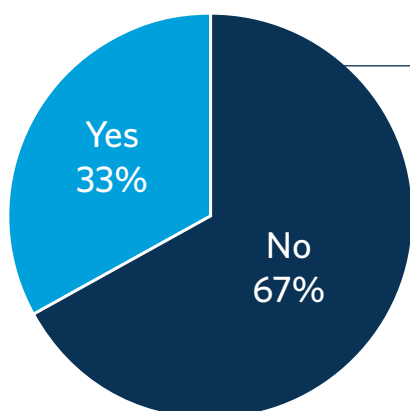
Survey respondents were probed on whether their plans differentiated between gene therapies and gene-targeted therapies when reviewing for utilization management. While a third of payers indicated that this difference was acknowledged in some capacity, those payers explained that differences did not impact the process by which these products were evaluated for coverage. Thus, further clarity is also needed to delineate between gene and gene-targeted therapies. As the market for rare disease therapies continues to evolve, payers described the importance of collaboration between the payer and the provider community to establish standardized definitions for these complex terms.

In discussing nuances between the therapeutic modalities of gene therapies and gene-targeted therapies, payers indicated little differentiation in their review process and little to no use of standardized definitions. While some acknowledge the mechanisms of action to be different, payers noted this had very little impact on their evaluation of new products today, given the few available therapies. As more gene therapies enter the market, the distinction may become more important and may play a greater role in payer evaluation of emerging rare disease drugs. As a Pharmacy Director at a national health plan described,

“We do not differentiate between gene and gene-targeted therapies in our review process currently, but I anticipate we might in the next 18–24 months **as more of these therapies become available** and we need to be able to better distinguish.”

Differentiating between gene therapies and gene-targeted therapies can have substantial implications for payer management of a disease, both from clinical and budgetary perspectives. Because a curative therapy will have a finite, one-time cost for a payer instead of the ongoing cost of a chronic therapy, the short- and long-term impact on the payer’s budget model will differ significantly.

**FIGURE 2:
Differentiation
Between Gene
Therapy and Gene-
Targeted Therapies**



Payers who cited differences, explained that they consider the cost implications of a one-time administration therapy, but that it does not affect management

Additionally, payers today see little management and evaluation differences when it comes to reviewing gene silencing therapies (such as RNA interference, or RNAi), further demonstrating the need for standardized guidelines and definitions for payers to leverage for these emerging classes of therapies.

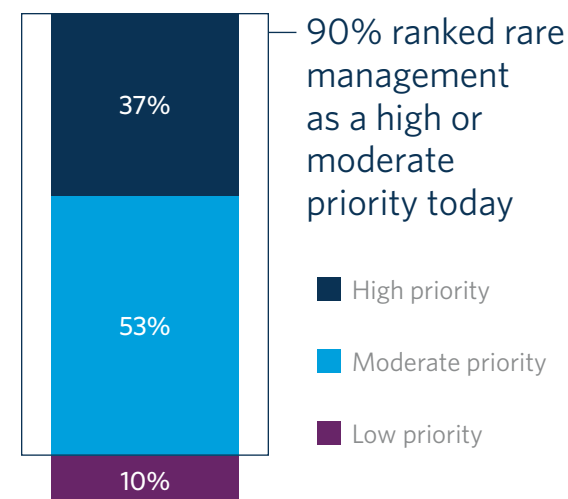
How do payers assess rare disease management?

Payers consider rare disease management to be of high priority today, primarily due to the impact of these products on their budget management and cash flow predictability. While rare disease product costs are rising, these costs can be even greater for one-time gene therapies, which often have high upfront costs and can therefore pose unique budgetary challenges for payers. Commercial payers cite one-time therapies as concerns for transient beneficiaries, as patients may move to another plan after payers have already made an investment in their high-cost case.

Most payers considered rare diseases to be at least as much of a priority as other, non-rare diseases. One-third of payers considered the rare disease category to be a higher priority than non-rare diseases, largely due to the high costs associated with the category of rare disease patients. Over half of all payers noted no dramatic difference in prioritization between the two broadly-defined areas of rare vs. non-rare.

In general, rare diseases are a low management priority for stakeholders at smaller, regional plans, largely due to the low prevalence of these populations within their plans. Considering the relatively substantial administrative effort that goes into management of rare disease products, it is reasonable that smaller plans will choose to consider rare disease products on a case-by-case basis. However, this is likely to change as more rare disease products come to the market and even smaller plans start seeing greater demand for innovative therapies.

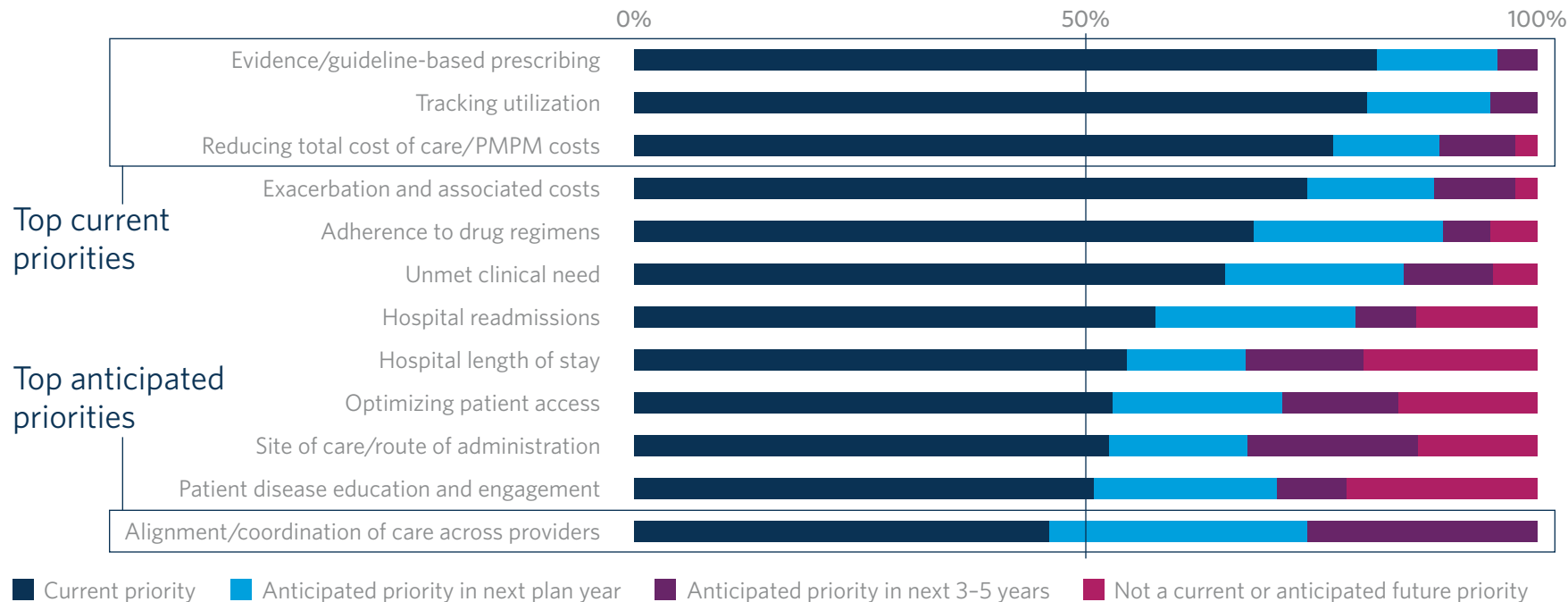
FIGURE 3: Prioritization of Rare Management Today



When asked to reflect on the effectiveness of their plan's rare disease management, over half of respondents (60%) felt management was moderately effective. An additional third (30%) felt that rare diseases were managed in a highly effective manner, with the remaining 10% indicating they felt that rare diseases were poorly managed today.

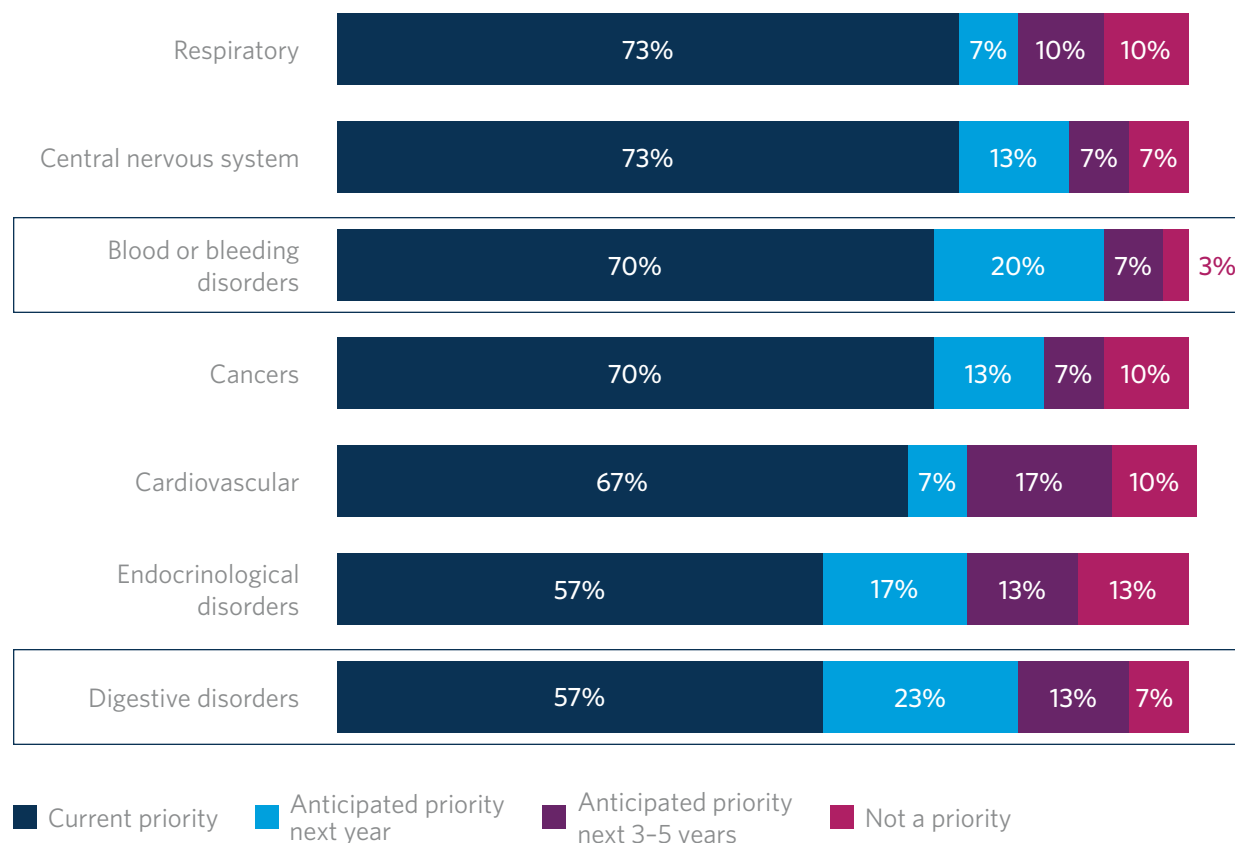
Respondents were further asked to reflect on the specific factors prioritized in management. Evidence-based prescribing and clinical guidelines were the factors most widely prioritized by payers within the rare disease space today. When asked to think about the next plan year, all respondents indicated that both evidence-based prescribing and utilization tracking were anticipated to be top priorities. Additionally, half of respondents indicated that coordination of care across providers and sites of care was anticipated to become a priority, especially as additional therapeutic options become available, with costs potentially varying by site of care.

FIGURE 4: Payer-Cited Priorities in Rare Diseases



Rare diseases affecting the central nervous system and respiratory system were most frequently cited (~73%) as current management priorities. Additionally, almost all payers anticipated that rare central nervous system indications and digestive disorders would be considered priorities in the future.

FIGURE 5: Priority Rare Disease Indications



Top priorities in next plan year

“We prioritize rare disease indications by looking at the total cost that is anticipated from both the therapy and treatment journey, and by assessing how many patients will benefit from this novel treatment.”

MD, National, Commercial

“Our priorities are in unmet clinical need and reducing total cost of care, so we prioritize rare indications that have a high impact to the budget and where patients do not have other options.”

MD, Regional, Commercial

The variety of treatment modalities for rare diseases differ not only by FDA indication, but also by frequency of treatment and route of administration, amongst other factors.

While virtually all payers surveyed were at least somewhat willing to manage various treatment options today, the majority anticipated increased willingness to manage the same treatment options in the future.

What resources and evidence primarily inform rare disease policy development?

Evidence-based guidelines are crucial for effective payer review of emerging products, especially as there is little standardization in defining and categorizing the different types of rare disease therapies today. Given the growing number of innovative therapies for rare diseases, payers look for guidance from the provider community and other advocacy/research

organizations such as the NORD on how best to address the needs of the rare population.

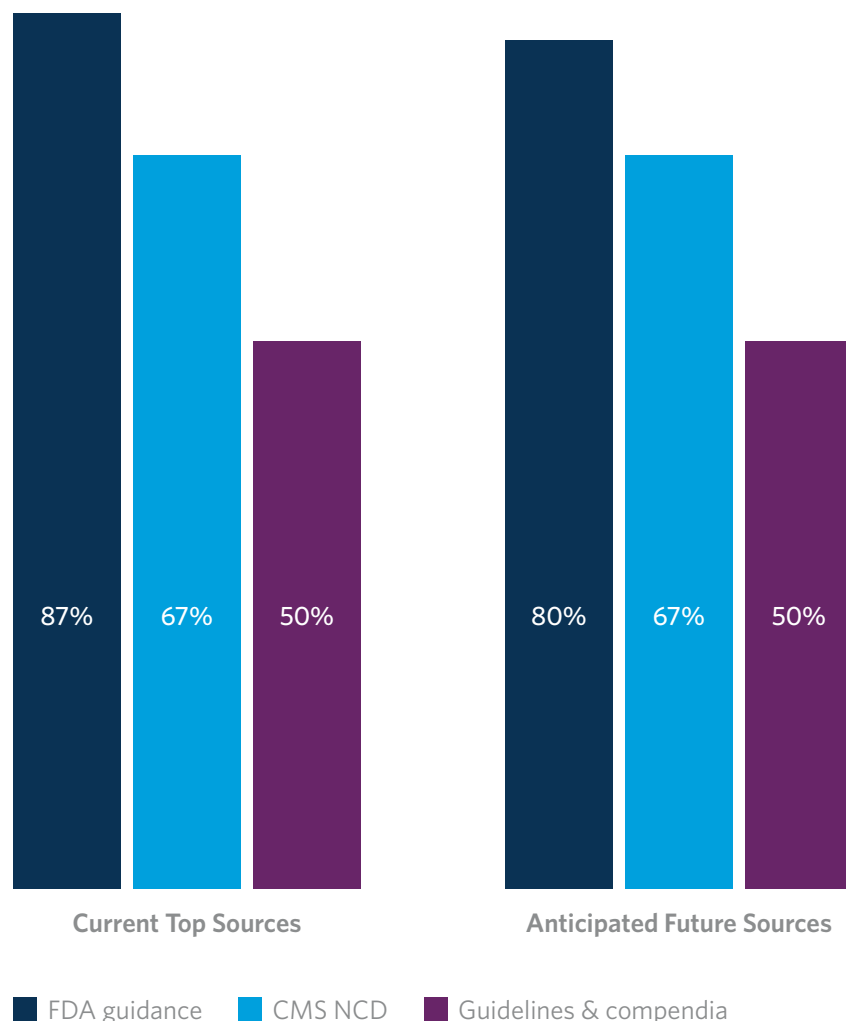
There has been increasing discussion in the U.S. regarding the role of non-clinical evidence in determining coverage and access. In contrast to countries like the United Kingdom that formally employ health-economic metrics to inform decision making, U.S. payers prioritize clinical evidence and typically avoid outwardly integrating cost impact in their decision-making processes. Survey results demonstrated that while payers continue to rely most heavily on sources that are clinically focused (such as FDA guidance documents and the Centers for Medicare and Medicaid's National Coverage Determinations), they anticipate incorporating formal health technology assessments (HTAs) in the future, given the growing budget impact of rare disease products.

HTAs evaluate more than just safety and efficacy data, and payers maintain their reliance on these tools to provide insights on clinical comparative effectiveness of emerging therapies against standards of care and/or competitive products. For example, respondents believe that the Institute for Clinical and Economic Review (ICER) may play an even more significant role in the review process as it attempts to shape

the conversation around price and value of new high-cost therapies.

“ICER will **work with drug manufacturers, patients, and clinical experts** to get supplemental information of newly approved drugs,” explained Dr. Steven Pearson, ICER's president at the Academy of Managed Care Pharmacy conference in 2019.

FIGURE 6: Top Resources for Informing Policy Development



Payers noted the growing impact of ICER assessments with cautious optimism. While ICER’s influence on payer management is expected to increase in the coming years, the group’s methodology has often been criticized. Payers expressed that ICER does not effectively address the challenges related to evaluating rare diseases. In response to criticism, ICER published a value assessment framework for more effectively examining the clinical, economic, and humanistic value of rare disease products. Stakeholders within the research and medical communities continue to question the viability of the model, raising concerns with some of its assumptions and conclusions.

While data from the FDA label will continue to influence payer decisions regarding coverage, more than half of respondents indicated that they refer to compendia or specialty society guidelines to inform coverage and access determinations. When asked how treatment guidelines are used to inform such decisions within the rare disease space, about one-quarter of respondents replied that they defer to clinical guidelines. A majority of payers (73%), noted that although guidelines are considered, the plan ultimately makes an internal decision.

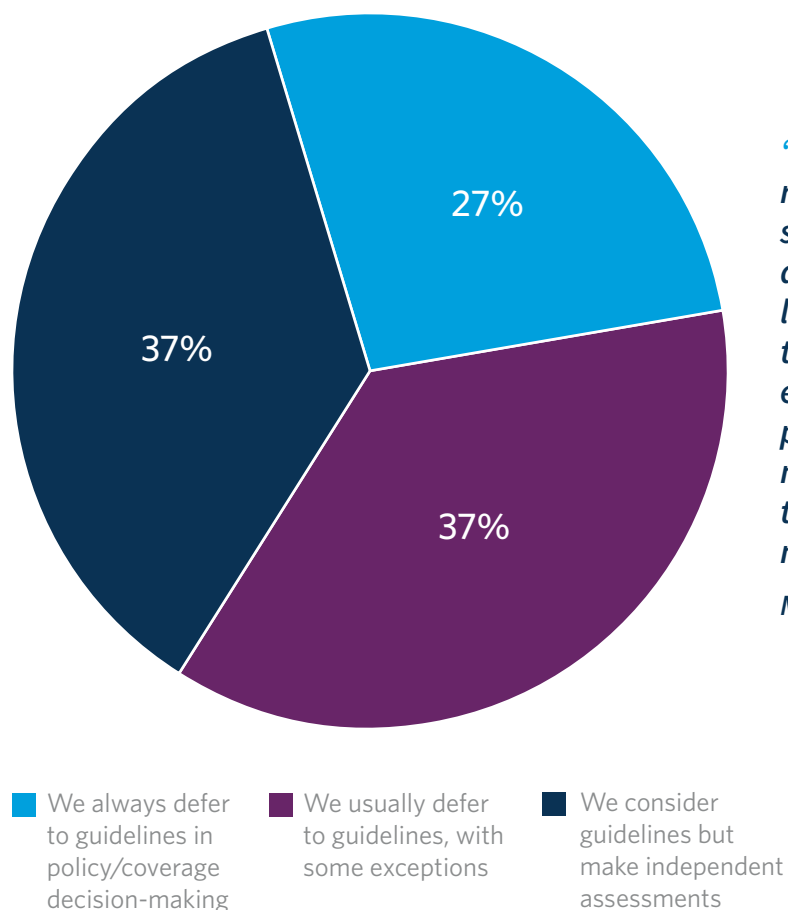
“The most important source today are FDA label and guidelines, and I do not anticipate these will change dramatically in the future for rare disease products given their influence on our review of new products.”

MD, National, Commercial

In a review of existing clinical practice guidelines (CPG) for rare disease products, authors cited that “CPGs for rare diseases are scarce... and may vary in quality depending on the source and methodology used.”⁶ Given the limited availability of distinct treatment guidelines for rare disease products today, payers may find it challenging to review these products that come to the market with only clinical trial data and an FDA-approved indication. When clinical guidelines do not exist, payers describe leveraging key opinion leaders (KOL) and industry expert input into their review process to ensure an appropriate understanding of the clinical benefits.

Outside of FDA guidance, clinical trial inclusion criteria, and clinical guidelines when available, payers may consider manufacturer input or sponsored data during their review process; however, this information is typically considered in addition to provider/KOL guidance in order to ensure an unbiased and independent review.

FIGURE 7: Use of Treatment Guidelines in Coverage Policy Decision-Making



“We always go to the relevant specialty societies or guidelines and peer-reviewed literature to see what they recommend, especially as more products are coming to market and the cost of the drug becomes more challenging.”

MD, National, Commercial

Broadly, payers expressed that they anticipate an increase in the use of health economic data to inform policy decisions for any therapeutic area, with three-quarters of payers already incorporating health economic evidence to some degree in policy decision-making. The rising costs of rare disease therapies and orphan drugs are likely to lead to increased usage of health economic data by payers. Specifically, 47% of payers noted that their plans may consider such assessments to support the initial internal review, but that they are unlikely to independently impact management decisions. This viewpoint is distinct from the 27% of payers who consistently look to health technology reports as part of the review process. The specific types of health economic evidence that payers deemed most impactful on policy development were budget impact analyses and cost-effectiveness analyses.

In general, though health economic evidence is limited, it is likely to support payer evaluation of emerging products. High-quality health economic studies are difficult to produce, particularly in the rare disease space, where there is very little information available on the short- and long-term clinical impact, direct/indirect cost, and humanistic value of these products. Additionally, payers note that health economic data can vary substantially depending on the assumptions used in model development, further diminishing their influence on management decisions.

To date, HTAs are considered to be insignificant in coverage decision-making, as the role of these tools has largely been to validate clinical decisions and are less frequently leveraged upstream to guide policy determinations.

FIGURE 8: Use of Health Technology Assessment Reports in Coverage Policy Decision-Making

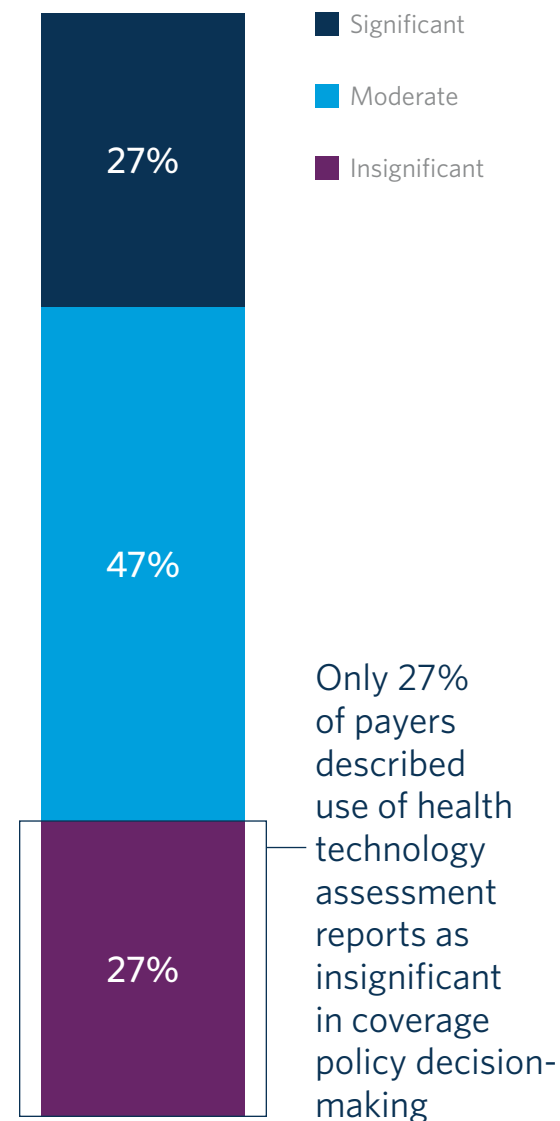
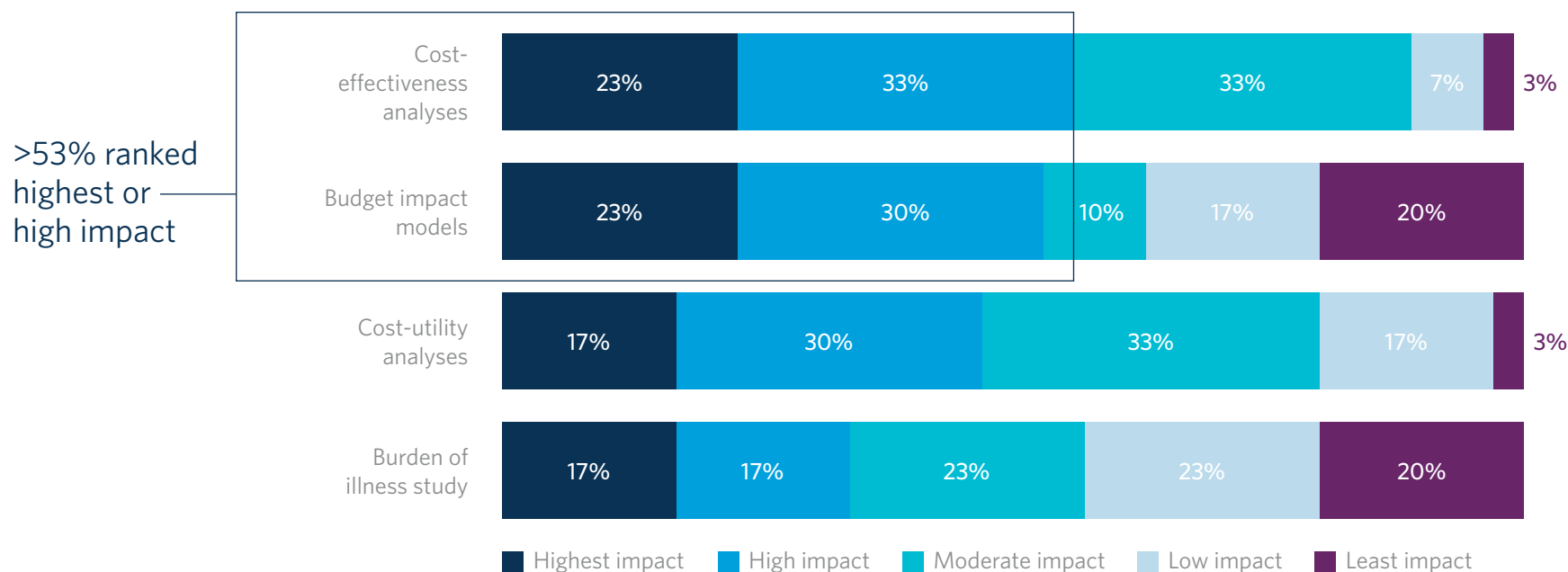


FIGURE 9: Impact of Health Economic Data on Policy Development, By Evidence Type

“We don’t really look at HTAs or ICER because the methodology can be all over the map. It’s not part of our framework. We want to see what published studies show and then will do our own internal analysis.”

MD, Regional, Commercial

“We generally look at ICER’s cost-effectiveness analysis because it gives us a good framework to start with. We may then try to plug in some of our own costs and do our own analysis.”

MD, Regional, Commercial

“Today we look at ICER cost-effectiveness, but honestly for rare we’re looking at what the big players are doing. Within 5 years you’ll see more emphasis on ICER cost-effectiveness just because of product cost.”

MD, Regional, Medicaid

What proportion of payer spend is attributable to rare diseases?

Respondents were asked to assess whether rare diseases make up 1–20%, 21–40%, 41–60%, or over 60% of their annual budgets today and within the next 5 years (Figure 10). The vast majority of payers responded that <20% of their overall budget is currently attributable to the category. These payers expect this share will likely increase to 21–40% in the future.

In assessing specifically rare disease pharmacy spend, about one-quarter of payers expected that spend would rise to 21–40% in the next five years, and

an additional 10% of payers expected that pharmacy costs would rise to over 50% of their overall budget within five years.

Medical benefit drug spend is expected to see a similar shift, with less than a quarter of payers indicating that rare disease spend would be likely to rise to 21–40% of their medical benefit budgets within the next five years.

With payers expecting spending increases upwards of 40% on both the medical and pharmacy benefits, rare disease spending will continue to be a priority topic. The potential budget impact of rare disease spending likewise may encourage more collaborative and innovative ways of managing overall costs of care.

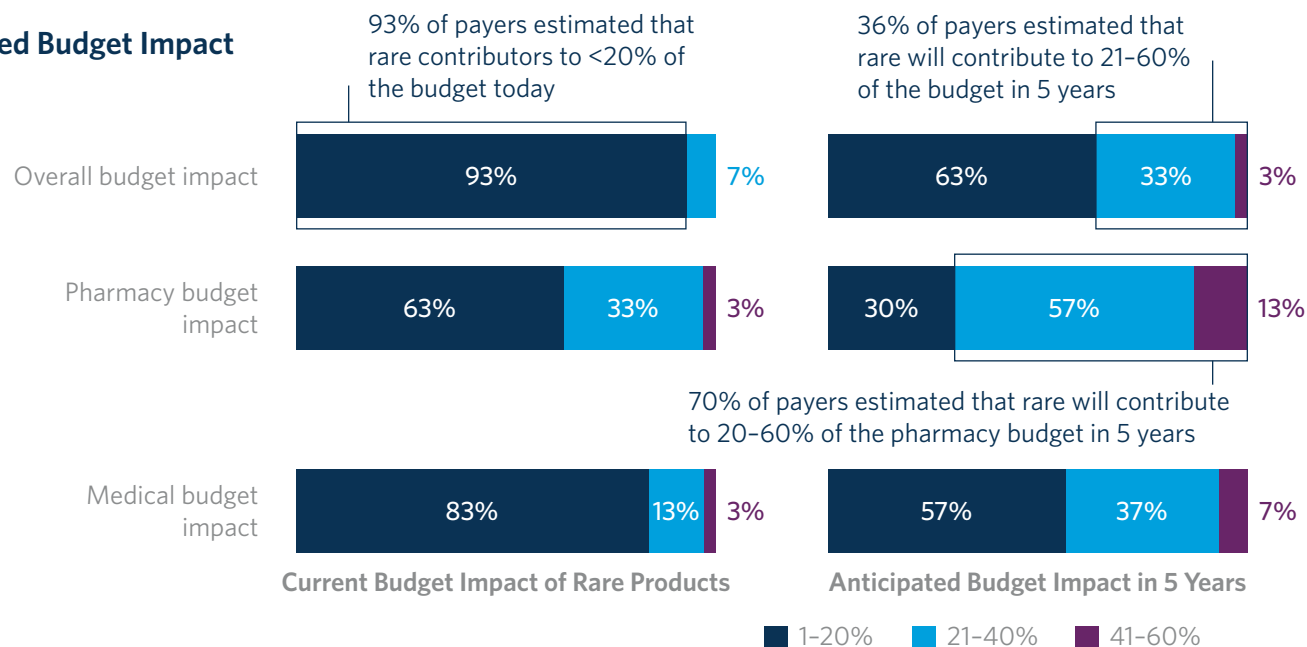
FIGURE 10: Rare Disease-Related Budget Impact

“Today almost 10% of our pharmacy budget is from rare disease products, but that will only increase as more options become available.”

PD, National, PBM

“The growing contribution to pharmacy budget mainly comes down to the cost of the product. We are going to cover these rare products, but the challenge is the price of the drug.”

MD, Regional, Commercial







What challenges do payers face when developing rare disease coverage policies?

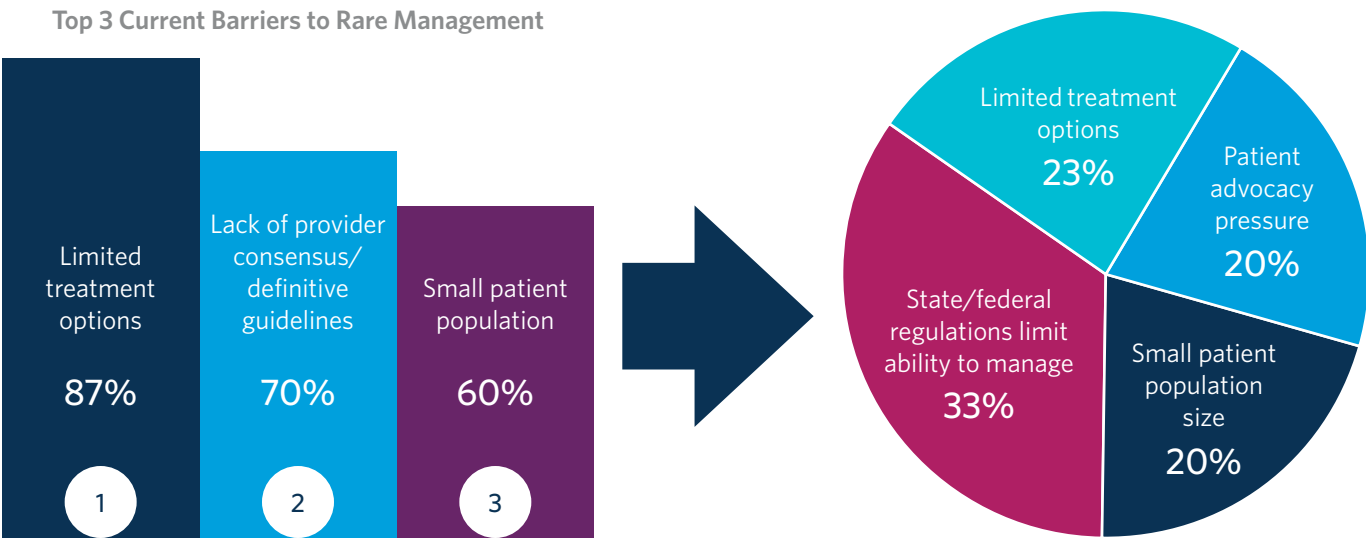
Compared to non-rare conditions, rare diseases are associated with several challenges that may make management more difficult. The main barrier cited by payers is the limited number of available treatment options that leads to fewer opportunities for management. A large portion of payers (over 80%) indicated the lack

of competition within a therapeutic area to be a present concern, with an additional seven percent noting this to be a likely concern in the future. Other factors most widely expected to be future barriers included a lack of definitive epidemiological data and guidelines, and increased legislation limiting a payer’s ability to manage rare disease therapies.

Of the top three perceived barriers to rare disease management cited by payers, they

consider the availability of guidelines to be the most easily addressable in the future. This further underscores the critical need for provider consensus on treatment and definitive guidelines. With the payer community so focused on rare disease management, there is an opportunity to empower guidelines organizations and rare disease patient groups, such as NORD, to take a leadership role in developing guidance for management.

FIGURE 11: Barriers to Utilization Management



“We look to guidelines today, but sometimes for these products the guidelines aren’t there yet. In the future I believe there will be more definitive guidelines published for rare products.”

MD, Regional, Managed Care

“Rare diseases are high priority due to the anticipated product cost, but as more products come out and small subsets of patients will benefit from the costly therapies it will be more challenging to manage.”

MD, National, Commercial

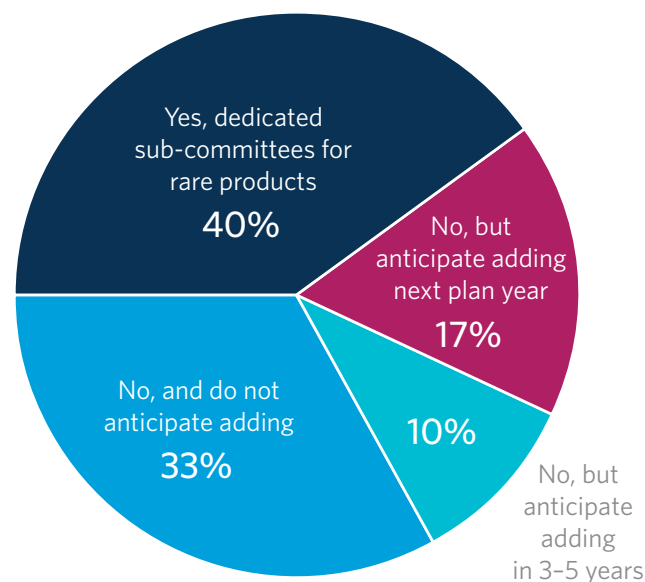
Given the distinct challenges associated with effective management of rare diseases, payers have begun to establish subcommittees to oversee coverage and clinical management decision-making. Almost half of survey respondents indicated that their organization already had a subcommittee dedicated to rare diseases, and a quarter anticipated establishing one within the next five years.

These subcommittees are largely tasked with reviewing pipeline products and anticipating budget impact, but also focus on forecasting the potential eligible patient populations given some of the uncertainty associated with rare disease populations. While some of these subcommittees are new additions to the review process, these strategic teams can be incorporated into the decision-making processes regarding value-based care, utilization management, and managing total cost of care for rare diseases moving forward.

Utilization Management: *How do benefit category assignment and payer active management strategies impact patient access?*

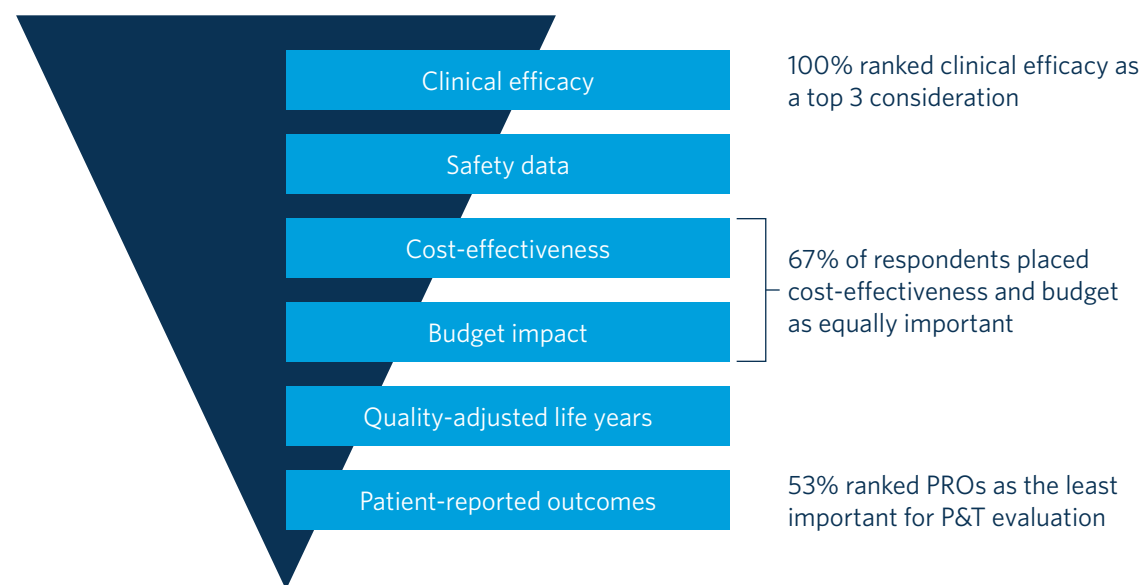
Respondents were asked about the primary considerations influencing P&T evaluations. Within pharmacy and therapeutics (P&T) committees that structure plan-specific formularies dictating drug access, payers cited that, beyond safety and efficacy, which are respectively the first- and second-most influential factors informing P&T committee evaluation, cost-effectiveness data have a strong impact on the evaluation of rare disease products.

FIGURE 12: Sub-Committees Dedicated to Rare Disease Management



“We now have a subcommittee monitoring rare agents that presents to the pharmacy or medical policy committees quarterly with recommendations about pipeline agents that they feel are going to have an impact on the plan. We’re going to have to implement stronger management as more of these high-cost products come to market.”

MD, National, Commercial

FIGURE 13: Priority Considerations for Pharmacy and Therapeutics (P&T) Committee Evaluation

“Rare and non-rare products go through the same P&T thought and operational process. Everything starts with clinical efficacy and safety data from the label, then we look through detailed published studies and specialty society guidelines that may also discuss cost-effectiveness. We need to see the information published in a major journal, so we don’t really consider HTAs.”

MD, Regional, Commercial

In certain instances when there is demonstrated medical necessity, however, medical exceptions are made to allow access to drugs that would otherwise not be covered by the plan. Such exceptions allow patients to access either off-formulary drugs or non-preferred drugs on more favorable cost-sharing terms. For rare disease products, approximately three-quarters of payer respondents indicated that medical exceptions are made on a case-by-case basis through an evaluation of medical necessity.

How are benefits within the rare disease space assigned?

There are several ways in which the structures and administrative processes that enable adjudication of claims differ between the medical and pharmacy benefits. Whether a drug falls under the medical or pharmacy benefit holds potentially different out-of-pocket responsibilities for the patient.

The assigned benefit category under which a therapy is covered is typically dictated by a combination of care setting and provider involvement in drug administration, along with the benefit design structure itself. Drugs prescribed by the provider and self-administered by the patient in his or her home (e.g., oral pharmaceuticals or self-administered injections) generally fall under the pharmacy benefit, whereas healthcare professional-administered

treatments are generally covered under the medical benefit. However, there may be wide variability in whether a particular product falls under the medical vs. pharmacy benefit, particularly for rare disease therapies.

The complex nature of rare diseases and diversity in treatment modalities for these conditions results in coverage under different benefit categories across different payers. Thirty-seven percent of payers indicated that rare disease products are mostly covered under the medical benefit, yet almost half of all respondents noted they currently see an even distribution of coverage for rare disease therapies under the medical and pharmacy benefits.

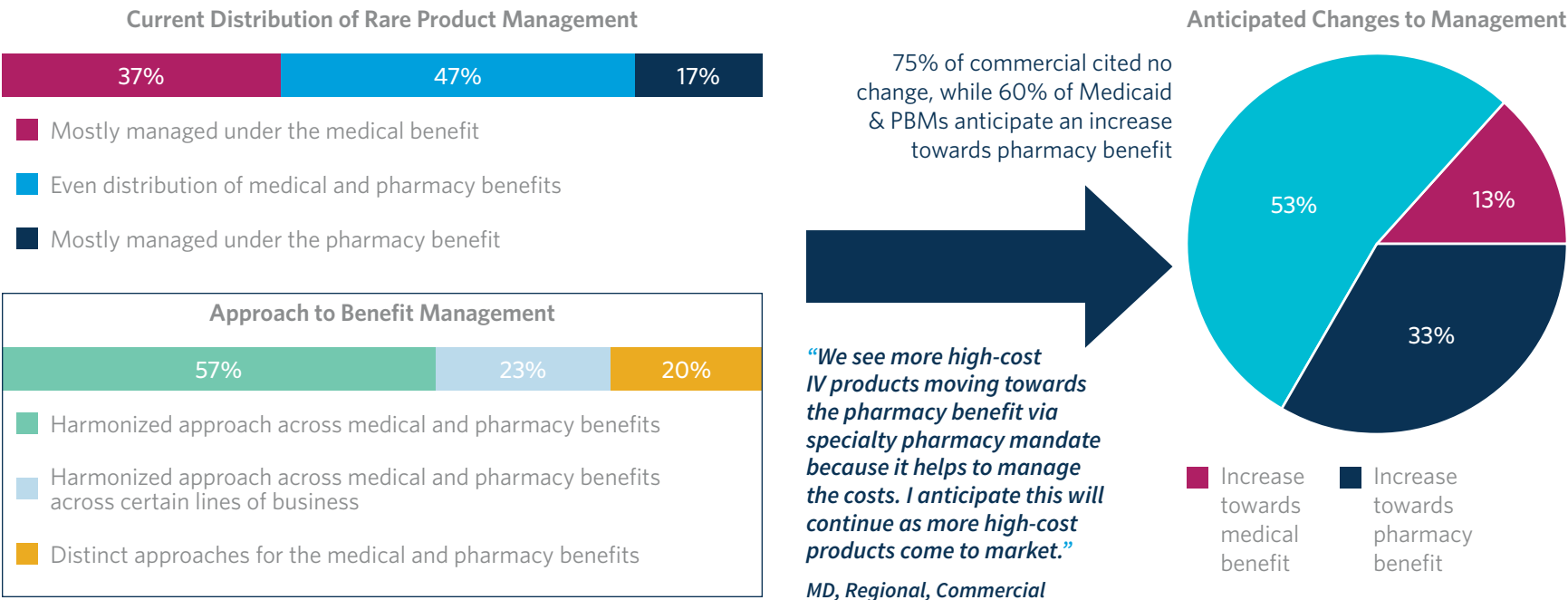
When asked how the benefit determination of rare disease therapies might change in the future, one-third (32%) of respondents expected to see an increase in the proportion of products managed under the pharmacy benefit, while slightly over half of respondents (53%) expected no significant changes from today.

The expected evolution of benefit coverage largely stems from the increased use of specialty pharmacy as a distribution model, which typically covers drugs under the pharmacy benefit. Additional details on specialty pharmacy will be addressed later in this report. The 13% of respondents who anticipate an increase in coverage under the medical benefit mostly cited uncertain safety profiles for new rare disease products, which may dictate a particular site of care (e.g., inpatient administration) or require—at a minimum—healthcare professional administration.

The flexibility in benefit category assignment holds implications for variations in coverage requirements and evaluation processes across the medical and pharmacy benefits. When asked to speak to the degree of harmonization for management across benefits, over half of payers indicated employing a consistent approach across benefit categories, and an additional 23% of payers noted process synchronization for select lines of business.

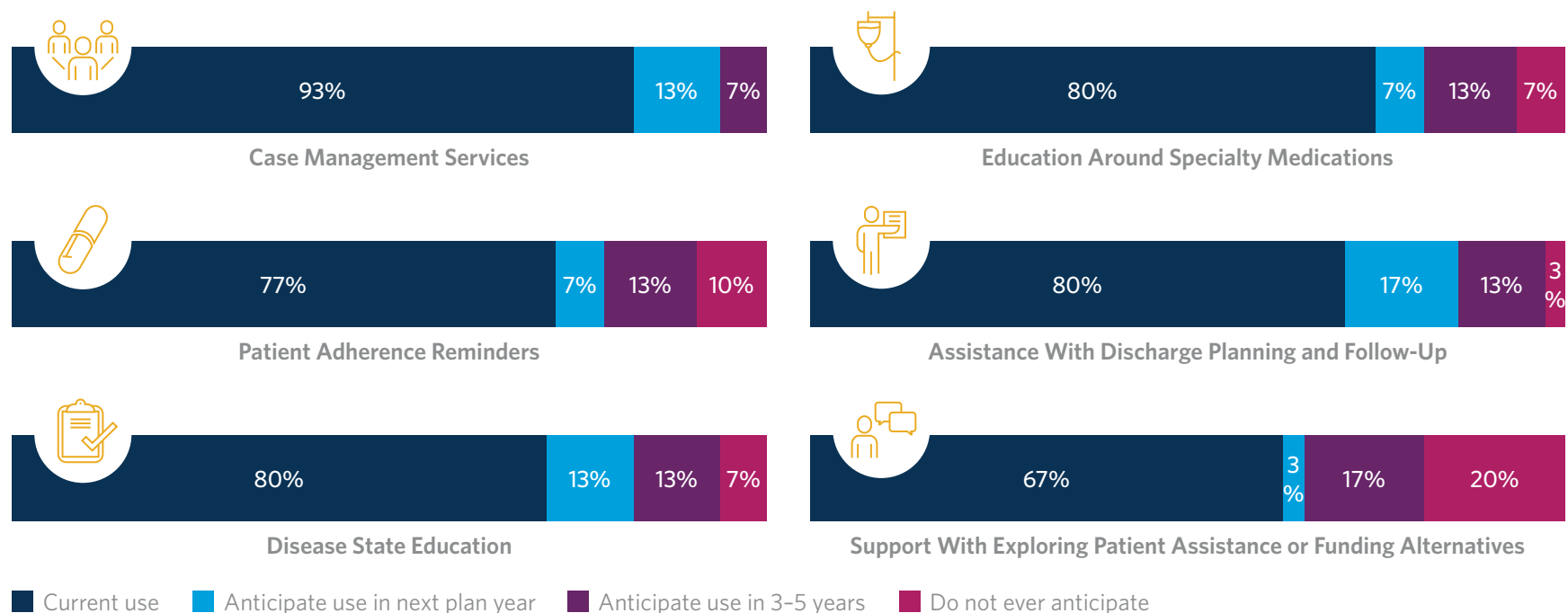


FIGURE 14: Benefit Distribution



Availability of Ancillary Benefits

With the hope of improving patient engagement, coordination, quality of care, and health outcomes, payers have begun to offer additional ancillary services to rare disease patients (Figure 15). For example, almost all payers (over 90%) indicated that they offer case management services. In addition, 80% of payers also noted that they play a role in assisting patients with discharge planning and follow-up. While these services (case management and discharge planning/follow-up) are expected to be more widely adopted in the future by virtually all payers, other ancillary services such as disease state education, specialty medication education, and patient adherence reminder services are also expected to become more prevalent. These latter three services may be attributed to expectations for increased patient ownership and involvement in their disease and treatment decisions.

FIGURE 15: Ancillary Services Offerings


What factors drive payers to implement active utilization management strategies?

The primary goals of utilization management (UM) strategies are to manage the cost of healthcare benefits and to enable patient access to the most effective therapies. However, implementation of these goals can be particularly challenging for payers in the rare disease space due to the relatively small patient populations and the limited availability of treatment options. Furthermore, the financial risk associated with paying for rare conditions leads payers to more active management to the extent feasible.

Over 50% of payer respondents noted that rare diseases are more actively managed than non-rare diseases today (Figure 16). In fact, 40% cited minimizing financial risk as the most important driver of active UM (Figure 17). Virtually all payers who were interviewed ranked forecasting eligible patient populations as one of the three most important factors to consider when managing rare diseases, given the anticipated budget impact. Additionally, the incorporation of innovative payments for these high-cost products was cited as the most important consideration by 30% of payer respondents, allowing for the identification of useful metrics for building innovative payment models in the future.

FIGURE 16: Rare Management Relative to Non-Rare Indications

- More actively managed
- Similar management
- Less actively managed

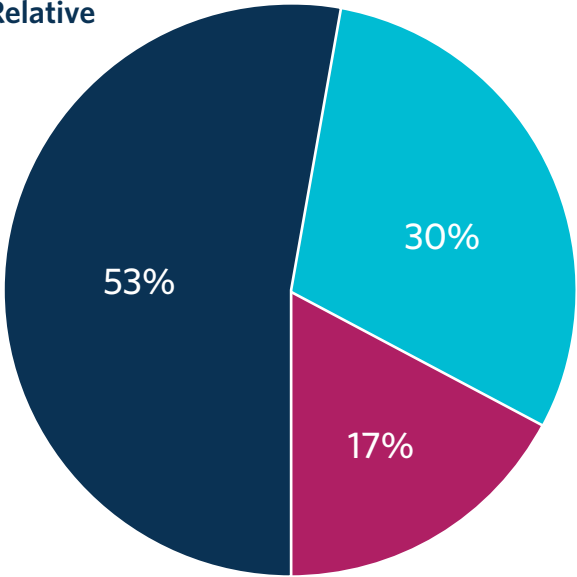
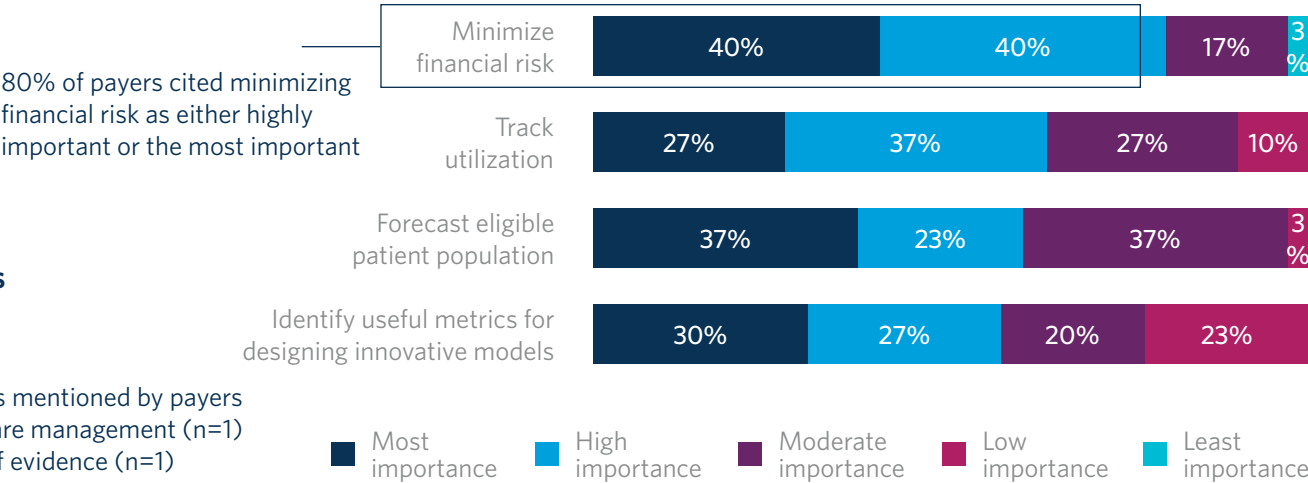


FIGURE 17: Goals of Utilization Management for Rare Diseases

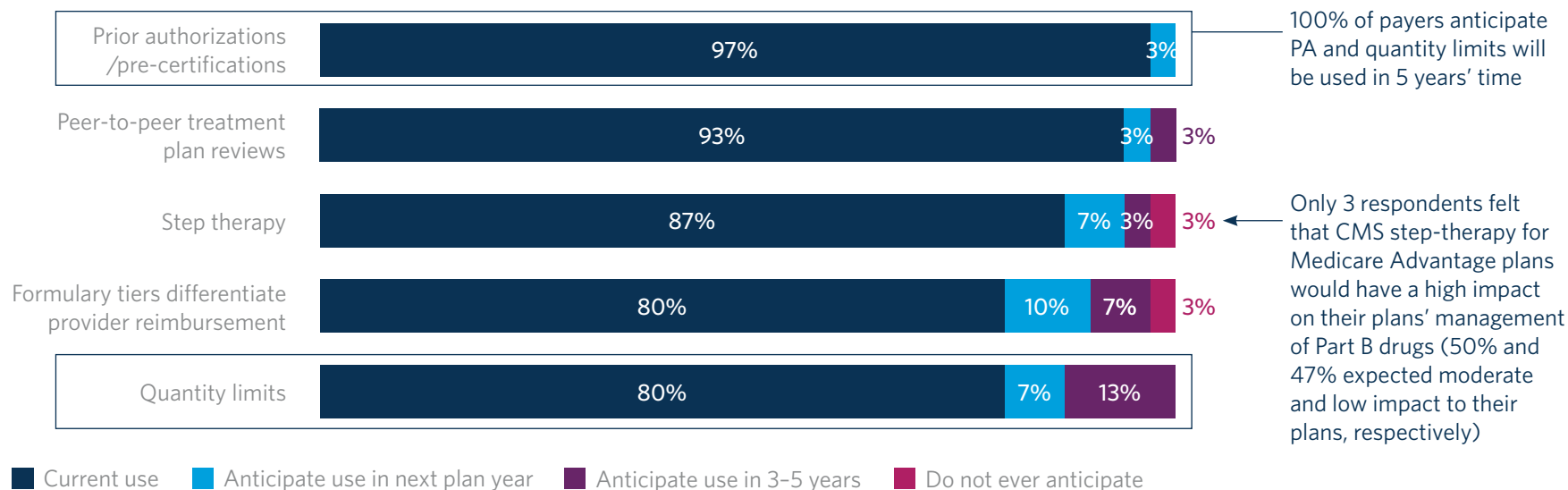


Does benefit category assignment impact utilization management technique?

Payers have implemented an array of tools to help manage comprehensive care for rare diseases. These tools can inform patient selection, reduce wastage of drugs or other supplies, and guide setting of care decisions. The exact type of management tool used may differ by the benefit category under which the product is covered.

On the medical benefit, virtually all payers currently require prior authorization (PA) or peer-to-peer treatment plan reviews before granting coverage for rare disease products (Figure 18). These management tools were expected to remain in use in the future, along with an increase in the use of quantity limits for rare disease drugs.

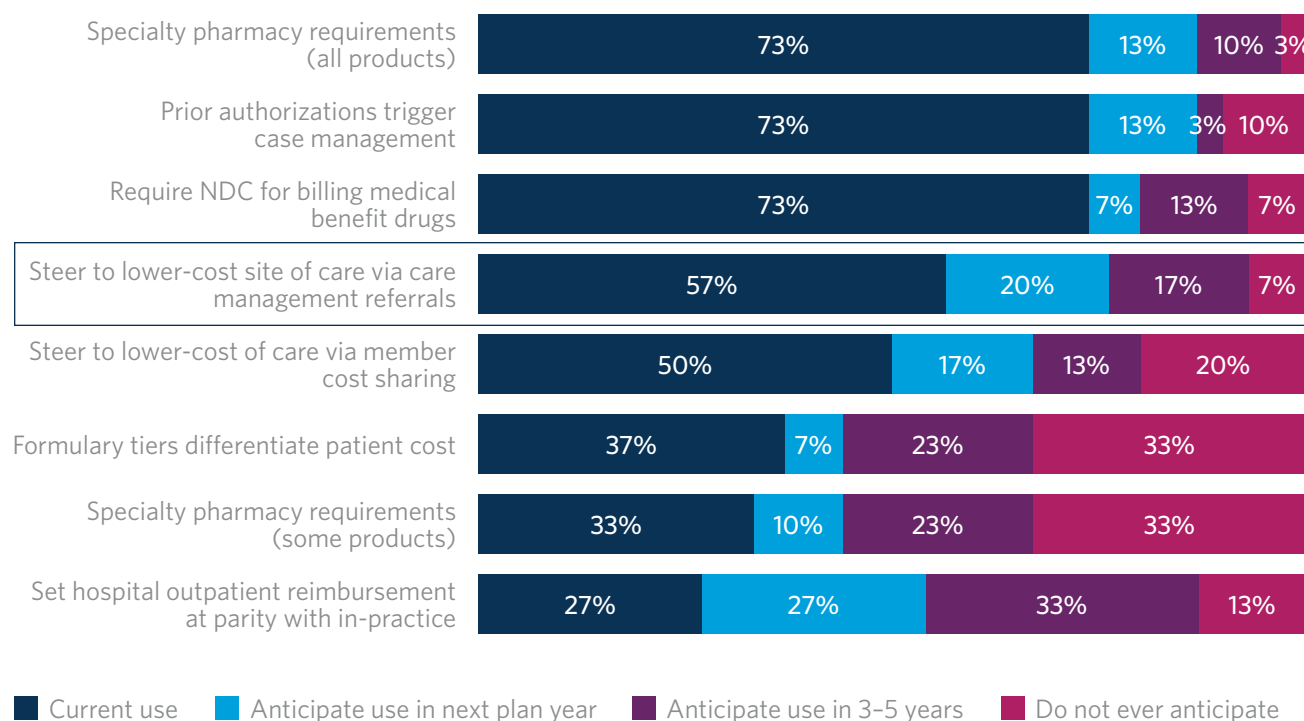
FIGURE 18: Top Medical Benefit Management Tools



As of January 2019, Medicare Advantage plans have been permitted to impose step therapy requirements on Part B drugs. This regulatory change was implemented as part of the Trump Administration's efforts to lower drugs costs while maintaining patients' access to medicines. When asked how this change has impacted internal decision-making, very few indicated it will have a high impact on plan management of healthcare professional-

administered and other Part B drugs. One potential reason for this response is due to the requirement that Medicare Advantage (MA) policies cannot be more restrictive than their Fee-for-Service counterparts, where a coverage policy exists. Therefore, the MA plan sponsor's ability to implement more stringent UM tools, such as step therapy, is limited.

FIGURE 19: Other Medical Benefit Management Tools



“About half of specialty drugs are covered under the pharmacy benefit for billing purposes, but for those covered under medical benefit, physician-administered subcutaneous is primarily done in the physician office or via home health while infusion is most likely to be done in outpatient infusion space. We are currently looking at internal claims and site of care to treat at the most cost-effective site of care.”

MD, Regional, Commercial

“We are looking at claims internally to direct patients to cost-effective sites of care, but this will only be more important in the future as more high-cost products come.”

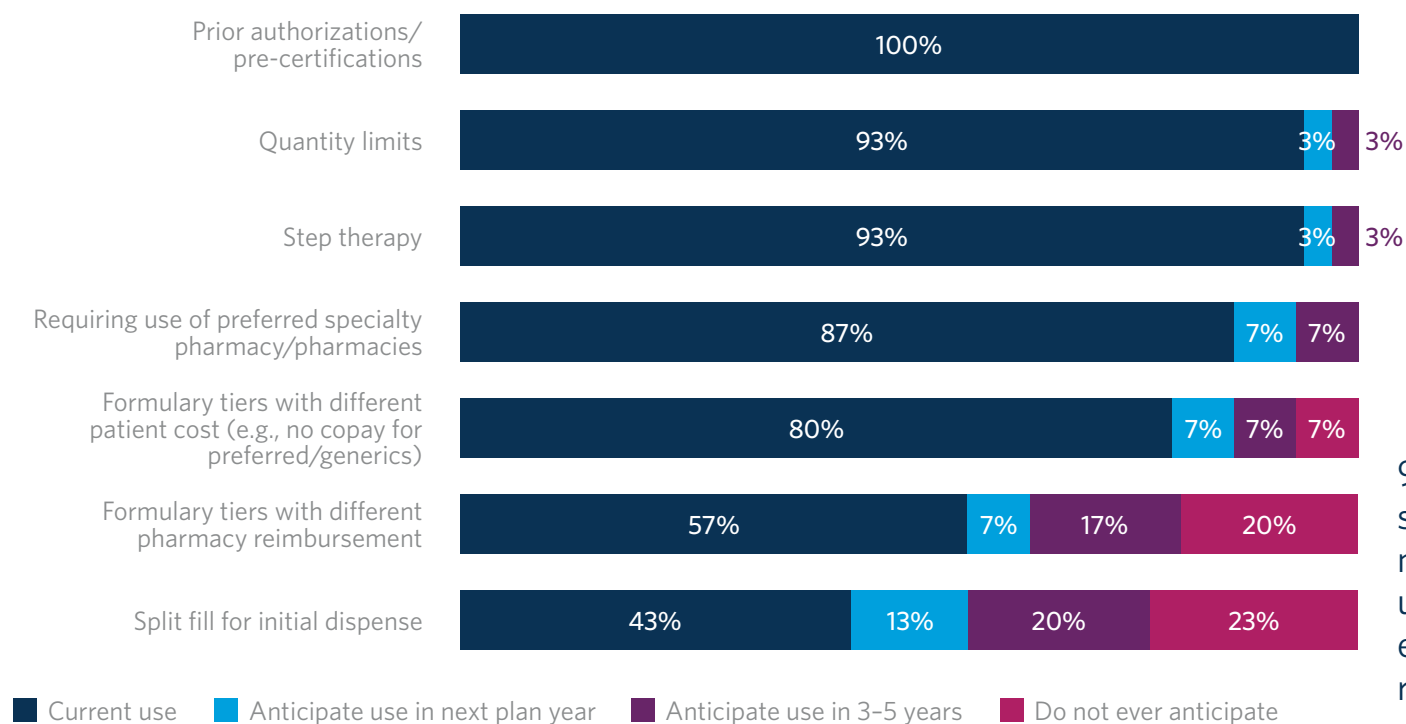
PD, Regional, Medicaid

Note: Respondents who indicated use of a specific management tool were assumed to continue use in the future

When asked about the use of pharmacy benefit management tools, all respondents indicated that they currently require prior authorization before granting coverage of rare disease therapies under the pharmacy benefit. What's more, approximately 93% of respondents currently impose quantity limits and require step therapy. In fact, payers anticipate quantity limits and step therapy to be used when possible in the future given the

limited competition in the rare disease space. The vast majority of payers (93%) also plan to rely on preferred specialty pharmacies (SPPs) in the future, noting that SPPs play an active role in supporting patient adherence and care coordination, as well as improving the overall quality of care and reducing healthcare costs.

FIGURE 20: Use of Pharmacy Benefit Management Tools



Note: Respondents who indicated use of a specific management tool were assumed to continue use in the future

“If the product is only available via an out-of-network specialty pharmacy, then we would have to approve it on an exceptions basis.”

MD, National, Commercial

97% of payers noted some degree of medical exceptions use to ensure or expedite access to rare disease products

What impact does site of care have on benefit category assignment and utilization management?

Given the high variability in costs based on site of care, payers can attempt to control costs with policies guiding procedures to settings that are intrinsically less costly, such as a service at a hospital outpatient department (HOPD) in lieu of an inpatient hospital stay. By way of example, certain healthcare professional (HCP)-administered drugs in ophthalmology may be provided in both HOPD and ambulatory surgical centers (ASC). For oncology and autoimmune disorders, infusion centers are often more cost-effective than the hospital inpatient or outpatient settings. In this latter case, payers may restrict coverage to the infusion centers or other lower cost settings. At present, 43% of payers have an established site-of-care policy for rare disease specialty products, and an additional 50% expect to incorporate this type of policy within five years from now.

FIGURE 21: Site-of-Care Policy Implementation

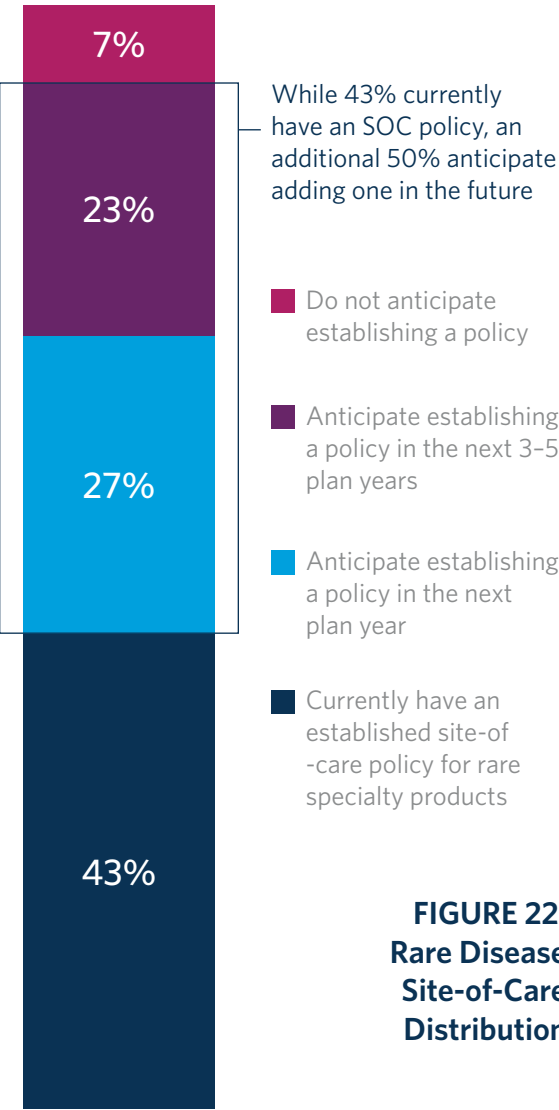
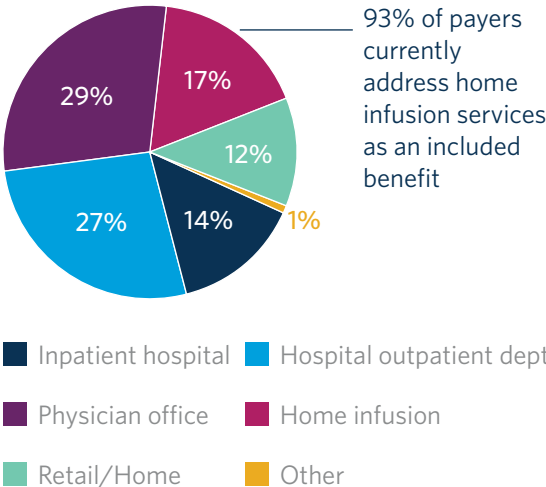


FIGURE 22: Rare Disease Site-of-Care Distribution

Today, 27% of patients receive care for rare diseases in the HOPD setting, which is the second most expensive setting of care, after the hospital inpatient setting. Given the proportion of payers who expect to implement site-of-care policies in the future, non-critical care may move to the office setting from the hospital in the future. Potential ramifications of these trends may lead payers to prefer products that can be used in lower cost settings, when appropriate competition and little clinical differentiation exist in the market. While site of care policies differ by plan, patients are typically able to choose from a number of lower cost sites.



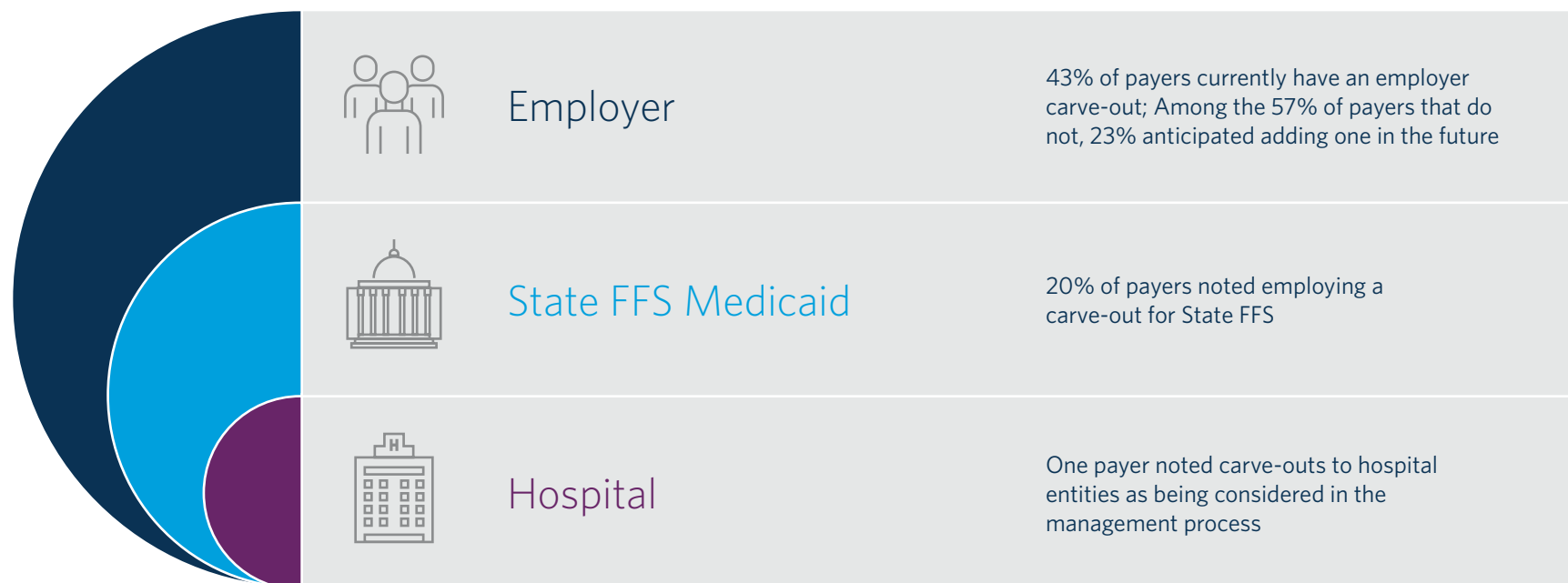
Currently, around 30% of all infusion procedures are performed in relatively low-cost settings, with 17% performed in the home and an additional 13% performed in dedicated infusion centers (Figure 22).

How prevalent are rare disease health plan carve-outs?

There are specific instances in which decisions related to certain books of business, such as employer groups or Medicaid, are carved out of

management to the state or to third-party vendors. While these carve-outs are motivated by different factors, they are typically implemented in situations where State Medicaid may want to assume greater control over costs, leading to a managed care plan “carving out” drug-related costs back to their State Medicaid. About half of respondents (~43%) factor employer carve-outs into their management of rare disease products today, whereas only 23% considered carve-outs to State Medicaid. States will differ on their use of drug carve-outs from Managed Medicaid contracts due to differences in program administration.

FIGURE 23: Consideration of Carve-Out Payments in Rare Disease Management



Distribution: What distribution channels are preferred by payers?

Distribution of Rare Disease Products

Some rare disease products are complex and, as such, require specific distribution and storage capabilities. While manufacturers are primarily responsible for establishing distribution networks for their products, payers are frequently responsible for ensuring that drugs are made available to providers through their respective distribution networks.

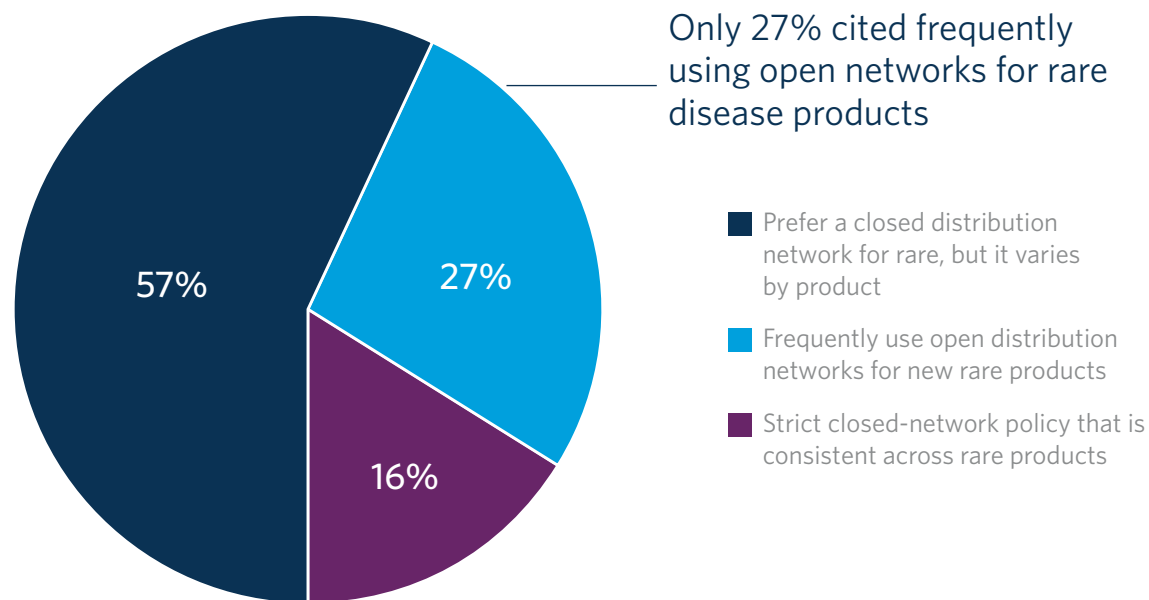
Payers frequently contract with networks of pharmacies from which patients may obtain prescriptions. However, these networks may not always include pharmacies that distribute specific rare disease products, in which case patients may be required to obtain their products from out-of-network pharmacies.

Over half of survey respondents noted that a closed distribution network was preferred by payers for rare disease products. However, in real world settings, distribution networks are rarely completely closed. The lack of completely closed

networks allows patients to access medically necessary drugs that may not be available through an in-network provider. Sixteen percent of respondents mandate that patients obtain

rare disease products from within a plan's network, while 27% of payers cite frequent use of open distribution networks for rare disease products (Figure 24).

FIGURE 24: Most Common Channels for Rare Distribution



“Distribution models are largely dictated by the manufacturer. If we have a choice, we redirect to an available product in our preferred SP network, otherwise we would have to approve the product on a medical exceptions basis.”

MD, National, Commercial

In a scenario where multiple products exist for a given rare therapeutic area, payers prefer products that are distributed by in-network pharmacies. Given the control and potential for cost-saving synergies—especially at health plans that are vertically integrated with pharmacy benefit managers (PBMs) and specialty pharmacies (SPs)—payers prefer in-network products,

but are willing to approve out-of-network rare products based on a medical necessity request made by providers. Notwithstanding payer preference, respondents widely anticipate an increase in manufacturer use of closed distribution networks for rare disease products in the future (Figure 25).

FIGURE 25: Anticipated Changes to Distribution Networks

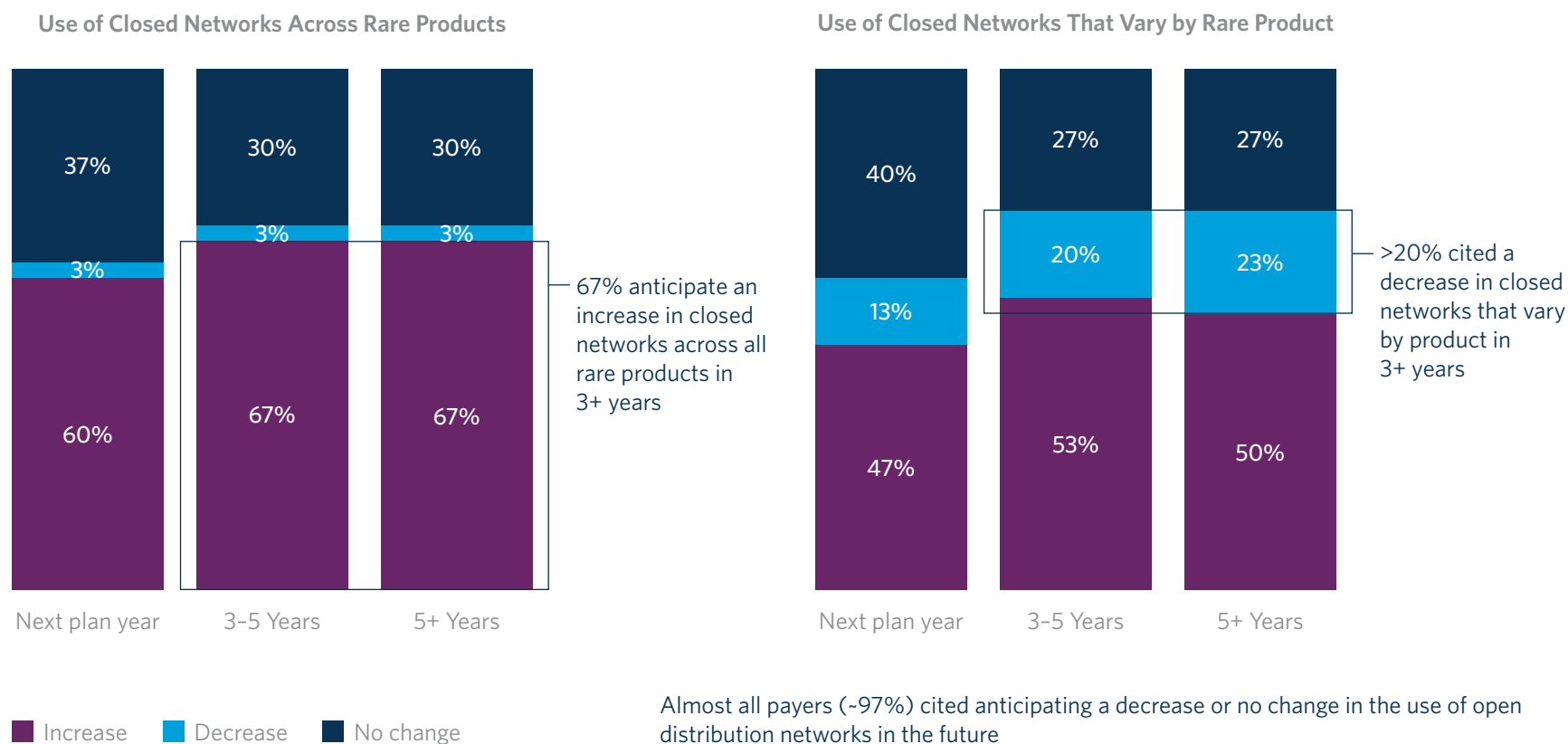
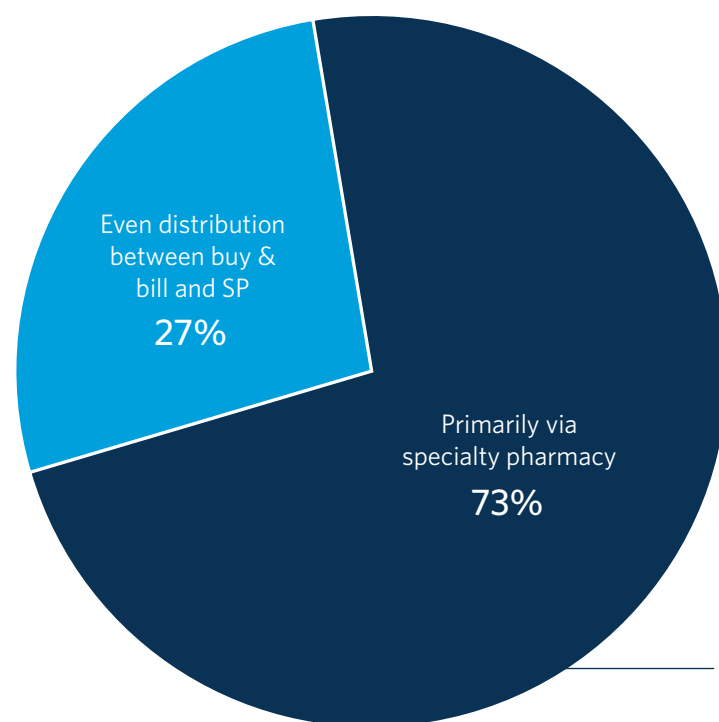


FIGURE 26: Distribution Network Preferences



“Our preference is SP distribution for rare products through our SP partner. This comes down to lower costs and also the ability to drop-ship to the site of care.”

MD, National, Commercial

Payers described SP capabilities such as ensuring timely delivery, optimizing PA, and managing distribution as equally important for effective rare disease management

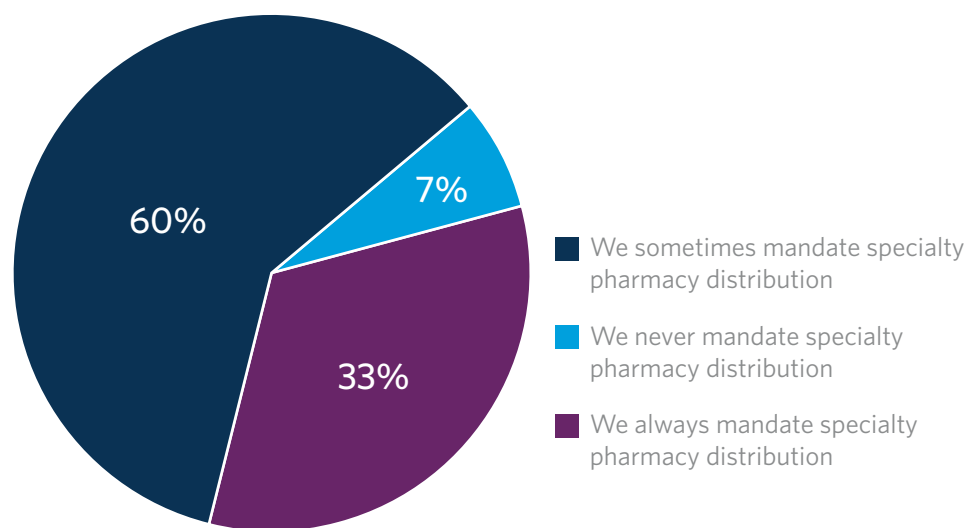
What is the role of the specialty pharmacy?

Payers may mandate that patients obtain drugs from a certain SP, especially in situations in which SPs have capabilities to more effectively manage rare diseases. Nearly three-quarters (73%) of payer respondents cite SP as the primary distribution channel for rare disease products, citing the SP’s ability to increase efficiency of the PA process, avoid product surplus and shortages, and to ensure convenient and flexible product delivery.

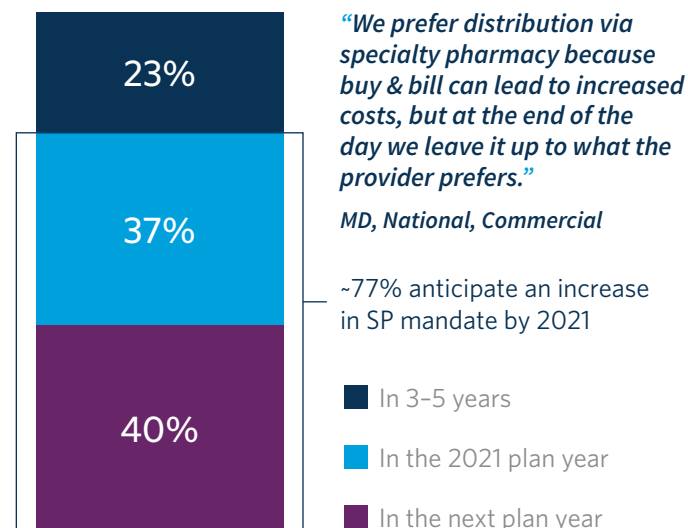
Nearly all payers mandate some form of SP distribution, with 60% employing mandates only for select rare products and 33% always employing these mandates for rare disease products (Figure 27). Such requirements may serve as rationale for the fact that 73% of payers identified SP as the primary distribution channel for rare disease products. All respondents anticipate a rise in the use of SP-mandated distribution over the next five years, with most expecting to see an increase in their use as early as the next plan year.

FIGURE 27: Use of a Specialty Pharmacy Mandate

Mandate of Specialty Pharmacy Distribution for Rare/Orphan Products



Timeframe for Anticipated Increase in Specialty Pharmacy Mandate



Innovative Payment Models: How are innovative payment models used today and what is the potential for future use?

Innovative Reimbursement Models for Rare Diseases

The concept of innovative contracting among payers and manufacturers, such as risk- or cost-sharing agreements, has become increasingly popular as more innovative therapies come to market. Payers look to these models to mitigate some of the financial risks they assume, particularly for rare

disease therapies. Such models have been explored primarily for high-cost treatments, particularly where clinical outcomes are able to be measured easily. In these models, payment can be provided for a drug meeting (or not meeting) clinical milestones. In the case where a drug doesn't meet clinical outcomes, payment is generally in the form of a back-end rebate to the payer by the manufacturer.

Innovative models may take on many forms, such as value-based, outcomes-based, and annuity payments. These examples have not been used frequently for rare diseases given the small patient populations and potentially significant administrative lift for payers.



Either the manufacturer or payer most often initiate this conversation due to their financial stake in both pricing and reimbursement (Figure 28).

How widely are innovative payment models leveraged in rare diseases?

Innovative contracting is a key interest among payers, particularly as it relates to rare diseases. Payers voiced interest in any type of contracting process that alleviates some of the financial risks related to rare disease management. With respect to manufacturer use of these payment models, apprehension of risk sharing is seen as a leading factor for their limited use today.

Today, about 50% of payers employ innovative payment models for rare disease products, with value-based contracts (VBCs) being the most popular (Figure 29). To date, most VBCs have been established in oncology, which allow for targeted biomarker tracking and offer a large body of clinical evidence to support its design. Outside of oncology, there is limited participation in innovative payment arrangements for rare products.

FIGURE 28: Stakeholder Who Initiates Innovative Contracting Conversation

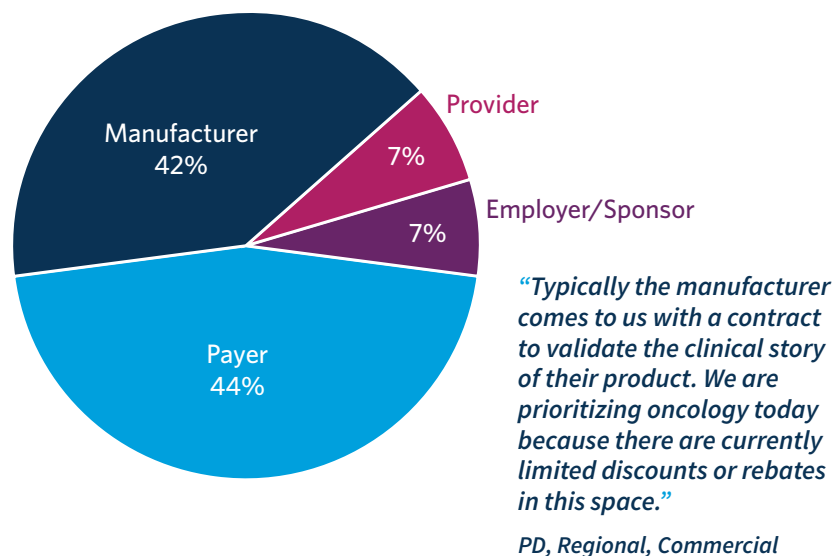
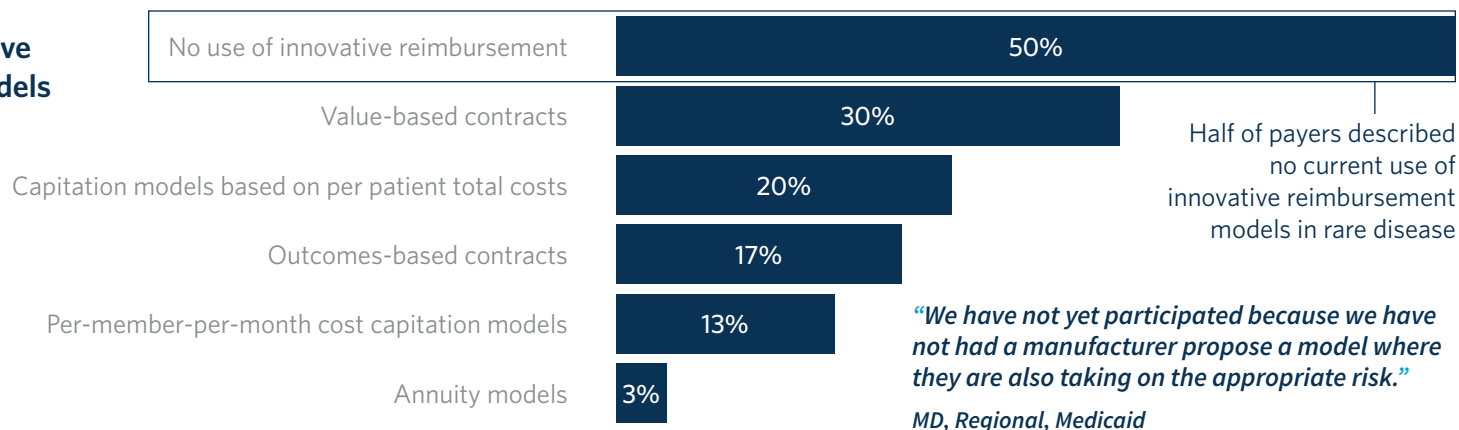


FIGURE 29: Innovative Reimbursement Models Employed Today



Despite broad interest in VBCs, payers largely perceive these models to be administratively burdensome and to encompass significant challenges related to tracking outcomes in order to appropriately share risk. Several operational challenges, such as data privacy, data sharing across claims and prescription history, and appropriate measuring of outcomes at agreed-upon milestones were noted by payers.

These challenges are heightened in the rare disease environment due to the dearth of clinical evidence available to design effective models and the small patient populations. While traditional volume-based rebates are driven by financial risk, rebates from VBCs are likely to be driven by clinical data. Given the lack of clinical evidence typically available for rare diseases, VBCs may pose greater challenges for payers to implement in these categories.

The line between value- and outcomes-based contracting is often blurred by payers' inconsistent definitions of the terms. Some payers consider "value" to be a derivative of clinical, economic, and humanistic impact of a product on patients. Whereas, outcomes may be more strictly defined by the review of agreed-upon clinical biomarker metrics to measure the efficacy (and potentially safety) of a product.

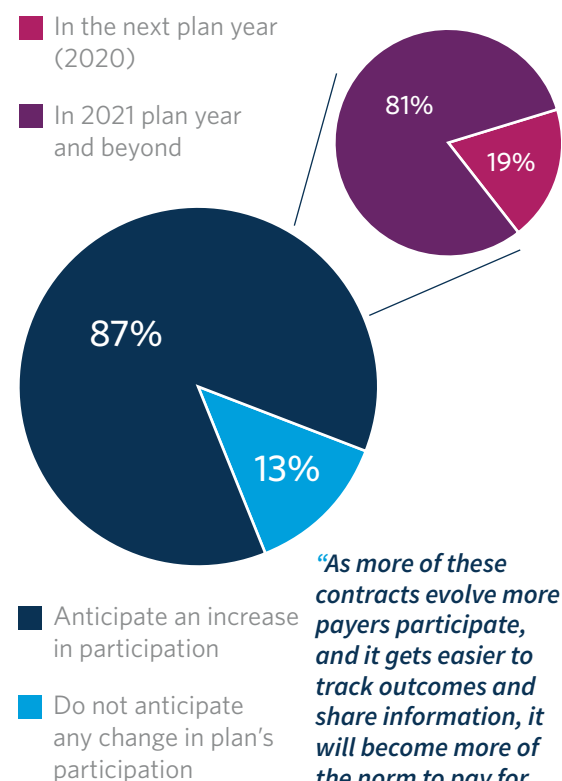
Still others consider both value- and outcomes-based contracts to be used interchangeably, particularly under conditions where discrete outcomes may not be available.

While there are no consistent definitions of or strong consensus on these terms, one thing is clear—payers are increasingly interested in pursuing these models to more effectively manage rare disease patient populations. In fact, 87% of survey respondents expect to see an increase in payer participation in innovative payment and contracting agreements for rare disease products in 2021 or later, specifically with a focus on value-based contracts and outcomes-based contracts (Figure 30).

Payers seek to employ these models in the near future due to the need to control total cost of care in recognition that many more of these high-cost products will soon be commercially available. Of the 13% of payers who responded that they do not anticipate any change to their participation level in VBCs, this cohort may either be already participating in innovative reimbursement models or may not believe they are able to overcome the administrative burden in the near future. Several smaller regional payers cite a wait-and-see approach to VBC implementation, anticipating that some of the

larger plans may be able to iron out operational challenges to enable broader adoption.

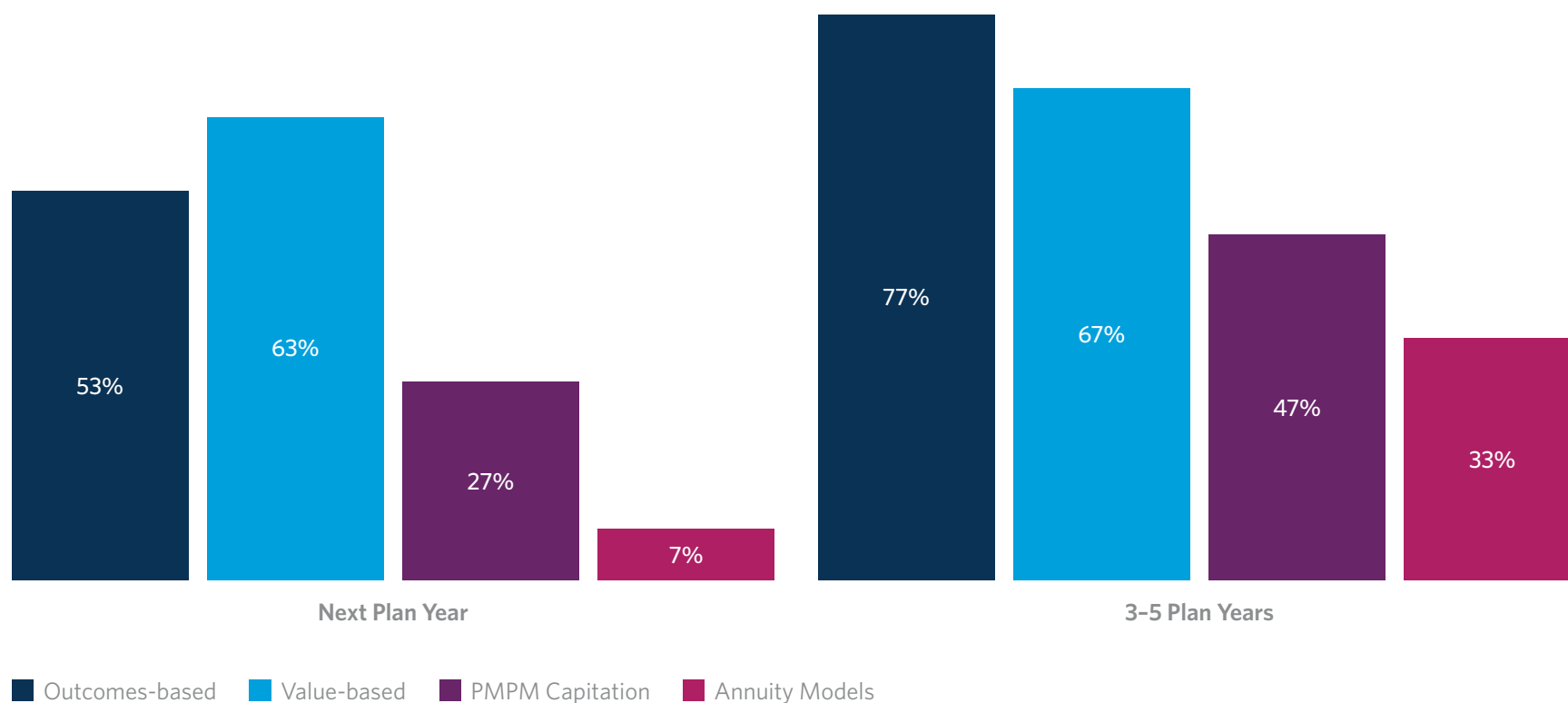
FIGURE 30: Anticipated Future Participation



"As more of these contracts evolve more payers participate, and it gets easier to track outcomes and share information, it will become more of the norm to pay for these products."

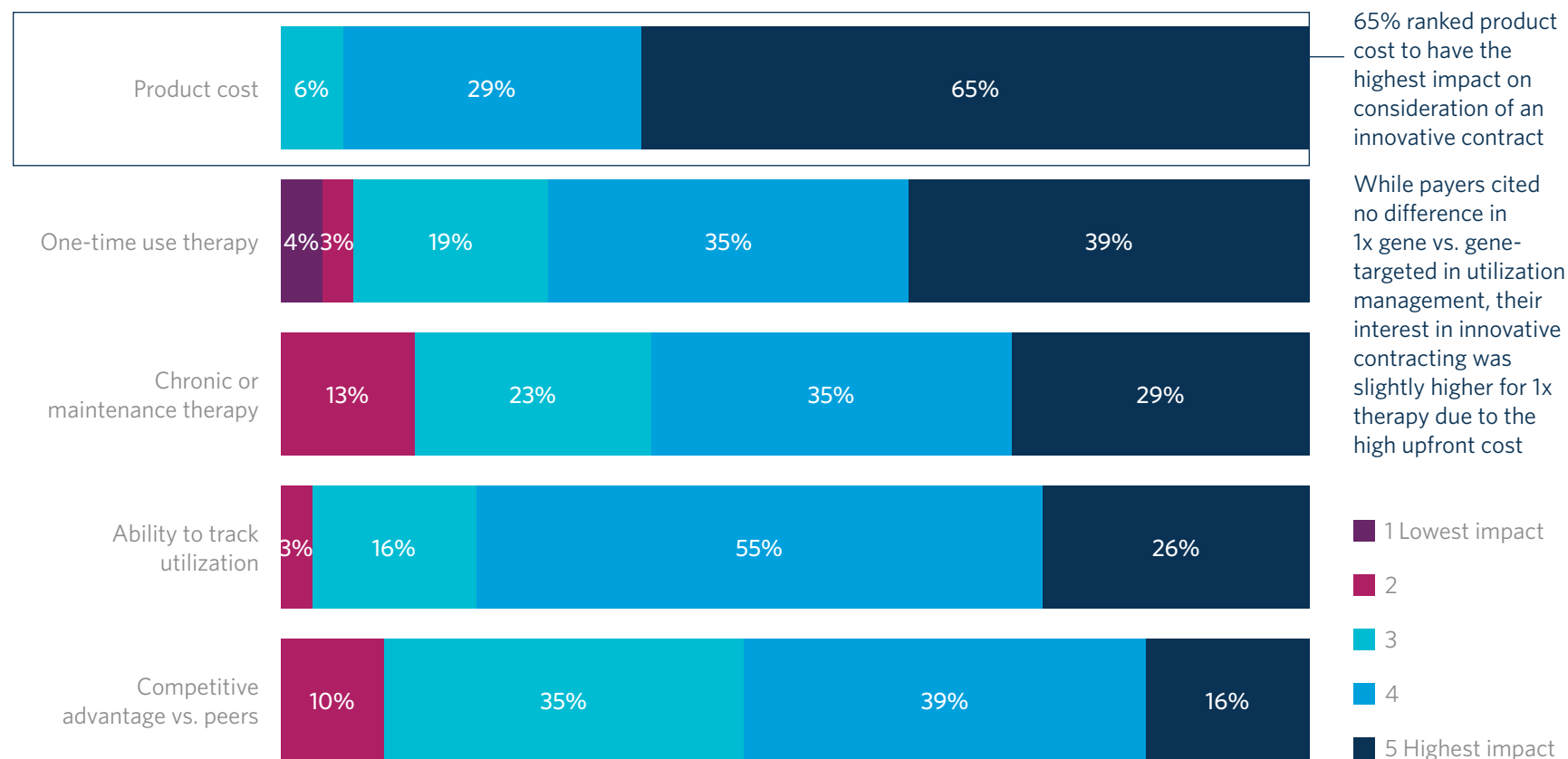
MD, National, Commercial

FIGURE 31: Anticipated Participation in Different Models



What factors support payer engagement and participation in innovative contracting?

Two thirds of respondents (67%) view product cost as the most influential factor for a payer's decision to pursue innovative contracting (Figure 32). Virtually all payers note that they would consider entering innovative reimbursement agreements for single-dose gene therapies, multi-dose gene therapies, and maintenance therapies given their high costs.

FIGURE 32: Factors Impacting Interest in Innovative Reimbursement Contracting

“Innovative reimbursement models tend to be more relevant for these 1x high-cost treatments because it gives some protection if they do not work. We want to see more of these contracts for those 1x therapies because we want to pay for outcomes.”

MD, Regional, Commercial

“Our goal is to align innovative reimbursement strategies with the health systems so we can build models where we’re jointly responsible for the total cost of care. We’re in the process of developing a strategy for rare diseases to reduce year-over-year spend.”

MD, Regional, Commercial

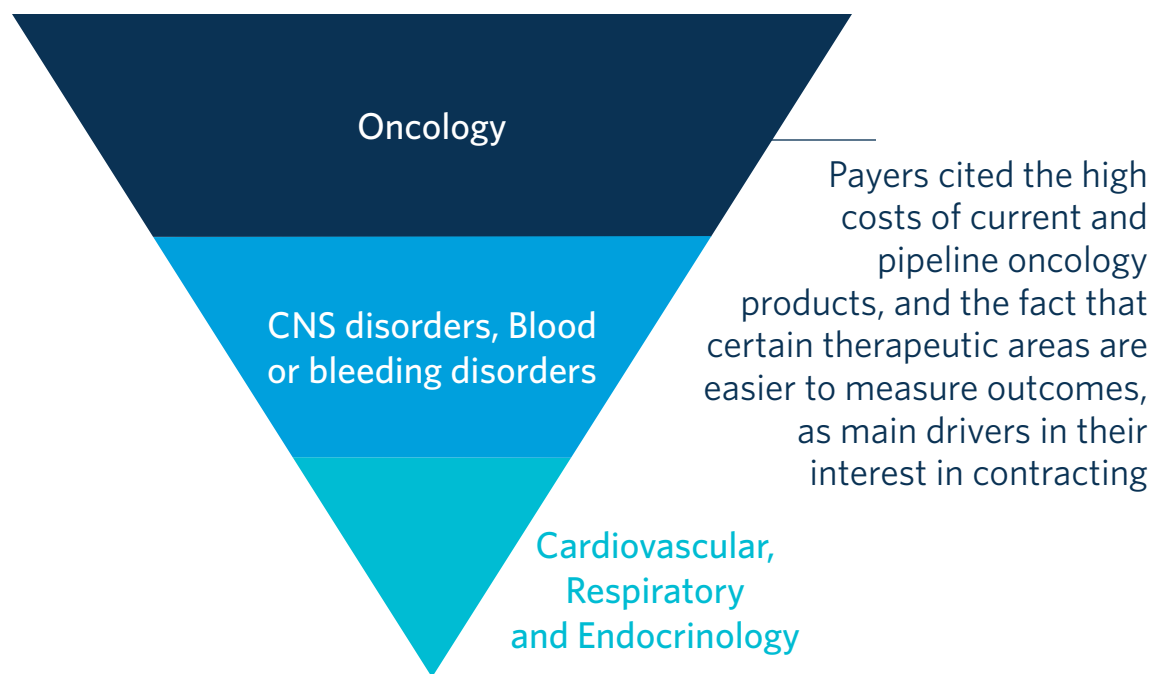


Many payers identify priority therapeutic areas to be rare oncology, central nervous system disorders, and blood or bleeding disorders (Figure 33). Payers cited the high costs of rare oncology products to be the major driver behind an interest in innovative contracting. The other primary motivators for engaging in VBCs within these therapeutic areas are: 1) the availability of clearly defined value metrics by which risks can be measured and a contract can be developed; and, 2) manufacturer-driven conversations on how best to structure new VBCs.

With respect to the availability of defined metrics for measurement, as mentioned above, oncology has seen the most success in developing VBCs to-date, as there are clearly defined, consistent, and measurable ways by which payers can track outcomes. Clinical research focused on identifying specific biomarkers that contribute to disease progression, in addition to treatments linked to those specific biomarkers enabled VBCs to be established in oncology. As research continues to grow in rare diseases, the opportunities for VBCs are likely to expand as well.

While payers seek clarity on the application, utility, and structure of VBCs as it relates to different therapeutic areas, manufacturers tend to be a driving force in identifying new

FIGURE 33: Priority Indications for Innovative Reimbursement Contracting



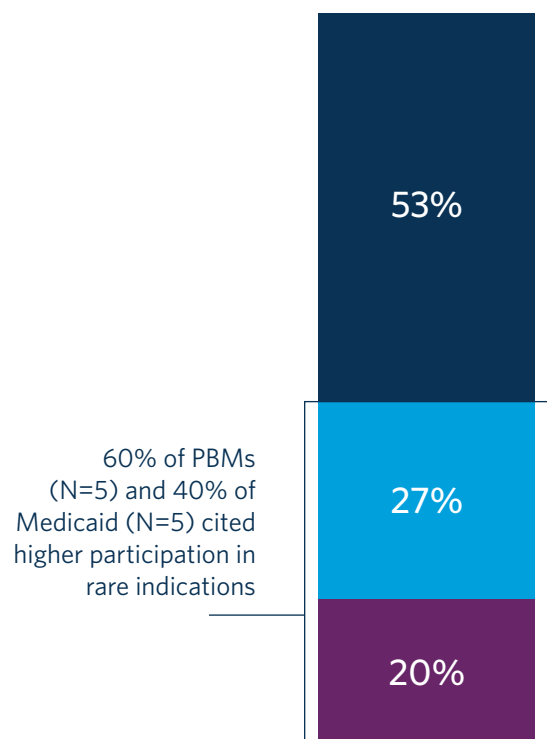
methods and opportunities for implementing VBCs. Indeed, payer respondents note that manufacturer and other stakeholder insights are critical as they broach the use of VBCs for disease management.

Interestingly, the drivers for payer engagement in an innovative reimbursement model did

not differ between rare and non-rare diseases, and 53% of payer respondents noted no differentiation in the extent to which they participate in the arrangements for rare and non-rare diseases. PBMs and managed Medicaid sponsors cited higher participation in innovative reimbursement schemes in rare indications.

FIGURE 34: Participation Differences Between Rare and Non-Rare Indications

- No differences between rare and non-rare indications
- Participate in innovative reimbursement more in rare indications
- Participate in innovative reimbursement more outside of rare



One major concern raised by commercial payers for high-cost drugs, particularly one-time administered gene therapies, is the understanding that patients will move between plans every few years. The risk of covering a high-cost treatment for a rare disease patient without realizing the long-term cost savings presents an additional challenge when it comes to agreeing to innovative reimbursement and contracting arrangements. Lack of patient “stickiness” under a commercial health plan may also limit payer willingness to participate in innovative contracting where the risk sharing is spread over time. For example, several payers raised the example of extended payment for Spark Therapeutics Inc.’s gene therapy product LUXTURNA® (voretigene neparvovec-rzyl), whose publicly announced installment payment model spreads out the payment over time, even potentially after a patient transfers to another insurance plan. As such, extended payment models could mitigate payer concerns with high cost drugs moving forward.

What barriers exist to implementation of innovative reimbursement models?

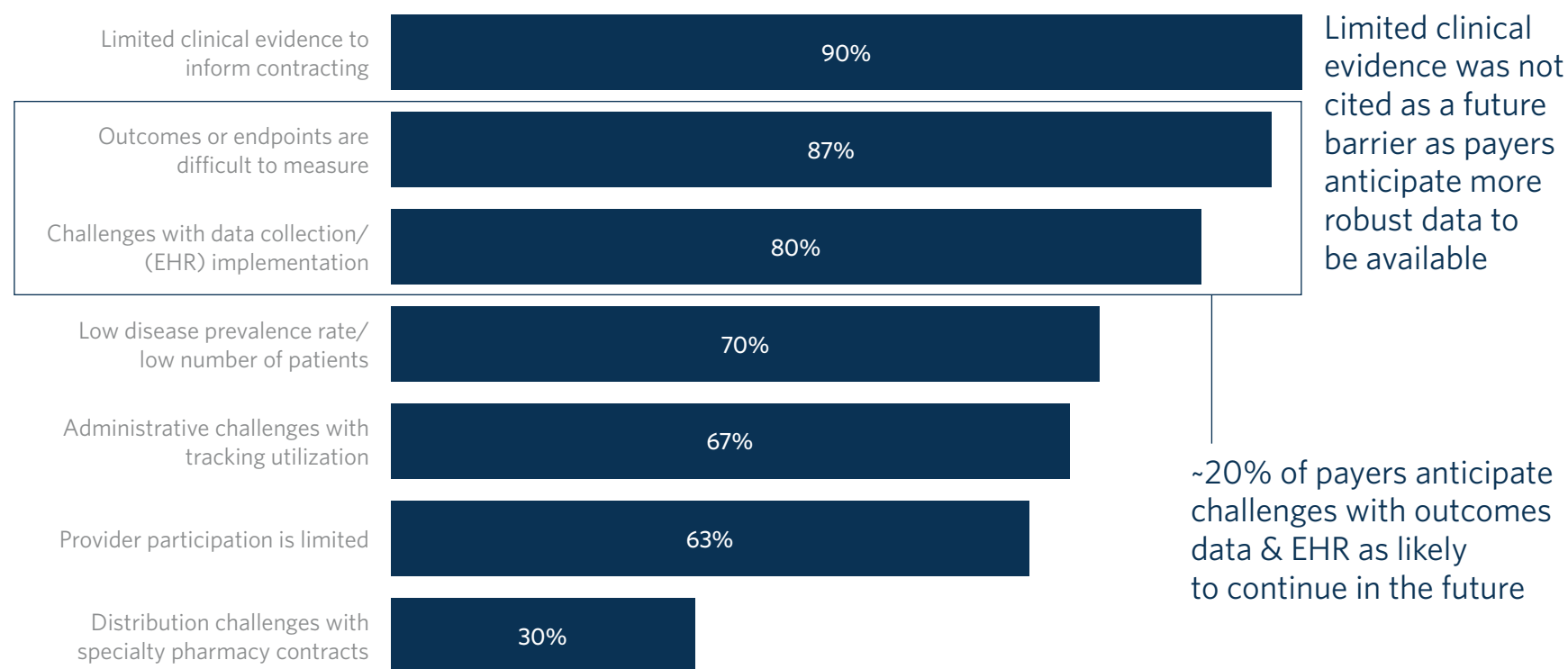
Despite the increasing interest in innovative payment models, there are several perceived barriers inhibiting their widespread adoption.

The most widely recognized barrier is the limited clinical evidence available today to inform the terms of a contract. Specifically, the outcomes or endpoints that may demonstrate clinical success can be challenging to consistently measure and adjudicate.

Payers also acknowledge several administrative barriers that present difficulties for designing and implementing these agreements. Data collection and electronic health record (EHR) implementation challenges are cited by 87% of payer respondents, and administrative challenges associated with tracking utilization are recognized by 80% of payers.

Patient Cost Impact on Payer Management: How do payers consider patient cost burden associated with rare disease management?

The patient out-of-pocket (OOP) costs for their prescription drugs has been an ongoing focus of public discourse. For drugs covered under the pharmacy benefit, patients may be responsible for up to 40% of drug costs. For patients with rare disease, high OOP costs can

FIGURE 35: Barriers to Executing Innovative Reimbursement Contracts

“We aren’t participating in a lot of these models because while conceptually they make sense, the reality, where the endpoints are, and when you measure efficacy when it crosses from one plan year to another and they’re no longer your member can be challenging.”

MD, Regional, Commercial

“The biggest hurdles are agreeing on the outcomes and ensuring integrity of the data. Tracking the outcomes and getting an understanding of the clinical situation can be challenging, especially if there isn’t a requirement for the patient to have a follow-up study with a registry. Unfortunately there isn’t a central body that will track outcomes at this time.”

MD, Regional, Commercial

be significantly burdensome and may decrease medication adherence.

When asked how concerned payers are about the impact of rising OOP costs on patients, almost half of payers cited that their organization was somewhat concerned, noting that manufacturer support plays a critical role. Payers described their patients as having the opportunity to receive financial support from a foundation or manufacturer assistance program, especially

for rare diseases where advocacy presence is strong. Manufacturer-based programs may be available for certain types of patients, depending on their insurance.

Manufacturer support programs were seen as beneficial in reducing patient OOP burden, and over 70% of payer respondents expect to see an increase in manufacturer-sponsored patient copay support programs over the next five years. When payers were asked the extent to which the

availability of manufacturer assistance programs is considered when determining how a new rare disease product would be managed, 40% noted considering such programs, and the remaining 60% noted that manufacturer assistance programs did not affect management.

FIGURE 36: Current Consideration of Out-Of-Pocket Costs

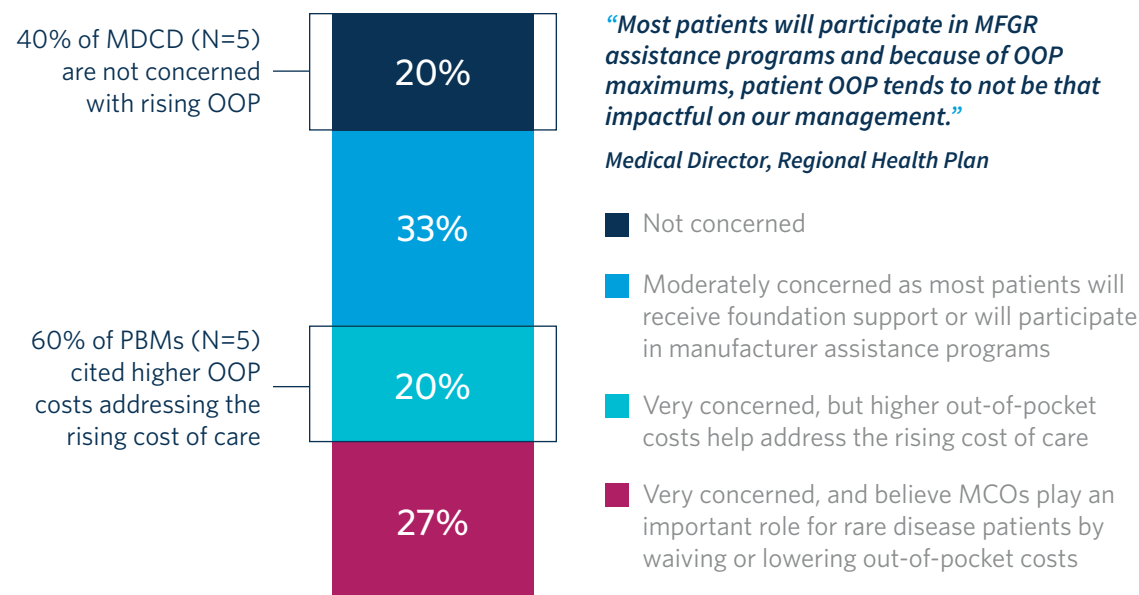
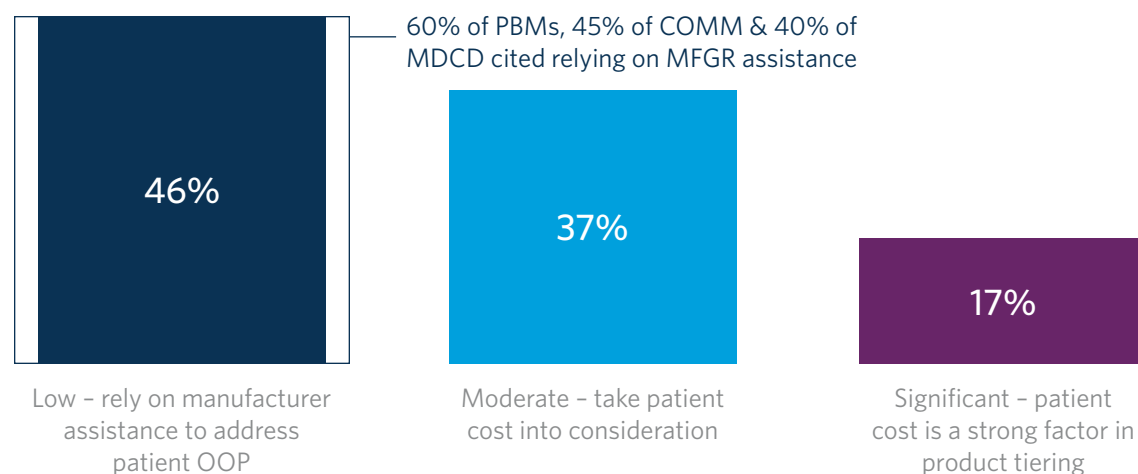


FIGURE 37: Payer Consideration of Manufacturer Assistance Programs



FIGURE 38: Impact of Patient Cost Burden on Formulary Tiering Decisions

“We don’t really consider manufacturer assistance programs in our management. We have considered including copay mitigation programs such as copay accumulators, but the assistance does help the patients that are in need so for now we have not included them.”

MD, Regional, Commercial

How can payer action impact patient cost burden?

Commercial payers may use mechanisms such as formulary tiering and copay accumulator programs to manage drugs, but these tools can also impact patient OOP. By placing a drug on a lower formulary tier, for example, patients may experience more favorable cost-sharing terms as compared to a drug placed on a higher formulary tier. While 54% of payer respondents noted that patient OOP costs are considered when designing formulary tiers to some degree, the remaining 46% noted that patient cost

share was not considered and that they relied on manufacturer assistance programs to offset patient out-of-pocket costs.

Copay accumulator programs prohibit manufacturer-provided financial support from being applied towards a patient’s OOP maximum calculation, thereby increasing the amount a patient must pay until the OOP maximum is reached. While 43% of respondents do not have any copay accumulator programs today, 63% expect to deploy these programs in the next 3–5 years. Copay accumulators have not been introduced without controversy; payers have

employed these tools to respond to concerns that manufacturer copay programs circumvent benefit design, and therefore take out any “skin in the game” that patients have in selecting therapies that may be more cost effective, which could include generics. Other stakeholders, such as patients and manufacturers, however, contend that these programs could disproportionately impact individuals with rare diseases, who may rely on orphan drugs for treatment. Even with copay accumulators in place, maximum OOP amounts are generally federally regulated, so patients have some protection from high OOP exposure.

FIGURE 39: Anticipated Changes to Patient Cost-Sharing Arrangements

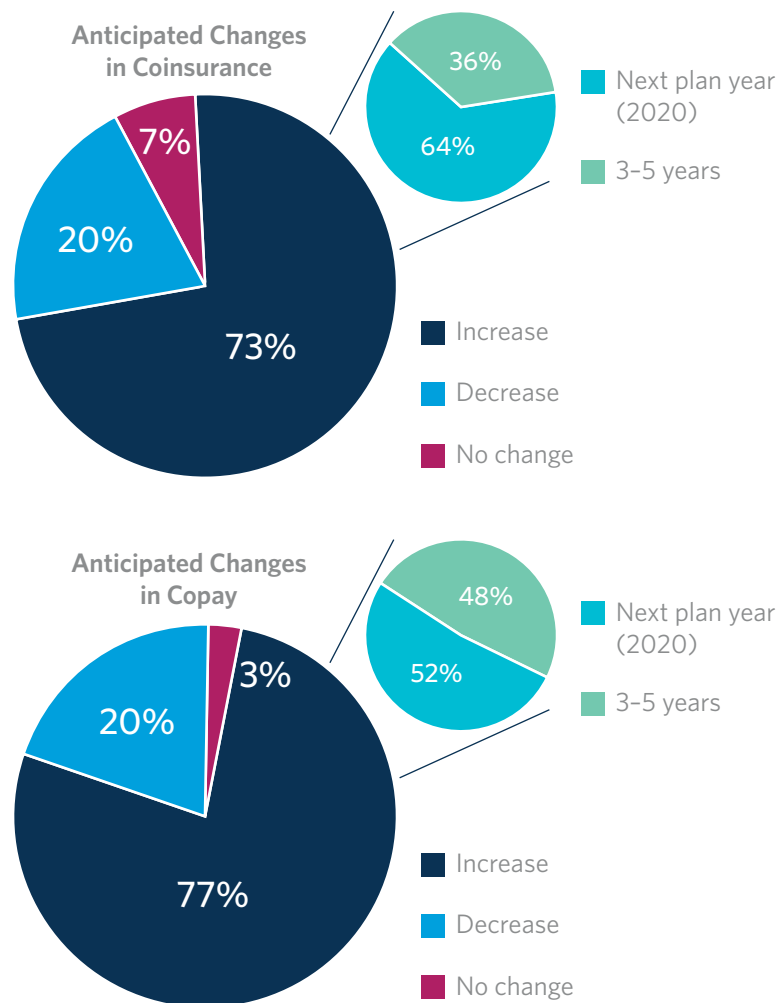
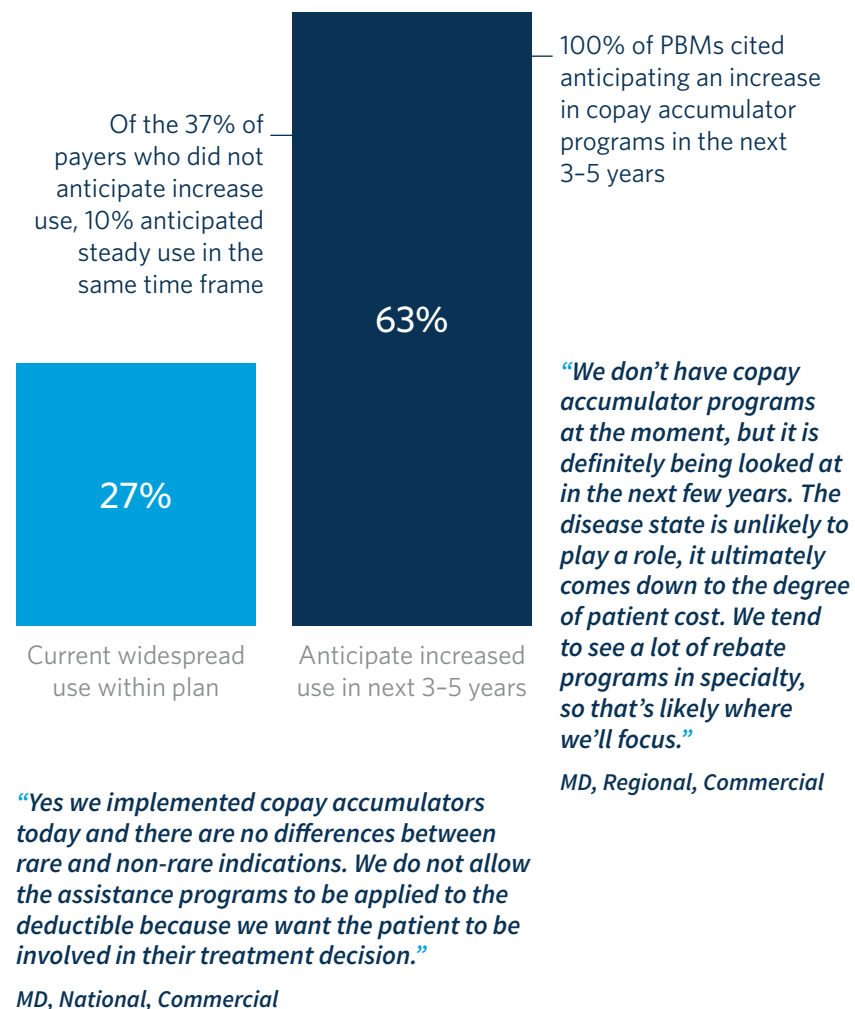


FIGURE 40: Current and Anticipated Future Use of Copay Accumulator Programs



Conclusions & Feedback

Growing research into rare diseases continues to result in clinical breakthroughs and new treatments for complex conditions. Given the high cost and limited treatment options for rare disease, payers are prioritizing and actively managing rare disease and orphan drugs today with a trend towards management under pharmacy benefit. Furthermore, they anticipate needing to leverage more stringent utilization management techniques in the future as more high-cost therapies come to market. In addition to treatment costs, payers anticipate needing to manage the high overall cost of care for these patient populations.

Considering the potential rise in spending on rare diseases, payers are actively discussing potentially innovative ways to pay for these therapies, with the opportunity for multi-disciplinary stakeholders to share in the risk. Payers frequently look to manufacturers to initiate discussions around innovative contracting and require both explicit and measurable outcomes—as well as the infrastructure to share and analyze data—in order to feel comfortable engaging in these arrangements. The components of value-based contracting can be challenging

to operationalize, and are further complicated by potential patient attrition, which makes upfront payment for a high-cost therapy largely burdensome for the payer community.

Additionally, while the growing costs associated with rare disease treatment impact patient adherence, patient cost sharing has had little influence on payer management of these products to date. Payers assume manufacturers will provide copay assistance and patient engagement programs.

Lastly, rare disease comprises an evolving class of therapies and payers continue to seek new ways to actively manage these products. Subsequent research will be required to accurately track payer management trends within this therapeutic area. As such, follow-up publications can explore the considerations, challenges, and opportunities for rare disease management at greater length and detail.

References

1. Code of Federal Regulations, Orphan Drug Act, 21 CFR Part 316
2. NORD IQVIA Institute Orphan Drug Trends in the United States 2018 Report
3. EvaluatePharma Orphan Drug Report 2019, 6th Edition
4. REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 16 December 1999 on orphan medicinal products
5. U.S. Food & Drug Administration Consumer Updates. What is Gene Therapy? How Does It Work?. Accessed October 5, 2020. <<https://www.fda.gov/consumers/consumer-updates/what-gene-therapy-how-does-it-work>>
6. Clinical Practice Guidelines for Rare Diseases: The Orphanet Database. January 18, 2017

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





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