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Lysosomal Storage Diseases and Other Rare Diseases: A Path to Better Management

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Of the approximately 7000 known rare diseases, about 1% are lysosomal storage diseases (LSDs).^{1,2} These inherited metabolic conditions include Fabry disease, Gaucher disease, Tay-Sachs disease, Farber disease, and other diseases (Table).²⁻²⁵ Incidences of LSDs in the United States align with those reported internationally; in 2018, the global incidence of all LSDs related to defects in lysosomal enzymes or integral membrane proteins was 18.2 to 20 cases per 100,000 people.^{2,26} The diagnosis of these ultrarare/rare diseases involves identification of clinical symptoms and testing, such as enzymatic analysis and genetic sequencing.² Treatments are varied and they can be costly.² Although they affect a small patient population, LSDs are progressive, difficult to diagnose, and often life-threatening (Table).²⁷ Disease education and earlier communication between manufacturers and payers as endorsed in the 2022 Pre-Approval Information Exchange (PIE) Act²⁸ may foster a path to better management of LSDs and other rare diseases.

CLINICAL AND ECONOMIC IMPACT

LSDs are associated with substantial clinical and economic impact.^{2,29} These diseases affect the cell's ability to break down substrates within lysosomes and may also impair the transport of lipids and metabolites inside the lysosome. Secondary storage of substrates can also occur in LSDs, which may be a result of trafficking defects.^{2,30} When there are pathogenic variants on genes encoding lysosomal proteins, the consequent accumulation of substrates in cells can lead to cellular dysfunction and damage to tissues and organs, such as the skeleton, skin, heart, lungs, and central nervous system (Table).^{2,6,8,12}

LSDs such as Fabry and Gaucher disease can progress subclinically for several years, delaying diagnosis; this can exacerbate the impact of the disease.^{5,31} Moreover, the rarity of LSDs like Fabry, Pompe, Gaucher disease, and mucopolysaccharidosis type I (MPS I); the heterogeneity of their symptoms; and the similarity of their symptoms to those of other conditions can lead to delays in diagnosis or misdiagnosis.^{6,8,32,33}

The direct and indirect economic costs of LSDs can be considerable. Results of a study of 2016 Healthcare Cost and Utilization Project data demonstrated that, of 35.6 million national hospital weighted discharges, total charges for all rare diseases in the United States (\$768 billion, 2016 US\$) nearly equaled total charges for common conditions (\$880 billion) ($P < .0001$).³⁴ The results of a 2022 analysis of claims data and a primary survey of the rare disease community found that direct medical costs and indirect costs contribute almost equally (45% and 44%, respectively) to the estimated \$997 billion (2019 US\$) total economic impact of 379 rare diseases in the United States in 2019.²⁹

A cohort study of prospective and retrospective clinical- and patient-reported data in adults and children in the United Kingdom diagnosed with Fabry disease, Gaucher disease, MPS I, MPS type II, Pompe disease, or Niemann-Pick type C disease (N = 1106) found that costs associated with LSDs were varied and extensive. Patients living with LSDs typically incurred costs related to medication, emergency department visits, inpatient stays, and office or home visits with health care professionals.³⁵

Given the progressive nature of LSDs, early treatment may be most effective.² For patients with Gaucher disease type 1, for example, a missed diagnosis can lead to treatment delays of up to 10 years.⁸ Associated effects of untreated disease that can occur during that delay (eg, growth failure, pathologic fractures, and progressive liver disease) can be permanent, thus reinforcing the need for timely, appropriate diagnosis and connection to treatment.⁸

MANUFACTURER AND MANAGED CARE PAYER CONSIDERATIONS

Disease education and earlier communication between manufacturers and payers may foster a path to better management of LSDs.^{2,20} Utilization management strategies related to early communication with drug manufacturers, consultation with key opinion leaders,

Table. Global Epidemiology, Characteristics, and Clinical Burden of Select Lysosomal Storage Diseases²⁻²⁵

Lysosomal storage disease	Epidemiology: estimated incidence or prevalence	Characteristics and clinical burden
Hurler disease (MPS-1-H)	Estimated incidence: <ul style="list-style-type: none"> • 0.2 to 1 cases / 100,000 live births 	<ul style="list-style-type: none"> • Accumulation of glycosaminoglycans is associated with widespread cell, tissue, and organ dysfunction, which can be debilitating or life-threatening. • Cardiorespiratory failure and progressive neurologic disease usually cause death in the first decade of life in untreated patients with the severe phenotype. • Substantial morbidity occurs in untreated patients with the attenuated phenotype.
Gaucher disease (all types)	Estimated incidence: <ul style="list-style-type: none"> • 1 to 2 cases / 100,000 people • 100 to 200 cases of type 1 disease / 100,000 people of Ashkenazi Jewish descent 	<ul style="list-style-type: none"> • For patients with Gaucher disease type 1 (the most common form of the disease in the US), glucosylceramide buildup can be asymptomatic. • Disease is associated with thrombocytopenia, anemia, hepatosplenomegaly, bone pain, bone disease, and an increased risk of certain cancers. • Neuropathic disease (type 2 or type 3) is also associated with neurological features including gaze palsy, seizures, and ataxia. <ul style="list-style-type: none"> › Patients with type 2 present in infancy and death occurs before age 3. › Patients with type 3 present in childhood and have a reduced life span.
Fabry disease (classic and nonclassic/late-onset)	Estimated incidence (classic disease): <ul style="list-style-type: none"> • 2.5 cases / 100,000 males • 5 cases / 100,000 females 	<ul style="list-style-type: none"> • Progressive accumulation of lipids GL3 and lyso-GL3 contributes to heart disease including cardiac arrhythmias, renal failure, TIAs, and stroke, resulting in reduced life expectancy. • Other symptoms are life altering and include neuropathic pain, angiokeratomas, gastrointestinal complications, exercise intolerance, and intolerance to heat and cold.
Pompe disease	Estimated incidence: <ul style="list-style-type: none"> • 2.5 cases / 100,000 people • Varies by ethnic group 	<ul style="list-style-type: none"> • Children with untreated, infantile-onset Pompe disease often die before reaching 2 years of age. • In untreated, late-onset Pompe disease, progressive loss of muscle function and respiratory failure hasten mortality.
ASMD (A, A/B, and B) Niemann-Pick disease (A, A/B, and B)	Estimated incidence: <ul style="list-style-type: none"> • about 0.5 cases / 100,000 live births 	<ul style="list-style-type: none"> • Disease exists on a spectrum with 3 subtypes: <ul style="list-style-type: none"> › Type A: infantile neurovisceral ASMD (Niemann-Pick disease type A; NPD-A) › Type A/B: chronic neurovisceral ASMD (intermediate form; NPD-A/B) › Type B: chronic visceral ASMD (Niemann-Pick disease type B; NPD-B) • Patients with ASMD type B have few or no neurologic symptoms; however, they often present with splenomegaly, hepatomegaly, and pulmonary dysfunction with a life expectancy in the range of childhood to later in adulthood. • ASMD type A presents in infancy and is fatal.
Farber disease (Farber lipogranulomatosis)	Estimated prevalence: <ul style="list-style-type: none"> • ≤0.0001% of population 	<ul style="list-style-type: none"> • Caused by pathogenic variants on <i>ASAH1</i> gene, encoding acid ceramidase. • There are 7 types of this disease; patients with type 1 have a life expectancy of approximately 3 years, and those with type 4 have a life expectancy of a few weeks. • Symptoms include hoarse voice, arthralgia, laryngeal nodule formation, joint deformities, neurologic dysfunction, and respiratory insufficiency.
Tay-Sachs disease	Estimated incidence: <ul style="list-style-type: none"> • 1 case / 100,000 live births 	<ul style="list-style-type: none"> • Involves GM2 ganglioside accumulation in the lysosomes of nerve cells. • Patients with the infantile form exhibit acute neurodegeneration; mostly manifests during infancy. • Juvenile and adult-onset forms are less common.

ASMD, acid sphingomyelinase deficiency; GL3, globotriaosylceramide; lyso-GL3, globotriaosylsphingosine; MPS-1, mucopolysaccharidosis type 1; TIAs, transient ischemic attacks; US, United States.

case management, drug benefit design, and site of care are needed within the rare disease space. The PIE Act, which was signed into law in December 2022, clarifies how information about a drug's investigational use can be exchanged between health care entities and drug manufacturers prior to launch.^{28,36} Information sharing is particularly important when considering rare diseases, as the small sample sizes or small treatment effects lead to underpowered studies.³⁷ Utilization of PIE-supported communication may allow payers to foresee the approval of a rare disease therapeutic, estimate the size of the treatment population, establish appropriate preauthorization steps, forecast budget implications of coverage, and expedite treatment to all eligible plan members.³⁸ This AJMC® Profiles in Care focuses on best practices and models to improve and enhance delivery and access to care for LSDs and other rare diseases in the United States. •

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Managing Treatments for Rare Diseases: Payer Insights

Editors from *AJMC* spoke with Steve Evans, MD, chief medical officer of Centene Corporation in Las Vegas, Nevada, and James T. Kenney, RPh, MBA, founder and president of JTKenney, LLC, of Waltham, Massachusetts, to discuss payer strategies and challenges involved when managing treatments for rare diseases.

AJMC: In your experience, how do health plans identify patients with rare or ultrarare diseases, such as lysosomal storage diseases?

Both Evans and Kenney shared that because the population of patients with rare diseases is so small, health plans do not actively monitor members to identify cases. Patients are identified mostly through their primary care provider or if they receive a diagnosis during hospitalization. Patients with rare diseases also may come to a plan's attention when there is a request for treatment. Ideally, these requests come from physicians who are treating the patients (eg, geneticists, hematologists, pediatricians, cardiologists).

In addition, Kenney noted that "cases also come to a plan's attention when a manufacturer brings a unique product to market, especially if there are no existing treatment options. In this case, standard practice is to search the medical claims system for ICD (*International Classification of Diseases*) codes to estimate the size of the affected population. For example, a product was coming to market a few years ago for Duchenne muscular dystrophy (DMD). An ICD-10 code for DMD was not available in the current ICD-10 coding reference; however, there was a general ICD-10 code for muscular dystrophy that included DMD with many other conditions. Our plan pulled patient data using this code and applied additional criteria to estimate the size of the population affected by DMD. This method also helps to project the financial risk of paying for a recently approved expensive treatment or to estimate the impact of a potential pipeline product for a rare disease."

AJMC: Why is appropriate disease management important to payers?

Evans: Appropriate disease management ensures that there is expected benefit [to the patient] for the cost to the payer. A challenge with many treatments for rare diseases is that there is almost no financial return for the health plan. There is the medical impact, but the cost offsets are just not there. Patients are provided with the best possible treatment with existing therapies. However, it must be recognized that there is a cost to the health plan; there are no cost offsets. Payers understand that and cover the therapy, but they want to ensure the health plan resources are going to the best possible use for the patient. For example, we want to minimize waste of medication and ensure that patients adhere to their treatment regimens.

One of the reasons that many payers started in this field was to help ensure people—in particular, those who are most vulnerable—have access to care. It is our responsibility to ensure all patients have access to the best appropriate treatment and that money and resources are not wasted. It is simply the cost of being in this business that we will have certain patients who require extremely expensive medications. As long as we ensure that we are not wasting resources, it is our duty to also ensure that these patients receive the treatment that will best benefit them.

AJMC: In your experience, how are treatments for rare or ultrarare diseases typically managed?

Kenney: Payers and insurers evaluate each rare disease product using a standard approach: a medical policy team typically reviews physician-administered treatments, and a pharmacy and therapeutics (P&T) committee reviews everything else. At some payers, the P&T committee may evaluate all products whether they are HCP- (health care practitioner-) administered or self-administered. The processes are similar: members of these committees examine the treatment's efficacy, safety, and tolerability. Committee members review the current standard of care for the disease, where the treatment fits in therapy, and the cost of the treatment and any clinical comparators. During this process, rare disease therapies are treated similarly, regardless of prevalence or indication.

Plans will require prior authorization (PA) for coverage of these treatments, which means certain requirements must be met before payers will cover them. PAs help ensure that patients are appropriate candidates for treatment and prevent plans from paying for a treatment that is not supported by clinical data. There are 2 approaches to developing PA criteria. Many plans will write PA criteria in line with the FDA-approved product labeling. If, for example, the label for an enzyme replacement therapy indicates that it is FDA-approved for Fabry disease, a label-based PA would not allow coverage for a different lysosomal storage disease. Other payers go deeper into the clinical data and build up their PAs beyond the label. They look at the trials' inclusion criteria, exclusion criteria, and clinical elements like end points, and they may incorporate these elements into the PA.

Sometimes, payers rely on a subject matter expert or key opinion leader (KOL) in the market to help evaluate products and develop coverage criteria. The disease state and its rarity inform whether to involve an outside KOL. Utilization management (UM) goals are another consideration. In my experience, if a payer has decided on a standard coverage policy, they will not reach out to a KOL. They will build coverage criteria based upon the drug and its label. One reason a payer might consult a KOL is if they are looking to do something

unconventional. For example, a payer might seek to require that patients with a particular rare disease be treated with a standard-of-care product that is not specifically indicated for that disease. Steroids are a common example. A payer might seek to require proof of steroid use before covering a treatment indicated for that rare disease. The payer might ask a KOL if that requirement is appropriate. Payers seek to avoid creating policies that providers do not support. KOL advice can help in this regard.

KOLs also can advise when an existing treatment is the standard of care only because no other treatment exists. A coverage policy that requires [step therapy with the existing] treatment prior to covering a new therapy can foster provider resistance. A KOL will know if a new therapy is going to supplant the existing drug. For example, products like immunoglobulins and rituximab are often used off-label. This use is compendia-supported and appropriate. Compendia may support that use because there are no treatment alternatives. Payers will seek to determine whether a specialist who treats a particular rare disease supports that off-label use as a prerequisite to use of a new FDA-approved therapy.

AJMC: How do payers determine whether to cover a therapy under the pharmacy benefit or the medical benefit, or both?

Evans: There are rules from Medicare as to which treatments are covered under the medical benefit (ie, Part B) vs the pharmacy benefit (ie, Part D) and, to keep things simple, we tend to follow those same rules for patients with commercial insurance as well as those covered by Medicaid.

In general, medications or therapies for rare diseases are not restricted unless there is a large cost disparity between treatments. In that instance, step therapy may be required. But, because there are many fewer patients, we leave it up to the specialists. Often, these treatments are weight-based (eg, 1 mg/kg), which is ideal to minimize product waste. Mode of administration can be considered, for example, between therapies of equal efficacy for a pediatric disease that are required to be self-injected, or administered subcutaneously, intravenously, or orally. We know that for some pediatric patients, injections or infusions can be challenging, and so mode of administration can be considered in coverage decisions in addition to cost. That being said, for Medicare, self-injectable or oral treatments are generally preferred to be covered under Part D.

AJMC: What challenges do payers face when developing coverage policies for treatments for rare diseases?

Both Kenney and Evans noted that a major challenge for payers and plans in the management of therapies for rare and ultrarare diseases is a lack of experience with the disease. If a million-member plan has only 1 or 2 patients with a given rare disease, the plan does not gain much experience with a particular treatment. Kenney added that in cases such as this, plans and payers look to the manufacturer to provide real-world evidence from other plans and settings, which can help define the clinical value of that therapy.

Furthermore, Kenney noted that the FDA's "breakthrough" designation and other paths to bring rare-disease products to market early

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—Steve Evans, MD

can pose a challenge. He explained that products may have been approved via these paths based on results from early-phase clinical trials, so payers may not have all the information that they ideally would like to have when making coverage decisions. For example, a drug approved under the FDA's accelerated approval process may come to market after only phase 2 data have been evaluated. "The accelerated approval signals that phase 2 results were positive, but payers seek confirmation from phase 3 study results that a drug is safe and effective. We may not have a high level of confidence in the efficacy of a product granted accelerated approval," remarked Kenney.

AJMC: What role can dossiers play in payers' review of a recently approved treatment?

Kenney: A dossier is developed by the manufacturer utilizing the AMCP (Academy of Managed Care Pharmacy) Format for Formulary Submissions. The AMCP dossier format is publicly available and it supports preapproval and postapproval clinical and economic information and evidence. A dossier contains clinical information about a product. It also may contain clinical information that is not in the FDA-approved labeling and is, therefore, off-label. As a result, a manufacturer cannot offer a dossier to a payer; that would be off-label promotion. The only way a payer can receive a dossier is to request it from the manufacturer. Typically, a P&T clinical team requests a dossier from a manufacturer. If the manufacturer does not have a dossier, it commonly has a formulary monograph that contains clinical and trial information on the therapy. The formulary monograph may also include information about distribution and patient services.

The manufacturer alone has the clinical information on a new therapy unless it has been approved elsewhere in the world or is licensed by multiple companies. Clinical information is also available in peer-reviewed publications. Payers may request clinical information directly from the manufacturer and may review the FDA-approved label. If additional information is needed, they can connect with the manufacturer's medical science liaison and make a request.

AJMC: Do plans provide case management services for members with rare or ultrarare diseases?

Evans: The costs of therapies for these diseases can have a substantial impact on a plan's pharmacy or medical budget; therefore, plans

should ensure that each patient has appropriate case management resources and is being treated by a qualified team of specialists. This team includes more than just the physician—a successful disease management team includes the staff of the physician’s office, nurses, medical assistants, pharmacists, and case managers. The patient may need medication management support—for example, patient assistance programs, waste management, and adherence support. If treatment is required on a regular basis, the plan will connect the patient with a specialty case manager. Although there are different categories of rare diseases, we do not have case managers that are specialized in, for example, leukocyte adhesion deficiency. The case managers will manage any complex case. Personally, I do not see a benefit of separating rare cancers from other rare diseases. In a health plan of our size, there are not enough patients with rare diseases to build up significant expertise in any particular rare disease.

AJMC: How could a manufacturer-provided case management program best work in tandem with an existing payer-provided case management program?

Evans: Although our health plan does not [officially] work directly with the manufacturer case managers, we do not discourage patients from working with them. A case manager who works in the rare disease division for the manufacturer is going to have more experience, for example, noticing whether a patient is improving on treatment or knowing more about certain adverse events than do our case managers who do not have that experience. The best possible scenario is when both the health plan case manager and the specialist case manager work together. This can occur via a conference call, when all the providers who work with that patient meet and discuss ideas and concerns and, together, they develop the best care plan for that patient. These meetings can include the manufacturer case managers, the health plan case managers, the physician(s), nursing staff, and even a representative from the specialty pharmacy. Although it is difficult to measure return on investment in rare diseases, intuitively, it

makes sense that patient outcomes should be improved if the patient is being managed by a team that specializes in that rare disease.

AJMC: How has the Pre-Approval Information Exchange Act changed the relationship between payers and manufacturers?

Kenney: The PIE Act was signed into law in December of 2022. That codified the opportunity to exchange information between manufacturers and payers or health plans prior to FDA approval. The manufacturer has always been able to provide payers and plans with published clinical data about its therapies—anything in the prescribing information, for instance. PIE provides a new opportunity for decision makers at a health plan to communicate directly with the manufacturer prior to approval of a treatment. A manufacturer can share information even if the therapy never gets approved. Plan decision makers may review a PIE presentation in advance of approval to learn about the therapy and to gain a sense of the size of the treatment population. Based on these presentations, decision makers can draft UM criteria prior to a potential drug launch.

Prior to the signing of the PIE Act, some manufacturers resisted PIE-like presentations because they feared that they would be accused of off-label promotion. The FDA had finalized some PIE guidance in 2018, but there was still concern from manufacturers. The PIE Act expanded this exchange which should assuage those concerns.

AJMC: In the context of ultrarare diseases, how can a lack of communication between payer and manufacturer hinder the development of effective policies?

Kenney: A lack of communication can prompt unnecessarily stringent coverage policies. Typically, a payer or health plan monitors the pipeline for drugs that may be coming to market. This can occur internally, given a large enough plan size and a dedicated staff. This can also happen externally, via contracts with specialty pharmacies or a pharmacy benefit manager; these companies typically have extensive pipeline-monitoring capabilities and can share this information.

A gene therapy for hemophilia A is a good example. Because there are a fair number of patients with hemophilia A in a typical plan, payers are certainly aware of and monitoring the development of newer treatments that are being investigated. Payers might even be communicating with a manufacturer (eg, BioMarin), which has a hemophilia A gene therapy currently under FDA review. BioMarin received a 3- or 4-month decision delay because the FDA needed more time to review.¹ The payer’s internal monitoring team would make them aware of this delay.

Conversely, monitoring the treatment pipeline for a very rare disease, such as Niemann-Pick disease, can be more challenging because the payer may be unfamiliar with the disease. If a treatment and the corresponding disease is unknown at launch, the payer may develop and implement a more stringent UM strategy with many steps. Payers accept that a patient with an ultrarare disease may need a million-dollar therapy because it is the only one available. However, they also want to confirm that each patient is an appropriate candidate for the drug, that the patient cannot be treated with

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—James T. Kenney, RPh, MBA

another therapy that is comparably effective and less expensive, and that the patient is responding to the treatment.

When manufacturers share information with payers about a therapy in advance—through a PIE dialogue or otherwise—this helps payers to develop appropriate UM criteria, which benefits payers, manufacturers, and, most importantly, patients.

AJMC: In your view, has the treatment of rare diseases improved in the past several years?

Kenney: Rare disease treatment has greatly improved in the past several years. AMCP deserves much credit, having pushed for PIE. In 2022, more than 50% of the drugs that the FDA approved were expensive specialty drugs for rare diseases. Managing these new therapies as they come to market is challenging, and PIE is a helpful educational tool. I've used PIE to learn about diseases and drugs, to prepare outcomes-based agreements prior to approval, and to implement such agreements quickly and efficiently after launch. The process has improved payers' uptake and coverage for new treatments; payers know where these treatments fit and the expected population size. This allows draft criteria to be created based on this information. Payers are prepared for the launch, criteria are tied to

the approved label, and the treatment is then readily available with minimal hindrance to providers and patients. Manufacturers can help payers and plans prepare for drug approval by supplying information in advance. All stakeholders can benefit from having access to as much information as possible, as early as possible.

AJMC: Are there any programs being developed or new therapies in the pipeline for lysosomal storage diseases that may change the treatment landscape?

Evans: Obviously, gene therapy is exciting. Instead of a lifetime of treatment, the patient is cured with 1 treatment. These therapies are projected to be quite costly, and this needs to be weighed against the overall lifetime cost for the patient who does not receive the therapy. My hope is that health plans—together with manufacturers, specialists, and lawmakers—can work together on pricing decisions for these ultrarare therapies. •

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