



October 2021

# RARE DISEASES

Although Limited,  
Available Evidence  
Suggests Medical and  
Other Costs Can Be  
Substantial

# GAO@100 Highlights

Highlights of [GAO-22-104235](#), a report to congressional committees

## Why GAO Did This Study

By definition, few people have any specific rare disease. But there are many different rare diseases—about 7,000—and as a result, an estimated 30 million people in the United States have one or more of them. About half of those with a rare disease are children. Often genetic, many rare diseases are chronic, progressive (they worsen over time), and life-threatening. Relatively little is known about the costs of rare diseases, either individually or collectively.

The Joint Explanatory Statement for the Further Consolidated Appropriations Act, 2020, includes a provision for GAO to study the costs of rare diseases within the U.S. GAO examined, among other things, the challenges to diagnosing rare diseases and what is known about their costs.

GAO reviewed documents from two agencies in HHS—the National Institutes of Health (NIH) and Food and Drug Administration (FDA) and published literature, including studies on the costs of rare diseases in the United States and elsewhere published from 2000 through 2021. GAO also interviewed NIH and FDA officials; selected researchers and experts on rare diseases, health care, and health economics; and officials of organizations representing those with rare diseases. The organizations included two devoted to rare diseases in general and six representing those with a specific rare disease or sets of related rare diseases.

View [GAO-22-104235](#). For more information, contact John Dicken at (202) 512-7114 or [dickenj@gao.gov](mailto:dickenj@gao.gov).

October 2021

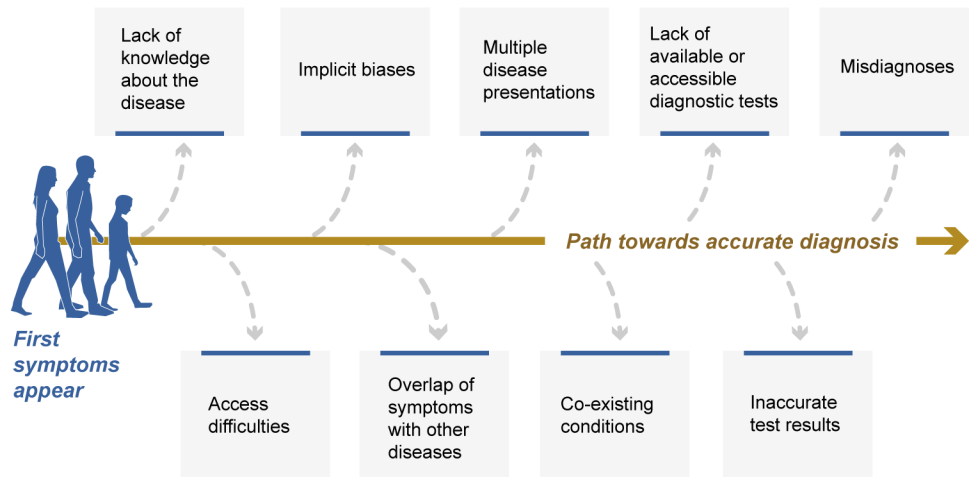
## RARE DISEASES

### Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial

## What GAO Found

According to the literature GAO reviewed, diagnosis of any disease can be complicated, and diagnosis of rare diseases can be particularly difficult because of a variety of factors. (See figure.) Although some rare diseases may be detected quickly, in other cases years may pass between the first appearance of symptoms and a correct diagnosis of a rare disease, and misdiagnoses—and treatments based on them—occur with documented frequency. According to the literature GAO reviewed and GAO's interviews, those with undiagnosed, misdiagnosed, or untreated rare diseases may face various negative outcomes. For example, a person's health can suffer when appropriate, timely interventions are not provided or when interventions based on misdiagnoses cause harm. In addition, multiple diagnostic tests, medical appointments, and ultimately unwarranted interventions can add to the costs of the disease.

#### Examples of Factors That May Interfere with Accurate Diagnosis



Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

Research on the costs of rare diseases is limited, in part because of the difficulty of diagnosing them. Nonetheless, the costs can be substantial, as indicated by available research from the U.S. and elsewhere and the experts, researchers, and organization officials GAO interviewed. These costs—to those with rare diseases, health care payers, the U.S. government, or a combination—can include direct medical costs (e.g., costs of outpatient visits or drugs), direct nonmedical costs (e.g., costs to modify one's home to accommodate a wheelchair), or indirect costs (e.g., loss of income or diminished quality of life). Peer-reviewed studies of specific rare diseases estimated costs for people with rare diseases that are multiple times higher than costs for people without those diseases. One recent study, which has not yet been peer-reviewed, estimated \$966 billion as the total cost (including medical and other nonmedical and indirect costs) in the United States for an estimated 15.5 million people with 379 rare diseases in 2019.

The Department of Health and Human Services (HHS) provided technical comments on a draft of this report, which GAO incorporated as appropriate.

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## Abbreviations

FDA	Food and Drug Administration
GARD	genetic and rare diseases
ICD	International Classification of Diseases
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
PPPY	per person, per year

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October 18, 2021

The Honorable Patty Murray  
Chair  
The Honorable Roy Blunt  
Ranking Member  
Subcommittee on Labor, Health and Human Services, Education, and  
Related Agencies  
Committee on Appropriations  
United States Senate

The Honorable Rosa L. DeLauro  
Chair  
The Honorable Tom Cole  
Ranking Member  
Subcommittee on Labor, Health and Human Services, Education, and  
Related Agencies  
Committee on Appropriations  
House of Representatives

By definition, few people have any specific rare disease. In the United States, a rare disease is typically defined as any condition that affects less than 200,000 people in this country. There are many different rare diseases, however—about 7,000—and, as a result, 30 million people in the United States likely have one or more of them.<sup>1</sup> According to the National Institutes of Health (NIH), about half of those with a rare disease are children. Often genetic, many rare diseases are chronic, progressive (that is, worsening over time), and life threatening. They are also more

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<sup>1</sup>See, for example, GAO, “*Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue*,” [GAO-19-83](#) (Washington, D.C.: Nov. 30, 2018). We use the term “disease” to refer to diseases, disorders, syndromes, complexes, and other health conditions except when one of those other terms is part of the name of a disease. The exact number of rare diseases is not known, but the number is growing—on average, about 200 new rare diseases are identified each year. One reason for differences in estimates of the number of rare diseases is that diseases can be named and identified in different ways; for example, by focusing on their clinical presentation (such as the pattern of signs and symptoms) or the cause (such as a specific genetic defect) or some combination of the two.

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difficult to diagnose and less likely to be treatable than common diseases.<sup>2</sup>

The federal government has provided incentives to support the development of drugs for rare diseases. In particular, the Orphan Drug Act provides tax credits and exclusive marketing rights to manufacturers of drugs that the Food and Drug Administration (FDA) has designated as orphan drugs, which are those intended to treat a rare disease.<sup>3</sup>

Rare diseases can have a substantial societal impact in terms of mortality, morbidity, and utilization of health care services. They often disrupt work and school and can create financial hardship for patients and their families.<sup>4</sup> Nonetheless, relatively little is known about the costs of rare diseases, either individually or collectively.

The Joint Explanatory Statement for the Further Consolidated Appropriations Act, 2020, includes a provision for us to study what is known about the total effect rare diseases have on the U.S. economy and

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<sup>2</sup>See, for example, Institute of Medicine Committee on Accelerating Rare Diseases Research and Orphan Product Development; M. J. Field and T. F. Boat, editors, *Rare Diseases and Orphan Products: Accelerating Research and Development* (Washington, D. C.: National Academies Press, 2010).

<sup>3</sup>See Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified in pertinent part as amended at 21 U.S.C. §§ 360aa et seq. and 26 U.S.C. § 45C). Under the Orphan Drug Act, as amended in 1984, an orphan drug is one that is intended to treat a disease or condition that affects less than 200,000 persons in the United States, or affects more than 200,000 persons in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from sales in the United States. 21 U.S.C. § 360bb(a)(2). Both drugs approved under 21 U.S.C. § 355(b) and biological products licensed under 42 U.S.C. § 262 may be designated as for a rare disease or condition under the Orphan Drug Act. In the early 1980s, the U.S. population was about 236 million, so a disease that affected about 1 in 1,200 people was considered rare under the numerical standard in the Act. As of April 2020, the U.S. population was about 331 million, so a disease affecting about 1 in 1,657 people is now considered rare under that standard. In this report, we use the term “drug” to include drugs and biologics and we use the term “rare disease” to refer to diseases that affect less than 200,000 in this country.

<sup>4</sup>In a report issued in 1989, the National Commission on Orphan Diseases reported that 42 percent of patients with a rare disease said their disease prevented them from working or attending school, and another 32 percent reported that the amount or type of work they could do was limited as a result of their disease; 43 percent of the patients said that the disease imposed an extreme financial burden on their families. Department of Health and Human Services, *Report of the National Commission on Orphan Diseases* (Feb. 27, 1989).

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the societal consequence of undiagnosed and untreated rare disease.<sup>5</sup>  
This report describes

1. the challenges to diagnosing rare diseases;
2. the challenges to identifying the costs of rare diseases;
3. what is known about the costs of rare diseases in the United States;  
and
4. what is known about the effects of rare diseases that are  
undiagnosed, misdiagnosed, or untreated.

To address our objectives, we reviewed publications from 2010 and later that described challenges to diagnosing rare diseases or identifying their costs, the costs of rare diseases, and the effects of undiagnosed, misdiagnosed, or untreated disease in any country. We also conducted a more focused search of peer-reviewed studies of the costs of rare diseases in the United States published in 2000 or later. (App. I provides a more detailed description of our methods for identifying these studies.) In addition, we reviewed documents from NIH and FDA, which are part of the Department of Health and Human Services, about their programs that focus on rare diseases. For example, NIH provides public information about rare diseases through its Genetic and Rare Diseases (GARD) Center; we used GARD information as our primary source of descriptions of specific rare diseases.<sup>6</sup> For the purposes of this report, we consider costs to those with rare diseases and their families, health care payers (such as insurance companies or government health care programs), the U.S. government, or combinations of them, and we define costs to include direct medical costs (e.g., costs of outpatient visits or drugs), direct nonmedical costs (e.g., costs to modify one's home to accommodate a wheelchair or for transportation to medical appointments), and indirect costs (e.g. loss of income or diminished quality of life).

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<sup>5</sup>See Pub. L. No. 116-94, § 4, 133 Stat. 2534, 2536 (2019); Joint Explanatory Statement regarding H.R. 1865, the Further Continuing Appropriations Act, 2020, Congressional Record, 165 Cong. Rec. H11061, H11074 (Daily ed., Dec. 17, 2019).

<sup>6</sup>NIH is the key federal agency involved in sponsoring and conducting biomedical research within the United States. Many of its institutes and centers support research on rare diseases. In fiscal year 2020, the last year for which actual amounts have been reported, NIH allocated \$5,947 million to research on rare diseases. The Office of Rare Diseases Research, within the National Center for Advancing Translational Sciences (NCATS), is the primary office responsible for coordinating rare diseases research across NIH. FDA's Office of Orphan Products Development also supports rare disease research, awarding \$18.5 million for rare disease clinical trials and natural history studies in fiscal year 2020.

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We also interviewed (1) NIH and FDA officials; (2) selected researchers and experts on rare diseases, health care, and health economics—namely, three groups of researchers who have studied costs of multiple rare diseases, two experts on rare diseases who are currently affiliated with NIH, and three members of the GAO Comptroller General’s Advisory Board; and (3) officials from eight organizations representing those with rare diseases. These organizations are two devoted to rare diseases in general—the EveryLife Foundation for Rare Diseases and the National Organization for Rare Disorders—and six organizations representing those with specific rare diseases or sets of related rare diseases. We selected this sample to provide coverage of a wide range of rare diseases—those with differing prevalence, causes, age of typical onset, disease course, typical time from first symptoms through confirmed diagnosis, treatment options, and outcomes. The six organizations that focus on specific rare diseases or sets of diseases are

- the Aneurysm and AVM Foundation (AVM stands for arteriovenous malformation);
- the Creutzfeldt-Jakob Disease Foundation;
- the Cystic Fibrosis Foundation;
- the Ehlers-Danlos Society;
- the National PKU Alliance (PKU stands for phenylketonuria); and
- NTM Info & Research (NTM stands for nontuberculous mycobacteria).<sup>7</sup>

See appendix II for brief descriptions of the rare diseases that are the focus of these organizations, along with brief descriptions of all other rare diseases mentioned in this report.

We conducted this performance audit from April 2020 to October 2021 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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<sup>7</sup>In our interview with the Aneurysm and AVM Foundation, we focused on intracranial arteriovenous malformations. Officials from this foundation invited three people with arteriovenous malformations or caring for people with them to participate in our interview.



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## Background

### Examples of Rare Monogenic Diseases—Diseases Due to a Single Genetic Aberration

**Cystic fibrosis.** Cystic fibrosis is a disease caused by mutations in the gene encoding a specific protein called the cystic fibrosis transmembrane conductance regulator protein; more than 900 mutations of this gene have been found. This disease causes mucus to build up and damage organs in the body, particularly the lungs, pancreas, and digestive tract. Over time, mucus buildup and infections can lead to permanent lung damage, as well as other symptoms and health risks. Most people with cystic fibrosis are diagnosed by age 2, in part because newborn screening can often detect it, but the disease might not be detected until adulthood.

**Duchenne muscular dystrophy.** Duchenne muscular dystrophy is a disease in which a specific gene—the DMD gene—does not function properly, resulting in a deficiency of dystrophin—a protein involved in maintaining the integrity of muscle. The disease results in progressive muscle wasting, and muscle weakness is usually noticeable in early childhood. Most children with Duchenne muscular dystrophy use a wheelchair by their early teens. Heart and breathing problems also begin in the teen years and lead to serious, life-threatening complications.

Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

Rare diseases include a wide range of diseases that vary in cause, age of onset, affected organs, and other features. For example, potential causes include infection, bites or other exposures to poison, complications from transplants, and malformations during embryonic or fetal development. In some cases, the causes are not known. However, most rare diseases—often estimated at 80 percent—are genetic.<sup>8</sup> And in contrast to most common diseases, rare diseases are often due to a single genetic mutation. For information about other attributes that often distinguish rare from common diseases, see appendix III.

Research indicates that rare genetic diseases have a disproportionate effect on children, often by compromising the nervous system and so producing chronic, progressive, and degenerative effects.<sup>9</sup> For example, these diseases may involve a deficiency in a substance the body needs or an excess of a substance that disrupts the body's functioning. In either case, the result is generally a chronic, progressive, and potentially life-threatening disease. The age of symptom onset depends on the time it takes for the effects of the deficiency to become clear or for the accumulation of a toxic substance to interfere with functioning. Depending on the substance, the results might involve multiple organ systems.

Although rare diseases often affect children, they can affect people of any age. They can also affect people of any racial or ethnic group, but some rare diseases (like some common diseases) occur more frequently in certain groups than others. See the text box for examples of rare diseases that are more common in people of specific racial or ethnic groups than others.<sup>10</sup>

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<sup>8</sup>See, for example, NIH, *NCATS Rare Diseases Are Not Rare! Challenge Details*, accessed Apr. 16, 2021, //https.ncats.nih.gov/funding/challenges/rare-diseases-challenge-2020. Estimates of the percentage of rare diseases that are genetic vary. For a discussion of the estimates and reasons for differences among them, see C. R. Ferreira, "The Burden of Rare Diseases," *American Journal of Medical Genetics*, vol. 179A (2019): pp. 885-892.

<sup>9</sup>According to one recent analysis, 83 percent of rare genetic disorders affect children, and nearly 90 percent of rare pediatric disorders have negative effects on the nervous system. See C. E. Lee, et al., 2020, "Rare Genetic Diseases: Nature's Experiments on Human Development," *iScience*, vol. 23 (2020): pp. 1-15.

<sup>10</sup>Diseases can vary in prevalence across countries. For example, certain tropical infections—such as the parasitic disease, leishmaniasis—are common in some parts of the world, but are rare in the United States.

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### Examples of Rare Diseases Linked to Specific Racial or Ethnic Groups

**Kawasaki disease** involves inflammation of the blood vessels. Typically diagnosed in young children, the disease usually begins with a fever that lasts at least 5 days. If the disease affects the coronary arteries, serious heart problems can result. The cause is unknown. Kawasaki disease is most common in people of Asian or Pacific Island descent.

**MPV17-related hepatocerebral mitochondrial DNA depletion syndrome** is a progressive, life-threatening disease. Liver problems develop in the first weeks of life and may quickly progress to liver failure. Many affected infants also develop neurological problems. This inherited disease is most common in Native American Navajos.

**Niemann-Pick disease type A** is an inherited disease in which lipids (fats) accumulate in the spleen, liver, lungs, bone marrow, and brain. It appears during infancy and involves progressive deterioration of the nervous system. There is no treatment, and most people with the disease do not survive past early childhood. This disease is most common in Ashkenazi Jewish families.

**Recombinant chromosome 8 syndrome** is a disease that involves abnormalities in the heart and urinary tract and moderate to severe intellectual disability. Because of the heart abnormalities, many children with this disease do not survive past early childhood. Caused by a chromosomal abnormality, most people with this disease are Hispanic, specifically, from a Hispanic population originating in the San Luis Valley area of southern Colorado and northern New Mexico.

**Sickle cell anemia** is an inherited disease in which the body produces red blood cells that are abnormally shaped—they are a sickle shape, rather than a disc shape. These abnormal cells do not last as long as normal red blood cells, causing anemia. In addition, the sickle cells can become stuck in blood vessels, blocking blood flow, and that can cause stroke, infections, episodes of pain, or eye problems. (Sickle cell anemia is the most common cause of stroke in children.) In the United States, most people who have sickle cell anemia are of African ancestry or identify themselves as Black.

Source: GAO analysis of descriptions of rare diseases published by the National Institutes of Health. | GAO-22-104235

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## Treatment

Currently, there are no treatments or cures for most rare diseases. Despite federal incentives for development of products to treat them, there are FDA-approved treatments for only about 5 percent of rare diseases.<sup>11</sup> Few of these treatments—which include drugs and medical devices—are cures; instead, most are intended to address specific

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<sup>11</sup>See, for example, [GAO-19-83](#). NIH officials estimate that there are FDA-approved treatments for a slightly smaller percent of rare diseases—because some FDA-approved treatments for rare diseases are for the same rare diseases. They estimate that there are FDA-approved treatments for about 300 unique rare diseases—about 4 percent of rare diseases. The number of drugs that FDA has approved for rare diseases has increased over time, and a substantial proportion of new drug approvals from 2010 through 2020—44 percent—were for rare diseases. For a recent review of the development of drugs for rare diseases, see K. L. Miller, L. J. Fermaglich, and J. Maynard, “Using Four Decades of FDA Orphan Drug Designations to Describe Trends in Rare Disease Drug Development: Substantial Growth Seen in Development of Drugs for Rare Oncologic, Neurologic, and Pediatric-Onset Diseases,” *Orphanet Journal of Rare Diseases*, vol. 16 (2021): pp. 265-274.

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symptoms or lower the risk of possible complications.<sup>12</sup> Even when a drug is available for off-label use, NIH officials explained that the drug would only be available to patients with a rare disease if a physician prescribed it (which they might be unwilling to do in the absence of clear evidence of effectiveness for the patient's specific situation) and, if prescribed, it might not be covered by insurance.<sup>13</sup> Other interventions, such as surgery, may be available in some cases, but the frequency is difficult to estimate.<sup>14</sup> According to NIH officials, because most rare diseases are single-gene disorders that manifest at the cellular level, surgical approaches would generally only be able to ameliorate or help manage physical manifestations of an otherwise untreated progressive disease.<sup>15</sup>

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<sup>12</sup>Medical devices can be used in the diagnosis or treatment of disease and to improve patients' quality of life. Research indicates that physicians who have experience with rare diseases perceive a substantial need for innovative medical devices for use with those with rare diseases. See, for example, V. Peiris, et al., "Children and Adults with Rare Diseases Need Innovative Medical Devices," *Journal of Medical Devices*, vol. 12 (2018), 0347011–347018. <https://doi.org/10.1115/1.4040489>

<sup>13</sup>Before approving a drug for marketing in the United States, FDA evaluates evidence to ensure that it is safe and effective for its intended use. Use of an FDA-approved drug for an unapproved use is known as "off-label" use. Childhood cancers provide an example of rare diseases for which physicians might prescribe drugs for off-label use. These treatments could involve off-label use of drugs approved to treat adults (not children) with the same cancer; approved for children with a different cancer; approved for use at a different dose or frequency than the child's physician prescribes; or included as part of non-approved chemotherapy combination.

<sup>14</sup>Disease-modifying therapies have been identified for some rare diseases, with effects that range from modest effects on morbidity and mortality to allowing a nearly normal life (even though these therapies are not cures). For most rare diseases, the only current options are to treat symptoms, for example, by managing pain or preventing complications, such as infection. End-of-life care may also be important. See, for example, Institute of Medicine, *Rare Diseases and Orphan Products*, pp. 55-69.

<sup>15</sup>Some rare diseases are preventable, for example, by limiting risk of exposure to toxic substances, such as heavy metals, or by encouraging women of childbearing age to take folic acid supplements to reduce the risk that a child might have certain birth defects, such as spina bifida. Preventive measures can also affect whether a disease meets the definition of a rare diseases in the United States. For example, several diseases that were once common, such as mumps, are now rare in the United States because of preventive immunizations.

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## Costs

Costs of any disease fall into three categories:




- **Direct medical costs.** The expenditures and use of resources for medical services (such as costs for doctor's appointments).<sup>16</sup>
- **Direct nonmedical costs.** The expenditures and use of resources that are the result of the disease, but are not for medical services *per se* (such as payments to modify one's home to accommodate a wheelchair).
- **Indirect costs.** The costs of the disease in terms of effects on earnings, productivity, opportunities, or quality of life (such as loss of income due to unpaid sick leave).

As figure 1 illustrates, there are direct medical costs, direct nonmedical costs, and indirect costs for all payers, which can include not just patients and their families, but also health care payers and the U.S. government.

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<sup>16</sup>When referring to costs, we use the term "medical" to include all health care costs, whether specifically associated with medical professions or associated with other health professions (such as clinical psychology or respiratory therapy).

**Figure 1: Types of Disease-Related Costs Incurred by Different Payers**

Type of cost	Payers		
	Patients and their families	Health care payers (such as insurance companies or government health care programs)	The U.S. government
 <p><b>Direct medical costs</b></p> <p>Expenditures and use of resources for medical services.</p>	<p>Out-of-pocket health care expenses, including</p> <ul style="list-style-type: none"> <li>• copayments, deductibles, and costs not covered by applicable insurance (those for experimental treatments or hired caregivers).</li> </ul>	<p>Paid health care expenses, including costs for</p> <ul style="list-style-type: none"> <li>• hospitalizations, outpatient care, drugs, medical devices, and rehabilitative services.</li> </ul>	<p>Use of government resources, including</p> <ul style="list-style-type: none"> <li>• costs of government-supported health care programs, and costs of government-supported health care training programs.</li> </ul>
 <p><b>Direct nonmedical costs</b></p> <p>Expenditures and use of resources that are the result of the disease but are not for medical services.</p>	<p>Out-of-pocket costs associated with the disease but not for health care itself, including</p> <ul style="list-style-type: none"> <li>• transportation to health care services, modifications to one's home or vehicle to accommodate limitations imposed by disease, and legal expenses secondary to the disease (such as fees for establishing guardianship).</li> </ul>	<p>Administrative costs, including costs for</p> <ul style="list-style-type: none"> <li>• claims processing, database maintenance, and for some health care payers, certain covered transportation costs.</li> </ul>	<p>Costs to the government for services and programs other than those for health care <i>per se</i>, including costs for</p> <ul style="list-style-type: none"> <li>• government-supported medical and basic science research programs, special educational services, public health programs, and community support programs.</li> </ul>
 <p><b>Indirect costs</b></p> <p>Consequences of the disease for earnings, productivity, opportunities, or quality of life.</p>	<p>Indirect costs due to consequences of the disease, including</p> <ul style="list-style-type: none"> <li>• productivity losses (such as lost income due to unpaid time off work, reduced on-the-job productivity, and temporary or permanent disease-related unemployment), and intangible effects (such as decreased quality of life or loss of opportunities for employment, promotion, or education).</li> </ul>	<p>Indirect costs due to consequences of the disease, including</p> <ul style="list-style-type: none"> <li>• opportunity costs associated with using limited resources for some, rather than other, health care needs, and intangible effects (such as decreased employee morale if needs exceed resources).</li> </ul>	<p>Indirect costs due to consequences of the disease, including</p> <ul style="list-style-type: none"> <li>• opportunity costs of using government funds for some, rather than other, health care services or government programs, and lost tax revenue due to foregone income to patients or their families.</li> </ul>

Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

Note: When referring to costs, we use the term “medical” to include all health care costs, whether specifically associated with medical professions or associated with other health professions (such as clinical psychology or respiratory therapy). Other payers could also be considered, for example, businesses. This categorization of costs is illustrative, not definitive. For example, expenditures for paid home health services can include both direct medical costs (e.g., intermittent skilled nursing care) and direct nonmedical services (e.g., homemaker cleaning or laundry services). When people participate in clinical trials, some costs—those that would be incurred whether the person participates in the trial or not, such as doctor visits or lab tests—are generally covered by health insurance. Costs

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associated with the clinical trial itself—such as the costs of an experimental drug or lab tests that are performed only for research purposes—are not normally covered by health insurance but may be covered by the sponsor of the research. If participation in the clinical trial results in extra visits to a physician (e.g., to check for possible side effects), these extra visits can add to the patient’s direct nonmedical costs (e.g., for transportation) or the patient’s indirect costs (e.g., for child care or time off work).

Researchers who study any disease must make decisions about which costs to consider, including who incurs the costs and which specific costs are to be analyzed.

**Costs to Patients and Their Families: The Example of Intracranial Arteriovenous Malformations**

GAO interviewed a man who reported that he woke up in bed one day, when he was about 40 years old, to find that he had suffered a major stroke due to a previously undiagnosed intracranial arteriovenous malformation—an abnormal connection between arteries and veins in the brain. Unexpected strokes are not uncommon with this rare disease. As he described it, his brain surgery left him with thousands of dollars in expenses that were not covered by his health insurance. The consequences he described included loss of his business (and loss of his employees’ jobs), the end of his marriage and other family problems, ongoing struggles to put his skills and experience to productive use, and the draining of resources that he and his extended family had accumulated.

Source: GAO interview with the Aneurysm and AVM Foundation. | GAO-22-104235

- **Costs to whom?** The costs that are studied depend on the perspective taken for the specific purpose of the research—whether the focus is on costs to the individuals with the diseases and their families, costs to health care payers, costs to the government, or some combination (which could include an attempt to identify all costs—the cost to the society). For example, FDA’s fiscal year 2020 allocation for its Office of Orphan Products Development was \$33,260,000—an amount that includes funds for grants to study diagnostics and treatments for rare diseases, and that could be included in the costs of rare diseases to the government or to society but not in the costs to those with the disease.<sup>17</sup> Conversely, the costs of parking for medical appointments—one study estimated that parking for a single hospitalization due to acute myeloid leukemia in 2019 ranged from \$0 to \$1,680—could be included in costs to patients but not costs to the government.<sup>18</sup>
- **Costs for what?** The costs that are studied reflect several decisions about which costs to consider, including
  - **Type of cost.** Researchers must decide whether to study direct medical costs, direct nonmedical costs, indirect costs, or some combination. Moreover, for any specific type of cost, they must decide which specific costs to analyze. For example, researchers might limit their study of direct medical costs to costs for treatment or limit their study of indirect costs to productivity losses.

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<sup>17</sup>FDA’s Office of Orphan Products Development advances the evaluation and development of products (drugs, biologics, devices, and medical foods) that demonstrate promise for the diagnosis, prevention, or treatment of rare diseases. It operates designation programs that provide incentives for development of rare disease products and provides grants to promote development of products for rare diseases.

<sup>18</sup>Cost estimates were for parking at a center designated as a cancer treatment center by the National Cancer Institute. See A. Lee, K. Shah, and F. Chino, “Assessment of Parking Fees at National Cancer Institute–Designated Cancer Treatment Centers,” *JAMA Oncology*, vol. 6, no. 8 (2020): pp. 1295-1297.

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- **Disease specificity.** Researchers must decide whether to study costs that are specific to the disease or costs that could have been associated with any health concerns the person has—not just the rare disease but also general health care and comorbid conditions. When costs of general health care and comorbid conditions were included, we refer to them as “all-cause” costs. For example, the direct medical cost of a visit to a medical specialist about a person’s rare disease would be disease-specific; the cost of that same person’s annual physical would not be specific to the rare disease but could be included in all-cause costs. Reasons for limiting the analyzed costs to those that are disease-specific could include an intent to identify a specific type of disease-related cost (such as the cost of a treatment specific to a disease) or to distinguish costs for the disease from those for comorbid conditions. Reasons for analyzing all-cause costs could include prior knowledge that a disease is associated with an array of comorbid conditions and identifying the difference in costs between people who do and don’t have the disease (to identify the additional or excess cost posed by the rare disease).
  - **Costs defined by a disease-related event.** Researchers must decide whether to study costs that were incurred during a time period defined by a specific disease-related event, such as initiation of treatment—an event-based approach—or without regard to specific disease-related events. Event-based methods can provide information about costs that are specific to the effect of that event or can ensure that those who are studied have that event in common. Methods that are not event-based, in contrast, identify costs without regard to specific disease-related events; for example, costs incurred during a particular calendar year for all people identified as having the disease.

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## Multiple Factors Make Diagnosing Rare Diseases Challenging

Our review of published literature indicates that accurately diagnosing any disease, rare or common, can be complicated by many factors, some of which are more likely to affect the diagnosis of rare diseases than common ones. These factors include

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### Evolving Understanding of Rare Diseases: The Example of Central Precocious Puberty

Central precocious puberty is a disease in which sexual and physical characteristics develop and mature earlier than normal—before age 8 for girls or before age 9 for boys. It is also a disease that illustrates that some rare diseases have not been fully understood by medical professionals: While studying the costs of this disease, researchers discovered that children with it had more comorbid conditions than those without the disease, adding to what was known about the disease. (Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called “comorbid conditions.”) Specifically, they found that endocrine, nutritional, metabolic, or immunity diseases were five to ten times more common among those with central precocious puberty, and diseases of the nervous system were five to six times more common among those with central precocious puberty than in a group of similar children who did not have the disease.<sup>a</sup>

<sup>a</sup>K. Klein, et al., “Health Care Utilization and Economic Burden in Patients with Central Precocious Puberty: An Assessment of the Commercially Insured and Medicaid Populations,” *Journal of Managed Care & Specialty Pharmacy*, vol. 25, no. 7 (2019): pp. 836-846.

Source: GAO and Klein, et al., *Journal of Managed Care & Specialty Pharmacy*. | GAO-22-104235

- **Lack of knowledge.** Precisely because rare diseases are rare, they may not be well understood.<sup>19</sup> The signs and symptoms of many rare diseases have not been fully described, nor has their course—their natural history.<sup>20</sup> As a result, neither patients nor clinicians may recognize the significance of symptoms or the diseases they represent.<sup>21</sup> For example, patients might not recognize the significance of their initial symptoms and, as a result, not seek medical attention until the symptoms become problematic for them. Similarly, physicians might have limited experience with rare diseases and might not know the rare disease or diseases they encounter, particularly if the symptoms are non-specific (such as weight loss, fatigue, or fever). In addition, clinicians who are not familiar with certain rare disease manifestations may discount patients’ reports of their experiences.
- **Access difficulties.** Diagnosis of a rare disease might require consultation with specialists, but access to these specialists can be difficult for some people, such as those who live some distance from a knowledgeable specialist. For example, researchers who studied the cost of hemophilia B noted that children who did not have a follow-up examination tended to have a severe form of the disease and to be

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<sup>19</sup>Rare diseases differ in prevalence, with only about 100 rare diseases accounting for about 80 percent of all patients with rare diseases. In contrast, some diseases are so rare that only a few cases have been identified so far worldwide. Thus, some rare diseases are much more likely to be understood than others. See, for example, W. R. Evans and I. Rafi, “Rare Diseases in General Practice: Recognizing the Zebras Among the Horses,” *British Journal of General Practice*, vol. 66 (2016): pp. 550-551.

<sup>20</sup>FDA administers a grant program, the Natural History Grants Program, to support research on the course of rare diseases over time, as well as to identify the demographic, genetic, environmental, and other variables that influence their development and outcomes.

<sup>21</sup>A common adage in medical practice is, “Where you hear hoof beats, think horses not zebras,” suggesting that a common disease is a more likely explanation of symptoms than a rare disease. Several experts caution that the diagnostician should not forget that zebras exist. See, for example, R. N. Kliegman, et al., “How Doctors Think: Common Diagnostic Errors in Clinical Judgment—Lessons from an Undiagnosed and Rare Disease Program,” *Pediatric Clinics of North America*, vol. 64 (2017): pp. 1-15.



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from poorer households, leading the researchers to question whether access might have prevented follow-up.<sup>22</sup>

- **Implicit biases.** Implicit biases—beliefs outside conscious awareness that involve preexisting judgments about considerations that are irrelevant to the diagnosis, such as race or gender when the disease is not linked to race or gender—can interfere with a physician’s ability to accurately diagnose a disease. For example, a physician with such a bias might be inclined (without conscious awareness) to discount reports of symptoms from certain people or fail to order diagnostic tests they would order for other patients and, as a result, fail to provide an accurate diagnosis.<sup>23</sup>
- **Overlap with other diseases.** Symptoms of rare diseases may overlap with those of other diseases, whether common or rare, and this overlap can complicate diagnosis, particularly if they are non-specific symptoms. For example, the main symptoms of nontuberculous mycobacterial lung disease include cough, fatigue, fever, and weight loss, all of which are also symptoms of many diseases, including tuberculosis. Researchers have reported on the misdiagnosis of nontuberculous mycobacterial lung disease, with results that include unnecessarily lengthy, costly, and potentially toxic treatments.<sup>24</sup>
- **Multiple disease presentations.** Many rare diseases manifest in different ways in different people, and symptoms may change over time, so that no single set of symptoms may be consistently associated with the disease—that is, there are multiple disease presentations. Moreover, when a disease affects multiple organ systems—as is the case with many rare diseases—patients may consult a number of specialists who provide incorrect diagnoses

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<sup>22</sup>C. X. Chen, J. R. Baker, and M. B. Nichol. “Economic Burden of Illness Among Persons with Hemophilia B from HUGS Vb: Examining the Association of Severity and Treatment Regimens with Costs and Annual Bleed Rates.” *Value in Health*, vol. 20 (2017): pp. 1074-1082. In this example, the children had already been diagnosed.

<sup>23</sup>See, for example, C. Fitzgerald and S. Hurst, “Implicit Bias in Healthcare Professionals: A Systematic Review,” *BMC Medical Ethics*, vol. 18 (2017): pp. 19-36. This review addressed common diseases but suggests a mechanism that could complicate any diagnosis. For a discussion of other biases that can influence diagnosis of rare diseases, such as a tendency to seek only information that affirms a preliminary diagnosis—a confirmation bias—see Kliegman, et al., “How Doctors Think,” pp. 1-15.

<sup>24</sup>See, for example, Y. D. S. Sarro, et al., “Simultaneous Diagnosis of Tuberculous and Nontuberculous Mycobacterial Diseases: Time for a Better Patient Management,” *Clinical Microbiology and Infectious Diseases*, vol. 3, no. 3 (2018): pp. 1-4.

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based on the limited set of symptoms they see. Ehlers-Danlos syndromes provide an example of a rare disease with multiple disease presentations: there are 13 recognized subtypes of the disease, with signs and symptoms that vary by type, although most involve some degree of joint hypermobility.

- **Comorbid conditions.**<sup>25</sup> Comorbid conditions can complicate the diagnosis of any disease because the diagnostician would generally be trying to identify a single disease that would explain the person's signs and symptoms but, in fact, the person has the signs and symptoms of two or more diseases. Diagnosis can be particularly complicated if one or more of the diseases are rare, and people can have two or more rare diseases.<sup>26</sup> Some rare diseases are associated with an increased risk of comorbidities. For example, acromegaly, a hormonal disease, is frequently accompanied by specific comorbid conditions, such as diabetes or cardiovascular disease. This rare disease follows a slow progressive course, so that by the time of diagnosis—typically years after the first presentation of symptoms—the person may have an advanced state of the disease and multiple comorbid conditions that resulted from the disease.<sup>27</sup>
- **Lack of available or accessible diagnostic tests.** Diagnostic tests are not available or readily accessible for many rare diseases, and the diagnostic tests that are available may not necessarily be sufficiently

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<sup>25</sup>Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called “comorbid conditions.”

<sup>26</sup>An expert we interviewed described several possible reasons that a person might have two or more rare diseases. For example, some rare diseases are due to genetic deletions, and the portion of genetic material that is missing could include several genes that are each associated with a rare disease.

<sup>27</sup>See, for example, S. Liu, et al., “Patient-Centered Assessment on Disease Burden, Quality of Life, and Treatment Satisfaction Associated with Acromegaly,” *Journal of Investigative Medicine*, vol. 66 (2018): pp. 653-660. Diseases that interfere with the immune system increase the risk for a variety of other diseases and so are also generally associated with complicated clinical presentations, with symptoms reflecting any of several comorbid conditions. For example, primary immune deficiency diseases are genetic disorders that impair the immune response. As a result, people with these diseases may be subject to chronic, debilitating—and potentially fatal—infections. See, for example, M. Dilley, et al., “Primary Immunodeficiency Diseases Treated with Immunoglobulin and Associated Comorbidities,” *Allergy and Asthma Proceedings*, vol. 42, no. 1 (2021): pp. 78-86.

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specific or sensitive to permit conclusive results, instead offering suggestive information.<sup>28</sup>

- For example, there is no test that is specific for fetal valproate syndrome, a rare disease involving congenital abnormalities. Diagnosis depends on ruling out the other possible causes of the signs and symptoms shown by infants whose mothers took valproic acid during pregnancy (as they might have done to treat diseases such as epilepsy, bipolar disorder, or migraines).
- Access to tests can also be an issue: One publication noted that because there are no treatments for many rare diseases, tests for them might not be considered to affect health outcomes and, therefore, may not be covered by some insurance companies on the grounds that they are “not medically necessary.” For example, whole exome sequencing—a method for identifying variations in the protein-coding regions of genes—has proven useful in testing patients for suspected genetic diseases, but insurance companies do not necessarily cover its use.<sup>29</sup> Moreover, experts told us that insurance company requirements for pre-approval may result in delays associated with preparation and review of preauthorization paperwork and any appeals of denied claims—a situation that can be particularly problematic if the disease is progressive and a number of tests must be conducted in sequence.
- **Inaccurate test results.** Because no test is always accurate, some test results will be inaccurate, and inaccurate test results complicate

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<sup>28</sup>See, for example, Institute of Medicine, “*Rare Diseases and Orphan Products*,” pp. 123–125. Tests differ in their sensitivity (their ability to correctly identify people with a particular disease) and their specificity (their ability to correctly identify people who do not have the disease).

<sup>29</sup>In one study, whole exome sequencing was provided to undiagnosed patients participating in a research program designed, in part, to facilitate diagnosis. Results indicated that 35 percent of undiagnosed patients who had faced insurance coverage barriers to clinical whole exome sequencing prior to their participation in the program were diagnosed with use of that test. The insurance barriers these patients had faced included denial of coverage because the service was deemed experimental or investigational or because it was deemed “not medically necessary.” See C. M. Reuter, et al., “Yield of Whole Exome Sequencing in Undiagnosed Patients Facing Insurance Coverage Barriers to Genetic Testing,” *Journal of Genetic Counselling*, vol 28 (2019): pp. 1107–1118. Whole exome sequencing does not detect certain chromosomal deletions (when part of chromosome is missing), duplications (when there is an extra segment of a chromosome), or certain other genetic disorders. The costs of genome sequencing have declined over the last two decades. See, for example, NIH, *The Cost of Sequencing a Human Genome*, accessed July 13, 2021, <https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost>.

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the diagnostician's task, which is—at core—to evaluate the evidence in a patient's medical record to assess the possibilities. Our review of the literature and our interviews indicated that in addition to complicating the task, inaccurate test results can contribute to misdiagnosis.<sup>30</sup> And, when the diagnostic process involves multiple tests (as is not uncommon when the disease is rare), the probability of an error or a misleading test outcome increases.<sup>31</sup>

- **Misdiagnoses.** By definition, misdiagnoses are another type of erroneous information that can be entered into the medical record, complicating the diagnostician's task.<sup>32</sup> While misdiagnosis can occur for any of the reasons mentioned above, one analysis also suggests that children with an undiagnosed rare disease may be at risk for a particular misdiagnosis: because of their families' persistent attempts to obtain a diagnosis for an unusual pattern of symptoms (among other things), they may be given an erroneous diagnosis of Munchausen syndrome by proxy—a form of child abuse in which a child's caretaker either makes up symptoms or causes real symptoms to make it seem that the child is ill.<sup>33</sup>

Figure 2 illustrates the ways in which these factors complicate and disrupt diagnosis of a rare disease.

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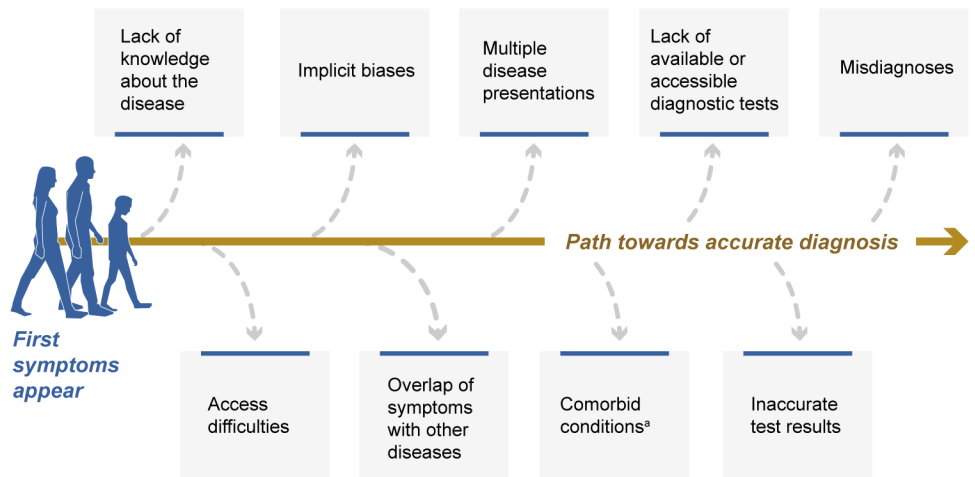
<sup>30</sup>Inaccurate test results include both false positive results (which indicate the presence of a disease, when that disease is not, in fact, present) or false negative results (which indicate that the disease is not present, when that disease is, in fact, present).

<sup>31</sup>See, for example, F. Shen and H. Liu, "Incorporating Knowledge-Driven Insights into a Collaborative Filtering Model to Facilitate the Differential Diagnosis of Rare Diseases," *AMIA ... Annual Symposium proceedings. AMIA Symposium*, vol. 2018 (2018): pp. 1505-1514.

<sup>32</sup>Erroneous information in a medical record can also result from clerical or other error.

<sup>33</sup>See Kliegman, et al., "How Doctors Think," pp. 4-5.

**Figure 2: Examples of Factors That May Interfere with Accurate Diagnosis**



Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

Note: Complicating factors may disrupt the path towards accurate diagnosis of any disease and can occur in any sequence. Diagnosis of a rare (or other) disease does not necessarily take a long time.

<sup>a</sup>Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called “comorbid conditions.”

In part because of these factors, the time it takes to arrive at an accurate diagnosis varies across rare diseases and across people. Some rare diseases are relatively easy to diagnose—for example, some can be detected through routine newborn screenings—and others are diagnosed relatively quickly, for example, when infants with certain rare diseases are hospitalized with acute symptoms. But in many cases, obtaining an accurate diagnosis for a rare disease can be an expensive process that takes many years and may involve mistaken diagnoses before obtaining a correct one.<sup>34</sup> For example, a study examining the survey responses of people who had been diagnosed with one of 18 rare diseases in 24 European countries found that

- 25 percent of people with a rare disease waited (depending on the disease) between 15 months (for cystic fibrosis) and 28 years (for

<sup>34</sup>See, for example, Institute of Medicine, *Rare Diseases and Orphan Products*, pp. 59. The Department of Health and Human Services makes recommendations for the screening of newborns for certain diseases, such as phenylketonuria, basing those recommendations on considerations such as the ability of states to screen for the disease and the availability of treatment. States can choose which diseases to screen, and they differ in which diseases they include in their newborn screening programs. In addition, carrier screening—a type of genetic testing that allows people to learn their likelihood of passing certain heritable diseases on to their children—is available for certain diseases.

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Ehlers-Danlos syndromes) from the time of their first symptoms until diagnosis.

- 41 percent of those with a rare disease were misdiagnosed first, and many of them were treated for that mistaken diagnosis.
- 7 percent of those with a rare disease reported inappropriate psychological or psychiatric treatment, and those who were given a false psychological or psychiatric diagnosis had longer delays to accurate diagnosis than those who did not.<sup>35</sup>

See the text box for examples of initiatives that are underway to improve the diagnosis of diseases, including rare ones.

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<sup>35</sup>See A. Kole and F. Faurisson, "Rare Diseases Social Epidemiology: Analysis of Inequalities," in *Rare Diseases Epidemiology, Advances in Experimental Medicine and Biology*, vol. 686, eds. M. Posada de la Paz and S. Groft (Dordrecht: Springer, 2010), pp. 223-250. The definition of a rare disease varies across countries. In the European Union, a rare disease is defined as one that affects no more than 1 person in 2,000.

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### Examples of Initiatives Underway to Improve Diagnosis of Diseases

**The Undiagnosed Disease Network.** The Undiagnosed Disease Network brings multidisciplinary experts and advanced technologies to bear on undiagnosed diseases. Supported by funding from National Institutes of Health (NIH), this Network currently includes clinical sites in 12 U. S. cities. Patients who are accepted into the program undergo a comprehensive evaluation; about 30 percent of participants have obtained a diagnosis. The program has also yielded advances in the scientific understanding of disease processes. For example, by studying arterial calcification due to deficiency of CD73 (a vascular disorder), the program's researchers discovered the function of adenosine in preventing vascular calcification—a discovery that could also shed light on other diseases.<sup>a</sup>

**The Undiagnosed Diseases Network International.** The Undiagnosed Diseases Network International, modeled in part on the NIH-funded Network, currently has members from dozens of countries. Its aims include diagnosing otherwise undiagnosed people (both individually and by establishing standards for doing so) and learning about the causes of novel diseases.<sup>b</sup>

**Artificial Intelligence, Machine Learning, and Data Mining.** Researchers are exploring ways to use various artificial intelligence processes, machine learning strategies, and data mining techniques to improve understanding of rare diseases and develop better ways to diagnose them. These efforts include a variety of knowledge-based and data-driven strategies and may be applied to a variety of diagnostic materials (such as information in electronic medical records and images).<sup>c</sup>

<sup>a</sup>W. A. Gahl, et al., "The NIH Undiagnosed Diseases Program and Network: Applications to Modern Medicine," *Molecular Genetics and Metabolism*, vol. 117 (2016): pp. 393-400.

<sup>b</sup>D. Taruscio, et al., "The Undiagnosed Diseases Network International: Five Years and More!," *Molecular Genetics and Metabolism*, vol. 129 (2020): pp. 243-254.

<sup>c</sup>See, for example, C. Faviez, et al., "Diagnosis Support Systems for Rare Diseases: A Scoping Review," *Orphanet Journal of Rare Diseases*, vol. 15 (2020): pp. 94-109, and Q. Zhu, et al., "An Integrative Knowledge Graph for Rare Diseases, Derived from the Genetic and Rare Diseases Information Center (GARD)," *Journal of Biomedical Semantics*, vol. 11 (2020): pp. 13-25.

Source: GAO analysis of publications on rare diseases. | GAO-22-104235

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## Challenges to Identifying the Costs of Rare Diseases

Conducting research on the costs—direct and indirect—of any disease, rare or common, requires identifying costs and linking them to people with the disease. More specifically, researchers must not only decide which costs to study, they must also identify reliable data sources for information about them, and they need to link that information to an appropriate group of people with the disease (and possibly, for comparison, to those without the disease or with a different disease). According to our review of the literature and our interviews, there are challenges associated with these decisions for all cost-of-illness research, and some aspects of rare diseases may make research on their costs particularly challenging.

Selecting an appropriate data source can pose challenges for any study of the costs of a disease (rare or common) because data sources are often incomplete or of limited reliability. These issues can interfere with

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the usefulness of the data for identifying the direct medical, direct nonmedical, or indirect costs of a disease.

- **Direct medical costs.** Databases that capture direct medical costs in the United States, such as those recording Medicare or private insurance health care claims, vary in comprehensiveness and may preclude capture of certain data.<sup>36</sup> For example, these databases may capture only reimbursable expenses and do not necessarily cover all direct health care costs, such as costs for over-the-counter drugs or medical foods that are critical for those with some rare diseases.<sup>37</sup> Moreover, complete records of medical costs are unlikely for people who lose or change their insurance or who were never insured—circumstances that our literature review indicated are not uncommon for people with rare diseases or the parents of children with them.<sup>38</sup> Specifically,
  - Private health insurance companies, including those that offer employer-sponsored health care plans, would not necessarily capture health care data for those who lose employment or change jobs (and so change health care insurance plans or become uninsured).
  - Medicare databases capture information about costs for those it covers but do not generally capture costs for those under age 65, and rare diseases may result in death prior to that age. Costs for those who are age 65 or older may differ from those of younger patients.

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<sup>36</sup>Medicare is a federally financed program that provides health insurance coverage to people age 65 and older, certain individuals with disabilities, and those with end-stage renal disease (permanent kidney failure requiring dialysis or a transplant).

<sup>37</sup>Medical foods are formulated to be consumed or administered under the supervision of a physician and are intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Among other uses, medical foods are used as treatments for a number of rare inborn errors of metabolism, such as phenylketonuria.

<sup>38</sup>For example, Wilson found that 10 percent of patients with systemic sclerosis reported job loss due to their disease, and Whittington, et al., found that nearly two-thirds of the caregivers of children with Dravet syndrome—often the parents—reported a job change (lost job, quit job or retired early, or switched jobs) due to their caregiving responsibilities. See L. Wilson, “Cost-of-Illness of Sclerosis: The Case for Rare Diseases,” *Seminars in Arthritis and Rheumatism*, vol. 27, no. 2 (1997): pp. 73-84; and M. D. Whittington, et al., “The Direct and Indirect Costs of Dravet Syndrome,” *Epilepsy & Behavior*, vol. 80 (2018): pp. 109-113.



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- Medicaid databases capture information about costs for those it covers but do not generally capture costs for those with employee-sponsored health insurance, and so they will not generally include information about the costs of rare diseases prior to any effect of that rare disease on employment status.<sup>39</sup>
  - **Direct nonmedical costs.** Few databases capture direct nonmedical costs, so studies of these costs generally rely on surveys of patients or their caregivers.<sup>40</sup>
  - **Indirect costs.** Similarly, few databases capture information about indirect costs, and so studies of these costs also generally rely on survey data. Indirect costs can be quantified (for example, by estimating years of potential life lost and likely income during those years or by developing estimates of the effect of health effects, including psychological effects, on quality of life), but they can rarely be precisely quantified.<sup>41</sup>

In addition, research on the costs of rare diseases must link cost data to people who have the disease or diseases of interest, a task that can be challenging for at least three reasons: (1) most rare diseases are not specifically encoded in health care databases, (2) the sample of people identified as having a rare disease might not be representative of the population of those with the disease, and (3) the identified costs for a

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<sup>39</sup>Medicaid is a joint federal-state program that finances health care coverage for low-income and medically needy individuals.

<sup>40</sup>We use the term “caregiver” to refer to family members or others who provide care without receiving compensation for doing so. Some databases contain information about certain direct nonmedical costs. For example, Medicaid provides coverage for non-emergency medical transportation—a direct nonmedical cost—under certain circumstances, and when it does provide coverage, claims for this service are included in Medicaid data.

<sup>41</sup>Some databases capture information that can be used to estimate certain indirect costs. For example, the Centers for Disease Control and Prevention’s Compressed Mortality File includes information about ages and causes of death. In conjunction with assumptions regarding likely life span in the absence of a disease, researchers can use this data to estimate likely years lost and, with additional assumptions about likely income, estimate the indirect costs of lost income due to premature death. See, for example, P. D. Frenzen, “Economic Cost of Guillain-Barré Syndrome in the United States,” *Neurology*, vol. 71 (2008): pp. 21-27.

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group of people might not be representative of the costs for the entire population of people with the disease.<sup>42</sup>

- **Most rare diseases are not specifically encoded in health care databases.** Health care databases usually indicate diagnoses using International Classification of Diseases (ICD) codes, and it is estimated that ICD codes cover a limited number of rare diseases; according to one analysis, as little as five percent of rare diseases can be specifically identified using ICD codes.<sup>43</sup> Researchers can use a combination of diagnostic and procedural codes to identify some rare diseases, but the overlap of symptoms of many rare diseases with other diseases, including common diseases, makes it impossible to use ICD codes to clearly identify most rare diseases.<sup>44</sup> In addition, data in claims databases are generally collected to support payment decisions, rather than research purposes and, as a result, these data are not necessarily fully aligned with the coding requirements for diagnosis. For example, the data may indicate that a person is in need of airway clearance without specifying the person's diagnosis, and because the need for airway clearance could arise from several different diseases, the data would not necessarily permit identification of the patient's disease. Even when ICD codes are linked to specific rare diseases, problems have been noted in the consistency and accuracy of their use by those responsible for data entry, perhaps in

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<sup>42</sup>Research on rare diseases, including research designed to test possible treatments, is complicated by disease rarity. For example, it took 10 years to enroll 39 patients in a clinical trial of a treatment to prevent severe fungal infections in people with chronic granulomatous disease, an immunodeficiency. For a discussion of the issues, see S. W. Lagakos, "Clinical Trials and Rare Diseases," *New England Journal of Medicine*, vol. 348 (2003): pp. 2455-2456. FDA and NIH have efforts underway to facilitate timely research through use of non-traditional clinical trial designs.

<sup>43</sup>C. E. Walker, et al., "The Collective Impact of Rare Diseases In Western Australia: An Estimate Using a Population-Based Cohort," *Genetics in Medicine*, vol. 19, no. 5 (2017): pp. 546-552. NIH officials told us that about 50 percent of rare diseases can be mapped to ICD codes, but with overlap. For example, they said that various inborn errors of metabolism may map to the same code.

<sup>44</sup>In the version of ICD codes in place since 1990 (ICD-10), one code may be used for multiple rare and common diseases, or a single disease may be identified by a specific combination of codes. A new version (ICD-11) has been adopted and is to go into effect in 2022; ICD-11 is expected to improve the ability to identify rare diseases in databases that use these codes.

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part because the rarity of these codes means that coders are inexperienced in their use.<sup>45</sup>

- **Patient sample may not be representative.** To the extent that the sample is not representative, any identified costs might not be representative of the costs incurred by, or attributable to, the broader population of all people with that disease. Reasons for possible lack of representativeness include diagnostic delays and non-continuous insurance enrollment. As described earlier, by the time of diagnosis, some people with rare diseases may have developed comorbid conditions or more severe symptoms and so they might not be representative of all people who have the disease. In addition, non-continuous insurance enrollment can result in a sample that is not representative: Causes of disenrollment before the end of that period could include patient death or loss of employment due to progression of the disease, either of which could (according to our literature review) involve higher costs than patients who remain enrolled—costs that would not be captured in an insurance database due to disenrollment.<sup>46</sup>
- **Costs may not be representative.** Even if the sample of patients is representative of the population with a disease, identified costs may not be typical of the relevant costs, so that any identified costs might not be representative of the costs incurred by, or attributable to, people with that disease. For example, researchers who identify patients who are receiving medical services at a center that specializes in a specific rare disease may not have access to information about costs incurred before those patients were treated at the center or for services received at other facilities.

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<sup>45</sup>See, for example, Walker, et al., “The Collective Impact of Rare Diseases in Western Australia,” pp. 546-552. Another limitation of insurance databases is that they might not capture data that would allow meaningful analysis of distinctions among those with a disease; for example, those with different manifestations of the disease.

<sup>46</sup>Researchers who study cost data from insurance databases typically require that people were continuously enrolled in the same health care plan for a specific period of time (e.g., a year) to ensure that costs for different people can be meaningfully compared.

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## Although Limited, Available Research Suggests the Costs of Rare Diseases Can Be Substantial

Although limited research has been conducted on the costs of rare diseases in the United States, either individually or collectively, available research (in the United States and elsewhere) and our interviews suggest that the costs of rare diseases can be substantial.<sup>47</sup>

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## There Is Limited Research on the Costs of Rare Diseases in the United States

Our review of the literature indicated—and the experts, researchers, and officials we interviewed agreed—that research on the costs of rare diseases is limited due in part to the challenges to diagnosing them and conducting research on their costs. We found that rare disease studies addressed different diseases and different costs, and they did so using different methods.<sup>48</sup> As a result, they are not generally directly comparable, and their results cannot necessarily be assumed to be applicable to other rare diseases (individually or collectively).

We reviewed 36 peer-reviewed studies of the costs of rare diseases in the United States that were published on or after January 1, 2000.<sup>49</sup> (See app. I for more information about these studies.)

- The studies addressed 33 different rare diseases or groups of rare diseases, diseases that differed in cause, age of typical onset, major organ system or systems affected, disease course, typical time from first symptoms through confirmed diagnosis, treatment options, and outcomes.<sup>50</sup>

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<sup>47</sup>For reviews of worldwide research on the costs of rare diseases, see A. Angelis, D. Tordrup, and P. Kanavos, “Socio-Economic Burden of Rare Diseases: A Systematic Review of Cost of Illness Evidence,” *Health Policy*, vol. 119 (2015): pp. 964-979, and R. Linertová, L. García-Pérez, and I. Gorostiza, “Cost-of-Illness in Rare Diseases,” in *Rare Diseases Epidemiology: Update and Overview, Advances in Experimental Medicine and Biology*, vol. 1031, eds. M. Posada de la Paz, D. Taruscio, and S. Groft (Cham: Springer, 2017), pp. 283-297.

<sup>48</sup>For a recent review of the differences among cost-of-illness studies worldwide, see L. García-Pérez, et al., “Cost-of-Illness Studies in Rare Diseases: A Scoping Review,” *Orphanet Journal of Rare Diseases*, vol. 16 (2021).

<sup>49</sup>Although we searched for articles published on or after January 2000, only one of the 36 studies we identified was published before 2010. It was published in 2008.

<sup>50</sup>Some diseases were examined in more than one study, and some studies addressed groups of rare diseases, such as rare childhood-onset epilepsies.

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### Direct Medical Costs Can Include Various Expenses: The Example of Friedrich Ataxia

Direct medical costs for a rare disease can include a wide range of expenditures, as illustrated by the types of costs associated with Friedrich ataxia—a progressive, inherited disease affecting the nervous system and causing movement problems. Those with this rare disease may require: consultations with, or the services of, general practitioners, neurologists, cardiologists, ophthalmologists, physical or speech therapists, and others.

- surgery or hospitalization.
- medical devices such as walking aids, braces, wheelchairs, and hearing aids.
- drugs to manage problems with nervous, musculoskeletal, cardiovascular, genitourinary, metabolic, or other systems.
- paid home care and stays in long-term care facilities.

See B. Polek, et al., "Burden of Friedrich's Ataxia to the Patients and Healthcare Systems in the United States and Canada," *Frontiers in Pharmacology*, vol. 4 (2013): pp. 1-7.

Source: GAO and Polek et al., *Frontiers in Pharmacology*. | GAO-22-104235

- Each of these studies addressed direct medical costs—that is, expenditures and use of resources for medical services—but they did not necessarily address all direct medical costs. For example, some studies excluded costs for drugs or addressed only costs for hospitalization.
- Of the direct medical costs that were analyzed, most studies (32 of 36) examined all-cause costs (that is, costs for all health care, whether specifically linked to the disease or not).
- Fewer studies (six of 36) examined direct nonmedical costs—expenditures and use of resources that are the result of the disease but are not for medical services—or indirect costs—that is, consequences of the disease for earnings, productivity, opportunities, or quality of life (10 of 36 studies).
- Few studies (12 of 36) calculated costs with reference to a specific disease-related event, such as diagnosis or initiation of a specific treatment; of these, five studies provided information about costs before and after that event.
- Few studies (nine of 36) analyzed costs for a comparison group of people without the disease, and another four studies provided information allowing comparisons of costs for people with one of two or more different diseases.

Thus, the studies we reviewed addressed some (but not necessarily all) of the direct medical costs of 33 of the estimated 7,000 or more rare diseases that have been identified to date. These studies used different methods and, therefore, highlighted different aspects of the costs—how costs change with therapy, for example. Each study provides specific information about the costs of rare disease, but, as already noted, the conclusions from any one study do not necessarily apply more generally to other rare diseases.

In addition to these peer-reviewed studies of specific rare diseases or groups of rare diseases, our interviewees told us about two large-scale studies of multiple rare diseases that were designed to obtain information about the costs of rare diseases in the United States. One is a study of the direct and indirect costs of rare diseases collectively being conducted by the EveryLife Foundation (an organization that represents rare diseases in general) and Lewin Group (a firm that offers health policy analysis and consulting services)—a study known as The National Economic Burden of Rare Disease Study. The researchers have released a summary of their findings and methodology but have not yet published the full study and, therefore, it has not been peer reviewed. The other is a

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pilot study, known as the Impact of Rare Diseases on Patients and Healthcare Systems study, of the direct medical costs of 14 rare diseases being conducted by researchers with NIH's National Center for Advancing Translational Sciences (NCATS) and others; this study has also not yet been published or peer-reviewed.<sup>51</sup> We reviewed the methodology of both of the studies and found them to be sufficiently reliable for our purposes.

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## Available Research Suggests the Costs of Rare Diseases Can Be Substantial

Although the studies we reviewed differ from each other in important ways, research from the United States and elsewhere indicates that the costs of rare diseases are often substantial. These studies provided information about various aspects of the costs of rare disease—comparisons of costs for people who do and do not have a rare disease, the direct medical costs of treating rare disease, the direct nonmedical costs of rare diseases, the indirect costs of rare diseases, and variation in the costs of rare diseases. The researchers, experts, government officials, and officials of organizations representing people with rare disease organizations who we interviewed agreed that the available research indicates that the costs of rare diseases can be substantial.

## Comparisons of Costs for People Who Do and Do Not Have a Rare Disease

The study by the EveryLife Foundation and Lewin Group was intended to estimate the costs of rare diseases in the United States—direct medical costs, direct nonmedical costs, and indirect costs to people with rare diseases and their families and to payers. This study addressed direct, all-cause medical costs for 379 rare diseases using claims from Medicaid, Medicare, and a large private insurance database.<sup>52</sup> In addition, surveys completed by people with those rare diseases or their caregivers provided information about direct nonmedical and indirect costs. Results of this study (which has not yet been peer-reviewed) indicated that in 2019:

- The total cost in the United States for the estimated 15.5 million people with these 379 rare diseases was \$966 billion.
- Roughly equal amounts were for direct medical costs (\$418 billion) and indirect costs associated with productivity losses (\$437 billion); direct nonmedical costs totaled \$111 billion.

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<sup>51</sup>The researchers responsible for these studies told us that they intend to seek publication of their results in peer-reviewed journals. Because these two studies have not yet been published in peer-reviewed journals, we do not include them in appendix I.

<sup>52</sup>All-cause medical costs include medical costs without regard to disease, and so can include costs for rare disease, comorbid conditions, and general health care.

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- Annual direct medical costs for a person with a rare disease were substantially more—\$26,887, on average—than for a person without a rare disease.<sup>53</sup>

Research examining specific rare diseases also indicated that costs can be substantial. For example, the NCATS study examined the direct medical costs of 14 rare diseases using data spanning 2002 through 2020. Preliminary results indicated that annual costs for those with these diseases were, on average, from 1.5 to 23.9 times the costs for comparison groups of people without those diseases.

Although most of the peer-reviewed studies of costs in the United States that we reviewed did not compare costs for those with a rare disease to costs for similar people without the disease, nine of 36 studies did. In these comparisons, various costs for those with the rare disease were substantially more than costs for those without the disease, sometimes multiple times higher. Examples of comparisons of direct, all-cause medical costs—expenditures and use of resources for medical services without regard to disease, and so including costs for the rare disease, comorbid conditions, and general health care—include the following:

- The average direct, all-cause medical costs in 2016 U.S. dollars over a 2-year period were substantially higher for those with the neurological disease, chronic inflammatory demyelinating polyneuropathy (\$116,330) than for those without the disease (\$15,586).<sup>54</sup>

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<sup>53</sup>EveryLife Foundation and the Lewin Group, “*The National Economic Burden of Rare Disease Study*” (Feb. 25, 2021), accessed Feb. 25, 2021, <https://everylifefoundation.org/burden-study/>. The authors note that their estimate of the cost of these 379 rare diseases can serve as a lower-bound estimate of the total cost of rare diseases in the United States, given that there are thousands of other rare diseases. They also note that their estimate of the total cost in the United States of these 379 rare diseases is higher than estimates for specific chronic diseases, although the methods of the studies differ enough to preclude direct comparison. According to the Centers for Disease Control and Prevention, costs for heart disease and stroke were estimated to total \$352 billion in 2018; costs for diabetes were estimated to total \$327 billion in 2017; and costs for cancer were projected to be \$174 billion in 2020. See the Centers for Disease Prevention and Control, *Health and Economic Costs of Chronic Diseases*, accessed April 26, 2021, <https://www.cdc.gov/chronicdisease/about/costs/index.htm>.

<sup>54</sup>V. Divino, et al., “The Economic Burden of [Chronic Inflammatory Demyelinating Polyneuropathy] in the United States: A Case-Control Study,” *PLoS ONE*, vol. 13, no. 10 (2018): pp. 1-7.

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## Direct Medical Costs of Treating Rare Diseases

- The annual average direct, all-cause medical costs in 2017 U.S. dollars were substantially higher for those with a severe childhood-onset epilepsy, Lennox-Gestaut syndrome (\$63,930 to \$65,026 for Medicaid beneficiaries and commercially insured patients, respectively) than for those without the disease (\$3,849 to \$2,442).<sup>55</sup>
- The annual average direct, all-cause medical costs, based on data from 2009 through 2014, were substantially higher for those with a disease due to a chromosomal abnormality, Prader-Willi syndrome (\$40,868 to \$28,712 for Medicaid beneficiaries and commercially insured patients, respectively) than for those without the disease (\$5,306 to \$3,246).<sup>56</sup>

Treatments for rare diseases can be expensive, but some studies indicate that treating a rare disease can result in lower direct medical costs compared with not treating the disease. For example, a comparison of costs incurred by people with pulmonary arterial hypertension (a disease affecting the heart and lungs) in the year after initiation of drug therapy to an estimate of their costs in the year before initiation of drug therapy suggests potential cost savings. Results indicated that, despite the increase in costs for drugs (from an average of \$6,440 to \$38,514 per person, in 2011 U.S. dollars), overall direct, all-cause medical costs decreased after initiation of drug therapy (from an average of \$116,681 to \$98,243 per person).<sup>57</sup>

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<sup>55</sup>N. L. Reaven, et al., "Burden of Illness in Patients with Possible Lennox-Gastaut Syndrome: A Retrospective Claims-Based Study," *Epilepsy & Behavior*, vol. 88 (2018): pp 66-73.

<sup>56</sup>A. J. Shoffstall, et al., "The High Direct Medical Costs of Prader-Willi Syndrome," *Journal of Pediatrics*, vol. 175 (2016): 137-143. The published article does not state whether costs were adjusted to reflect dollar values for a particular year.

<sup>57</sup>M. Sikirica, et al., "The Economic Burden of Pulmonary Arterial Hypertension (PAH) in the [United States] on Payers and Patients," *BMC Health Services Research*, vol. 14, (2014): pp. 676-686.



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### Potential Cost Savings from Use of a Costly Diagnostic Method: Rapid Whole-Genome Sequencing of Infants

Rapid whole-genome sequencing is a diagnostic procedure that can allow faster diagnosis than standard genetic tests. A study examined its use in infants hospitalized from November 2018 to May 2020. The infants were in their first year of life and had an acute illness without a clear non-genetic cause.

Rapid whole-genome sequencing yielded a diagnosis in 74 of 184 infants. The authors noted that most of these diagnoses were of very rare disorders that their providers would not likely have seen before. Rapid precision medicine (use of information about a person's genes and other factors to determine specific interventions) resulted in a change in the medical care of 58 infants, for example, by adding or canceling a surgical procedure or changing the infant's medication or diet. According to the authors, the diagnoses allowed treatment early in the course of care, when less irreversible damage had occurred, and also allowed clinicians and parents to make decisions with greater confidence.

The total cost of the testing and precision medicine for these 184 children was \$1.7 million (about \$9,492 per infant). The researchers estimate savings of \$2.2 to \$2.9 million through reduced costs for hospitalization and professional fees—savings of \$12,041 to \$15,786 per infant.<sup>a</sup>

<sup>a</sup>D. Dimmock et al., "Project Baby Bear: Rapid Precision Care Incorporating rWGS in 5 California Children's Hospitals Demonstrates Improved Clinical Outcomes and Reduced Costs of Care," *American Journal of Human Genetics*, vol. 108 (2021): pp. 1-8.

Source: Dimmock et al. and Cell Press. | GAO-22-104235

When multiple treatments are available, research can also compare the direct and indirect costs of each. For example, a study of two different treatments for severe hemophilia A (a bleeding disease) indicated that a treatment intended to prevent bleeding episodes was associated with average annual direct medical costs related to the disease that were higher, in 2011 U.S. dollars (\$292,525) than a treatment provided in response to bleeding episodes (\$184,518). The researchers noted, however, that there could be nonmonetary benefits associated with the more costly preventive treatment, such as improvements in the patients' quality of life. These hypothetical benefits were not included in the costs estimated for this study but, according to the researchers, they should be considered when evaluating the costs of the two treatments.<sup>58</sup>

## Direct Nonmedical Costs of Rare Diseases

Six of the 36 studies we reviewed documented direct nonmedical costs of rare diseases—expenditures and use of resources as a result of a disease, but not for medical services *per se*. These estimates indicate

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<sup>58</sup>Z.-Y. Zhou, et al., "Burden of Illness: Direct and Indirect Costs among Persons with Hemophilia A in the United States," *Journal of Medical Economics*, vol. 18, no. 6 (2015): pp. 457-465. For a discussion of methods for comparing the cost of an intervention to either another intervention or no intervention, see J. López-Bastida and J. Oliva-Moreno, "Cost of Illness and Economic Evaluation in Rare Diseases," *Rare Diseases Epidemiology, Advances in Experimental Medicine and Biology*, eds. M. Posada de la Paz and S. Groft (Dordrecht: Springer, 2010), pp. 273-282.

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that direct nonmedical costs, which are typically borne by the people with the disease or their families, can be substantial. For example,

- One study examined three different rare neuromuscular diseases and found that the average of direct nonmedical costs per year in 2010 U.S. dollars was \$17,889 for those with amyotrophic lateral sclerosis, \$12,939 for those with Duchenne muscular dystrophy, and \$5,517 for those with myotonic dystrophy.<sup>59</sup> For this study, nonmedical costs included costs for moving or modifying one's home, purchasing or modifying a vehicle, and travel.
- A study of people with Merkel cell carcinoma (an aggressive cancer) found that the average one-way distance traveled by patients to a specialized treatment center from 2012 through 2017 was 1,137 miles; the median was 813 miles.<sup>60</sup>

## Indirect Costs of Rare Diseases

Ten of the 36 studies we reviewed estimated indirect costs—costs of the disease in terms of effects on earnings, productivity, opportunities, or quality of life. Some of these studies found that indirect costs were not only substantial, but were also greater than direct costs.<sup>61</sup> For example:

- A study of the costs for those with Dravet syndrome, a severe epilepsy, indicated that average annual indirect costs to patients and their caretakers in 2016 U.S. dollars (\$81,582) exceeded direct, all-cause, medical costs (\$27,276). One contributor to these indirect

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<sup>59</sup>J. Larkindale, et al., "Cost of Illness for Neuromuscular Diseases in the United States," *Muscle & Nerve*, vol. 49 (2014): pp. 431-438. Other researchers elaborated on the nonmedical costs to those with Duchenne muscular dystrophy, including costs that might not be captured in databases that include most medical costs. These costs could include "assistive devices, such as electric beds, alternating pressure relieving mattresses, patient lifts, custom shower and toilet chairs, power wheelchairs, pressure relieving cushions, mobile arm supports, upper extremity robotics, environmental control units, computer access interfaces, automotive access lifts and ramps, and other adaptations to housing...." See S. Thayer, C. Bell, and C. M. McDonald, "The Direct Cost of Managing a Rare Disease: Assessing Medical and Pharmacy Costs Associated with Duchenne Muscular Dystrophy in the United States," *Journal of Managed Care & Specialty Pharmacy*, vol. 23, no. 6 (2017): pp. 633-641.

<sup>60</sup>R. Jain, et al., "Travel Burden Associated with Rare Cancers: The Example of Merkel Cell Carcinoma," *Cancer Medicine*, vol. 8 (2019): pp. 2580-2586.

<sup>61</sup>Indirect costs do not always exceed direct costs. Some researchers suggest that indirect costs are generally higher for rare diseases that are debilitating. See Angelis, Tordrup, and Kanavos, "Socio-Economic Burden of Rare Diseases," pp. 964-979. The indirect costs we report are per patient. Because many rare diseases are genetic, some families have two or more children with the disease, and so costs per family can be higher.

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costs was the amount of time caregivers spent caring for a child with the disease—the equivalent of 380 eight-hour days per year (more than days in a year).<sup>62</sup>

- A study of the costs for those with frontotemporal degeneration, which includes certain dementias and other diseases involving progressive loss of function, indicated that average annual indirect costs to patients and their caregivers in 2016 U.S. dollars (\$71,737) exceeded average direct costs (\$47,916). Average annual costs varied with the person's age, disease type and progress, and sex.<sup>63</sup>
- A study of the costs for those with Guillain-Barré syndrome, an autoimmune disease, estimated that the total cost of the disease to the United States was \$1.7 billion in 2004 U.S. dollars: \$200 million in direct medical costs and \$1.5 billion in indirect costs. The authors attributed 60 percent of the total annual cost to the premature death of those with the disease. For those disabled by the disease, the estimated cost of foregone earnings averaged \$186,416 per year.<sup>64</sup>

## Variation in the Costs of Rare Diseases

The costs for any one rare disease are not necessarily consistent, and can instead vary across time, location, or person. More generally, studies on health care spending typically find that a small percentage of individuals account for a large portion of expenditures, and the available research on costs of rare diseases typically show that costs for some people are higher than costs for others.<sup>65</sup> Complications and comorbid conditions can contribute to such differences, and other factors can also contribute to variation in costs. (See table 1 for examples of factors that can contribute to variation in the cost of rare diseases.)

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<sup>62</sup>Whittington, et al., "Costs of Dravet Syndrome," pp. 109-113.

<sup>63</sup>J. E. Galvin, et al., *The Social and Economic Burden of Frontotemporal Degeneration.* *Neurology*, vol. 89 (2017): pp. 2049-2056.

<sup>64</sup>Frenzen, "Economic Cost of Guillain-Barré Syndrome," pp. 21-27.

<sup>65</sup>See, for example, GAO, *Medicaid: A Small Share of Enrollees Consistently Accounted for a Large Share of Expenditures*, [GAO-15-460](#) (Washington, D.C.: May 8, 2015) and Angelis, Tordrup, and Kanavos, "Socio-Economic Burden of Rare Disease," p. 975. One expert suggested that costly, catastrophic clinical presentations—very high cost events—might provide a diagnostic clue to the presence of a rare disease.

**Table 1: Factors That Can Cause Variation in the Costs of a Rare Disease**

Factor	Example of the Effect on Variation in Costs
Complications	A study of the direct medical costs of hospitalizations for certain treatments of a spinal arteriovenous malformation (abnormal connections between arteries and veins) indicated an average cost in 2014 U.S. dollars of \$36,562 for those with no recorded complications, compared to an average of \$67,571 if there were inpatient complications. <sup>a</sup>
Comorbid conditions <sup>b</sup>	A study of the direct, all-cause medical costs of hospitalization for cardiac dysfunction in adults with cardiac amyloidosis (a heart disease) indicated that the average cost in 2016 U.S. dollars was higher for those with both cardiac amyloidosis and renal disease (\$24,238) than for those without renal disease (\$16,041). <sup>c</sup>
Disease severity	A study of the costs of treatment for acute attacks among those with hereditary angioedema (an immunodeficiency) found that average total (direct and indirect) costs in 2007 U.S. dollars varied with attack severity, from \$14,379 for those with mild attacks to \$96,460 for those with severe attacks, generally reflecting an increase in hospital stays and emergency department visits with severe attacks. <sup>d</sup>
Location	A study of the direct non-medical costs of travel to a specialty center for the treatment of Merkel cell carcinoma (an aggressive cancer) estimated that travel costs from 2012 through 2017 for patients who lived more than 300 miles from the center averaged \$1,448 per patient compared to a cost of \$416 for those traveling 300 miles or fewer. <sup>e</sup>
Payer	A study of direct, all-cause medical costs for those with fragile X syndrome (a chromosomal abnormality) who had one or more outpatient visits during 1 year in the period from 2004 through 2009 found that the average annual cost was \$12,608 for Medicaid beneficiaries and \$4,643 for those with commercial insurance or Medicare. <sup>f</sup>
Patient's age	A study of the direct medical costs from 2008 through 2010 for those with myasthenia gravis (a neuromuscular disease) indicated that average costs were greatest for those ages 20 to 39 (\$37,522) compared to costs for those ages 0 to 19 (\$7,906), ages 40 to 64 (\$27,610), or age 65 and older (\$20,686). <sup>g</sup>
Race or ethnicity	A study of direct medical costs for an acute hospitalization for those with dermatomyositis (an autoimmune disease) indicated that the average costs from 2002 through 2012 was higher for Asians than for other people. <sup>h</sup>
Time	A study of the costs in 2016 U.S. dollars of cystic fibrosis documented an increase in average all-cause medical costs per person from 2010 (\$61,591) to 2016 (\$130,879), a time period during which new treatments that prevent or slow disease progression were becoming available. <sup>i</sup>

Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

<sup>a</sup>The studied treatments were a specific surgical intervention or endovascular embolization. See J. K. Yue, et al., "Hospital Complications and Costs of Spinal Arteriovenous Malformations in the United States from 2002-2014," *Journal of Neurosurgical Sciences*, vol. 65, no. 1 (2021): pp. 54-62.

<sup>b</sup>Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called "comorbid conditions."

<sup>c</sup>T. P. Quock, et al., "Untangling the Clinical and Economic Burden of Hospitalization for Cardiac Amyloidosis in the United States," *Clinicoeconomics and Outcomes Research*, vol. 11 (2019): pp. 431-439.

<sup>d</sup>D. A. Wilson, et al., "Economic Costs Associated with Acute Attacks and Long-Term Management of Hereditary Angioedema," *Annals of Allergy, Asthma & Immunology*, vol. 104 (2010): pp. 314-320.

<sup>e</sup>Costs were measured from January 1, 2012, until January 1, 2017, or until the patient's last follow-up appointment or death. See R. Jain, et al., "Travel Burden Associated with Rare Cancers: The Example of Merkel Cell Carcinoma," *Cancer Medicine*, vol. 8 (2019): pp. 2580-2586. Location can also cause variation in the costs of any disease because of regional variation in health care costs. See, for example, W. C. Johnson and J. F. Biniek, "Sources of Geographic Variation in Health Care Spending Among Individuals with Employer Sponsored Insurance," *Medical Care Research and Review* (July 2020), accessed on Jul. 6, 2021, <https://doi.org/10.1177/1077558720926095>.

<sup>f</sup>The reasons for differences in costs for different payers were not clear, although the researchers discuss several possibilities. See P. Sacco, et al., "The Economic Burden of Fragile X Syndrome:

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Healthcare Resource Utilization in the United States," *American Health & Drug Benefits*, vol. 6, no. 2 (2013): pp. 73-83. The published article does not state whether costs were adjusted to reflect dollar values for a particular year.

<sup>g</sup>J. T. Guptill, et al., "Cost Analysis of Myasthenia Gravis from a Large U.S. Insurance Database," *Muscle & Nerve*, vol. 44 (2011): pp. 907-911.

<sup>h</sup>M. C. Kwa, et al., "Predictors of Hospitalization, Length of Stay, and Cost of Care among Adults with Dermatomyositis in the United States," *Arthritis Care & Research*, vol. 69, no. 9 (2017): pp. 1391-1399.

<sup>i</sup>S. D. Grosse, et al., "Healthcare Expenditures for Privately Insured [U.S.] Patients with Cystic Fibrosis, 2010-2016," *Pediatric Pulmonology*, vol. 53 (2018): pp. 1611-1618. See also A. Angelis, D. Tordrup, and P. Kanavos, "Socio-Economic Burden of Rare Diseases: A Systematic Review of Cost of Illness Evidence," *Health Policy*, vol. 119 (2015): pp. 964-979.

The costs of a rare disease can extend beyond treatment. See the text box for information about the health and financial costs experienced by survivors of childhood cancer.

**Long-Term Health and Financial Costs Experienced by Survivors of Childhood Cancers**

Cancer is the leading cause of death by disease among children, and although childhood cancers are life threatening, the likelihood of survival for 5 years or more has increased from about 62 percent in the mid-1970s to about 86 percent in the mid-2010s.<sup>a</sup> As a result, the number of survivors of childhood cancer has increased, and research has begun to indicate long-term effects for these survivors.

Survivors of childhood cancer are at risk for early mortality from secondary cancers (cancers that are different from their original ones), cardiac events, and pulmonary conditions. Some health effects seem to be linked to treatment of the original cancer—for example, long-term adverse effects of radiation or chemotherapy—and in some cases, these effects emerge many years after completion of therapy. Certain treatment protocols have been changed in light of follow-up data (for example, the use of cranial irradiation has been limited in light of evidence of long-term effects).<sup>b</sup>

Research on the psychological effects of childhood cancers—effects on the patients and their families—suggests substantial resilience in general, but some individuals are at risk for long-term deleterious effects. For example, those who survive brain tumors or who undergo treatments focused on the central nervous system may be at particular risk for adverse psychological effects.<sup>c</sup>

Studies also suggest that many survivors of childhood cancers experience financial hardship as a result of the costs of subsequent health problems, educational disruption, an inability or limited ability to work, or a combination of those factors.<sup>d</sup>

Source: GAO analysis of research on childhood cancers. | GAO-22-104235

Note: For more information, see GAO, *Survivors of Childhood Cancer: Factors Affecting Access to Follow-up Care*, [GAO-20-636R](#) (Washington, D.C.: July 31, 2020).

<sup>a</sup>See [GAO-20-636R](#). Survival rates vary with the type of cancer, ranging from almost 0 percent for diffuse intrinsic pontine glioma (a type of brain cancer) to about 90 percent for children under the age of 15 with acute lymphoblastic leukemia, the most common childhood cancer. See NIH, "Cancer in Children and Adolescents," accessed on Nov. 20, 2020, <https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet>, and R. Aziz-Bose and M. Monje, "Diffuse Intrinsic Pontine Glioma: Molecular Landscape and Emerging Therapeutic Targets," *Current Opinion in Oncology*, vol. 31, no. 6 (2019): pp. 522-530.

<sup>b</sup>See, for example, L. L. Robison and M. M. Hudson, "Survivors of Childhood and Adolescent Cancer: Life-Long Risks and Responsibilities," *Nature Reviews Cancer*, vol. 14 (2014): pp. 61-70.

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<sup>c</sup>See, for example, A. E. Kazak and R. B. Noll, "The Integration of Psychology in Pediatric Oncology Research and Practice," *American Psychologist*, vol. 70 (2015): pp. 146-158.

<sup>d</sup>See, for example, P. C. Nathan, et al., "Financial Hardship and the Economic Effect of Childhood Cancer Survivorship," *Journal of Clinical Oncology*, vol. 36 (2018): pp. 2198-2206.

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## Effects of Undiagnosed, Misdiagnosed, and Untreated Rare Diseases

Our literature review and our interviews indicated that the effects of undiagnosed, misdiagnosed, or untreated rare diseases can include negative health outcomes, both physical and psychological. In addition, multiple diagnostic tests, medical appointments, and other interventions that may turn out to be unnecessary can add to the costs—direct and indirect—of the disease.

### Negative Health Outcomes

According to the literature we reviewed, failure to diagnose or treat rare diseases can lead to negative health outcomes, including disease progression and an increased risk of comorbid conditions or mortality. Similarly, misdiagnosis can lead to these negative outcomes and also increase the risk of inappropriate interventions. These health effects can stem from failure to obtain appropriate, timely intervention; effects of treatments that are inappropriate; and effects of inaccessible or denied treatment. In addition, those with undiagnosed, misdiagnosed, and untreated rare diseases may experience various adverse psychological effects.

#### Misdiagnosis: The Example of Creutzfeldt-Jakob Disease

A study of patients ultimately determined to have sporadic Creutzfeldt-Jakob disease indicated that the average number of misdiagnoses prior to correct diagnosis was 3.8, most commonly including viral encephalitis, paraneoplastic disorder, and depression. The time from first symptoms to correct diagnosis was, on average, 6.7 months—about two-thirds of the way through the course of this inevitably fatal disease, which is due to the accumulation of abnormal prion proteins in the brain. The negative consequences of this diagnostic delay included potential infection control issues, extensive and costly evaluations of the patient, failure to allow families to focus on patient care and end-of-life planning, and limiting opportunities to enroll in clinical trials.<sup>a</sup>

Conversely, a study of tissue from the brain autopsies referred to a prion disease surveillance center found that 32 percent were negative for prion disease, and of those, 23 percent had a potentially treatable disease—diseases for which appropriate treatment had not been provided after misdiagnosis as Creutzfeldt-Jakob disease.<sup>b</sup>

<sup>a</sup>R. W. Paterson, et al., "Differential Diagnosis of Jakob-Creutzfeldt Disease," *Archives of Neurology*, vol. 69 (2012): pp. 1578-1582.

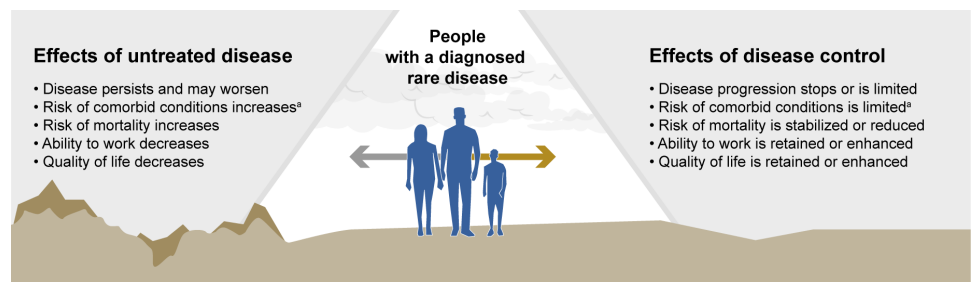
<sup>b</sup>N. Chitravas, et al., "Treatable Neurological Disorders Misdiagnosed as Creutzfeldt-Jakob Disease," *Annals of Neurology*, vol. 70 (2011): pp. 437-444.

Source: GAO analysis of published literature on rare diseases. | GAO-22-104235

- **Lack of appropriate treatment.** People with undiagnosed or misdiagnosed diseases are unlikely to receive appropriate treatment, and so their disease may persist. For progressive diseases—including many rare diseases—lack of treatment results not only in worsening of symptoms or an increase in the scope or severity of the disease, but also a likely increase in comorbid conditions and risk of mortality,

along with reduced ability to work and poorer quality of life.<sup>66</sup> (See fig. 3 for an illustration of the advantages of controlling a diagnosed disease—treating it or limiting its effects—as opposed to leaving a disease untreated.)

**Figure 3: Advantages of Controlling a Diagnosed Disease versus Leaving a Disease Untreated**



Source: GAO analysis of published literature on undiagnosed and untreated disease. | GAO-22-104235

<sup>a</sup>Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called “comorbid conditions.”

- **Untimely treatment.** NIH officials told us that many rare diseases, particularly those that affect the nervous system, can be treated effectively only during a limited, disease-specific time period. For example, late infantile metachromatic leukodystrophy, a neurometabolic disease, normally results in death by age 5. Preliminary data from an experimental gene therapy shows promise as an intervention, but those data also suggest that to be effective, treatment must be given before the symptoms become evident, normally in the second year of life.<sup>67</sup> Similarly, early intervention can be critical for those with rare diseases that affect cognitive

<sup>66</sup>If appropriate interventions are not provided, a complete economic analysis would acknowledge cost avoidance, and some treatments for rare diseases are very expensive. It does not necessarily follow that the costs of those expensive interventions would have been greater than the costs of an untreated or mistreated disease.

<sup>67</sup>M. Sessa, et al., “Lentiviral Haemopoietic Stem-Cell Gene Therapy in Early-Onset Metachromatic Leukodystrophy: An Ad-Hoc Analysis of a Non-Randomised, Open-Label, Phase 1/2 Trial,” *Lancet*, vol. 388 (2016): pp. 476-487.

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development by helping limit progressive cognitive deterioration and, in some cases, improving cognitive development.<sup>68</sup>

- **Inappropriate interventions.** In the case of both common and rare diseases, if they are misdiagnosed, patients might receive interventions that are inappropriate for the patient’s actual disease and that may produce adverse health results. For example, abdominal attacks from hereditary angioedema, an immunodeficiency, can mimic acute abdominal emergencies, often resulting in exploratory procedures or unnecessary surgery.<sup>69</sup> Our literature review also indicated that, in some cases, the inappropriate interventions that follow misdiagnosis may carry particular risks associated with the person’s actual disease. For example, Ehlers-Danlos syndromes are often misdiagnosed, and surgeries are sometimes performed as a result of misdiagnoses.<sup>70</sup> For some people with Ehlers-Danlos syndromes, the disease may increase the risk of surgical complications, such as wound healing problems, excessive bleeding, dissection, and hernias.<sup>71</sup>
- **Lack of access to medical and other services.** Our review of the literature and our interviews indicate that access to certain medical services and to necessary rehabilitative, educational, or supportive services may be difficult for those with undiagnosed or misdiagnosed rare diseases—or even for people with a diagnosed rare disease. These difficulties can minimize the health benefits that would otherwise be associated with these services.
  - Access to treatment can depend on whether FDA has approved the treatment for use for the rare disease. For example, nontuberculous mycobacterial lung disease illustrates a potential problem with lack of access to treatment even for people with a diagnosed rare disease: the only antibacterial drug approved for

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<sup>68</sup>See, for example, G.-A. Kuiper, et al., “Failure to Shorten the Diagnostic Delay in Two Ultra-Orphan Diseases (Mucopolysaccharidosis Types I and III): Potential Causes and Implications,” *Orphanet Journal of Rare Diseases*, vol. 13 (2018): pp. 2-14, and Kole and Faurisson, “Rare Diseases Social Epidemiology,” pp. 223-250.

<sup>69</sup>One study of people with hereditary angioedema found that the median time from first symptom to confirmed diagnoses was 4 years, ranging to as many as 53 years, and that reports of improper treatments prior to correct diagnosis were not uncommon. See D. A. Wilson, et al., “Acute Attacks and Long-Term Management of Hereditary Angioedema,” *Annals of Allergy, Asthma & Immunology*, vol. 104 (2010): pp. 314-320.

<sup>70</sup>Kole and Faurisson, “Rare Diseases Social Epidemiology,” pp. 223-250.

<sup>71</sup>See, for example, GARD, “*Ehlers-Danlos Syndromes*,” accessed on May 24, 2021, <https://rarediseases.info.nih.gov/diseases/6322/ehlers-danlos-syndromes>.



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treatment of this disease, Arikayce, was approved specifically to treat refractory disease—that is, disease for which conventional treatments have failed for 6 months. However, an official of an organization representing those with this disease told us that insurance companies may deny coverage of the conventional treatments necessary to demonstrate that the disease is refractory (and thereby qualify for the one FDA-approved treatment for this disease), because the conventional treatments have not been specifically approved for use with nontuberculous mycobacterial lung disease. This official told us that most insurance companies will cover those conventional treatments if the patient and physician appeal denial of coverage.

- Access to certain rehabilitative, educational, or supportive services (including certain Social Security benefits and individualized education programs) may depend on having a diagnosis—specifically, a diagnosis that is recognized as one for which those services are considered appropriate. Undiagnosed individuals and diagnosed individuals lacking one of these specific, recognized diagnoses may be unable to obtain these services or they may be able to access them only by assuming the full cost.<sup>72</sup>
- Access to age-appropriate services can also be difficult for some people with a diagnosed rare disease. For example, our literature review indicated that the transition from pediatric to adult health care for those with rare, serious, and chronic diseases that emerge in childhood can involve disruptions to, or difficulties with, access to necessary health care services because adult health

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<sup>72</sup>Our literature review and interviews indicated that well-intentioned clinicians may document diagnoses specifically to allow patients access to necessary services, for example, by diagnosing a child who may have an unidentified rare disease with autism spectrum disease (which is not rare) to allow that child access to critical services, even if all criteria generally necessary for that diagnosis have not been confirmed. Even if well intentioned, documentation of an inaccurate diagnosis might inadvertently further delay identification of the correct diagnosis by introducing erroneous information into the patient's medical record.

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care facilities might not have specialists with experience treating diseases that often result in death before adulthood.<sup>73</sup>

In some cases, the negative health outcomes for those with rare diseases that are undiagnosed, misdiagnosed, or untreated—and for their family members—are psychological. According to our literature review and interviews, these effects are common and important and typically include frustration, anxiety, a sense of isolation, and diminished confidence in health care providers.<sup>74</sup> These psychological effects are not just unpleasant—anxiety and depression may be seen as comorbid conditions. For example, a survey of patients with hereditary angioedema conducted from November 2007 to January 2008 indicated that 42 percent reported at least mild depressive symptoms, and nearly 20 percent reported taking medications that would be used for depression or other psychiatric disease.<sup>75</sup>

Other health-related effects of undiagnosed, misdiagnosed, and untreated disease can include

- Diminished confidence in health care providers, which can further prolong the diagnostic process and can have broader public health effects—for example, if it causes people to fail to follow public health recommendations.<sup>76</sup>

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<sup>73</sup>In addition, the transition from childhood to adulthood may involve a change in insurance coverage with possible effects on access to services. Medicaid, for example, covers a range of special services for children that are not usually covered for adults, services that may be particularly important for those with severely debilitating conditions. See, for example, Institute of Medicine, “*Rare Diseases and Orphan Products*,” pp. 67-69. Similarly, our literature review and one of our interviews indicated that adults who experience progressive dementias or stroke while in their prime earning years, while they may have dependent children, may have difficulty accessing age-appropriate services because services for those with dementia or stroke are often geared to people who are older and who no longer have wage-earning or dependent care responsibilities. See, for example, Galvin, et al., “Burden of Frontotemporal Degeneration,” p. 2049.

<sup>74</sup>See, for example, W. A. Gahl and C. J. Tiff, “The NIH Undiagnosed Diseases Program,” *Journal of the American Medical Association*, vol. 305, no. 18 (2011): pp. 1904-1905.

<sup>75</sup>Wilson, et al., “Acute Attacks and Long-Term Management of Hereditary Angioedema,” pp. 314-320.

<sup>76</sup>The study of rare diseases in Europe mentioned above found that 19 percent of respondents reported a loss of confidence in the health care system as a result of delayed diagnosis. See Kole and Faurisson, “Rare Diseases Social Epidemiology,” pp. 223-250.

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- Concerns about future pregnancies based on unanswered questions about possible genetic causes—concerns that can delay or complicate family planning decisions.
  - Frustration among health care professionals who are unable to diagnose or treat the patients with whom they work.

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### Undiagnosed, Misdiagnosed, and Untreated Rare Diseases Can Pose Other Financial Costs

According to our review of the literature and our interviews, the costs associated with undiagnosed, misdiagnosed, or untreated rare diseases include costs in addition to those that would be incurred if the disease had been diagnosed upon first presentation. For example, there could be costs for consultations with specialists, costs for unnecessary treatment of an incorrectly diagnosed disease, and costs associated with the progression of an untreated disease.<sup>77</sup> Similar costs would occur with any undiagnosed, misdiagnosed, or untreated disease, whether rare or common, but the difficulties of diagnosing rare diseases and the absence of clear treatments for many of them underscore an increased potential for such costs with rare diseases. Quantifying these costs can be even more difficult than quantifying the costs of the rare diseases once diagnosed—costs of undiagnosed or misdiagnosed disease are, by definition, not linked in databases to the rare disease because there may be no indication in the data that the recorded diagnosis was incorrect or that a diagnosis had not been determined.

According to the published (but not yet peer-reviewed) summary of its survey of 1,360 patients with 379 rare diseases, the EveryLife Foundation and Lewin Group obtained some information about their experiences prior to receiving a diagnosis of their rare disease—experiences that involved direct and indirect costs. These patients reported that before receiving a diagnosis of their rare disease, they

- saw an average of 4.2 primary care physicians and 4.8 specialists for rare disease diagnosis;
- made an average of 2.4 out-of-state trips related to their diagnosis; and

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<sup>77</sup>Among the costs to physicians and health care payers are opportunity costs—that is, the loss of the opportunity to use health care resources (such as a physician’s time or a hospital bed) for other purposes when these resources are used unnecessarily for people with undiagnosed, misdiagnosed, or untreated rare diseases. In addition, one expert noted that health care providers may experience negative psychological reactions if they are not able to diagnose a patient or provide treatment.

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- visited an emergency room an average of 3.7 times and were hospitalized an average of 1.7 times for reasons related to their rare disease, but prior to diagnosis.<sup>78</sup>

The costs to people who have not received a treatment appropriate to their disease can also include costs of interventions that are not considered appropriate. For example, one study examined use of a particular treatment—hematopoietic stem-cell transplantation—in patients with a pediatric leukodystrophy, a group of diseases of the central nervous system. This technique has been shown to be an effective treatment for a limited set of leukodystrophies, but the study examined its use with other patients. Despite significant risks of morbidity and mortality, the study found that from October 2015 through June 2017, the procedure was used on about 10 percent of those with types of pediatric leukodystrophy for which the procedure was not otherwise indicated, at an average cost of \$786,846 per patient.<sup>79</sup> As another example of costs of unnecessary treatment, one expert with whom we spoke noted that the desperation of patients and their family members when faced with an undiagnosed or untreated disease can make them vulnerable to charlatans, with results that include not only financial cost, but also potential side effects and further diagnostic confusion.

Our review of the literature and our interviews indicated that the costs to people with undiagnosed, misdiagnosed, or untreated disease can also involve the time and energy those people and their families exert in pursuit of a diagnosis or treatment. In part because little is known about many rare diseases, it is often the patients and their families who bear the burden of seeking a diagnosis, identifying and seeking necessary resources, and developing support networks for those with similar problems—efforts that can add to both direct and indirect costs of the disease. For example, a study of people referred to an academic center specializing in inherited kidney disease from 1996 through 2017 found that 27 percent of its 665 referrals were from people who believed that they or a family member might have autosomal dominant tubulointerstitial kidney disease, resulting in the diagnosis of 116 people with this disease—a diagnosis described by the researchers as one that would not

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<sup>78</sup>EveryLife Foundation and the Lewin Group, “*National Economic Burden of Rare Disease*.” p 19.

<sup>79</sup>J. L. Bonkowsky, J. Wilkes, and D. C. Shyr, “Scope and Burden of Non-Standard of Care Hematopoietic Stem Cell Transplantation in Pediatric Leukodystrophy Patients,” *Journal of Child Neurology*, vol. 33, no. 14 (2018): pp. 882–887.

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have been identified without the efforts of these patients to pursue a diagnosis.<sup>80</sup>

Our literature review and interviews also indicated that rare disease support groups and organizations have often been founded and are sustained by the people who have rare diseases and their families—an effort that imposes additional costs, such as the indirect costs associated with the time they and their families invest. These organizations may represent and advocate for those with rare diseases and often provide information and social support to those with rare disease—a substantial benefit in light of the isolation many rare disease sufferers experience. In addition, some of these groups have advanced the cause of, and promoted attention to, rare disease through supporting research benefiting those with rare diseases, advocating for legislative action, or establishing disease registries to facilitate research.<sup>81</sup>

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## Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review and comment. The department provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the appropriate congressional committees, the Secretary of the Department of Health and Human Services, and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

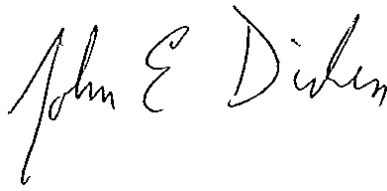
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<sup>80</sup>A. J. Bleyer, et al., “Outcomes of Patient Self-Referral for the Diagnosis of Several Rare Inherited Kidney Diseases,” *Genetics in Medicine*, vol. 22, no. 1 (2020): pp. 142-149.

<sup>81</sup>For example, the National Organization for Rare Disorders provides small grants for clinical research related to the development of new diagnostics or treatments for rare diseases, including funding for research that ultimately yielded an FDA-approved titanium rib—a device used to treat children with thoracic insufficiency syndrome (a congenital condition in which severe deformities of the chest, spine, and ribs prevent normal breathing and lung development). The EveryLife Foundation supported a major study of the costs of rare diseases in the United States and has an active legislative advocacy component. The Cystic Fibrosis Foundation developed diagnostic criteria and established centers of care for that disease. Registries of people with rare diseases by organizations help researchers identify people who might be candidates for participation in studies, among other things.

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If you or your staff have any questions about this report, please contact me at (202) 512-7114 or [dickenj@gao.gov](mailto:dickenj@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix IV.

A handwritten signature in black ink that reads "John E. Dicken". The signature is written in a cursive style with a large initial "J" and "D".

John E. Dicken  
Director, Health Care

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# Appendix I: Selected Studies of the Costs of Rare Diseases in the United States

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This appendix describes how we selected studies of the costs of rare diseases in the United States and provides information about those studies.<sup>1</sup>

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## Selection of Studies for Review

We identified a total of 36 peer-reviewed studies of the costs of rare diseases in the United States published during or after 2000, as follows:

- To identify an initial set of studies of the costs of rare diseases in the United States, we conducted a search of peer-reviewed articles that included the key terms “rare disease” and “cost” (or another word or word stem related to cost).<sup>2</sup> We searched for articles published from January 2000 through February 2021.<sup>3</sup> We used this search to identify empirical studies of the costs of rare diseases conducted within the United States that included descriptions of methods in sufficient detail to allow an understanding of key methodological features, such as the types of costs that were considered. We identified 16 studies conducted in the United States that provided information about the costs of rare disease published in or after 2000. Our search would not have identified research that focused on one or more of the 7,000 or so rare diseases without using the term “rare disease” in the article’s abstract or keywords.
- We supplemented the studies we identified through this literature search with 20 peer-reviewed studies identified by our interviewees. We asked our interviewees—officials of the National Institutes of Health (NIH) and Food and Drug Administration (FDA); selected researchers and experts on rare diseases, health care, and health economics; and officials of organizations representing those with rare diseases—if there were specific studies they recommended for review.

Our methods were not designed to provide a comprehensive review of the empirical literature on costs of rare diseases in the United States.

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<sup>1</sup>We use the term “disease” to refer to diseases, disorders, syndromes, complexes, and other health conditions except when one of those other terms is part of the name of the disease.

<sup>2</sup>In addition to the term “rare disease,” our search criteria included the terms “cost” or “economic\*” or “noneconomic\*” or “burden\*” or “challeng\*,” where \* indicates that the full word can include additional letters. The databases we searched, chosen for their comprehensive coverage, included EBSCO, ProQuest, ProQuest Dialog, and Scopus.

<sup>3</sup>Although we searched for articles published on or after January 2000, only one of the 36 studies we identified was published before 2010. It was published in 2008.

The studies we reviewed addressed some (but not necessarily all) of the direct medical costs of 33 of the estimated 7,000 or more rare diseases that have been identified to date. These studies used different methods and, therefore, highlighted different aspects of the costs. Each study provides specific information about the costs of rare disease, but the conclusions from any one study do not necessarily apply more generally to other rare diseases (individually or collectively).

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## Information Included in This Appendix

For each of the studies we reviewed, we provide the following information, in alphabetical order by the name of the disease or group of diseases under investigation:<sup>4</sup>

- **Citation.** We identify each study’s authors, article title, journal name, volume, year, and pages.
- **Disease.** We provide a brief description of the rare disease based on information published on NIH’s Genetic and Rare Diseases (GARD) Information Center website (unless otherwise indicated).<sup>5</sup>
- **Cost data.** We summarize several features of the cost data used by the researchers.
  - Type or types of costs, which could include:
    - Direct medical costs (costs for health care, such as costs for physician services or drugs).<sup>6</sup>
    - Direct nonmedical costs (costs attributable to disease, but not medical *per se*, such as costs for transportation to specialized treatment centers or for home modifications to accommodate disabilities).

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<sup>4</sup>When a specific rare disease was one of several diseases covered by a particular study, we present the study under the name of the group of diseases. We include the name of the specific disease in our alphabetical list with a cross-reference to the name of the group of diseases.

<sup>5</sup>Department of Health and Human Services, National Institutes of Health, National Center for Advancing Translational Sciences, *Genetic and Rare Diseases Information Center (GARD)*, accessed July 8, 2021, <https://rarediseases.info.nih.gov>. We interpreted listing of a disease on the GARD web-site, in the absence of a statement that the disease is not rare, as evidence that the disease is rare in the United States

<sup>6</sup>When referring to costs, we use the term “medical” to include all health care costs, whether specifically associated with medical professions or associated with other health professions (such as clinical psychology or respiratory therapy).



- Indirect costs (costs that do not correspond to payments but are indirect costs resulting from disease, such as lost income or diminished quality of life).<sup>7</sup>
- Source of the cost data (such as health care database or self-report).
- Year or years covered by the cost data that were accessed by the researchers (for example, the researchers might have accessed Medicaid data for the year 2010 or commercial insurance claims from 2008 through 2012).
- **Methods.** We note several features of the methods used in each study. This information includes
  - Whether costs were calculated with reference to a specific disease-related event.
    - Event-based methods identify the costs incurred by those with the disease during a time period defined by a specific event related to the disease—such as diagnosis or initiation of treatment—and can provide information about costs that are specific to the effect of that event or can ensure that those who are studied have that event in common.
    - Methods that are not event-based, in contrast, identify costs without regard to specific disease-related events—for example, costs incurred during a particular calendar year for people with the disease.<sup>8</sup>
  - Whether the costs that were studied were specific to the disease or could have been associated with any health concerns the person has—not just the rare disease, but also general health care and coexisting diseases often referred to as comorbid conditions. When costs of general health care and comorbid conditions were included, we refer to them as “all-cause” costs. As examples, the direct medical cost of a visit to a medical specialist about a person’s rare disease would be disease-specific; the cost

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<sup>7</sup>Whether direct medical, direct nonmedical, or indirect, the costs covered by any particular study do not necessarily include all possible relevant costs. For example, the costs of experimental drugs (those that are investigational and so do not yet have FDA approval to be marketed in the United States) would be considered direct medical costs but are not necessarily captured in cost databases. We do not provide full details about which specific costs were addressed in the studies we reviewed.

<sup>8</sup>We describe studies as event-based only if they were linked to a specific disease-related event that would be the same for all people about whom cost data were collected, such as costs immediately after diagnosis or after initiation of a treatment.

of that same person's annual physical or treatment for a comorbid condition would not be specific to the rare disease and so would be an all-cause cost. Similarly, direct nonmedical costs can be specific to the disease (e.g., transportation to a specialty clinic) or all-cause (e.g., transportation to one's annual physical or for treatment of a comorbid condition), and indirect costs can be specific to the disease (e.g., time without pay because of the rare disease) or all-cause (e.g., time without pay because of one's annual physical or a comorbid condition).

- Whether a comparison group was included, and, if so, what it was.
- **Estimated costs.** We provide key estimates of the costs of the studied rare disease(s) that were presented in the published article, such as estimates of the average annual cost per person—the per person, per year (PPPY) cost—or estimates of the cost per hospitalization. We also present similar data for any comparison group included in the study.<sup>9</sup>

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## Reviewed Studies on the Costs of Rare Diseases, by Disease

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### Acromegaly

- **Citation.** Liu, S., D. T. Adelman, Y. Xu, J. Sisco, S. M. Begelman, S. M. Webb, X. Badia, T. K. Thethi, V. Fonseca, and L. Shi. Patient-Centered Assessment on Disease Burden, Quality of Life, and Treatment Satisfaction Associated with Acromegaly. *Journal of Investigative Medicine*, vol. 66 (2018): pp. 653-660.
- **Disease.** Acromegaly is a disease in which the pituitary gland produces too much growth hormone. Signs and symptoms can include abnormal growth of the hands and feet, joint pain, and backbone fractures. It is usually caused by non-cancerous tumors on the pituitary gland. Treatment may include hormones, drugs, radiotherapy, or surgery. If untreated, it can result in serious illness,

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<sup>9</sup>Unless otherwise specified, the average we report was the arithmetic mean, which is calculated by summing a set of numbers and dividing by the number of numbers in the set.

comorbid conditions, such as diabetes or cardiovascular disease, and premature death.<sup>10</sup>

- **Cost data.** Out-of-pocket, direct medical costs specifically for acromegaly and indirect costs as assessed by a survey distributed to adults with acromegaly from August to October 2014. The survey asked about the last 3 months.
- **Methods.** Out-of-pocket medical costs specifically for acromegaly as well as indirect costs. The latter were estimated by multiplying reported units of impact (such as numbers of days of sick leave or days when the person needed to hire assistance with household chores) by typical wages. There was no comparison group of people without acromegaly.
- **Estimated costs** (in 2014 U.S. dollars).
  - The average self-reported out-of-pocket medical cost was \$1,790 PPPY.
  - Indirect costs, which averaged \$25,145 PPPY, varied with the person's symptoms: Compared to those who reported three or fewer symptoms over the past 3 months, those who reported four or more symptoms had higher indirect costs for such things as loss of job and inability to perform household chores.
  - Family members also experienced indirect costs averaging \$472 PPPY as a result of taking days off work to take care of the person with acromegaly.

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## Alpha-1 Antitrypsin Deficiency

- **Citation.** Sieluk, J., J. F. Slejko, H. Silverman, E. Perfetto, and C. D. Mullins. Medical Costs of Alpha-1 Antitrypsin Deficiency-Associated [Chronic Obstructive Pulmonary Disease] in the United States.<sup>11</sup> *Orphanet Journal of Rare Diseases*, vol. 15 (2020): pp. 260-271.
- **Disease.** Alpha-1 antitrypsin deficiency is an inherited disease that increases the risk of chronic obstructive pulmonary disease, liver disease, skin problems, and inflammation of the blood vessels. Although some people do not experience any problems, liver and skin problems may begin in childhood, while lung problems are most likely in adults. In addition to treatments for the comorbid conditions and to ameliorate symptoms, some people with lung problems due to alpha-1

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<sup>10</sup>When the tumors that result in excess growth hormone occur in childhood, the disease is called gigantism, rather than acromegaly.

<sup>11</sup>Here and elsewhere, we use brackets to replace abbreviations or acronyms with the full names of the diseases for which they stand.

antitrypsin deficiency may be given infusions of alpha-1 antitrypsin protein to prevent progression of lung disease.

- **Cost data.** Direct medical costs paid by insurance plans between January 2000 and August 2017 as indicated by claims in a national database covering commercially insured adults enrolled in large, private plans and some Medicare Advantage beneficiaries.<sup>12</sup>
- **Methods.** Event-based, counting all-cause medical costs for adults ages 30 to 65 with chronic obstructive pulmonary disease who did and did not have alpha-1 antitrypsin deficiency. These groups were matched on gender, race or ethnicity, region, and several disease-related variables; results were reported as the incremental cost of alpha-1 antitrypsin deficiency above and beyond costs for chronic obstructive pulmonary disease. Costs were assessed for 1 year before and 1 year after the diagnosis of chronic obstructive pulmonary disease.
- **Estimated costs** (in 2018 U.S. dollars).
  - Among people with chronic obstructive pulmonary disease, PPPY all-cause medical costs for those with alpha-1 antitrypsin deficiency were about twice the costs for those without that deficiency.
  - The average incremental cost of alpha-1 antitrypsin deficiency (i.e., the cost exceeding the cost for chronic obstructive pulmonary disease) was \$6,861 PPPY before diagnosis and \$5,772 PPPY after diagnosis.

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Amyotrophic Lateral  
Sclerosis

See neuromuscular diseases.

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Arteriovenous  
Malformations of the  
Central Nervous System

- **Disease.** Arteriovenous malformations of the central nervous system involve abnormal connections between arteries and veins in the central nervous system (the brain—intracranial arteriovenous malformations—or spinal cord—spinal arteriovenous malformations). Most people with brain or spinal arteriovenous malformation have few, if any, major symptoms. About 12 percent of people with this condition

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<sup>12</sup>Medicare beneficiaries may choose to enroll in Medicare Advantage plans, which are the private health care insurance plan alternative to Medicare's traditional fee-for-service program. Medicare is a federally financed program that provides health insurance coverage to people age 65 and older, certain individuals with disabilities, and those with end-stage renal disease (permanent kidney failure requiring dialysis or a transplant).

Intracranial Arteriovenous  
Malformation

have symptoms, which vary in severity; seizures and headaches are the most common symptoms. The cause of the malformations is not well understood, but they most often seem to arise during embryonic or fetal development.<sup>13</sup>

- **Citation.** Rutledge, C., J. Nelson, A. Lu, P. Nisson, S. Jonzzon, E. A. Winkler, D. Cooke, A. A. Abla, M. T. Lawton, and H. Kim. “Cost Determinants in Management of Brain Arteriovenous Malformations.” *Acta Neurochirurgica*, vol. 162 (2020): pp. 169-173.
- **Disease.** Intracranial arteriovenous malformations are in the brain. These malformations can rupture, causing a hemorrhage, which in turn can cause a stroke or death. Symptoms most commonly occur in adulthood, particularly in those ages 20 through about 50. Treatment can involve medications to address symptoms or surgery.
- **Cost data.** Direct medical costs between 2012 and 2015, as indicated in a database maintained by a San Francisco hospital where people can receive treatment for intracranial arteriovenous malformation.
- **Methods.** Event-based, counting direct medical costs for certain surgical or radiosurgical treatments specifically for intracranial arteriovenous malformation.<sup>14</sup> There was no comparison group of people without the disease.
- **Estimated costs** (in 2015 U.S. dollars).
  - The median direct medical cost specifically for the studied surgical treatments for intracranial arteriovenous was \$77,865 per person.<sup>15</sup>
- **Citation.** Yue, J. K., H. Deng, E. A. Winkler, A. Ordaz, E. M. Gillis-Buck, Y. M. Lee, M. M. Safaee, A. A. Abla, M. C. Huang, and S. S. Dhall. “Hospital Complications and Costs of Spinal Arteriovenous

Spinal Arteriovenous  
Malformation

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<sup>13</sup>We supplement the description of arteriovenous malformations of the central nervous system from GARD with information from an NIH institute, the National Institute of Neurological Disorders and Stroke.

<sup>14</sup>People who were treated for intracranial arteriovenous malformation using surgery, surgery with preoperative embolization, or radiosurgery were included in the study; those treated with embolization alone or other combinations of surgery, embolization, and radiosurgery were excluded.

<sup>15</sup>This study presented the median cost, rather than the average (or mean) cost. The median value is sometimes preferred when there are outliers, as the average can be dragged up or down by the presence of outliers. Outliers don't influence the median since it is just a middle value in a distribution.

Malformations in the United States from 2002-2014.” *Journal of Neurosurgical Sciences*, vol. 65, no. 1 (2021): pp. 54-62.

- **Disease.** Spinal arteriovenous malformations are in the spinal cord and can cause sudden and severe back pain; sensory disturbances, muscle weakness, or degeneration of nerves and paralysis in the parts of the body below the malformation. Treatment can involve surgery or endovascular embolization, an alternative to open surgery in which the blood supply to the relevant artery is cut off.
- **Cost data.** Direct medical costs for hospitalizations between 2002 and 2014, as estimated using a large, national, inpatient database.
- **Methods.** Event-based, counting direct, all-cause medical costs of hospitalizations for certain treatments of a spinal arteriovenous malformation.<sup>16</sup> There was no comparison group of people without the disease.
- **Estimated costs** (in 2014 U.S. dollars).
  - The average cost of a hospitalization for treatment of a spinal arteriovenous malformation was \$41,216.
  - Complications had an effect on costs: When there were no recorded complications, the average cost was \$36,562. For the 15 percent of people who experienced inpatient complications, the average cost was \$67,571.

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## Cardiac Amyloidosis

- **Citation.** Quock, T. P., T. Yan, R. Tieu, A. D’Souza, and M. S. Broder. Untangling the Clinical and Economic Burden of Hospitalization for Cardiac Amyloidosis in the United States. *Clinicoeconomics and Outcomes Research*, vol. 11 (2019): pp. 431-439.
- **Disease.** Cardiac amyloidosis is a disease in which an abnormal protein called amyloid builds up in heart tissue. Over time, the amyloid deposits take the place of normal heart muscle, causing dysfunction.<sup>17</sup> According to the study authors, the prognosis for cardiac amyloidosis is poor—the disease is severe and progressive, and death without treatment typically occurs within about 6 months of the development of symptomatic cardiac dysfunction.

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<sup>16</sup>These treatments were a specific surgical intervention or endovascular embolization.

<sup>17</sup>Because cardiac amyloidosis is not listed in GARD under that name, this description is based on information from MedlinePlus, a website provided by NIH and the National Library of Medicine.

- **Cost data.** Direct medical costs for hospitalizations from 2014 to 2016 as indicated by a database covering about 600 hospitals.
- **Methods.** Direct, all-cause medical costs of hospitalizations for cardiac dysfunction for adults with cardiac amyloidosis.<sup>18</sup> The study presents information about the costs of certain re-hospitalizations, but the main data set included only one hospitalization per person. There was no comparison group of people without the disease.
- **Estimated costs** (in 2016 U.S. dollars).
  - The average cost of a hospitalization for cardiac dysfunction among those with cardiac amyloidosis was \$20,584.
  - More than half (55.4 percent) of those who were hospitalized also had renal disease, a common comorbid condition when heart disease results in low cardiac output. The average hospitalization cost was higher for those with both cardiac amyloidosis and renal disease (\$24,238) than for those without renal disease (\$16,041).
  - The in-hospital mortality rate was 9 percent; for those discharged alive and for whom 30-day follow-up data were available, 16.8 percent were readmitted within 30 days at an average per-person cost of \$18,536.

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## Central Precocious Puberty

- **Citation.** Klein, K., A. M. Soliman, M. Bonafede, J. K. Nelson, and E. Grubb. "Health Care Utilization and Economic Burden in Patients with Central Precocious Puberty: An Assessment of the Commercially Insured and Medicaid Populations." *Journal of Managed Care & Specialty Pharmacy*, vol. 25, no. 7 (2019): pp. 836-846.
- **Disease.** Central precocious puberty is a disease in which sexual and physical characteristics develop and mature earlier than normal—before age 8 for girls or before age 9 for boys. Although it can be inherited, the cause is not always known. Treatment involves medications that stop the body from releasing sexual hormones. If untreated, results can include psychological and behavioral problems.<sup>19</sup>

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<sup>18</sup>People with hereditary amyloidosis were excluded from the study, as were people with an inflammatory amyloidosis.

<sup>19</sup>We supplemented the description of precocious puberty from GARD with information from MedlinePlus.

- **Cost data.** Costs were direct medical costs as indicated in claims in a commercial insurance database and a database covering Medicaid beneficiaries from January 2009 through September 2015.<sup>20</sup>
- **Methods.** Event-based, counting direct, all-cause medical costs for the year before and at least one year after the date of initiation of treatment. These costs were compared to costs for a group of people without central precocious puberty who were matched on age, sex, region, and other variables.
- **Estimated costs** (in 2015 U.S. dollars).
  - Direct, all-cause medical costs were higher for those with central precocious puberty after initiation of treatment than before initiation of treatment, and they were higher for those with the disease than for those without it both before and after diagnosis.<sup>21</sup>
    - For commercially insured patients, these PPPY costs for those with central precocious puberty averaged \$14,338 before initiation of treatment and \$37,135 after initiation of treatment, compared to PPPY costs for those without the disease of \$1,595 before the matched initiation-of-treatment date and \$1,665 afterwards.
    - For Medicaid beneficiaries, these PPPY costs for those with central precocious puberty averaged \$16,097 before initiation of treatment and \$29,249 after initiation of treatment, compared to PPPY costs for those without the disease of \$2,484 before the matched initiation-of-treatment date and \$2,665 afterwards.
    - The increase in PPPY averages for those with central precocious puberty after initiation of treatment was primarily attributable to increases in outpatient services and pharmacy costs.

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## Childhood-Onset Epilepsies

- **Disease.** Epilepsy is a brain disease marked by recurrent seizures. Seizures can result in injury, and certain childhood-onset epilepsies

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<sup>20</sup>Medicaid is a joint federal-state program that finances health care coverage for low-income and medically needy individuals,

<sup>21</sup>Those in the comparison group did not have an initiation-of-treatment date and had instead been assigned an initiation-of-treatment date based on the study's matching criteria.



Dravet Syndrome

are associated with substantially higher rates of treatment-resistant seizures than other epileptic diseases.<sup>22</sup>

- **Citation.** Whittington, M. D., K. G. Knupp, G. Vanderveen, C. Kim, A. Gammaitoni, and J. D. Campbell. "The Direct and Indirect Costs of Dravet Syndrome." *Epilepsy & Behavior*, vol. 80 (2018): pp. 109-113.
- **Disease.** Dravet syndrome is a type of severe epilepsy with seizures first occurring in infancy. In addition to seizures, symptoms include loss of motor skills, intellectual disability, speech impairment, and difficulty moving. Caused when a particular gene (called the SCN1A gene) is not working correctly, Dravet syndrome can be inherited, but most people with the disease do not have a family history of it. The main goal of treatment is to reduce the number and length of seizures, but the seizures of this type of epilepsy can be difficult to treat.
- **Cost data.** Direct medical costs and indirect costs as estimated based on answers to a survey. The survey was administered to caregivers of children (under age 18) with Dravet syndrome in Colorado. Direct medical costs (including both traditional health care services, such as outpatient doctor visits, and alternative health care services, such as multivitamin use) were estimated by multiplying reported health care service utilization by representative unit prices. Indirect costs (including lost productivity and lost leisure time) were reported for one week and assumed to be typical.
- **Methods.** Direct, all-cause medical costs and indirect costs for people with Dravet syndrome or their caregivers. There was no comparison group of people without the disease.
- **Estimated costs** (in 2016 U.S. dollars).
  - The average PPPY cost for direct, all-cause medical expenses was \$27,276.
  - The average PPPY indirect cost was \$81,582.
  - The average number of 8-hour work days that caregivers reported spending providing care to a child with Dravet syndrome was 380, more than the total number of work days in a year. Nearly two-thirds of caregivers reported a job change (lost job, quit job or retired early, or switched jobs).

Lennox-Gastaut Syndrome

- **Citation.** Reaven, N. L., S. E. Funk, G. D. Montouris, T. B. Saurer, and T. J. Story. "Burden of Illness in Patients with Possible Lennox-

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<sup>22</sup>Because childhood-onset epilepsies are not listed in GARD under that name, this description includes information from MedlinePlus and research we reviewed.

Gastaut Syndrome: A Retrospective Claims-Based Study.” *Epilepsy & Behavior*, vol. 88 (2018): pp 66-73.

- **Disease.** Lennox-Gastaut syndrome is a severe epilepsy that begins in childhood and is marked by multiple types of seizures and intellectual disability. It can be caused by brain malformations, perinatal lack of oxygen, severe head injury, infection of the central nervous system, or certain inherited degenerative or metabolic diseases; in about one-third of cases, no cause is identified. Treatment is generally intended to control seizures, which may be treatment resistant.
- **Cost data.** Direct medical costs between October 2010 and September 2015 as indicated by claims in a national database including commercially insured adults and Medicaid beneficiaries.
- **Methods.** Direct, all-cause medical costs over 2 years for those identified with possible Lennox-Gastaut syndrome.<sup>23</sup> Their costs were compared to costs for people without epilepsy or seizures who were matched for age, gender, geographic region, type of insurance, and approximate dates of insurance coverage.
- **Estimated costs** (in 2017 U.S. dollars).
  - Direct, all-cause medical costs were higher for those with possible Lennox-Gastaut syndrome than for those without a diagnosis of any childhood-onset epilepsy:
  - For Medicaid beneficiaries, the PPPY average was \$63,930 for those with Lennox-Gastaut syndrome and \$3,849 for those without childhood-onset epilepsy.
  - For commercially insured people, the PPPY average was \$65,026 for those with Lennox-Gastaut syndrome and \$2,442 for those without childhood-onset epilepsy.
- **Citation.** Reaven, N. L., S. E. Funk, P. D. Lyons, and T. J. Story. “The Direct Cost of Seizure Events in Severe Childhood-Onset Epilepsies: A Retrospective Claims-Based Analysis.” *Epilepsy & Behavior*, vol. 93 (2019): pp. 65-72.
- **Disease.** This study addressed three diseases associated with severe, treatment-resistant seizures:

Treatment-Resistant Seizure  
Disorders

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<sup>23</sup>Lennox-Gastaut syndrome could not be definitively diagnosed from the information in the health care databases used for this research.

- Dravet syndrome (a type of childhood-onset epilepsy described above);
- Lennox-Gastaut syndrome (a type of childhood-onset epilepsy described above); and
- Tuberous sclerosis complex (a disease involving tumor growth, described below).<sup>24</sup>
- **Cost data.** Direct medical costs as indicated by claims from 2010 to 2015 in a national database including commercially insured adults and Medicaid beneficiaries.
- **Methods.** Prevalence based, counting direct, all-cause medical costs for 2 years for people with one of the three studied diseases, as well as costs for seizure events requiring acute treatment during that time. There was no comparison group of people without childhood-onset epilepsies.
- **Estimated costs** (in 2017 U.S. dollars).
  - The all-cause medical cost per seizure event requiring acute treatment varied with disease and insurance type. Specifically, the average direct medical cost per event, counting all-cause costs, was lower for Medicaid beneficiaries than for commercially insured people. The cost for Medicaid beneficiaries is listed first below, followed by the cost for commercially insured patients.
    - For Dravet syndrome, the cost per event averaged \$4,637 or \$8,751.
    - For Lennox-Gastaut syndrome, the cost per event averaged \$8,147 or \$14,759.
    - For tuberous sclerosis complex, the cost per event averaged \$5,335 or \$9,672.
  - In general, when a seizure resulted in injury, the more severe the injury the higher the average costs per event.<sup>25</sup>

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<sup>24</sup>Because certain childhood-onset epilepsies could not be definitively diagnosed from the information in the health care databases used for this research, the authors presented their findings in terms of likely diagnoses. Although tuberous sclerosis complex is associated with treatment-resistant seizures, it is not identified as a childhood-onset epilepsy in GARD.

<sup>25</sup>All direct medical costs for a seizure, including costs for comorbid conditions, were defined as costs through hospital discharge if there was no injury, within 10 days of the event if there was minor injury, within 30 days if there was moderate injury, and within 90 days if there was severe injury.

- For people who had a seizure during the studied time period, the average direct all-cause medical costs, including all-cause costs, varied with disease and insurance type. The cost for Medicaid beneficiaries is again listed first below, followed by the cost for commercially insured patients.
  - For Dravet syndrome, these PPPY costs averaged \$31,278 or \$43,758.
  - For Lennox-Gastaut syndrome, these PPPY costs averaged \$71,512 or \$84,939.
  - For tuberous sclerosis complex, these PPPY costs averaged \$42,997 or \$48,330.

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### Chronic Inflammatory Demyelinating Polyneuropathy

- **Citation.** Divino, V., R. Mallick, M. DeKoven, and G. Krishnarajah. "The Economic Burden of [Chronic Inflammatory Demyelinating Polyneuropathy] in the United States: A Case-Control Study." *PLoS ONE*, vol. 13, no. 10 (2018): pp. 1-7.
- **Disease.** Chronic inflammatory demyelinating polyneuropathy is a neurological disease that causes progressive weakness and impaired sensory function in the legs and arms. It is thought to be caused by the immune system mistakenly attacking and damaging the myelin sheath that provides a protective cover for peripheral nerves. Several different treatment options exist; if not treated early, permanent damage can result.
- **Cost data.** Direct medical costs for adults (age 18 or older) between January 2010 and June 2016, as indicated by adjudicated claims in a national commercial insurance database.<sup>26</sup>
- **Methods.** Event-based, counting (a) direct, all-cause medical costs and (b) direct medical costs specifically for therapy to treat chronic inflammatory demyelinating polyneuropathy. Costs were measured from the time of first claim indicative of chronic inflammatory demyelinating polyneuropathy until at least 2 years later. Costs for those with chronic inflammatory demyelinating polyneuropathy were compared to costs for a group of people who did not have the disease and who had been matched for age, gender, geographic region, health plan type, payer type, and a measure related to comorbid conditions.

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<sup>26</sup>Adjudication is the process of determining if a claim should be paid based on the services rendered, the patient's covered benefits, and the provider's authority to render the services. Fully adjudicated claims are those for which this process has been completed.

- **Estimated costs** (in 2016 U.S. dollars).
    - Those with chronic inflammatory demyelinating polyneuropathy had higher average direct, all-cause medical costs over the two years of study (\$116,330) than those without the disease (\$15,586).
    - The average per person cost specifically for therapy for chronic inflammatory demyelinating polyneuropathy over the two years of study was \$59,619.
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### Chronic Myeloid Leukemia

- **Citation.** Doshi, J. A., P. Li, A. R. Pettit, J. S. Dougherty, A. Flint, and V. P. Ladage. "Reducing Out-of-Pocket Cost Barriers to Specialty Drug Use Under Medicare Part D: Addressing the Problem of 'Too Much Too Soon.'" *American Journal of Managed Care Supplement*, vol. 23, no. 3, (2017): pp. S39-S45.
- **Disease.** Chronic myeloid leukemia is a slow-growing cancer of the bone marrow, which produces blood cells. In chronic myeloid leukemia, the marrow produces too many white blood cells. As the disease progresses, immature white blood cells accumulate in the blood and bone marrow, impairing the development of other blood cells and resulting in a shortage of red blood cells and platelets. Chronic myeloid leukemia usually begins after age 60 and is caused by a genetic mutation that occurs during a person's lifetime. Serious infections and uncontrolled bleeding can be life threatening. Bone marrow transplantation is the only cure for this disease, but the FDA has approved several drugs for use in certain patients with chronic myeloid leukemia.
- **Cost data.** Direct out-of-pocket drug costs for Medicare fee-for-service beneficiaries who opted for the program's prescription drug benefit, as indicated by Medicare data from 2012.
- **Methods.** Out-of-pocket costs for all drugs (whether specific to the disease or not) that were incurred by patients being treated continuously throughout the year, with certain high-cost specialty drugs with an indication for use in the treatment of chronic myeloid leukemia. Similar costs were calculated for people being treated with other high-cost specialty drugs, namely, people with rheumatoid arthritis and people with multiple sclerosis who were treated throughout the year with high-cost, disease-specific, specialty drugs.
- **Estimated costs** (in 2012 U.S. dollars).
  - The average out-of-pocket drug cost for people with chronic myeloid leukemia was \$6,322 PPPY.

- The majority of this cost for all drugs—95 percent—represented costs for specialty drugs specifically for the treatment of chronic myeloid leukemia.
  - In comparison, out-of-pocket PPPY costs averaged \$3,949 for those with rheumatoid arthritis and \$5,238 for those with multiple sclerosis.
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Corticobasal Degeneration    See frontotemporal degeneration.

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### Cushing’s Syndrome

- **Citation.** Broder, M. S., M. P. Neary, E. Chang, D. Cherepanov, and W. H. Ludlam. “Burden of Illness, Annual Healthcare Utilization, and Costs Associated with Commercially Insured Patients with Cushing Disease in the United States.” *Endocrine Practice*, vol. 21, no. 1 (2015): pp. 77-86.
  - **Disease.** Cushing’s syndrome is an endocrine disease resulting from prolonged exposure of the body’s tissues to cortisol, a hormone produced by the adrenal gland. In rare cases, it is inherited; in most cases, it is not. Causes can include long-term use of corticosteroid medications or tumors in the pituitary or adrenal gland. Treatment could involve surgery to remove a tumor or medications to decrease cortisol levels. According to the study authors, elevated cortisol levels affect every organ system and therefore produce a variety of symptoms, with obesity, diabetes, depression, and osteoporosis among the more common ones.
  - **Cost data.** Direct medical costs as indicated by claims for services in 2010 recorded in either of two commercial insurance databases.
  - **Methods.** Total, all-cause medical costs for those with Cushing’s syndrome and, separately, costs specifically for Cushing’s syndrome. There was no comparison group of people without the disease.
  - **Estimated costs** (in 2010 U.S. dollars).
    - The average PPPY direct, all-cause medical cost was \$34,992 (median: \$18,031).
    - The average PPPY direct medical cost specifically for Cushing’s syndrome was \$14,310 (median: \$2,079).
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### Cystic Fibrosis

- **Citation.** Grosse, S. D., T. Q. N. Do, M. Vu, L. B., Feng, J. G., Berry, and G. S. Sawicki. “Healthcare Expenditures for Privately Insured [U.S.] Patients with Cystic Fibrosis, 2010-2016.” *Pediatric Pulmonology*, vol. 53 (2018): pp. 1611-1618.

- **Disease.** Cystic fibrosis is a genetic disorder that causes mucus to build up and damage organs in the body, particularly the lungs and pancreas. Over time, mucus buildup and infections can lead to permanent lung damage. Treatment generally aims to relieve symptoms, and there is currently no cure for the disease; but, as noted by the study authors, certain treatments intended to address the underlying genetic mutation—cystic fibrosis transmembrane conductance regulator modulators—hold promise for use with certain patients.<sup>27</sup> The first of these drugs received FDA approval for use with some cystic fibrosis patients in 2012.
- **Cost data.** Direct medical costs as indicated by claims for services from 2010 through 2016 recorded in a large commercial insurance database.
- **Methods.** Total all-cause costs incurred during at least one year by people with cystic fibrosis who were under age 65. There was no comparison group of people without the disease.
- **Estimated costs** (in 2016 U.S. dollars).
  - All-cause medical costs for those with cystic fibrosis increased from 2010 to 2016. The PPPY average more than doubled from \$61,591 in 2010 (expressed in 2016 dollars) to \$130,879 in 2016.
    - Costs began to increase in 2012 and then increased even more rapidly beginning in 2015.
    - Most of the growth in PPPY costs was due to an increase in the costs of outpatient drugs, which accounted for 36 percent of direct medical costs in 2010 and 64 percent of those costs in 2016. More specifically, the increase in costs for outpatient drugs was primarily due to spending for specialty drugs, including cystic fibrosis transmembrane conductance regulator modulators.<sup>28</sup>

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<sup>27</sup>Cystic fibrosis is caused by mutations in the gene encoding a specific protein called the cystic fibrosis transmembrane conductance regulator protein. More than 900 mutations of this gene have been found; these mutations can be grouped based on certain common features, such as the effect the mutation has on the length of the protein or the amount of the protein at the membrane. Cystic fibrosis transmembrane conductance regulator modulators are therapies that target specific types of mutations, potentially correcting the fundamental genetic defect.

<sup>28</sup>Specialty drugs costing \$1,000 or more per prescription or per month that may be used in addition to cystic fibrosis transmembrane conductance regulator modulators for people with cystic fibrosis include pulmonary medications to treat chronic infection, inflammation, and airway obstruction by mucus and pancreatic enzyme products.

- All-cause medical costs were greater for adults with cystic fibrosis than for children with the disease. For example, in 2016 the PPPY average for an adult was \$140,564, compared to the PPPY average for a child (under age 18) of \$116,171.
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## Dermatomyositis

- **Citation.** Kwa, M. C., K. Ardlan, A. E. Laumann, and J. I. Silverberg. "Predictors of Hospitalization, Length of Stay, and Cost of Care among Adults with Dermatomyositis in the United States." *Arthritis Care & Research*, vol. 69, no. 9 (2017): pp. 1391-1399.
  - **Disease.** Dermatomyositis is an autoimmune disease that causes skin changes and muscle weakness. It is most common in adults between ages 40 and 60 and in children between ages 5 and 15. Muscle weakness gets worse over time and can lead to stiff joints and muscle wasting. The cause is unknown. Treatment is focused on managing the symptoms and may include medications, physical therapy, and exercise.
  - **Cost data.** Direct medical costs from 2002 through 2012 as indicated by a national healthcare database.
  - **Methods.** Direct, all-cause medical costs for acute hospitalizations related to dermatomyositis compared to costs for a group of people without the disease.<sup>29</sup>
  - **Estimated costs** (in 2014 U.S. dollars).
    - The average costs of an acute hospitalization for people with a primary or secondary diagnosis of dermatomyositis were \$11,682 and \$9,712, respectively. In contrast, the average cost of an acute hospitalization for people without dermatomyositis was \$7,620.<sup>30</sup>
    - The average cost of an acute hospitalization for people with a primary diagnosis of dermatomyositis was higher for Asians, those in the western region of the United States, and those with multiple chronic conditions.
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## Dravet Syndrome

See childhood-onset epilepsies.

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<sup>29</sup>Dermatomyositis is associated with malignancies, infections, and cardiovascular disease, any of which may result in hospitalization.

<sup>30</sup>The term "average" normally refers to an arithmetic mean. When the numbers in the set include extreme outliers or when the largest values are many times larger than the smaller values, arithmetic means can be misleading. This study reported geometric means, which are better suited to such data than arithmetic means.



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Duchenne Muscular  
Dystrophy

See neuromuscular diseases.

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Fragile X Syndrome

- **Citation.** Sacco, P., G. Capkun-Niggli, X. Zhang, and R. Jose. "The Economic Burden of Fragile X Syndrome: Healthcare Resource Utilization in the United States." *American Health & Drug Benefits*, vol. 6, no. 2 (2013): pp. 73-83.
- **Disease.** Fragile X syndrome, a genetic disease involving changes in part of the X chromosome, causes a range of developmental problems, including learning disabilities and cognitive impairment. Other symptoms may include seizures or problems with communication and social interaction. There is no cure, but early physical and educational therapies are recommended.
- **Cost data.** Direct medical costs for claims from 2004 through 2009 as indicated by commercial insurance, supplemental Medicare, and Medicaid databases.
- **Methods.** Prevalence based, counting 1 year of direct, all-cause medical costs for people with fragile X syndrome. There was no comparison group of people without the disease.
- **Estimated costs.**<sup>31</sup>
  - Direct, all-cause medical costs for those with fragile X syndrome varied with type of health care need during the study period and type of insurance.
    - For those who had one or more hospitalizations during the year, the average PPPY cost was \$25,847 for Medicaid beneficiaries (median: \$4,468) and \$21,677 for those with commercial insurance or Medicare (median: \$7,740).
    - For those who had one or more outpatient visits during the year, the average PPPY cost was \$12,608 for Medicaid beneficiaries (median: \$3,355) and \$4,643 for those with commercial insurance or Medicare (median: \$1,751).

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Friedreich Ataxia

- **Citation.** Polek, B., M. J. Roach, W. T., Andrews, M. Ehling, and S. Salek. Burden of Friedreich's Ataxia to the Patients and Healthcare Systems in the United States and Canada. *Frontiers in Pharmacology*, vol. 4 (2013): pp. 1-7.

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<sup>31</sup>The published article does not state whether costs were adjusted to reflect dollar values for a particular year.

- **Disease.** Friedreich ataxia is an inherited disease that affects the nervous system and causes movement problems. People with the disease generally begin to experience signs and symptoms around puberty, although it can be much later. The disease is progressive: Difficulty walking and signs of impaired muscle coordination gradually worsen and spread; muscles—especially those in the extremities—begin to weaken and waste away; and other symptoms, including some life-threatening comorbid conditions (such as heart disease) may appear. People with Friedreich ataxia typically need to use a wheelchair consistently within 10 or 20 years of their first symptoms. According to the study authors, the life expectancy of those with the disease is 40 to 50 years.
- **Cost data.** Direct medical and nonmedical costs as reported on a survey completed by people with Friedreich ataxia or their caregivers. The survey covered costs for 1 year, primarily in 2010, asking participants about car and home adaptations and about health care utilization. Medical care costs were estimated by multiplying reports of health care utilization units by unit costs.
- **Methods.** Prevalence based, counting 1 year of direct, all-cause costs for people with Friedreich ataxia. The study did not collect data about costs for a comparison group of people without the disease.<sup>32</sup>
- **Estimated costs** (in 2010 U.S. dollars).
  - Total medical costs for those with Friedreich ataxia averaged \$12,850 PPPY.
  - For those patients with annual medical costs that exceeded \$100,000, the largest component of the costs was paid home health care.
  - PPPY costs for home health care, drugs, and car adaptations were greater for those who were reported being severely affected by the disease than for those reporting a less severe impact.

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## Frontotemporal Degeneration

- **Citation.** Galvin, J. E., D. H. Howard, S. S. Denny, S. Dickinson, and N. Tatton. "The Social and Economic Burden of Frontotemporal Degeneration." *Neurology*, vol. 89 (2017): pp. 2049-2056.
- **Disease.** This study addressed costs associated with several types of frontotemporal degeneration, each of which can involve the progressive loss of function, such as loss of movement or cognitive

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<sup>32</sup>The study compared costs for those with Friedreich ataxia within the United States to those in Canada. We report only the U.S. costs.

abilities. Changes in social behavior and personality or problems with language or both are also common.

- Corticobasal degeneration is a disease involving degeneration of parts of the brain including the cerebral cortex (which is involved in processing information) and the basal ganglia (involved in movement). Signs and symptoms include the progressive loss of movement, cognitive impairment, and speech impairment. The genetic basis of the disease is not fully understood.
- Frontotemporal dementias are a group of neurodegenerative diseases associated with shrinkage of the frontal and temporal anterior lobes of the brain. Symptoms include marked changes in social behavior and personality or problems with language or both. Some people with these dementias also develop problems associated with destruction of motor neurons, the cells that control muscle activity such as walking, breathing, and swallowing. These dementias have a strong genetic component.
- Progressive supranuclear palsy is a degenerative neurologic disease associated with damage to nerve cells in the brain. It is a progressive disease that is sometimes, but not usually, inherited. Signs and symptoms vary, and typically involve problems with balance, vision, eye movement; changes in mood, behavior, and judgment; cognitive decline; and problems with speech.

According to the study authors, all forms of frontotemporal degeneration cause progressive loss of function and independence over a period of 2 to 20 years. Many people with frontotemporal degeneration are diagnosed in their prime earning years, have dependent children, and have difficulty accessing services developed primarily for older adults with dementia.

- **Cost data.** Direct costs—medical and nonmedical—and indirect costs as estimated based on answers to a survey administered to primary caregivers of people with frontotemporal degeneration. Assessed indirect costs included unpaid home care provided by family and friends and the lost wages of those with the disease and their caregivers. Medical costs were estimated by multiplying service utilization, as reported on the survey, by representative unit prices. The reported frequencies of certain direct nonmedical effects were also assessed but not quantified in dollars.
- **Methods.** Costs associated with dementia for people with frontotemporal degeneration or their primary caregivers. Estimation of the loss in household income was event-based, comparing reported

income before and after diagnosis. There was no comparison group of people without frontotemporal degeneration.

- **Estimated costs** (in 2016 U.S. dollars).
  - The total average PPPY cost was \$119,654: \$47,916 in direct costs and \$71,737 in indirect costs.
    - Average annual costs varied with the person’s age, disease type and progress, and sex. For example, total direct costs were generally greater for those aged 65 or older than those under age 65, while total indirect costs were generally greater for those under 65 than for those age 65 or older).
  - Direct nonmedical costs included reported costs resulting from poor financial decisions and legal costs: Poor financial decisions were reported by 58 percent of survey respondents, and legal costs (such as costs for court appearances to establish legal guardianship or attorney fees for revising wills) were reported by 9.6 percent of respondents).<sup>33</sup>
  - Indirect costs included effects on income, quality of life, and caregiver health):
    - On average, household income was lower 1 year after diagnosis (ranging from \$50,000 to \$59,999) than it had been 1 year before diagnosis (ranging from \$75,000 to \$99,000), a decline attributed by the study authors to lost days of work and early departure from the workforce.
    - Reported quality of life declined with the severity of the disease.
    - Results also indicated that caregivers for those with frontotemporal degeneration often experienced adverse health effects and costs: 67 percent reported a decline in health, and 53 percent reported an increase in their personal health care costs.

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Frontotemporal Dementia

See frontotemporal degeneration.

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Guillain-Barré Syndrome

- **Citation.** Frenzen, P. D. “Economic Cost of Guillain-Barré Syndrome in the United States.” *Neurology*, vol. 71 (2008): pp. 21-27.
- **Disease.** Guillain-Barré syndrome is an autoimmune disease affecting the peripheral nervous system, which carries signals from the brain to

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<sup>33</sup>The study did not include a definition of “poor financial decision.”

the muscles. Symptoms such as muscle weakness, numbness, and tingling sensations can increase until paralysis occurs. The exact cause is unknown, although most cases follow viral infection. There is no cure, but symptoms can generally be improved. According to the study, most people recover spontaneously, but some will require mechanical ventilation or develop permanent motor or sensory impairments, and some people with Guillain-Barré syndrome die from it.

- **Cost data.**
  - Direct medical costs for people who had been hospitalized for Guillain-Barré syndrome in 2004. Costs were estimated using utilization data in a nationwide databases and multiplying health care service utilization units by representative unit prices.
  - Indirect costs:
    - Costs due to lost productivity were estimated based on prior survey responses from adults interviewed 25 to 50 months after onset of the disease.
    - Costs due to premature death were estimated based on data regarding deaths caused by Guillain-Barré syndrome and projections of the value of lost years.
- **Methods.** Direct, all-cause medical costs, but excluding outpatient medications. There was no comparison group of people without the disease.
- **Estimated costs** (in 2004 U.S. dollars).
  - The annual total cost to the United States of Guillain-Barré syndrome was \$1.7 billion: \$0.2 billion in direct medical costs and \$1.5 billion in indirect costs. The authors attributed 60 percent of the total annual cost to premature death.
  - The average PPPY cost of the disease, including direct and indirect costs, was \$318,966.
    - The average PPPY was \$45,301 for direct all-cause medical expenses.
    - For disabled workers, the estimated PPPY cost of foregone earnings was \$186,416.

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## Hemophilia

**Disease.** Hemophilia is a bleeding disease in which the blood does not clot normally. It ranges in severity; in severe cases, heavy bleeding occurs after minor injury or even when there is no injury, and bleeding into the joints, muscles, brain, or organs can cause serious

Hemophilia A

complications. The main treatment is replacement therapy, during which a medication that includes a substance to facilitate clotting—a clotting factor—is dripped or injected slowly into a vein. This treatment can be episodic, when the clotting factor replacement therapy is provided after a bleeding episode, or prophylactic, when the clotting factor replacement therapy is provided on a regular basis to prevent bleeding.

- **Citation.** Zhou, Z.-Y., M. A. Koerper, K. A. Johnson, B. Riske, J. R. Baker, M. Ullman, R. Curtis, J.-L. Poon, M. Lou, and M. B. Nichol. “Burden of Illness: Direct and Indirect Costs among Persons with Hemophilia A in the United States.” *Journal of Medical Economics*, vol. 18, no. 6 (2015): pp. 457-465.
- **Disease.** Hemophilia A is an inherited form of hemophilia that primarily affects males and involves a deficiency in a specific blood clotting factor called factor VIII. Some people with severe hemophilia A may have a shortened lifespan due to the presence of other health conditions and rare complications of the disease.
- **Cost data.**
  - Direct medical costs for people receiving care at hemophilia treatment centers who were recruited into the study between July 2005 and July 2007. Costs were estimated by multiplying health care service utilization units by their representative unit prices).
  - Indirect productivity costs were estimated based on responses to a survey and included wages for self-reported missed work for people with hemophilia A or their employed parents, lost wages for working part time or not working due to hemophilia, and unpaid caregiver costs.
- **Methods.** Costs specifically for hemophilia among those with hemophilia A. Costs for health care utilization (e.g., hospitalization and outpatient visits) were assessed for 1 year, and costs for replacement clotting factor medication were assessed for 2 years.<sup>34</sup> There was no comparison group of people without hemophilia.
- **Estimated costs** (in 2011 U.S. dollars).
  - For people with hemophilia A who had not developed antibodies that would require higher than usual doses of replacement clotting

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<sup>34</sup>The cost of the replacement clotting factor, which is specifically for the treatment of hemophilia, accounted for 92 percent of the total direct medical costs identified in this study)

factor, the average PPPY direct cost for medical services specifically for hemophilia A was \$185,256 (median: \$113,857).<sup>35</sup>

- Average PPPY medical costs specifically for hemophilia varied with severity and, if severe, the type of treatment—episodic or prophylactic: These costs were
  - \$53,907 (median: \$5,863) for those with mild hemophilia;
  - \$75,320 (median: \$32,687) for those with moderately severe hemophilia;
  - \$184,518 (median: \$125,385) for those with severe hemophilia treated episodically; and
  - \$292,525 (median: \$272,892) for those with severe hemophilia treated prophylactically).
- The average PPPY indirect cost for people who had not developed antibodies that would require higher doses of clotting factors than usual was \$10,076 (median: \$233). As with direct hemophilia-related medical costs, average indirect costs varied with severity and type of treatment. These costs were
  - \$5,195 (median: \$0) for those with mild hemophilia;
  - \$9,043 (median: \$0) for those with moderately severe hemophilia;
  - \$16,952 (median: \$301) for those with severe hemophilia treated episodically; and
  - \$8,867 (median: \$376) for those with severe hemophilia treated prophylactically).

## Hemophilia B

- **Citation.** Chen, C. X., J. R. Baker, and M. B. Nichol. “Economic Burden of Illness among Persons with Hemophilia B from HUGS Vb: Examining the Association of Severity and Treatment Regimens with Costs and Annual Bleed Rates.” *Value in Health*, vol. 20. (2017): pp. 1074-1082.
- **Disease.** Hemophilia B is an inherited form of hemophilia that primarily affects males and involves a deficiency in a specific blood clotting factor called factor IX.

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<sup>35</sup>Average annual direct medical costs for hemophilia for 10 people who had developed antibodies that would require higher doses of clotting factors than usual were \$978,955 (median: \$554,916).

- **Cost data.**
  - Direct medical costs for people receiving care at hemophilia treatment centers who were recruited into the study between 2009 and 2014. Costs were estimated by multiplying health care service utilization units by their representative unit prices.
  - Indirect productivity costs were estimated based on responses to a survey and included wages for self-reported missed work for people with hemophilia B or their employed parents, lost wages for working part time or not working due to hemophilia, and unpaid caregiver costs.
- **Methods.** Direct all-cause medical costs for people with hemophilia B. Costs for health care utilization (e.g., hospitalization and outpatient visits) were assessed for 1 year, and costs for replacement clotting factor medication were assessed for 2 years. There was no comparison group of people without hemophilia.
- **Estimated costs** (in 2014 U.S. dollars).
  - The average PPPY cost, including direct, all-cause medical costs and indirect costs, was \$140,240 (median: \$63,617) for people who had not developed antibodies that would require higher than usual doses of replacement clotting factor.<sup>36</sup>
    - For these people, PPPY costs were higher for those with severe hemophilia (\$198,733) than for those with mild or moderate hemophilia (\$85,852).
  - For those with severe hemophilia, average PPPY costs varied with the type of treatment—episodic or prophylactic.
    - Average medical costs were lower with episodic treatment (\$103,630) than with prophylactic treatment (\$256,775).
    - Average indirect costs were higher with episodic treatment (\$10,957) than with prophylactic treatment (\$6,477).

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## Hereditary Angioedema

- **Citation.** Wilson, D. A., K. Bork, E. P. Shea, A. M. Rentz, M. B. Blaustein, and W. E. Pullman. “Economic Costs Associated with Acute Attacks and Long-Term Management of Hereditary Angioedema.” *Annals of Allergy, Asthma & Immunology*, vol. 104 (2010): pp. 314-320.

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<sup>36</sup>Average PPPY medical costs for two people who had developed antibodies requiring higher than usual doses of clotting factors were \$1,424,364.



- **Disease.** Hereditary angioedema is characterized by recurrent and generally painful attacks of severe swelling of the skin and mucous membranes—the linings of many body cavities—including the gastrointestinal tract or upper airway. Swelling of the upper airway is potentially life-threatening. Attacks typically start in childhood or adolescence and can continue throughout life; treatment can reduce their frequency.
- **Cost data.** Direct and indirect costs based on answers to a survey administered to adults with hereditary angioedema from November 2007 to January 2008. Survey questions covered the respondent's most recent attack and use of medical resources over the past year; cost estimates were based on multiplying reported health care service utilization units by representative unit prices.<sup>37</sup>
- **Methods.** Costs specifically for the treatment of acute attacks among those hereditary angioedema, and also direct medical costs regardless of their link to acute attacks (i.e., all-cause medical costs) for those same people.<sup>38</sup> There was no comparison group of people without the disease.
- **Estimated costs** (in 2007 U.S. dollars).
  - The average PPPY total cost was \$41,992.
    - Average total costs varied with attack severity, from \$14,379 for those with mild attacks to \$96,460 for those with severe attacks, generally reflecting an increase in hospital stays and emergency department visits with severe attacks.
    - For those with mild attacks, indirect costs were the largest component of total costs; for those with severe attacks, emergency department and hospitalization costs were the largest component.

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<sup>37</sup>According to the researchers, abdominal attacks from hereditary angioedema can mimic acute abdominal emergencies, often resulting in exploratory procedures or unnecessary surgery. They note that reports of improper treatments were not uncommon among their survey respondents, but costs of improper procedures and medications were not assessed. Respondents reported that the median time from first symptom to confirmed diagnoses was 4 years, ranging to as many as 53 years.. The researchers also noted that 42.5 percent of respondents with hereditary angioedema reported at least mild depression, and 19.5 percent reported taking psychotropic or anti-depressant medication. The costs of treatment for depression were not included in the study.

<sup>38</sup>The survey responses did not permit allocation of lost productivity costs specifically to hereditary angioedema. To address that issue, the researchers reduced the reports of lost productivity by 25 percent.

- The average PPPY cost for medical expenses for those with hereditary angioedema was \$25,884, including an average of \$21,339 for treatment of acute attacks. Patients reported an average of 26.9 attacks per year, with 94 percent reporting at least one attack in the last year.
- The average PPPY indirect cost was \$16,108, including an average PPPY cost of \$3,402 for work missed specifically due to attacks. Of the study participants, 16.4 percent reported being unable to work full time because of hereditary angioedema; for these people, the average PPPY indirect cost of lost wages was \$39,683.

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Homocystinuria

See inborn amino acid metabolism disorders.

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Idiopathic Pulmonary  
Fibrosis

- **Disease.** Idiopathic pulmonary fibrosis is a disease in which tissues in the lungs become thick and stiff over time, causing the lungs to lose their ability to move oxygen to the brain and other parts of the body. The term “idiopathic” indicates that the cause is unknown. Many people with this condition live for 3 to 5 years after the diagnosis; the most common cause of death is respiratory failure.

Idiopathic Pulmonary Fibrosis:  
People Aged 65 or Older

- **Citation.** Collard, H. R., S.-Y. Chen, W.-S. Yeh, Q. Li, Y.-C. Lee, A. Wang, and G. Raghu. “Health Care Utilization and Costs of Idiopathic Pulmonary Fibrosis in U.S. Medicare Beneficiaries Aged 65 Years and Older.” *Annals of the American Thoracic Society*, vol. 12, no. 7 (2015): pp. 981-987.
- **Cost data.** Direct medical costs as indicated by reimbursed Medicare claims from 2000 through 2011 for people age 65 or older.
- **Methods.** Event-based, counting direct all-cause medical costs, but excepting costs for lung transplantation or outpatient drugs. These costs were counted for the year before and year after the time of diagnosis of idiopathic pulmonary fibrosis.<sup>39</sup> Costs for those with idiopathic pulmonary fibrosis were compared to similar costs for a group of people who did not have the disease and who had been matched for age, sex, race or ethnicity, and region.

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<sup>39</sup>The researchers stated that their data did not include the costs of lung transplantation because, in general, that procedure is performed on people younger than age 65, which was the minimum age of people in their study. Those who qualified for Medicare based on disability or end-stage renal disease were excluded.

Idiopathic Pulmonary Fibrosis:  
Hospitalizations and Urgent  
Outpatient Care

- **Estimated costs** (in 2012 U.S. dollars).
  - Those with idiopathic pulmonary fibrosis had higher average PPPY all-cause, direct medical costs both before diagnosis (\$10,124) and after diagnosis (\$20,887) than those without idiopathic pulmonary fibrosis (\$5,888 and \$8,932 for the latter group, recorded before and after the date of the diagnosis of the people to whom they had been matched).
- **Citation.** Yu, Y. F., N. Wu, C.-C. Chuang, R. Wang, X. Pan, N. N. Benjamin, G. Devercelli, and D. B. Coultas. "Patterns and Economic Burden of Hospitalizations and Exacerbations among Patients Diagnosed with Idiopathic Pulmonary Fibrosis." *Journal of Managed Care & Specialty Pharmacy*, vol. 22, no. 4 (2016): pp. 414-423.
- **Cost data.** Direct medical costs as indicated by paid claims from 2006 through 2011 in a national database including commercially insured adults and Medicare beneficiaries with supplemental insurance.
- **Methods.** Event-based, counting direct all-cause medical costs for urgent or emergency outpatient care, as well as hospitalizations specifically for idiopathic pulmonary fibrosis. The analyzed costs were for adults (age 18 or older) from the time of first diagnosis until as much as 1 year later; those with prior claims for lung cancer or claims for cystic fibrosis during the study period were excluded. There was no comparison group of people without the disease.
- **Estimated costs** (in 2012 U.S. dollars).
  - The average direct medical costs per event varied with the services needed, as follows:
    - \$13,987 for a hospitalization for any cause (i.e., whether related to idiopathic pulmonary fibrosis or not).
    - \$16,812 for a hospitalization specifically for idiopathic pulmonary fibrosis (including hospitalizations for exacerbations).<sup>40</sup>

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<sup>40</sup>According to the researchers, idiopathic pulmonary fibrosis involves disease progression as well as unpredictable acute exacerbations, and episodes of acute exacerbation requiring hospitalization are associated with significant morbidity and mortality. Acute exacerbations of idiopathic pulmonary fibrosis are defined as rapid and unpredictable deterioration not due to infection, pulmonary embolism, or heart failure; however, the diagnostic information in the databases did not always include all the information necessary to determine whether the person had experienced an acute exacerbation. The researchers identified hospitalizations and urgent or emergency outpatient visits that they suspected, based on the claims data, to have resulted from an acute exacerbation of the disease.

- \$14,731 for a hospitalization suspected to have resulted from exacerbation of the disease.
- \$444 for an urgent outpatient or emergency visit suspected to have resulted from exacerbation of the disease.

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## Inborn Amino Acid Metabolism Disorders

- **Disease.** Inborn amino acid metabolism disorders are diseases in which the body has trouble breaking down certain amino acids—the building blocks of proteins—or problems getting amino acids into one’s cells. As a result, harmful substances accumulate in one’s body. Over time, serious and sometimes life-threatening health problems can occur.<sup>41</sup>

## Homocystinuria and Phenylketonuria

- **Citation.** Sellos-Moura, M., F. Glavin, D. Lapidus, K. Evans, C. R. Lew, and D. E Irwin. “Prevalence, Characteristics, and Costs of Diagnosed Homocystinuria, Elevated Homocysteine, and Phenylketonuria in the United States: A Retrospective Claims-Based Comparison.” *BMC Health Services Research*, vol. 20 (2020): pp. 183-193.
- **Disease.** This study addressed two inborn amino acid metabolism disorders:
  - Homocystinuria includes a group of inherited diseases in which homocysteine and other amino acids accumulate. People with the disease may experience problems with their eyes, skeleton, central nervous system (with possible learning, intellectual, and psychiatric problems), or heart. Newborn screening in many states includes a test for the most common cause of homocystinuria. Treatment is primarily through diet and vitamin therapy.
  - Phenylketonuria is an inherited disease in which the body cannot convert phenylalanine, which is a natural part of foods, to tyrosine, a harmless amino acid. Without treatment, the accumulation of phenylalanine’s breakdown products causes permanent intellectual disability and may also cause seizures, developmental delays, and behavioral problems. Treatment is primarily through diet (specifically, dietary protein restriction and supplementation with medical foods), and even early and continuous dietary control

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<sup>41</sup>Because inborn amino acid metabolism disorders are not described in GARD, this description is based on information from MedlinePlus.

may not be sufficient to fully prevent cognitive and neurological disruptions.<sup>42</sup>

- **Cost data.** Direct medical costs between 2010 and 2016 as indicated by fully adjudicated claims in a large commercial insurance database and a Medicare supplemental health care database.
- **Methods.** All-cause, direct medical costs for people with homocystinuria or phenylketonuria from the date of the first claim with a diagnosis of one of those diseases. There was no comparison group of people without an amino acid metabolism disorder.<sup>43</sup>
- **Estimated costs.**<sup>44</sup> Direct all-cause medical costs depended on the disease:
  - For those with homocystinuria, the average monthly cost ranged from \$1,629 to \$2,570 (median: \$576 to \$614), depending on the strictness of the diagnostic criteria applied by the researchers.
  - For those with phenylketonuria, the average monthly cost was \$2,123 (median: \$365).
- **Citation.** Rose, A., M., S. D. Grosse, S. P. Garcia, J. Bach, M. Kleyn, N.-J. E. Simon, and L. A. Prosser. "The Financial and Time Burden Associated with Phenylketonuria Treatment in the United States." *Molecular Genetics and Metabolism Reports*, vol. 21 (2019) 100523.
- **Disease.** Phenylketonuria, described above.
- **Cost data.**
  - Direct, all-cause medical expenses indicated by administrative claims in a private insurance database from 2010 to 2015.

Phenylketonuria

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<sup>42</sup>We supplement the description of phenylketonuria from GARD with information from MedlinePlus and published research. See, for example, S. A. Berry, et al., "Newborn Screening 50 years Later: Access Issues Faced by Adults with [Phenylketonuria]" *Genetics in Medicine*, vol. 15, no. 8 (2013): pp. 591-599. We use brackets to replace the abbreviation, PKU, with the full name of the disease.

<sup>43</sup>As the researchers noted, the first claim identified in a database is not necessarily the first time a person was diagnosed with the disease, so this study's methods were not event-based. Although the study did not include a comparison group of people without an amino acid metabolism disorder, it did include data from a group of people with elevated levels of homocysteine but without a diagnosis of homocystinuria.

<sup>44</sup>The published article does not state whether costs were expressed in dollar values for a particular year.

- Out-of-pocket expenses specifically for phenylketonuria, as indicated by a survey distributed to people with phenylketonuria, or their parents, in Michigan in 2014. Assessed costs included medical costs (such as medical formula and prescribed low-protein foods), nonmedical costs (such as travel time and parking for medical appointments), and indirect costs (such as time for shopping for and preparing the necessary diet).<sup>45</sup>
- **Methods.** Direct, all-cause medical costs and certain other direct and indirect costs for people with phenylketonuria or their caregivers.<sup>46</sup> There was no comparison group of people without the disease.
- **Estimated costs** (in 2018 U.S. dollars).
  - Direct, all-cause medical costs varied with the person's age: The average PPPY costs were \$19,057 for children ages 0 to 11, \$54,147 for those ages 12 to 17, and \$40,705 for adults ages 18 and older.<sup>47</sup>
  - The average PPPY out-of-pocket costs for low-protein foods were \$1,651 for children and \$967 for adults.
  - Parents reported spending more than 300 hours per year shopping for and preparing special diet foods; 23 percent of parents reported that they or their partner had quit working due to their child's disease.

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Lennox-Gastaut  
Syndrome

See childhood-onset epilepsies.

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<sup>45</sup>According to the authors of this study, certain costs associated with phenylketonuria—such as the cost of medical formula for children and home blood monitoring tests—were covered by the state of Michigan at the time of the study. They also report that Michigan subsequently discontinued provision of medical formula to those with phenylketonuria. Findings regarding out-of-pocket expenses might therefore not be generalizable to other states or other times.

<sup>46</sup>We use the term “caregiver” to refer to family members or others who provide care without receiving compensation for doing so.

<sup>47</sup>A medication approved for use by those with phenylketonuria—sapropterin—is dosed to body weight and, therefore, its cost increases with the person's weight and, through childhood, age. The average annual per person cost of sapropterin (including both insurance plan and out-of-pocket costs) was \$9,312 for children ages 0 to 11, \$35,835 for those ages 12 to 17, and \$30,263 for adults ages 18 and older.

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## Myasthenia Gravis

- **Citation.** Guptill, J. T., A. Marano, A. Krueger, and D. B. Sanders. "Cost Analysis of Myasthenia Gravis from a Large U.S. Insurance Database." *Muscle & Nerve*, vol. 44 (2011): pp. 907-911.
- **Disease.** Myasthenia gravis is a chronic, autoimmune, neuromuscular disease characterized by weakness of the skeletal muscles. There is no cure, but treatment can result in improvement. The disease is not directly inherited, nor is it contagious, but a genetic predisposition to autoimmune disease can run in families. People can develop myasthenia gravis at any age.
- **Cost data.** Direct medical costs as indicated by claims between June 2008 and June 2010 recorded in a large U.S. insurance services database that focuses on management of certain rare, complex, chronic conditions.
- **Methods.** Direct, all-cause medical costs for those with myasthenia gravis. There was no comparison group of people without the disease.
- **Estimated costs** (in U.S. dollars from June 2008 through June 2010).
  - The average PPPY all-cause medical cost was \$24,988 (median: \$9,023).
  - These costs varied with age: Average PPPY costs were greatest for those ages 20 to 39 (\$37,522) compared to costs for those ages 0 to 19 (\$7,906), ages 40 to 64 (\$27,610), or age 65 and older (\$20,686).

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## Myotonic Dystrophy

See neuromuscular diseases.

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## Neuromuscular Diseases

Amyotrophic Lateral Sclerosis, Duchenne Muscular Dystrophy, and Myotonic Dystrophy

- **Disease.** Neuromuscular diseases are a group of diseases that can cause progressive muscle weakness. Many have no cure, but treatment can ameliorate some symptoms and prolong life.<sup>48</sup>
- **Citation.** Larkindale, J., W. Yang, P. F. Hogan, C. J. Simon, Y. Zhang, A. Jain, E. M. Habeeb-Louks, A. Kennedy, and V. A. Cwik. "Cost of Illness for Neuromuscular Diseases in the United States." *Muscle & Nerve*, vol. 49 (2014): pp. 431-438.
- **Disease.** Three different progressive and potentially life-threatening neuromuscular diseases were addressed in this study:
  - Amyotrophic lateral sclerosis is a progressive motor neuron disease causing problems with muscle control and movement.

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<sup>48</sup>Because neuromuscular diseases are not listed in GARD under that name, this description is based on information from MedlinePlus.

Death from respiratory failure often results within 2 to 10 years after the onset of symptoms. Most cases are not inherited.

- Duchenne muscular dystrophy is a genetic disease that affects primarily males and involves progressive muscle wasting. Muscle weakness is usually noticeable in early childhood. Most children with Duchenne muscular dystrophy use a wheelchair by their early teens. Heart and breathing problems also begin in the teen years and lead to serious, life-threatening complications.
- Myotonic dystrophy is an inherited, progressive disease involving muscle loss and weakness that usually begins in adulthood. The severity of the disease varies among those affected; treatment is aimed at symptom management.
- **Cost data.**
  - Direct medical costs were estimated using claims in a large, national, commercial insurance database in 2009 and in Medicare's database in 2008, along with information from other national health care databases.
  - Direct nonmedical costs (such as modifications to one's home or one's vehicle) and indirect costs due to lost productivity were estimated based on self-reports from people with the disease or someone in their family.
- **Methods.** Direct, all-cause medical costs for people with amyotrophic lateral sclerosis, Duchenne muscular dystrophy, or myotonic dystrophy, along with disease-specific costs that were nonmedical or indirect. There was no comparison group of people without neuromuscular disease.<sup>49</sup>
- **Estimated costs** (in 2010 U.S. dollars).
  - Average total PPPY costs, including direct and indirect costs, varied with the disease and were
    - \$63,693 for amyotrophic lateral sclerosis;
    - \$50,952 for Duchenne muscular dystrophy; and
    - \$32,236 for myotonic dystrophy.
  - Average PPPY costs for direct nonmedical expenses—a subset of the total costs—also varied with the disease and were

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<sup>49</sup>The authors state that the direct costs that were nonmedical were assessed per annum; income losses were estimated based on reports of total family income in the past year.



- \$17,889 for amyotrophic lateral sclerosis;
  - \$12,939 for Duchenne muscular dystrophy; and
  - \$5,157 for myotonic dystrophy.
  - Average annual estimated family income loss increased with the person's need for care.
  - Total annual estimated costs to the United States were
    - \$1,023 million for amyotrophic lateral sclerosis;
    - \$787 million for Duchenne muscular dystrophy; and
    - \$448 million for myotonic dystrophy.
- Duchenne Muscular Dystrophy
- **Citation.** Thayer, S., C. Bell, and C. M. McDonald. "The Direct Cost of Managing a Rare Disease: Assessing Medical and Pharmacy Costs Associated with Duchenne Muscular Dystrophy in the United States." *Journal of Managed Care & Specialty Pharmacy*, vol. 23, no. 6 (2017): pp 633-641.
  - **Disease.** Duchenne muscular dystrophy, described above.
  - **Cost data.** Direct medical costs were estimated using claims from 2000 through 2010 in a large, national, commercial insurance database.
  - **Methods.** Direct, all-cause medical costs for at least 1 year for males with muscular dystrophy who were less than 30 years old. Their data were compared to costs for a group of people without muscular dystrophy or certain other diseases and matched for age, gender, and geographic region.
  - **Estimated costs** (in 2010 U.S. dollars).
    - Direct all-cause PPPY medical costs averaged \$23,005 for Duchenne muscular dystrophy, compared to \$2,277 for those without the disease.
    - These direct medical costs for Duchenne muscular dystrophy generally increased with the person's age, particularly after age 14.<sup>50</sup>

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<sup>50</sup>The authors noted that higher costs after age 14 are consistent with what is known about the natural course of Duchenne muscular dystrophy: As the disease progresses, people generally have greater health care needs because of loss of the ability to walk and increased respiratory difficulty.

- The researchers noted that their cost estimates did not include a variety of expenses that are often associated with Duchenne muscular dystrophy. For example,
  - Direct medical expenses could include the cost of durable medical devices that may reduce complications of the disease, such as airway clearance devices or suction apparatuses.
  - Direct nonmedical expenses could include the costs of assistive devices that make it easier for patients or their caregivers to manage the disease, such as patient lifts or custom shower and toilet chairs.

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### Nontuberculous Mycobacterial Lung Disease

- **Citation.** Strollo, S. E., J. Adjemian, M. K. Adjemian, and D. R. Prevots. "The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States." *Annals of the American Thoracic Society*, vol. 12, no. 10 (2015): pp. 1458-1464.
- **Disease.** Nontuberculous mycobacterial lung disease is an infectious (acquired) disease caused by a bacteria found naturally in soil and water. Although most people who are exposed to these bacteria do not become sick, people who have a weakened immune system or certain other health conditions have an elevated risk of developing the disease. If untreated, it can result in lung damage. It is generally treated with a combination of antibiotics provided continuously over 1 year or more. According to the study authors, nontuberculous mycobacterial lung disease is chronic and slowly progressive.
- **Cost data.** Direct medical costs estimated for the year 2010. The estimates were based on information developed by other researchers regarding disease prevalence, medical encounters for those with the disease, and average costs for those encounters.
- **Methods.** Direct, all-cause costs associated with a single medical encounter for nontuberculous mycobacterial lung disease. There was no comparison group of people without the disease.<sup>51</sup>
- **Estimated costs** (in 2014 U.S. dollars).
  - The average direct all-cause medical cost for a single medical encounter for nontuberculous mycobacterial lung disease was \$9,451.

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<sup>51</sup>The study authors note that many people with nontuberculous mycobacterial lung disease could have more than one medical encounter per year, and so the costs could be higher than estimated.

- The total annual direct medical cost of this disease in the United States in 2010 was estimated to be \$815 million, with regional variation in annual costs ranging from North Dakota (\$0.5 million) to California (\$110.7 million).<sup>52</sup>

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## Pemphigus

- **Citation.** Hsu, D., J. Brieva, and J. I. Silverberg. "Costs of Care for Hospitalization for Pemphigus in the United States." *Journal of the American Medical Association: Dermatology*, vol. 152, no. 6 (2016): pp. 645-654.
- **Disease.** Pemphigus is a group of chronic autoimmune diseases that causes blistering of the skin and mucous membranes, including the mouth, nose, throat, eyes, and genitals. It can occur at any age but often affects people in middle or older age. Pemphigus is best controlled by early diagnosis and treatment, which can include drugs to reduce inflammation, drugs to suppress the immune system response, and antibiotics to treat associated infections.
- **Cost data.** Direct medical costs from 2002 through 2012 as indicated by a national healthcare database.
- **Methods.** All-cause direct costs of acute hospitalizations for admissions specifically related to pemphigus, with comparison to hospitalization costs for people without the disease.<sup>53</sup>
- **Estimated costs** (in 2014 U.S. dollars).
  - The average annual costs of an acute hospitalization for people with a primary or secondary inpatient diagnosis of pemphigus were \$14,521 and \$14,818, respectively. In contrast, the average annual cost of an acute hospitalization for people without pemphigus was \$9,949.

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<sup>52</sup>One possible reason for regional variation in costs for nontuberculous mycobacterial lung disease is regional variation in climatic conditions associated with risk for the disease. For example, the risk of the disease is greater in states with oceanic coastlines than in landlocked states. Because the researchers did not study direct nonmedical costs or indirect costs, their estimate is not an estimate of the total costs of the disease to the United States, but is instead an estimate of the total direct medical costs of nontuberculous mycobacterial lung disease in the United States.

<sup>53</sup>According to the study authors, people with pemphigus may be hospitalized because of intense pain, esophageal problems that lead to difficulty eating, opportunistic infections, medication-related complications, or comorbid autoimmune conditions associated with pemphigus.

- Among those with a primary inpatient diagnosis of pemphigus, higher hospitalization costs were associated with people who were older, non-white, or had other chronic conditions.
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Phenylketonuria

See inborn amino acid metabolism disorders.

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Prader-Willi Syndrome

- **Citation.** Shoffstall, A. J., J. A. Gaebler, N. C. Kreher, T. Niecko, D. Douglas, T. V. Strong, J. L. Miller, D. E. Stafford, D. E., and M. G. Butler. "The High Direct Medical Costs of Prader-Willi Syndrome." *Journal of Pediatrics*, vol. 175 (2016): pp. 137-143.
  - **Disease.** Prader-Willi syndrome is a life-threatening, genetic disease that affects many parts of the body. Infants with this disease have severe problems with muscle tone, feeding difficulties, and slow growth. Later, children with the disease typically begin to eat excessively and become obese. Other common symptoms include developmental delays, cognitive impairment, and behavioral problems, such as temper tantrums. Most cases are not inherited, instead occurring randomly. Management generally depends on the person's age and symptoms.<sup>54</sup>
  - **Cost data.** Direct medical costs from 2009 through 2014, estimated from adjudicated claims recorded in large databases covering commercial insurance (employer-sponsored private insurance and supplemental Medicare insurance) and Medicaid.
  - **Methods.** Direct, all-cause medical costs for those with Prader-Willi syndrome compared to costs for a group of people without the disease and matched for sex, age, and payer type.
  - **Estimated costs.**<sup>55</sup>
    - All-cause medical costs were greater for those with Prader-Willi syndrome than for those without it, with costs for Medicaid beneficiaries being higher than for commercially insured people:
      - For commercially insured people, the PPPY average was \$28,712 (median: \$14,907) for those with Prader-Willi syndrome compared to \$3,246 (median: \$819) for those without the disease.
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<sup>54</sup>We supplement the description of Prader-Willi syndrome from GARD with information from an NIH institute, the National Institute of Child Health and Human Development.

<sup>55</sup>The published article does not state whether costs were adjusted to reflect dollar values for a particular year.

- For Medicaid beneficiaries, the PPPY average was \$40,868 for those with Prader-Willi syndrome compared to \$5,306 for those without the disease.<sup>56</sup>
- The difference between costs for those with and without Prader-Willi syndrome was greatest in younger people.

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## Primary Immune Deficiency Diseases

- **Citation.** Runken, M.C., J. M. Noone, C. M. Blanchette, E. Zacherle, and R. Howden. Differences in Patient Demographics and Healthcare Costs of Patients with [Primary Immune Deficiency Diseases] Receiving Intravenous or Subcutaneous Immunoglobulin Therapies in the United States. *American Health & Drug Benefits*, vol. 12, no. 6 (2019): pp. 294-303.
- **Disease.** Primary immune deficiency diseases are genetic disorders that impair the immune response. As a result, people with these diseases may be subject to chronic, debilitating—and potentially fatal—infections.<sup>57</sup> According to the study authors, early diagnosis and treatment is critical for reducing infections, complications, and hospitalization. Treatment generally involves administration of immunoglobulin (which includes antibodies used by the immune system to fight infection) by injection into one's veins—intravenous administration—or underneath the skin—subcutaneous administration.
- **Cost data.** Direct medical costs from 2011 to 2013 estimated from claims recorded in a large, commercial insurance database.
- **Methods.** Event-based, including direct, all-cause medical costs and direct medical costs specifically for primary immune deficiency disease for people newly diagnosed with one of these diseases. Costs were counted for 1 year from the first date indicating treatment with immunoglobulin. There was no comparison group of people without a primary immune deficiency disease.

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<sup>56</sup>The study authors suggest that the comparatively high costs they observed for Medicaid beneficiaries with Prader-Willi syndrome may have reflected costs associated with Medicaid coverage in some states of day or residential care—services that accounted for about half of the outpatient Medicaid costs for adults with Prader-Willi syndrome.

<sup>57</sup>Because primary immune deficiency diseases are not listed in GARD under that name, this description is based on information from the NIH's National Institute of Allergy and Infectious Diseases.

- **Estimated costs** (in unadjusted U.S. dollars from 2011 through 2013).
  - Average all-cause medical costs in the year following initiation of treatment differed depending on the type of treatment administration: The PPPY averages were \$103,177 for those receiving intravenous treatment and \$71,949 for those receiving subcutaneous treatment.
  - Average direct medical costs specifically for primary immune deficiency diseases also differed depending on the type of treatment administration, but the differences were smaller and in the opposite direction: These PPPY averages were \$45,225 for those receiving intravenous treatment and \$48,517 for those receiving subcutaneous treatment.
  - Most of these observed differences in costs for the two types of treatment appear to have been due to differences between the patients who received the two treatments: Those who received intravenous immunoglobulin were more likely to be male and, on average, were older and had more comorbid conditions than those who received subcutaneous immunoglobulin.<sup>58</sup>

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Progressive Supranuclear  
Palsy

See frontotemporal degeneration.

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Pulmonary Arterial  
Hypertension

- **Disease.** Pulmonary arterial hypertension is a progressive and life-threatening disease that affects the heart and lungs. It is characterized by abnormally high blood pressure in the pulmonary artery. Most cases occur in people with no family history of the disease. The disease can occur for unknown reasons, can be secondary to another underlying disease such as connective tissue disease, or can be induced by certain toxins and drugs. There is no cure for the disease, but drugs can be used to manage it and help delay its progression.

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<sup>58</sup>Because the amount of immunoglobulin given to patients is based on their weight, the amount of immunoglobulin and so its costs would generally be greater for men than women. When the researchers analyzed their data in a way that controlled for differences between the treatment groups in age, sex, and certain comorbid conditions, their results suggested that all-cause medical costs did not differ as a function of treatment; median (but not mean) PPPY medical costs specifically for primary immune deficiency disease were lower for those who received intravenous treatment than those who received subcutaneous treatment.

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Pulmonary Arterial  
Hypertension—Costs Before  
and After Initiation of Drug  
Therapy

- **Citation.** Sikirica, M., S. R. Iorga, T. Bancroft, and J. Potash. “The Economic Burden of Pulmonary Arterial Hypertension (PAH) in the US on Payers and Patients.” *BMC Health Services Research*, vol. 14 (2014): pp. 676-686.
- **Cost data.** Direct medical costs as estimated by claims from January 2004 through June 2011 in the database of a large, national managed care organization.
- **Methods.** Event-based, counting direct, all-cause medical costs from time of the earliest claim for prescription of a medication indicated for treatment of pulmonary arterial hypertension until one year later, compared to costs incurred by those people in the 180 days prior to that claim.
- **Estimated costs** (in 2011 U.S. dollars).
  - Direct, all-cause medical costs were lower after initiation of a drug therapy for pulmonary arterial hypertension: The PPPY average was \$98,243 during the follow-up period (the year following the initiation of drug therapy) compared to \$116,681 during the baseline period (an annualized estimate based on the 180 days before initiation of drug therapy).
  - This decrease in the PPPY cost for direct medical costs (costs that included the costs for drugs) was observed despite an increase in the costs of drug therapy: The PPPY average for drugs was \$38,514 during the follow-up period compared to \$6,440 during the baseline period.<sup>59</sup>

Pulmonary Arterial  
Hypertension—Costs of  
Hospitalization

- **Citation.** Burke, J. P., E. Hunsche, E. Régulier, M. Nagao, P. Buzinec, and W. Drake. Characterizing Pulmonary Hypertension–Related Hospitalization Costs among Medicare Advantage or Commercially Insured Patients with Pulmonary Arterial Hypertension: A Retrospective Database Study. *American Journal of Managed Care*, vol. 21, no. 3 (2015): pp. S47-S58.
- **Cost data.** Direct medical costs as estimated by claims from January 2007 through October 2011 in a database covering commercial insurance and Medicare Advantage beneficiaries whose coverage included drug costs.
- **Methods.** Event-based, with direct, all-cause medical costs for hospitalizations related to pulmonary hypertension among adults who had at least one such hospitalization. Costs were counted for at least

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<sup>59</sup>Average costs for inpatient care, in particular, were higher before initiation of drug therapy than afterwards.

6 months from the time of the earliest claim for prescription of a medication indicated for treatment of pulmonary arterial hypertension. There was no comparison group of people without pulmonary arterial hypertension.

- **Estimated costs** (in 2011 U.S. dollars).
  - Direct, all-cause costs for hospitalizations related to pulmonary hypertension varied with type of insurance:
    - The average hospitalization cost for those with commercial insurance was \$46,118; the average for those with Medicare Advantage was \$16,319.
    - Average costs for the first recorded hospitalization (rather than readmission) were also higher for those with commercial insurance (\$39,576) than for those with Medicare Advantage (\$16,496).
  - Readmissions were not uncommon and were even more costly than initial hospitalizations: 42 percent of the patients were readmitted for a hospitalization related to pulmonary hypertension within 1 year of their initial hospitalization; their average readmission casts were \$95,254 for those with commercial insurance and \$36,543 for those with Medicare Advantage).

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### Tuberous Sclerosis Complex

- **Disease.** Tuberous sclerosis complex is an inherited disease characterized by the growth of benign tumors throughout the body, including in the heart, brain, and kidneys. Some symptoms, such as heart tumors, develop before birth. Other symptoms, such as developmental delays, become more obvious in childhood, and lung and kidney tumors are more likely to develop in adulthood. Treatment is generally intended to manage the symptoms and may include medications and surgery. Tuberous sclerosis complex can be life threatening.<sup>60</sup>

### Tuberous Sclerosis Complex— Costs to Patients or their Caregivers

- **Citation.** Skalicky, A. M., A. M. Rentz, Z. Liu, Q. Said, J. A. Nakagawa, M. D. Frost, J. W. Wheless, and D. W. Dunn. “Economic Burden, Work, and School Productivity in Individuals with Tuberous

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<sup>60</sup>We supplemented the description of tuberous sclerosis complex from GARD with information from MedlinePlus. Because tuberous sclerosis complex is associated with treatment-resistant seizures, Reaven et al. included this disease in their study, described in the section on childhood-onset epilepsies. Reaven, et al., “The Direct Cost of Seizure Events in Severe Childhood-Onset Epilepsies,” p. 65.



Sclerosis and Their Families.” *Journal of Medical Economics*, vol. 21, no. 10 (2018): pp. 953-959.

- **Cost data.** Out-of-pocket costs, including direct costs (both medical and nonmedical) and indirect costs (such as work or school absenteeism, measured without estimating dollar amounts) as estimated based on answers to a survey administered to adults with the disease and primary caregivers of children with it. Survey participants were recruited between May 2021 and June 2021 and were asked about times ranging from the prior month to the prior year.
- **Methods.** All-cause, direct out-of-pocket expenses and indirect costs for people with tuberous sclerosis complex. Data were not collected in this study from a group of people without the disease.
- **Estimated costs** (in 2011 to 2012 U.S. dollars).
  - In general, adults with tuberous sclerosis complex reported higher out-of-pocket expenses than were reported for children with the disease. For example:
    - Average PPPY out-of-pocket expenses for hospital expenses, doctor’s visits, and emergency room visits totaled \$3,650 for adults and \$2,475 for children; and
    - Average reported out-of-pocket expenses over the past month for tests and procedures, medications, and alternative treatments totaled \$2,480 for adults and \$550 for children.
  - In general, adults with tuberous sclerosis complex reported greater indirect costs (such as more overall work productivity loss) than caregivers of children with the disease.
- **Citation.** Sun, P., Z. Liu, D. Krueger, and M. Kohrman. Direct Medical Costs for Patients with Tuberous Sclerosis Complex and Surgical Resection of Subependymal Giant Cell Astrocytoma: A [U.S.] National Cohort Study. *Journal of Medical Economics*, vol. 18, no. 5 (2015): pp. 349-356.
- **Cost data.** Direct medical costs as indicated in two large, nationwide, commercial health claims databases covering costs from 2000 through 2011 and a Medicaid database covering costs from 2004 through 2010.
- **Methods.** Event-based, counting direct, all-cause medical costs for people with tuberous sclerosis complex who were aged 35 or younger and who had their first claim for the studied surgical procedure between 2000 and 2011. This surgical procedure was removal of a particular type of brain tumor that can obstruct spinal fluid flow,

Tuberous Sclerosis Complex—  
Direct Medical Costs Before  
and After a Surgical Treatment

increase cerebral pressure, and cause symptoms ranging from headaches and blurred vision through sudden death.<sup>61</sup> Costs were counted for 1 year before and 1 year after the surgery. Data were not collected in this study from a comparison group of people without the disease.

- **Estimated costs** (in 2010 U.S. dollars).
  - Direct medical costs for people with tuberous sclerosis complex increased after surgery: The average PPPY cost was \$8,543 before surgery and \$85,397 after surgery.
    - The majority of this difference was due to inpatient costs in the month immediately after the surgery. During that month, inpatient costs averaged \$55,486.
    - Costs were higher after surgery even when the costs of the month that included the surgery were excluded from the analysis: The average total direct medical costs in the first year following surgery was 3.1 times higher than in the year prior to surgery.<sup>62</sup>

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<sup>61</sup>The study authors report that from 5 percent to 20 percent of people with tuberous sclerosis complex have the particular type of tumor of concern—a subependymal giant-cell astrocytoma. They also reported that although surgical removal of that tumor is a traditional treatment, the surgery is often difficult and incomplete, and it can result in complications.

<sup>62</sup>Direct medical costs were higher in the post-surgery year than in the year before surgery for all studied categories of costs, namely, inpatient care, outpatient care, and drugs.

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# Appendix II: Descriptions of Selected Rare Diseases

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This appendix provides brief descriptions of the rare diseases and groups of rare diseases mentioned in this report.<sup>1</sup> These descriptions are based on information published on the National Institute of Health's (NIH) Genetic and Rare Diseases (GARD) Information Center website (unless otherwise indicated) and are alphabetized by the name.<sup>2</sup>

**Acromegaly** is a disease in which the pituitary gland produces too much growth hormone. Signs and symptoms can include abnormal growth of the hands and feet, joint pain, and backbone fractures. It is usually caused by non-cancerous tumors on the pituitary gland. Treatment may include hormones, drugs, radiotherapy, or surgery. If untreated, it can result in serious illness, comorbid conditions, such as diabetes or cardiovascular disease, and premature death.<sup>3</sup>

**Acute lymphoblastic leukemia** is a type of cancer in which the bone marrow produces too many lymphocytes, a type of white blood cell. The disease spreads to the blood fairly quickly and may then spread to other parts of the body, including the lymph nodes, liver, or central nervous system. Acute lymphoblastic leukemia is typically caused by random (rather than inherited) changes in immature lymphocytes, which are called lymphoblasts. A variety of treatment options may be used depending on factors such as the person's age and how advanced the cancer is.

**Acute myeloid leukemia** is cancer of the blood and bone marrow that develops quickly and has an aggressive course. It has various causes and is rarely diagnosed in people under the age of 40. Treatment can include chemotherapy, radiation therapy, bone marrow transplant, and combinations of these treatments.

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<sup>1</sup>We use the term "disease" to refer to diseases, disorders, syndromes, complexes, and other health conditions except when one of those other terms is part of the name of the disease.

<sup>2</sup>Department of Health and Human Services, National Institutes of Health, National Center for Advancing Translational Sciences, *Genetic and Rare Diseases Information Center (GARD)*, accessed July 8, 2021, <https://rarediseases.info.nih.gov>. Some diseases have multiple names, which we do not list.

<sup>3</sup>When the tumors that result in excess growth hormone occur in childhood, the disease is called gigantism, rather than acromegaly. Comorbidity refers to the presence of more than one distinct disease in a person at the same time. The co-existing diseases are called "comorbid conditions."

**Alpha-1 antitrypsin deficiency** is an inherited disease that increases the risk of chronic obstructive pulmonary disease, liver disease, skin problems, and inflammation of the blood vessels. Although some people do not experience any problems, liver and skin problems may begin in childhood, while lung problems are most likely in adults. In addition to treatments for the comorbid conditions and to address symptoms, some people with lung problems due to alpha-1 antitrypsin deficiency may be given infusions of alpha-1 antitrypsin protein to prevent progression of lung disease.

**Amyotrophic lateral sclerosis** is a progressive motor neuron disease causing problems with muscle control and movement. Death from respiratory failure often results within 2 to 10 years after the onset of symptoms. Most cases are not inherited.

**Arterial calcification due to deficiency of CD73** is an inherited disease in which calcium accumulates in large blood vessels and joints, causing progressive pain and cramping.

**Arteriovenous malformations of the central nervous system** involve abnormal connections between arteries and veins in the central nervous system (the brain—intracranial arteriovenous malformations—or spinal cord—spinal arteriovenous malformations). Most people with brain or spinal arteriovenous malformation have few, if any, major symptoms. About 12 percent of people with this condition have symptoms, which vary in severity; seizures and headaches are the most common symptoms. The cause of the malformations is not well understood, but they most often seem to arise during embryonic or fetal development.<sup>4</sup>

**Autosomal dominant tubulointerstitial kidney disease** is a group of genetic kidney diseases involving progressive loss of kidney function. Symptoms are often apparent by the teenage years; if untreated, the result is generally end-stage kidney disease between the ages of 20 and 70.

**Cardiac amyloidosis** is a disease in which an abnormal protein called amyloid builds up in heart tissue. Over time, the amyloid deposits take the place of normal heart muscle, causing dysfunction. The disease is severe

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<sup>4</sup>We supplement the description of arteriovenous malformations from GARD with information from an NIH institute, the National Institute of Neurological Disorders and Stroke.

and progressive, and without treatment, death typically occurs within about 6 months of the development of symptomatic cardiac dysfunction.<sup>5</sup>

**Central precocious puberty** is a disease in which sexual and physical characteristics develop and mature earlier than normal—before age 8 for girls or before age 9 for boys. Although it can be inherited, the cause is not always known. Treatment involves medications that stop the body from releasing sexual hormones. If untreated, results can include psychological and behavioral problems.<sup>6</sup>

**Childhood cancers** are diseases that are generally thought to result from mutations in genes, although only a small percent—5 to 10 percent—are thought to be heritable. The environmental causes of childhood cancers are, in general, poorly understood. The prognosis varies with the specific cancer, how advanced the cancer is, and the patient’s age and response to treatment. The likelihood of survival for 5 years or more has increased in recent years, but childhood cancers remain life threatening.<sup>7</sup>

**Chronic granulomatous disease** is an inherited immunodeficiency that affects certain white blood cells. Because people with this disease have immune systems that do not function properly, they are vulnerable to chronic inflammation and frequent bacterial and fungal infections. Treatment generally involves continuous drug therapies to prevent or address these infections.

**Chronic inflammatory demyelinating polyneuropathy** is a neurological disease that causes progressive weakness and impaired sensory function in the legs and arms. It is thought to be caused by the immune system mistakenly attacking and damaging the myelin sheath that provides a protective cover for peripheral nerves. Several different treatment options exist; if not treated early, permanent damage can result.

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<sup>5</sup>Because cardiac amyloidosis is not listed in GARD under that name, this description is based on information from MedlinePlus, a website provided by NIH and the National Library of Medicine, and from T. P. Quock, et al., “Untangling the Clinical and Economic Burden of Hospitalization for Cardiac Amyloidosis in the United States,” *Clinicoeconomics and Outcomes Research*, vol. 11 (2019): pp. 431-439.

<sup>6</sup>We supplement the description of central precocious puberty from GARD with information from MedlinePlus.

<sup>7</sup>Because childhood cancers are not listed in GARD under that name, this description is based on information from an NIH institute, the National Cancer Institute.

**Chronic myeloid leukemia** is a slow-growing cancer of the bone marrow, which produces blood cells. In chronic myeloid leukemia, the marrow produces too many white blood cells. As the disease progresses, immature white blood cells accumulate in the blood and bone marrow, impairing the development of other blood cells and resulting in a shortage of red blood cells and platelets. Chronic myeloid leukemia usually begins after age 60 and is caused by a genetic mutation that occurs during a person's lifetime. Serious infections and uncontrolled bleeding can be life threatening. Bone marrow transplantation is the only cure for this disease, but the Food and Drug Administration (FDA) has approved several drugs for use in certain patients with chronic myeloid leukemia.<sup>8</sup>

**Corticobasal degeneration** is a disease involving degeneration of parts of the brain including the cerebral cortex (which is involved in processing information) and the basal ganglia (involved in movement). Signs and symptoms include progressive loss of movement, cognitive impairment, and speech impairment. The genetic basis of the disease is not fully understood. Death often occurs within 7 years of the development of symptoms.

**Creutzfeldt-Jakob disease** is an extremely rare progressive brain disease caused by an accumulation of abnormal prion proteins in the brain. Early symptoms include memory lapses, behavior changes, impaired coordination, and visual disturbances; as the disease progresses, mental deterioration becomes severe, and symptoms may include involuntary movements, weakness, blindness, or coma. Onset of symptoms is typical at about age 60 and is inevitably fatal, often relatively soon after symptoms appear—70 to 90 percent of those with Creutzfeldt-Jakob disease die within 1 year. It is difficult to diagnose because it is hard to distinguish from other forms of dementia prior to autopsy. There is no treatment other than symptom relief and palliative care. In most cases, the cause is unknown; a few cases have a hereditary cause, and some variants appear to be acquired, for example, by eating meat from cattle affected by a similar disease.<sup>9</sup>

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<sup>8</sup>We supplement the description of chronic myeloid leukemia from GARD with information from MedlinePlus.

<sup>9</sup>We supplement the description of Creutzfeldt-Jakob disease from GARD with information from an NIH institute, the National Institute of Neurological Disorders and Stroke. The disease similar to Creutzfeldt-Jakob disease that affects cattle is bovine spongiform encephalopathy, commonly called "mad cow" disease.

**Cushing’s syndrome** is an endocrine disease resulting from prolonged exposure of the body’s tissues to cortisol, a hormone produced by the adrenal gland. In rare cases it is inherited; in most cases it is not. Causes can include long-term use of corticosteroid medications or tumors in the pituitary or adrenal gland. Treatment could involve surgery to remove a tumor or medications to decrease cortisol levels. Elevated cortisol levels affect every organ system and, therefore, produce a variety of symptoms, with obesity, diabetes, depression, and osteoporosis among the more common ones.<sup>10</sup>

**Cystic fibrosis** is a genetic disorder that causes mucus to build up and damage organs in the body, particularly the lungs and pancreas. Over time, mucus buildup and infections can lead to permanent lung damage, as well as other symptoms and health risks. Cystic fibrosis can be detected with genetic testing, including prenatal diagnosis of those at risk and newborn screening, and it is among the conditions that the Department of Health and Human Services recommends for newborn screening. Treatment generally aims to relieve symptoms, and there is currently no cure for the disease; but certain treatments intended to address the underlying genetic mutation—cystic fibrosis transmembrane conductance regulator modulators—hold promise for use with certain patients.<sup>11</sup>

**Dermatomyositis** is an autoimmune disease that causes skin changes and muscle weakness. It is most common in adults between ages 40 and 60 or in children between ages 5 and 15. Muscle weakness gets worse over time and can lead to stiff joints and muscle wasting. The cause is unknown. Treatment is focused on managing the symptoms and may include medications, physical therapy, and exercise.

**Diffuse intrinsic pontine glioma** is a fast-growing cancerous tumor that forms in a certain type of cells—glial cells—in a part of the brain stem—

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<sup>10</sup>We supplement the description of Cushing’s syndrome with information from M. S. Broder, et al., “Burden of Illness, Annual Healthcare Utilization, and Costs Associated with Commercially Insured Patients with Cushing Disease in the United States,” *Endocrine Practice*, vol. 21, no. 1 (2015): pp. 77-86..

<sup>11</sup>We supplement the description of cystic fibrosis from GARD with information from the Cystic Fibrosis Foundation and published research. See, for example, C. L. Ren, et al., “Cystic Fibrosis Foundation Pulmonary Guidelines,” *Annals of the American Thoracic Society*, vol. 15, no. 3 (2018): pp. 271-280.

the pons. Diffuse intrinsic pontine gliomas, which usually occur in children, tend to spread and are hard to treat, so the prognosis is poor.<sup>12</sup>

**Dravet syndrome** is a type of severe epilepsy with seizures first occurring in infancy. In addition to seizures, symptoms include loss of motor skills, intellectual disability, speech impairment, and difficulty moving. Caused when a particular gene (called the SCN1A gene) is not working correctly, Dravet syndrome can be inherited, but most people with the disease do not have a family history of it. The main goal of treatment is to reduce the number and length of seizures, but the seizures of this type of epilepsy can be difficult to treat.

**Duchenne muscular dystrophy** is a disease in which mutations of a specific gene—the DMD gene—result in a deficiency of dystrophin—a protein involved in maintaining the integrity of muscle. The disease, which affects primarily males, involves progressive muscle wasting. Muscle weakness is usually noticeable in early childhood. Most children with Duchenne muscular dystrophy use a wheelchair by their early teens. Heart and breathing problems also begin in the teen years and lead to serious, life-threatening complications.

**Ehlers-Danlos syndromes** are a set of inherited connective tissue disorders caused by abnormalities in the structure, production, or processing of collagen. Signs and symptoms vary across types of Ehlers-Danlos syndromes and range from mildly loose joints to life-threatening complications. Treatment varies with the type and generally involves relieving signs and symptoms and preventing serious complications.

**Fetal valproate syndrome** is a disease that can occur when a baby is exposed to valproic acid during pregnancy, as might happen if the mother is being treated with that substance for epilepsy, bipolar disorder, or another medical condition. Symptoms vary and can include congenital heart defects, genital or skeletal abnormalities, developmental delays, and learning and behavioral problems. There is no cure, but early intervention programs may be helpful.

**Fragile X syndrome**, a genetic disease involving changes in part of the X chromosome, causes a range of developmental problems, including learning disabilities and cognitive impairment. Other symptoms may

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<sup>12</sup>Because diffuse intrinsic pontine glioma is not specifically described in GARD under that name, this description is based on information from an NIH institute, the National Cancer Institute.



include seizures or problems with communication and social interaction. There is no cure, but early physical and educational therapies are recommended.

**Friedreich ataxia** is an inherited disease that affects the nervous system and causes movement problems. People with the disease generally begin to experience signs and symptoms around puberty, although it can be much later. The disease is progressive: Difficulty walking and signs of impaired muscle coordination gradually worsen and spread; muscles—especially those in the extremities—begin to weaken and waste away; other symptoms, including some life-threatening comorbid conditions (such as heart disease) may appear. People with Friedreich ataxia typically need to use a wheelchair consistently within 10 to 20 years of their first symptoms.

**Frontotemporal dementias** are a group of neurodegenerative dementias associated with shrinkage of the frontal and temporal anterior lobes of the brain. Symptoms include marked changes in social behavior and personality or problems with language or both. Some people with these dementias also develop problems associated with destruction of motor neurons, the cells that control muscle activity such as walking, breathing, and swallowing. These dementias have a strong genetic component. There are no treatments to slow or stop the progression of these diseases, but some symptoms can be managed.

**Guillain-Barré syndrome** is an autoimmune disease effecting the peripheral nervous system, which carries signals from the brain to the muscles. Symptoms such as muscle weakness, numbness, and tingling sensations can increase until paralysis occurs. The exact cause is unknown, although most cases follow viral infection. There is no cure, but symptoms can generally be improved, and most people regain muscle strength. In contrast, some people with the disease require mechanical ventilation, and about 30 percent continue to experience muscle weakness for years. In rare cases, people have died from complications due to Guillain-Barré syndrome.

**Hemophilia** is a bleeding disease in which the blood does not clot normally. It ranges in severity: in severe cases, heavy bleeding occurs after minor injury or even when there is no injury, and bleeding into the joints, muscles, brain, or organs can cause serious complications.

**Hemophilia A** is an inherited form of hemophilia that primarily affects males and involves a deficiency in a specific blood clotting factor called

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factor VIII. Some people with severe hemophilia A may have a shortened lifespan due to the presence of other health conditions and rare complications of the disease.

**Hemophilia B** is an inherited form of hemophilia that primarily affects males and involves a deficiency in a specific blood clotting factor called factor IX.<sup>13</sup>

**Hereditary angioedema** is characterized by recurrent and generally painful attacks of severe swelling of the skin and mucous membranes—the linings of many body cavities—including the gastrointestinal tract or upper airway. Swelling of the upper airway is potentially life-threatening. Attacks typically start in childhood or adolescence and can continue throughout life; treatment can reduce their frequency.

**Homocystinuria** includes a group of inherited diseases in which homocysteine and other amino acids accumulate. People with the disease may experience problems with their eyes, skeleton, central nervous system (with possible learning, intellectual, and psychiatric problems), or heart. Newborn screening in many states includes a test for the most common cause of homocystinuria. Treatment is primarily through diet and vitamin therapy.

**Idiopathic pulmonary fibrosis** is a disease in which tissues in the lungs become thick and stiff over time, causing the lungs to lose their ability to move oxygen to the brain and other parts of the body. The term “idiopathic” indicates that the cause is unknown. Many people with this disease live for only 3 to 5 years after the diagnosis; the most common cause of death is respiratory failure.

**Inborn amino acid metabolism disorders** are diseases in which the body has trouble breaking down certain amino acids—the building blocks of proteins—or problems getting amino acids into one’s cells. As a result, harmful substances accumulate in one’s body. Over time, serious and sometimes life-threatening health problems can occur. Phenylketonuria is an example of an inborn amino acid metabolism disorder.<sup>14</sup>

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<sup>13</sup>We supplement the description of hemophilia B from GARD with information from MedlinePlus.

<sup>14</sup>Because inborn amino acid metabolism disorders are not described in GARD, this description is based on information from MedlinePlus.

**Intracranial arteriovenous malformations** are abnormal connections between arteries and veins in the brain. Most people with intracranial arteriovenous malformation have few, if any, major symptoms. About 12 percent of people with this condition have symptoms, which vary in severity; seizures and headaches are the most common symptoms and most commonly occur in those aged 20 through about 50. An intracranial arteriovenous malformation can, however, rupture, causing a hemorrhage, and that can cause a stroke or death. The cause of the malformations is not well understood, but they most often seem to arise during embryonic or fetal development. Treatment can involve medications to treat symptoms (for example, for headache, back pain, or seizures) or surgery.<sup>15</sup>

**Kawasaki disease** involves inflammation of the blood vessels. Typically diagnosed in young children, the disease usually begins with a fever that lasts at least 5 days. If the disease affects the coronary arteries, serious heart problems can result. The cause is unknown. Kawasaki disease is most common in people of Asian or Pacific Island descent.

**Leishmaniasis** is a parasitic disease spread by the bite of an infected sand flea. The most common forms of this disease are a cutaneous type, which causes skin sores, and a visceral type that affects internal organs such as the liver, spleen, and bone marrow. Without treatment, the visceral type of leishmaniasis can be fatal. This disease is found in Central and South America, Asia, Africa, parts of the Middle East, and southern Europe, but it is rare in the United States.

**Lennox-Gastaut syndrome** is a severe epilepsy that begins in childhood and is marked by multiple types of seizures and intellectual disability. It can be caused by brain malformations, perinatal lack of oxygen, severe head injury, infection of the central nervous system, or certain inherited degenerative or metabolic diseases; in about one-third of cases, no cause is identified. Treatment is generally intended to control seizures, which may be treatment resistant.

**Leukodystrophies** are progressive, genetic disorders that affect the brain, spinal cord, or other nerves. They are caused by mutations in the

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<sup>15</sup>We supplement the description of arteriovenous malformations from GARD with information from an NIH institute, the National Institute of Neurological Disorders and Stroke.

genes involved in the production of myelin, the fatty covering that insulates nerves and is required for their normal functioning.

**Merkel cell carcinoma** is an aggressive skin cancer. Treatment may include surgery, radiation, chemotherapy, or a combination of those approaches. Treatment options and prognosis depend on factors such as the location, size, and recurrence of the cancer. The mutations that cause the disease do not appear to be inherited and occur randomly during a person's life.

**Metachromatic leukodystrophy** is an inherited disease in which certain fats, called sulfatides, accumulate in cells, particularly cells of the nervous system. This accumulation causes progressive destruction of the brain's white matter, resulting in progressive deterioration of intellectual functions, motor skills, and awareness of the environment until the person becomes unresponsive.

**MPV17-related hepatocerebral mitochondrial DNA depletion syndrome** is a progressive, life-threatening disease. Liver problems develop in the first weeks of life and may quickly progress to liver failure. Many affected infants also develop neurological problems. This inherited disease is most common in Native American Navajos.<sup>16</sup>

**Mucopolysaccharidosis** refers to a group of inherited conditions in which the body is unable to properly break down long chains of sugar molecules that exist throughout the body. As a result, these sugars accumulate in cells, blood, and connective tissue, which can lead to a variety of health problems. Most affected people appear healthy at birth and experience a period of normal development, followed by a decline in physical or mental function or both. As the disease progresses, it may affect appearance, physical abilities, organ and system functioning, and, in most cases, cognitive development.

**Mumps** is an infectious viral disease. Initial symptoms include fever, headache, muscle aches, and loss of appetite. After that, the salivary glands under the ears or jaw, to either or both sides of the face, swell and become tender. Symptoms last from 7 to 10 days. There is no cure, but it

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<sup>16</sup>We supplement the description of MPV17-related hepatocerebral mitochondrial DNA depletion syndrome from GARD with information from MedlinePlus.

can be prevented with a vaccine, and because of routine vaccination, it is now rare in the United States.<sup>17</sup>

**Myasthenia gravis** is a chronic, autoimmune, neuromuscular disease characterized by weakness of the skeletal muscles. There is no cure, but treatment can result in improvement. The disease is not directly inherited, nor is it contagious, but a genetic predisposition to autoimmune disease can run in families. People can develop myasthenia gravis at any age.

**Myotonic dystrophy** is an inherited, progressive disease involving muscle loss and weakness that usually begins in adulthood. The severity of the disease varies among those affected; treatment is aimed at symptom management.

**Niemann-Pick disease type A** is an inherited disease in which lipids (fats) accumulate in the spleen, liver, lungs, bone marrow, and brain. It appears during infancy and involves progressive deterioration of the nervous system. There is no treatment, and most people with the disease do not survive past early childhood. This disease is most common in Ashkenazi Jewish families.

**Nontuberculous mycobacterial lung disease** is an infectious (acquired) disease caused by a bacteria found naturally in soil and water. Although most people who are exposed to these bacteria do not become sick, people who have a weakened immune system or certain other health conditions have an elevated risk of developing the disease. It is chronic and progressive, and, if untreated, it can result in lung damage. It is generally treated with a combination of antibiotics provided continuously over 1 year or more.<sup>18</sup>

**Pemphigus** is a group of chronic autoimmune diseases that cause blistering of the skin and mucous membranes, including the mouth, nose, throat, eyes, and genitals. It can occur at any age but often affects people in middle or older age. Pemphigus is best controlled by early diagnosis and treatment, which can include drugs to reduce inflammation, drugs to

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<sup>17</sup>Because mumps is not described in GARD under that name, this description is based on information from MedlinePlus.

<sup>18</sup>We supplement the description of nontuberculous mycobacterial lung disease from GARD with information from published research. See, for example, S. E. Stollo, et al., "The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States," *Annals of the American Thoracic Society*, vol. 12, no. 10 (2015): pp. 1458-1464.

suppress the immune system response, and antibiotics to treat associated infections.

**Phenylketonuria** is an inherited amino acid metabolism disease in which the body cannot convert phenylalanine, which is a natural part of foods, to tyrosine, a harmless amino acid. Without treatment, the accumulation of phenylalanine's breakdown products causes permanent intellectual disability and may also cause seizures, developmental delays, and behavioral problems. Phenylketonuria can be detected with a simple blood test, and all U.S. states require newborn screening for phenylketonuria. Treatment is primarily through diet (specifically, dietary protein restriction and supplementation with medical foods), but even early and continuous dietary control may not be sufficient to fully prevent cognitive and neurological disruptions.<sup>19</sup>

**Prader-Willi syndrome** is a life-threatening genetic disease that affects many parts of the body. Infants with this disease have severe problems with muscle tone, feeding difficulties, and slow growth. Later, children with the disease typically begin to eat excessively and become obese. Other common symptoms include developmental delays, cognitive impairment, and behavioral problems, such as temper tantrums. Most cases are not inherited, instead occurring randomly. Management generally depends on the person's age and symptoms.<sup>20</sup>

**Primary immune deficiency diseases** are genetic disorders that impair the immune response. As a result, people with these diseases may be subject to chronic, debilitating—and potentially fatal—infections.<sup>21</sup>

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<sup>19</sup>We supplement the description of phenylketonuria from GARD with information from MedlinePlus and published research. See, for example, S. A. Berry, et al., "Newborn Screening 50 Years Later: Access Issues Faced by Adults with [Phenylketonuria]" *Genetics in Medicine*, vol. 15, no. 8 (2013): pp. 591-599. We use brackets to replace the abbreviation, PKU, with the full name of the disease. Medical foods are formulated to be consumed or administered under the supervision of a physician and are intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

<sup>20</sup>We supplement the description of Prader-Willi syndrome from GARD with information from an NIH institute, the National Institute of Child Health and Human Development.

<sup>21</sup>Because primary immune deficiency diseases are not listed in GARD under that name, this description is based on information from the NIH's National Institute of Allergy and Infectious Diseases.

**Progressive supranuclear palsy** is a degenerative neurologic disease associated with damage to nerve cells in the brain. It is a progressive disease that is sometimes, but not usually, inherited. Signs and symptoms vary and typically involve problems with balance, vision, eye movement; changes in mood, behavior, and judgment; cognitive decline; and problems with speech. There is no effective treatment for the disease.

**Pulmonary arterial hypertension** is a progressive and life-threatening disease that affects the heart and lungs. It is characterized by abnormally high blood pressure in the pulmonary artery. Most cases occur in people with no family history of the disease. The disease can occur for unknown reasons, can be secondary to another underlying disease such as connective tissue disease, or can be induced by certain toxins and drugs. There is no cure for the disease, but drugs can be used to manage it and help delay its progression.<sup>22</sup>

**Recombinant chromosome 8 syndrome** is a disease that involves abnormalities in the heart and urinary tract and moderate to severe intellectual disability. Because of the heart abnormalities, many children with this disease do not survive past early childhood. Caused by a chromosomal abnormality, most people with this disease are Hispanic, specifically, from a Hispanic population originating in the San Luis Valley area of southern Colorado and northern New Mexico.

**Sickle cell anemia** is an inherited disease in which the body produces red blood cells that are abnormally shaped—they are a sickle shape, rather than a disc shape. These abnormal cells do not last as long as normal red blood cells, causing anemia. In addition, the sickle cells can become stuck in blood vessels, blocking blood flow, and that can cause stroke, infections, episodes of pain, or eye problems. (Sickle cell anemia is the most common cause of stroke in children.) In the United States, most people who have sickle cell anemia are of African ancestry or identify themselves as Black.<sup>23</sup>

**Spina bifida** is a type of defect in which the neural tube—the structure in an embryo that becomes the brain and spinal cord—does not close

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<sup>22</sup>We supplement the description of pulmonary arterial hypertension from GARD with information from an NIH institute, the National Heart, Lung, and Blood Institute.

<sup>23</sup>We supplement the description of sickle cell anemia from GARD with information from an NIH institute, the National Heart, Lung, and Blood Institute.

completely prior to birth. Depending on the extent and location of the effects on the spinal cord, the signs and symptoms of spina bifida can range from mild to severe and may include weakness or paralysis of the feet or legs, problems with bowel or bladder control, and learning problems. In most cases, both genetic and environmental factors appear to have a causal role. Maternal folate deficiency increases the risk that a baby will have spina bifida, and women who take folic acid supplements before and during early pregnancy reduce this risk.

**Spinal arteriovenous malformations** are abnormal connections between arteries and veins in the spinal cord. The cause of the malformations is not well understood, but they most often seem to arise during embryonic or fetal development. Most people with brain or spinal arteriovenous malformation have few, if any, major symptoms. Spinal arteriovenous malformations can cause sudden and severe back pain; sensory disturbances, muscle weakness, or degeneration of nerves and paralysis in the parts of the body below the malformation.<sup>24</sup>

**Systemic scleroderma** is an autoimmune disorder that affects the skin and internal organs. The disease is marked by production of too much collagen, which results in accumulation of scar tissue in the skin and other organs, including the esophagus, heart, lungs, and kidneys. The cause or causes are currently unknown. It can be fatal.<sup>25</sup>

**Tuberous sclerosis complex** is an inherited disease characterized by the growth of benign tumors throughout the body, including in the heart, brain, and kidneys. Some symptoms, such as heart tumors, develop before birth. Other symptoms, such as developmental delays, become more obvious in childhood, and lung and kidney tumors are more likely to develop in adulthood. Treatment is generally intended to manage the symptoms and may include medications and surgery. Tuberous sclerosis complex can be life threatening.<sup>26</sup>

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<sup>24</sup>We supplement the description of arteriovenous malformations from GARD with information from an NIH institute, the National Institute of Neurological Disorders and Stroke.

<sup>25</sup>We supplement the description of systemic scleroderma from GARD with information from published research. See, for example, V. D. Steen and T. A. Medsger, "Changes in Causes of Death in Systemic Sclerosis, 1972-2002," *Annals of the Rheumatic Diseases*, vol. 66, (2007): pp. 940–944.

<sup>26</sup>We supplement the description of tuberous sclerosis complex from GARD with information from MedlinePlus.



# Appendix III: Attributes Experts Identified as Often Distinguishing Rare from Common Diseases

Rare diseases are more likely than common diseases to be due to a single genetic mutation, but rare diseases do not necessarily differ in any specific way from common diseases.<sup>1</sup> We asked officials with the Food and Drug Administration and National Institutes of Health, researchers, and experts about the differences between rare and common diseases. Attributes that experts identified as often (but not invariably) distinguishing rare from common diseases are presented in table 2.

**Table 2: Attributes Experts Identified as Often Distinguishing Rare from Common Diseases**

Attribute	How the attribute often distinguishes rare from common diseases
<b>Attributes linked to the disease itself</b>	
Familiarity	Because rare diseases are less prevalent than common diseases, they may be harder to study (for example, because it may be harder to identify people with the disease and enroll them in research), so there is often less information about them, and medical professionals tend to have less experience with them.
Functionality	People with rare diseases are typically symptomatic through most of the course of their disease, often with severe or serious manifestations of the disease from the time the symptoms first appear. In contrast, people with common diseases that are progressive (that is, common diseases that worsen over time)—diseases such as diabetes or hypertension—may be able to function reasonably well during what could be decades.
Genetic causation	Many rare diseases are genetic, and they are, therefore, life long, with clinical manifestations in infants, children, and young adults. Moreover, in the absence of a disease-modifying treatment, these diseases are generally chronic and progressive. In addition, when there is a genetic cause, there may be more than one affected member in a family,
Neurological involvement	Many rare diseases have a neurological component, with cognitive, developmental, and neurodegenerative manifestations. As a result, treatment may require not only comprehensive physical management but also psychosocial interventions, learning support, and, in some cases, life-long custodial or supervised care.
Physical anomalies	Rare diseases are more likely than common diseases to involve physical anomalies or congenital malformations that bring attention to the person.
Reversibility	Many rare diseases are progressive, and most progressive diseases are irreversible.
Severity	Many rare diseases are serious, life-threatening, or life-limiting.
<b>Attributes linked to diagnosing the disease</b>	
Diagnostic process	Diagnosis of rare disease is more likely to require highly specialized diagnostic techniques and highly specialized physicians than diagnosis of a common disease.
Diagnostic testing	Testing for many rare diseases (if available) is generally more costly and more complex (for example, requiring genomic analysis) than testing for common diseases, which is often readily available and relatively low-cost.

<sup>1</sup>In the United States, a rare disease is typically defined as any condition that affects less than 200,000 people in this country. Thus, the number of people who are affected generally differentiates rare from common diseases, but that number can change over time (for example, if a way to prevent a common disease—such as immunization—is successfully implemented or if a novel infectious disease spreads).

**Appendix III: Attributes Experts Identified as Often Distinguishing Rare from Common Diseases**

<b>Attribute</b>	<b>How the attribute often distinguishes rare from common diseases</b>
<b>Attributes linked to treating the disease</b>	
Availability of a treatment	There is a lower probability that there will be an available treatment for rare than for common diseases.
Interactions with health care systems	Manifestations of rare diseases are more likely than those of common diseases to result in frequent interaction with the health care system, including hospitalization and emergency room visits.
Multidisciplinary care	Many rare diseases involve multiple organ systems, and, as a result, their care requires multiple specialists who provide coordinated, comprehensive care in multidisciplinary teams.
Precision medicine	Medical professionals are more likely to turn to the techniques of precision medicine—the use of information about a person’s own genes or proteins—to prevent, diagnose, or treat rare diseases than common diseases, for which interventions generally exist already.
Time sensitivity	With certain rare genetic disorders, early interventions such as enzyme replacement therapy or dietary modifications can substantially limit the effects of the disease and so have a profound effect on long-term outcomes. There may be limited time periods—“windows of opportunity”—during which the course of the rare disease can be modified. Outside of those time periods, chances for meaningful intervention may be more limited.

Source: GAO analysis of interviews with experts on rare diseases, including officials with the Food and Drug Administration and National Institutes of Health, researchers, and others. | GAO-22-104235

Note. The listed attributes do not necessarily distinguish rare from common diseases in all cases. For example, there are patient registries for certain rare diseases, and these registries may make it easier to identify potential research participants than would be the case for a common disease in the absence of a registry. In addition, some common diseases are as complex or disruptive as some rare diseases.

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# Appendix IV: GAO Contact and Staff Acknowledgments

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## GAO Contact

John E. Dicken, (202) 512-7114 or [dickenj@gao.gov](mailto:dickenj@gao.gov).

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## Staff Acknowledgments

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