The Cost of Delayed Diagnosis in Rare Disease:

A Health Economic Study

EveryLife Foundation for Rare Diseases

In Partnership With:

The Lewin Group, part of Optum Serve

Expert Stakeholders

The Rare Disease Community

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EVERYLIFE FOUNDATION FOR RARE DISEASES

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The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study

Full Study Report

Prepared for:

EveryLife Foundation for Rare Diseases

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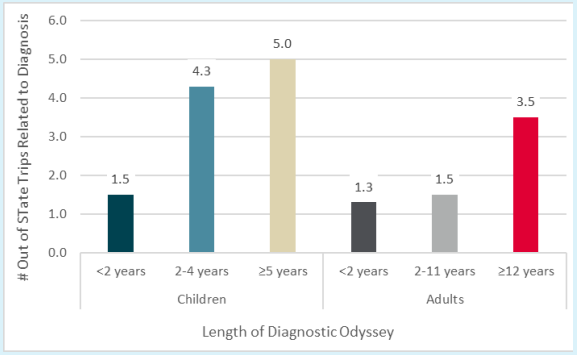
EXECUTIVE SUMMARY

Rare diseases (RD) affect an estimated 30 million children and adults in the US (Haendel, Vasileysky, & Unni, 2020; Genetic and Rare Diseases Information Center, 2023). The considerable excess burden on patients, families, and the health system is a matter of public health. Individuals with RD often undergo lengthy diagnostic odysseys resulting in delayed diagnoses and missed opportunities for timely and optimal treatment. Timely diagnosis can dramatically shorten or eliminate the diagnostic odyssey, resulting in prompt life-saving treatment of disease, and can save intangible cost savings for families, including time spent managing financials, time off work for healthcare visits, and in many cases, out-of-state trips to see rare disease specialists for diagnosis and treatment. Today, the transformative advances in technologies to screen, diagnose, treat and manage RD either presymptomatically or in the earliest stages of the disease process increase the need for timely diagnosis and intervention.

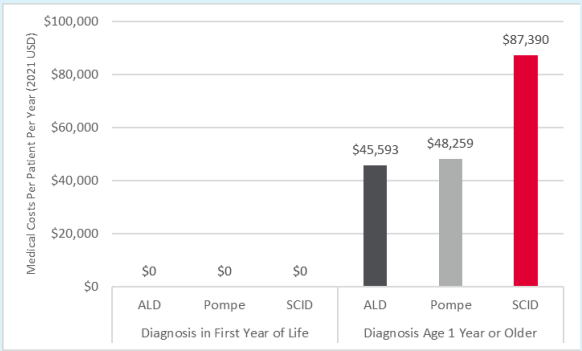
Out-of-State Trips Related to Rare Disease Diagnosis



Source: 2019 Rare Disease Impact Survey Analysis

This study uses real world data to examine healthcare utilization relative to timing of diagnosis in seven RDs based on anticipated costs, evidence for diagnostic odyssey, and potential for new therapies in adrenoleukodystrophy (ALD), infantile-onset and late-onset Pompe disease, Severe Compromised Immunodeficiency (SCID), Fragile X Syndrome (FXS), Duchenne Muscular Dystrophy (DMD), Wilson Disease, and generalized Myasthenia Gravis (gMG). In the three diseases (ALD, PD, SCID) where routine newborn screening has been implemented in some or all states, timely diagnosis can eliminate the diagnostic odyssey and its associated medical costs prior to diagnosis and provide the opportunity for optimal intervention and improved health outcomes.

Annualized Medical Costs Per Patient Prior to Rare Disease Diagnosis



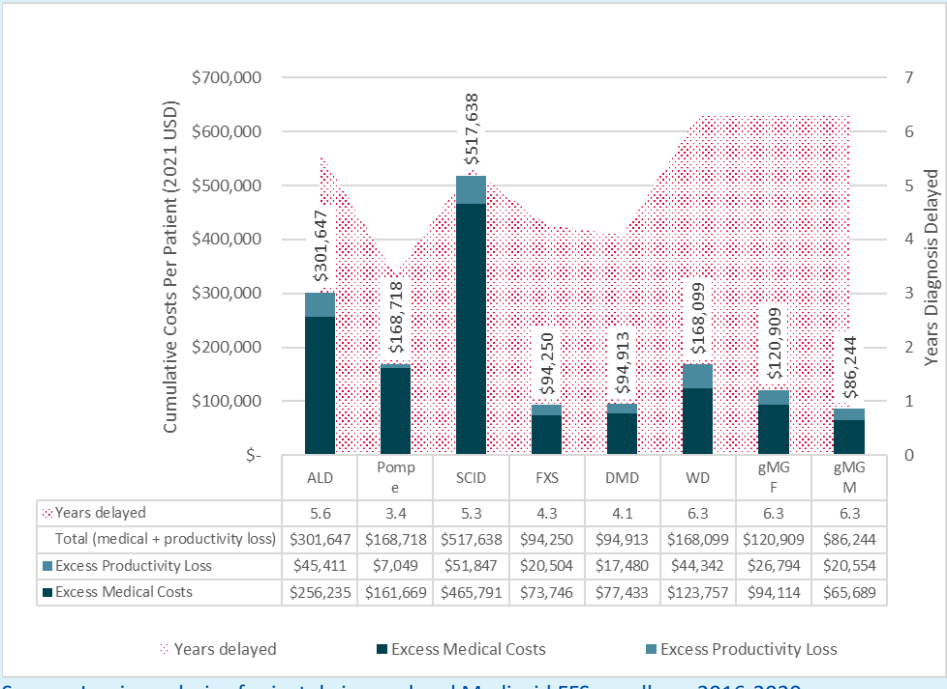
Source: Lewin analysis of privately insured and Medicaid FFS enrollees, 2016-2020

On average, RD patients spend more than 6 years searching for a diagnosis (Hendriksz, 2013; Benito-Lozano, Lopez-Villalba, Arias-Merino, Posada de le Paz, & Alonso-Ferreira, 2022; Yang, Cintina, & Pariser, 2022). We estimate that the avoidable costs attributable to delayed diagnosis, in terms of medical costs and productivity loss in the pre-diagnosis years, is

between $86,000 and $517,000 per patient cumulatively for the years of delay. This includes a conservative estimate of productivity loss based on healthcare visits and does not take into account travel time, which can be substantial for rare disease patients and their families.

Timely diagnosis is important when there are potentially disease-altering or life-saving treatments available. Even in the absence of such treatments, timely diagnosis can have a profound impact when irreversible symptom progression is delayed, treated, or managed; this ultimately improves health and reduces the cumulative burden of the diagnostic odyssey on patients and families with rare disease. While medical costs are unavoidable in RD, the avoidable costs attributable to delayed diagnosis represent the burden on patients and families searching for a diagnosis. Delayed diagnosis also prevents healthcare dollars from being better spent on treatment and supportive therapies that improve patient quality of life and may even increase workforce productivity.

Excess Medical Costs and Productivity Loss Attributed to Delayed Diagnosis



	ALD	Pompe	SCID	FXS	DMD	WD	gMGF	gMGM
Years delayed	5.6	3.4	5.3	4.3	4.1	6.3	6.3	6.3
Total (medical + productivity loss)	$301,647	$168,718	$517,638	$94,250	$94,913	$168,099	$120,909	$86,244
Excess Productivity Loss	$45,411	$7,049	$51,847	$20,504	$17,480	$44,342	$26,794	$20,554
Excess Medical Costs	$256,235	$161,669	$465,791	$73,746	$77,433	$123,757	$94,114	$65,689

Source: Lewin analysis of privately insured and Medicaid FFS enrollees, 2016-2020.

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BACKGROUND

An estimated 10,000 rare diseases (RDs) affect 25-30 million Americans (Haendel, Vasileysky, & Unni, 2020; Genetic and Rare Diseases Information Center, 2023). The results of our recent National Economic Burden of Rare Disease Study estimated the annual economic impact of RDs at $997 billion in 2019 USD. Less than half of those costs (45%, $449 billion) were direct costs to the healthcare system, with the remaining 55% of costs absorbed by individuals and families, employers, and society, as indirect and non-medical costs (Yang, Cintina, & Pariser, 2022). In addition, results from our survey of 1,360 respondents with confirmed RD diagnoses suggest an average time from symptom onset to diagnosis of over 6 years, including an average of 17 clinical encounters between symptom onset and RD diagnosis (Yang, Cintina, & Pariser, 2022). Referred to as the "diagnostic odyssey", these delays result in inappropriate clinical management and missed treatment windows for therapeutic interventions. The diagnostic odyssey contributes to irreversible disease progression and complications, ultimately putting patients at risk for preventable mortality and disability.

The challenges brought on by the diagnostic odyssey result in delayed or missed diagnoses. Delay in accurate diagnosis can yield inappropriate clinical management, unnecessary medical interventions, and missed treatment windows for therapeutic interventions to optimize health outcomes or prevent disease symptom onset. The diagnostic odyssey may contribute to increased probability of irreversible disease progression and complications, ultimately putting patients at risk for preventable mortality and disability.

Advancements in technologies to screen, diagnose, treat, and manage RD have the potential to dramatically shorten — or even eliminate — the diagnostic odyssey. This includes population-based newborn screening (NBS), which in some cases enables presymptomatic diagnosis, as well as genetic and genomic testing at the onset of clinical signs and symptoms of RD. These advancements facilitate timely diagnosis and have the potential to delay or prevent disease complications, or even death. Timely diagnosis may also save families from undue stress, save children from unnecessary tests and inappropriate treatments, and reduce the impact on the healthcare system. Shortening or eliminating the diagnostic odyssey in RD has been demonstrated to improve clinical health outcomes, lead to timely diagnoses of family members, and have significant economic benefits to individuals and society (Wu, McMahon, & Lu, 2020).

Patients and caregivers benefit from answers (Bauskis, Strange, Molster, & Fisher, 2022). Caregivers, in particular, may be empowered by knowledge of confirmed diagnosis even when treatment is not available and they are forced to make decisions about comfort care (Dimmock, et al., 2021). A growing body of evidence shows evaluations include many trips to specialists for diagnostic testing and treatment of symptoms (Yang, Cintina, & Pariser, 2022; Richards, Korgenski, Srivastava, & Bokowsky, 2015). A number of studies have made a case for early use of genomic testing, including comprehensive whole genome sequencing (WGS) and whole exome sequencing (WES), to shorten the diagnostic odyssey (Petrikin, et al., 2018), improve disease management (Sweeney, et al., 2021; Stark, et al., 2019; Dimmock, et al., 2021), and

subsequently reduce inpatient utilization and costs (Sweeney, et al., 2021; Farnaes, et al., 2018). Whole genome and whole exome sequencing, especially if early, has greater diagnostic and clinical utility (Clark, et al., 2018).

This study uses real world data to provide a detailed accounting of the diagnostic odyssey in seven RDs, three of which are part of routine NBS in the United States, and compares the healthcare utilization associated with timely vs delayed diagnosis. The study goal was to provide an estimate of potential cost-savings that may result from shortening or eliminating the diagnostic odyssey. Specifically, we aimed to understand the patient journey prior to diagnosis and quantify the medical costs and productivity loss of delayed diagnosis in seven RDs.

METHODS

The analysis was informed by detailed patient journey maps based on comprehensive literature review and consultation with an expert advisory group. We conducted a comprehensive literature review to understand disease epidemiology, disease milestones and progression, testing and procedures that can be part of the diagnostic odyssey, and economic burden. In collaboration with the EveryLife Foundation for Rare Diseases, we identified 27 experts to join a technical advisory panel, representing the research, clinical, and patient advocacy communities. The expert panel, including pediatricians, patients, family members, disease advocates, and researchers, reviewed patient journey maps and provided input to refine and finalize these. In addition, over the course of the project, we conducted 5 panel discussions to spearhead the project direction and to review interim output and study results. Disease-specific experts provided consultation and key insights throughout the project.

An IRB exemption was obtained via the New England IRB.

Data Sources

To estimate direct medical costs associated with the diagnostic odyssey, we used two data sources: Transformed Medicaid Statistical Information System (T-MSIS), which includes individuals covered by Medicaid Fee for Service (FFS) and Children's Health Insurance Program (CHIP); and Optum's large de-identified administrative claims database comprised of individuals enrolled in employer-sponsored and individual private insurance plans with a large national payer. Direct medical costs were assessed using enrollment data, medical and pharmacy claims.

We also analyzed the primary survey previously designed for the economic burden study — the RD Impact Survey (Yang, Cintina, & Pariser, 2022) — to estimate other indirect cost components that are potentially associated with the diagnostic odyssey.

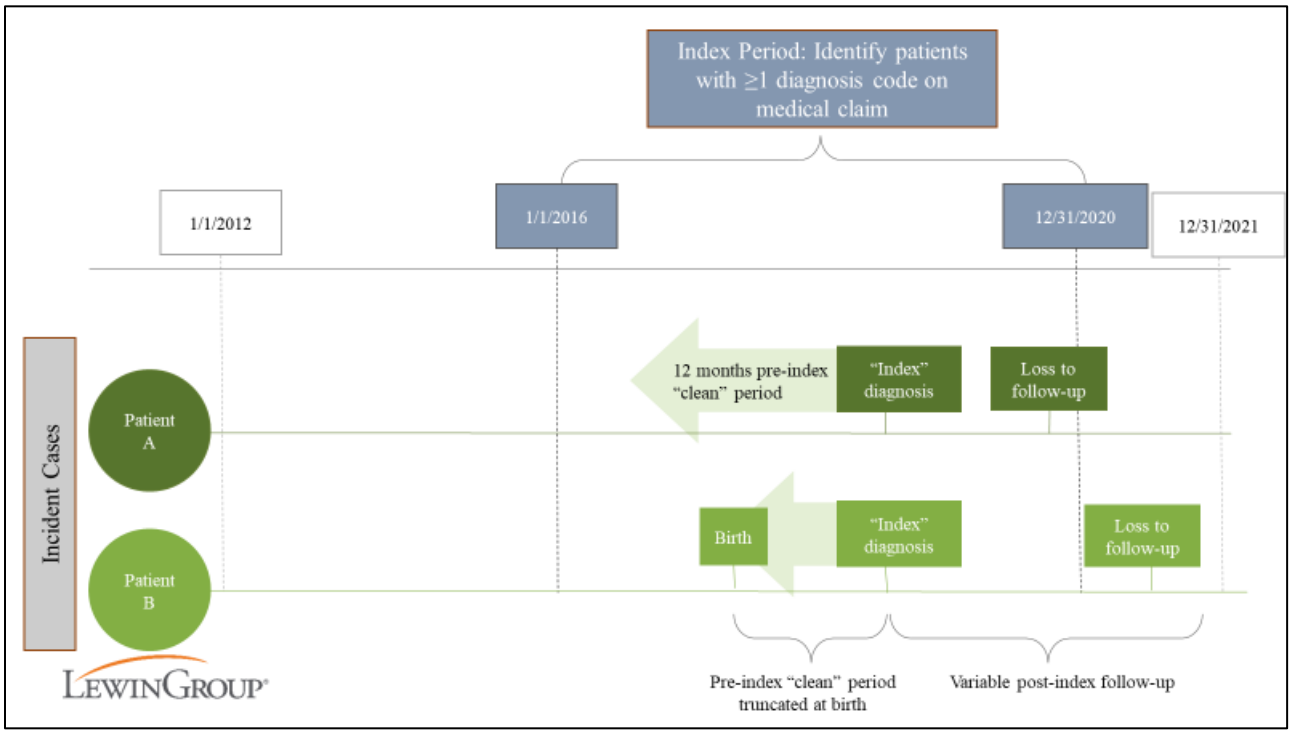
Direct Medical Costs

Study Population

The source population included patients diagnosed with any of the seven RDs of interest during the identification period of 2016-2020, or 2018-2020 for Duchenne Muscular Dystrophy when

the diagnosis code became available. Patients were identified by ≥1 medical claim with the respective International Classification of Disease 10th Edition (ICD-10) codes for a given disease (Exhibit 2). The first diagnosis within the identification period was considered the "index" diagnosis. Patients were required to have at least 12 months of continuous enrollment in the health plan (with both medical and pharmacy coverage) before the index date with no evidence of the respective RD. If a patient was born less than 12 months before the index date, the continuous enrollment requirement was truncated at birth.

Exhibit 1. Study Design



For each disease, we categorized patients as having "timely" or "delayed" diagnosis based on age at first diagnosis. For diseases where NBS has been implemented in some or all U.S. states (i.e., SCID, ALD, and Pompe), timely diagnosis was defined as a diagnosis before age 1. For other diseases the age threshold for timely diagnosis was derived from a combination of literature review, expert input, and empiric data (i.e., Fragile X Syndrome before age 3, Duchenne Muscular Dystrophy before age 5, Wilson before age 19, gMG before age 40 in females and age 50 in males). Cohorts were restricted to males for X-linked disorders (ALD, Duchenne Muscular Dystrophy, and Fragile X Syndrome).

Exhibit 2. Rare Disease Cohort Specifications

Disease	Source Population				Early and Late Cohorts	
	Identification Period Start	Identification Period End	Restrict to Males	ICD-10 for Disease Identification	Timely Diagnosis Definition (age in years)	Delayed Diagnosis Definition (age in years)
ALD	1/1/2016	12/31/2020	Y	E71511 E7152*	<1	≥1 and <12
Pompe[a]	1/1/2016	12/31/2020		E7402	<1	≥1 and <12
SCID	1/1/2016	12/31/2020		D810 D811 D812 D8131	<1	≥1 and <12
FXS	1/1/2016	12/31/2020	Y	Q992	<3	≥3 and <12
DMD	1/1/2018	12/31/2020	Y	G7101	<5	≥5 and <12
WD	1/1/2016	12/31/2020		E8301	<19	≥19
gMG	1/1/2016	12/31/2020		G7000 G7001	Females <40 Males <50	Females ≥40 Males ≥50

[a] Within timely and delayed diagnosis of Pompe, we further distinguish between infant onset (IOPD) and late onset (LOPD) by initiation of enzyme replacement therapy (ERT) within 120 days following diagnosis.

Healthcare Utilization and Costs

Per-patient-per-month healthcare utilization and costs were captured for the pre-diagnosis, year of diagnosis, and post-diagnosis periods. For ALD, Pompe, and SCID, the first year of life is the year of diagnosis. Costs and utilization were captured by type of healthcare setting: acute and non-acute inpatient stay (IP) where the entirety of a hospital stay is attributed to the time period in which the date of admission falls; emergency department (ED) visit; outpatient (OP) visit; physician office visit; and other. In general, the healthcare setting was determined by place of service, and a category of "Other" includes home-based services covered by insurance, ambulance, laboratory facilities, mobile and clinics in schools or places of employment (see Supplemental File S-1 for additional details). Prescription drug costs were also captured. Caregiver services covered by Medicaid FFS are also captured. Per-patient-per-month costs were annualized and adjusted to 2021 USD based on the medical care component of the Consumer Price Index (CPI). Medical costs included primary payer paid amount and patient out-of-pocket expenses (e.g., copay, co-insurance, deductibles). Costs attributed to a given RD diagnosis were defined as those with the respective diagnosis code in the primary position on the medical claim (Exhibit 2).

To estimate the cumulative direct medical costs during diagnostic odyssey, we multiplied the number of years the diagnosis was delayed (calculated as the difference between the mean age at diagnosis in the delayed group and the threshold for timely diagnosis) by the per-patient-per-year direct medical costs in the pre-diagnosis period for delayed diagnosis. For diseases with

typical adult onset, we used our results from our previous study that estimated 6.3 years as the length of the delay in diagnosis (Yang, Cintina, & Pariser, 2022).

Indicator variables were created for evidence of services such as genetic testing and specific treatments. Indicators for genetic testing were captured at any time during the study period and included: WGS, WES, single gene tests, genetic panel tests, and specific tests for diseases of interest. CPT and HCPCS code lists are in Appendix C. Exhibit C - 2. Supplemental Methods and Code Lists.

Indirect Costs

To quantify the cost of the diagnostic odyssey and delayed diagnosis incurred by patients and families, we used the method outlined by Mowitz (Mowitz, et al., 2022) to estimate the number of work hours missed due to medical appointments multiplied by the mean hourly wage in 2021 USD from the Bureau of Labor Statistics, where 1 IP day=1 day missed work, 1 OP or ED visit=0.5 days missed work, and one physician office visit=0.25 days missed work. We then estimated the cumulative productivity losses by multiplying the number of years diagnosis was delayed by the per-patient-per-year productivity loss in the pre-diagnosis period.

In addition, we analyzed data from the Rare Disease Impact Survey conducted in 2020. The Rare Disease Impact Survey included questions on several key domains, including: 1) health status, disease history and severity of RD; 2) demographics, socioeconomic characteristics and insurance of the person with RD; 3) informal caregiver profile and caregiver roles and responsibilities; and 4) non-medical costs.

Details of the survey development and sampling are described in detail elsewhere (Yang, Cintina, & Pariser, 2022). In summary, the survey was disseminated to a convenience sample of patients with over 350 unique RDs via more than 200 partner patient advocacy organizations. A total of 3,484 households responded to the survey, among them 1,409 (40.4%) completed the survey. From the original sample, 10 responses were dropped because the respondent did not have, or know anyone with, a RD and 39 were dropped because the name of the diseases entered was an invalid entry or it was not a RD (e.g., type 1 diabetes). For this examination of relationships with the diagnostic odyssey, we further excluded those without data necessary to calculate a diagnostic odyssey length (i.e., year of symptom onset and year of RD diagnosis). The final survey sample represented 1,300 RD patients, including 601 individuals diagnosed with RD before age 19 (of which, 492 surveys were completed by a caregiver or family member) and 699 who were adults at the time of diagnosis (of which, 63 surveys were completed by a caregiver or family member, Appendix B. Exhibit B - 1).

Because sample sizes for the seven diseases of interest were small, we included all survey respondents with data sufficient to calculate a diagnostic odyssey and stratified by self-reported age at time of diagnosis (<19 and ≥19 years). The length of diagnostic odyssey was calculated as the length of time in years from the year of symptom onset to the year of RD diagnosis and categorized as <2 years, 2-4 years, and ≥5 years for children and <2 years, 2-11

years, and ≥12 years for adults. We used these survey data to summarize patient-reported counts of healthcare events before RD diagnosis. Healthcare events included: number of primary care physicians seen for RD diagnosis; number of specialty physicians seen for RD diagnosis; number of ED visits related to RD before diagnosis; number of hospital admissions related to RD before diagnosis; and number of out-of-state trips related to RD diagnosis.

Sensitivity Analyses

To minimize risk of reidentification in the commercial data, we did not have access to date of birth and had to rely on year of birth to ascertain age. In order to more closely examine the potential impact of newborn screening in ALD, Pompe, and SCID, we conducted a sub-analysis of the Medicaid FFS study population using date of birth and a more refined definition of 4 months of age or earlier for timely diagnosis and older than 4 months for delayed diagnosis. This corresponds more closely with the timing of receipt of test results from newborn screening.

To preserve sample size, we required a minimum of 1 diagnosis code to be included in the analyses. However, this poses a risk of misclassification by disease status so we also conducted sensitivity analyses restricted to the subset with a second confirmatory diagnosis on a separate date of service.

RESULTS

Costs

We identified 4,828 individuals with ≥1 medical claim with a diagnosis code for one of the 7 RDs and enrolled in private or Medicaid FFS insurance between 1/1/2016 and 12/31/2020. Patient characteristics and mean post-diagnosis follow-up time for the timely and delayed cohorts are shown in Exhibit 3.

Exhibit 3. Study Population Characteristics Relative to Timing of Diagnosis

	Timely[a]					Delayed[b]				
	Total	Male, %	Age at Diagnosis, years	Medicaid, %	Post-diagnosis follow-up, months	Total	Male, %	Age at Diagnosis, years	Medicaid, %	Post-diagnosis follow-up, months
ALD	29	100%	0.0	41%	22.5	69	100%	6.6	78%	20.8
Pompe	51	63%	0.0	39%	19.8	40	48%	4.4	63%	18.6
SCID	54	57%	0.0	59%	21.5	73	66%	6.3	78%	24.1
FXS	75	100%	1.0	79%	21.2	272	100%	7.3	86%	24.4
DMD	86	100%	2.6	76%	20.4	652	100%	9.1	91%	20.3
WD	165	55%	11.6	78%	24.9	404	42%	39.6	46%	20.4
gMG, females	706	0%	25.8	60%	21.8	1073	0%	52.4	37%	21.8

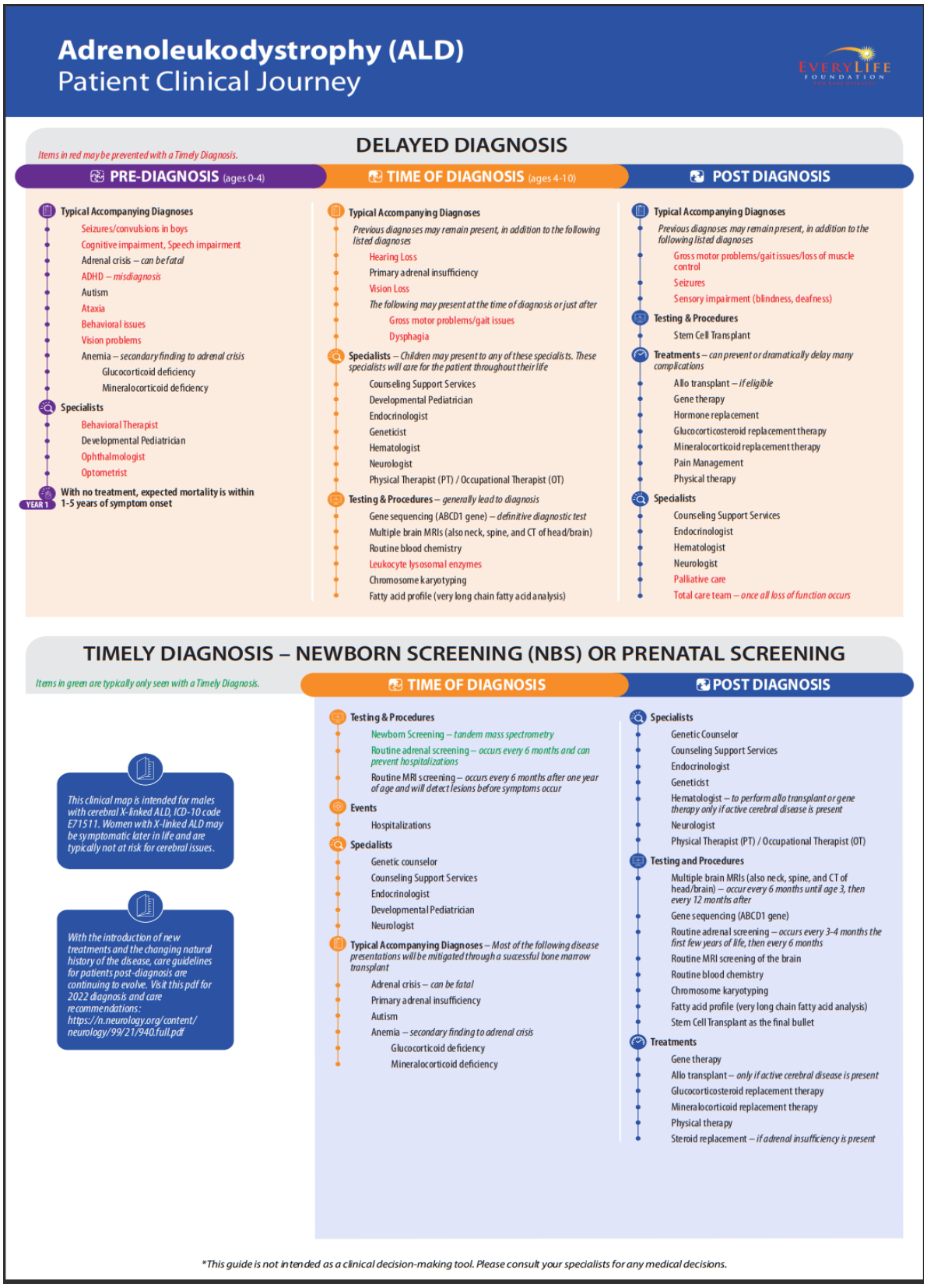
gMG, Males	524	100%	29.6	52%	22.3	556	100%	58.1	24%	21.1

[a] Timely diagnosis defined as: before age 1 in ALD, Pompe, and SCID; before age 3 in FXS, before age 5 in DMD; before age 19 in WD; before age 40 in females with gMG; and before age 50 in males with gMG.
[b] Delayed diagnosis defined as: age ≥1 year and <12 years for ALD, Pompe, and SCID; age ≥3 years and < 12 years for FXS; age ≥5 years and <12 years for DMD; age ≥19 and <65 for Wilson; and age ≥40 and <65 years for females in gMG and ≥50 years and <65 years for males with gMG.

Adrenoleukodystrophy

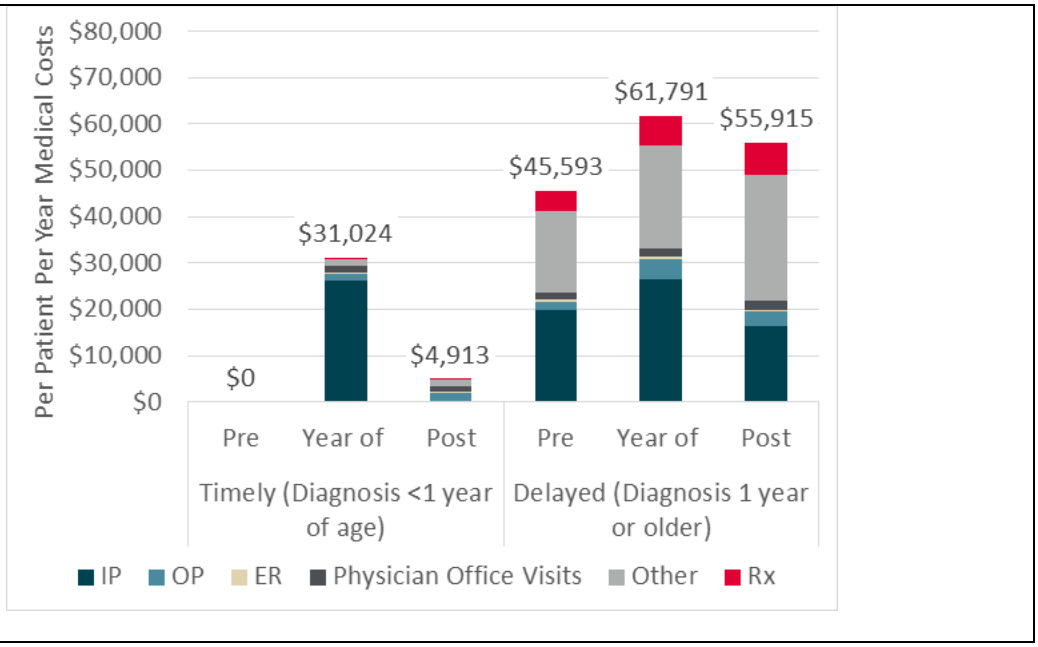
Adrenoleukodystrophy, or ALD, is a deadly genetic disease of the myelin sheath that affects 1 in 18,000 people, most severely affecting males. The most devastating form of ALD appears in childhood between the ages of four and ten years old when otherwise healthy boys suddenly begin to regress. At first, they simply show behavioral problems, such as withdrawal or difficulty concentrating, then symptoms progress to include loss of hearing and eyesight, seizures, loss of muscle control, and progressive dementia. This relentless downward spiral leads to either death or permanent disability, usually within 2 to 5 years from diagnosis. Analysis of ALD was informed by the patient journey map based on literature review, expert input, and empiric data observations. As illustrated in Exhibit 4, delayed diagnosis of ALD can result in additional, and potentially unnecessary testing. More importantly, a timely diagnosis widens the window for treatment that can prevent, or avoid, some of the complications of ALD such as adrenal crises and cognitive impairment. With timely diagnosis, children with ALD have the opportunity to benefit from lifesaving treatment. The stem-cell treatment for childhood-onset ALD can stop the progression of the disease, but it does not repair previous damage. ALD was added to the federal RUSP in 2016 and is currently screened for in 24 states in the U.S.

Exhibit 4. Adrenoleukodystrophy Patient Journey Map



We identified a total of 98 males with incident ALD in the commercial claims and Medicaid FFS data, of which 30% were diagnosed before age 1 year with the remaining 70% having delayed diagnosis (age 1 or older). The average post-diagnosis follow-up was 22.5 months for the timely group and 20.8 months for the delayed group (Exhibit 3). By definition, everyone in the timely diagnosis group was diagnosed before age 1. In the delayed diagnosis cohort, average age at diagnosis was 6.6 years. Among those with timely diagnosis, the mean annualized total direct medical costs were consistently lower in the year of and post-diagnosis relative to those with delayed diagnosis (Exhibit 5). This equated to absolute differences between the timely and delayed groups in the year of and post-diagnosis periods of $30,767 and $51,002 higher, respectively. Mean annualized per patient costs in the year of diagnosis were nearly 2-times greater among those with delayed diagnosis compared with timely diagnosis, ($61,791 and $31,024, respectively) and more than 10-times greater in the post-diagnosis period ($55,915 and $4,913, respectively). While mean per patient annualized costs were higher for each type of healthcare service including pharmacy, higher costs among those with delayed diagnosis appeared to be driven by Other utilization (Exhibit 6). In addition, in the year of diagnosis, considerably higher annualized per-patient costs attributed to ALD diagnosis were observed among those with delayed diagnosis compared to timely diagnosis ($17,854 and $589, respectively, Appendix A. Exhibit A - 1). While in the post-diagnosis period, the difference between delayed and timely diagnosis was lessened ($4,283 and $1,312, respectively). A sensitivity analysis using a definition for timely diagnosis of age 4 months or younger in ALD showed similar results for total costs and costs by type of service (Appendix A. Exhibit A - 2).

Exhibit 5. Annualized Per Patient Direct Medical Costs[a] Relative to Timing of Diagnosis of Adrenoleukodystrophy in Males, 2016-2020



[a] CPI adjusted to 2021 USD.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
Because the year of diagnosis is the first year of life, there are no pre-diagnosis costs in the diagnosed <1 year group.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and 2016-2020 T-MSIS files.

Exhibit 6. Annualized Per Patient Healthcare Utilization Counts Relative to Timing of Diagnosis of Adrenoleukodystrophy in Males, 2016-2020

	Timely Diagnosed Before Age 1				Delayed Diagnosed Age 1 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	29	23		69	69	50
IP Acute days	--	9.1	0.0		11.4	8.6	6.5
IP Non-acute days	--	0.0	0.0		9.2	5.3	14.3
OP[b]	--	2.8	6.9		13.7	12.6	15.6
ED	--	0.1	1.4		4.5	3.0	3.1
Office Visits[c]	--	7.6	12.0		25.3	14.4	24.6
Other[d]	--	9.0	13.1		137.8	81.7	152.9

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[b] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[c] Office visits include primary care and specialist.
[d] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

Total days of work missed for caregivers of patients with ALD were estimated to be highest in the year of diagnosis for timely diagnosis and in the pre-diagnosis period for delayed diagnosis (Exhibit 7). Furthermore, the total days of work missed and wages lost for caregivers during the post-diagnosis period were nearly twice as high for those with delayed diagnosis compared with timely diagnosis.

Exhibit 7. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with Adrenoleukodystrophy

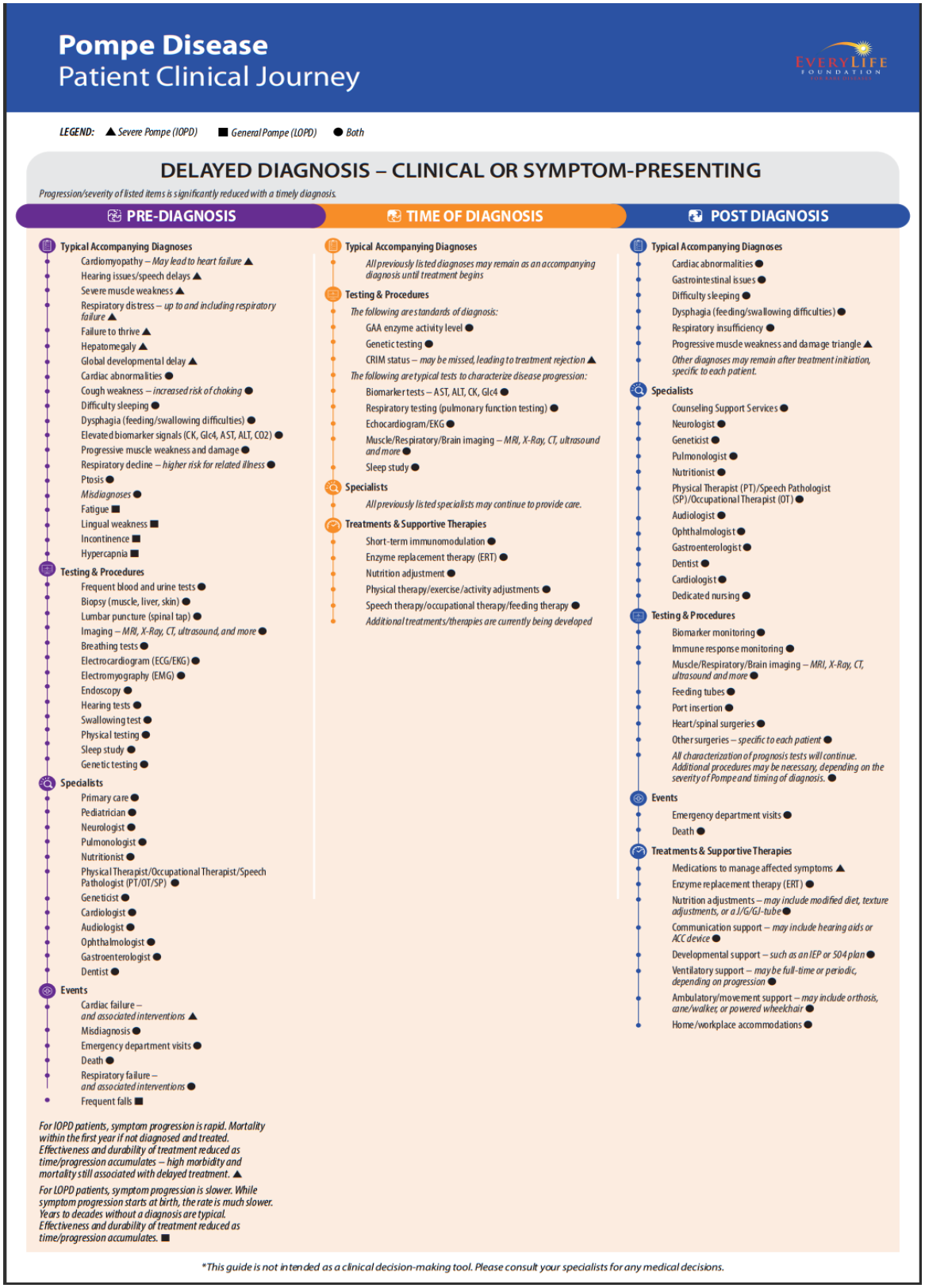
	Timely[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	0.0	12.4	7.1		36.1	25.3	36.3
Lost wages[c] per year	$0.00	$2,782.46	$1,597.03		$8,080.07	$5,662.16	$8,139.01

[a] Timely diagnosis in ALD is defined as before age 1 year; delayed diagnosis in ALD is defined as age 1 year or older.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

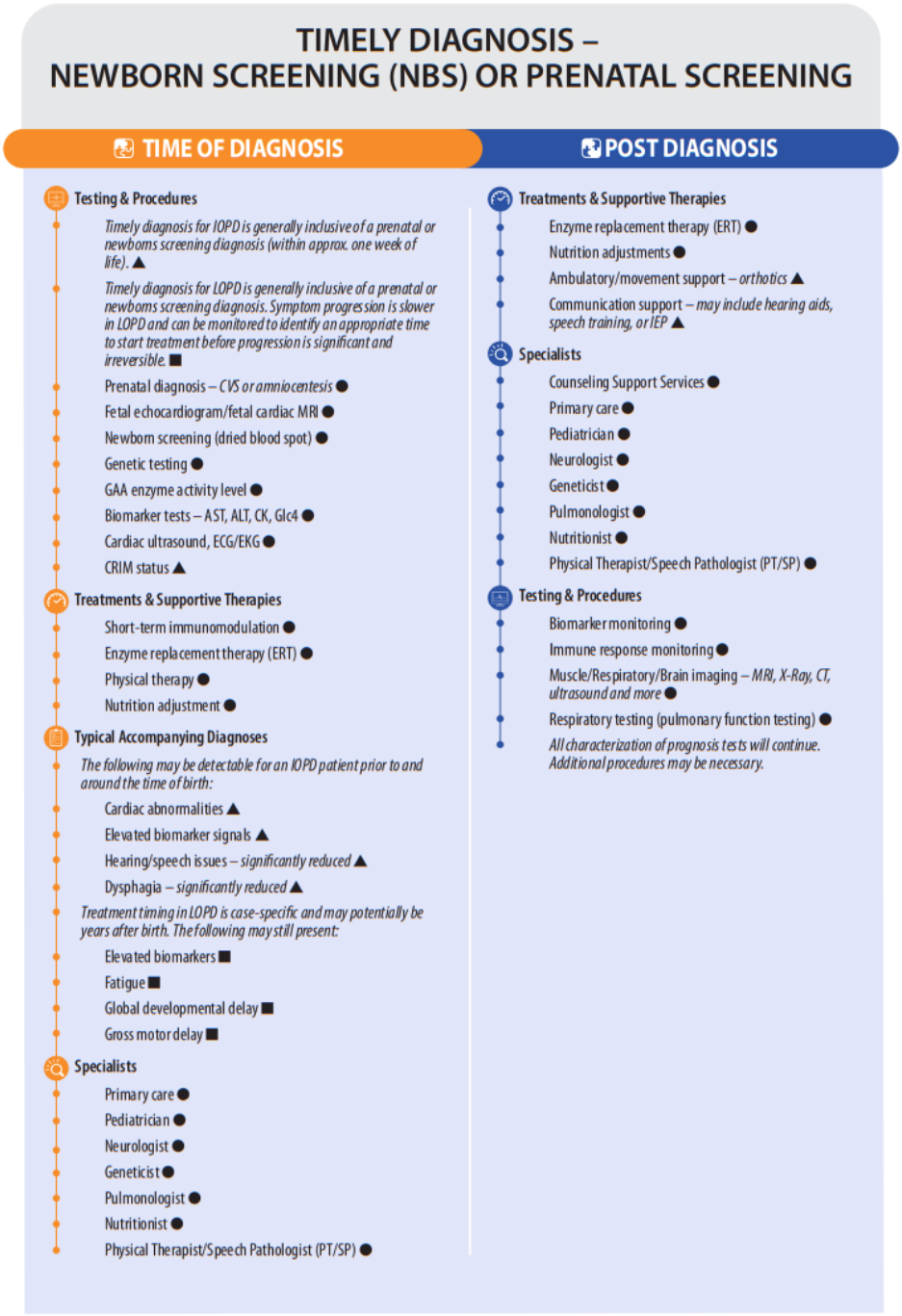
Pompe

Pompe disease is an inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The two subtypes of Pompe disease are infantile-onset and late-onset. The symptoms of infantile-onset Pompe disease (IOPD) typically manifest within a few months of birth. Infants with this disorder typically experience myopathy, hypotonia, an enlarged liver, heart defects, and may have breathing problems. Without timely recognition and treatment, the classic form of IOPD leads to death within the first year of life. The non-classic form of IOPD usually appears by age 1 and most children with this form live only into early childhood. With newborn screening, late-onset Pompe disease (LOPD) can be detected in infants, who can then be monitored for symptoms until treatment is needed, sometimes as late as adolescence or young adulthood (Stevens, Milani-Nejad, & Mozaffar, 2022). As illustrated in Exhibit 8, delayed diagnosis of Pompe can result in additional, and potentially unnecessary testing. More importantly, a timely diagnosis widens the window of opportunity for treatment that can prevent, or potentially avoid respiratory and cardiovascular complications associated with tissue build-up of glycogen. With timely diagnosis in infant-onset and late-onset Pompe disease, enzyme replacement therapy (ERT) can be initiated before disease progresses. Pompe disease was added to the federal Recommended Uniform Screening Panel (RUSP) in 2013 and by the end of 2020 was screened for in 29 states in the U.S.

Exhibit 8. Patient Journey Map for Pompe Disease



LEGEND: ▲ *Severe Pompe (IOPD)* ■ *General Pompe (LOPD)* ● *Both*

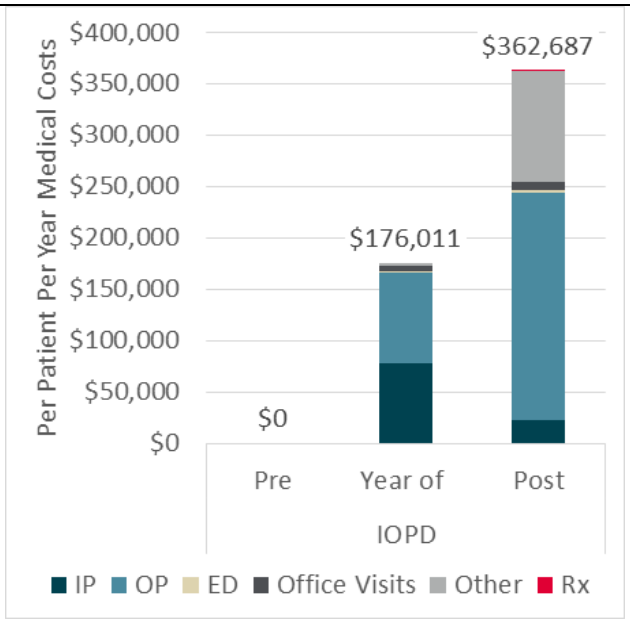


We identified 91 individuals with incident Pompe disease indicated by diagnosis code on a medical claim, of which 56% were diagnosed before age 1 (average post-diagnosis follow-up 19.8 months) with the remaining 44% diagnosed at age 1 year or older (average post-diagnosis follow-up 18.6 months). The ICD-10 diagnosis code for Pompe does not allow us to distinguish between subtypes, IOPD and LOPD, thus we identified IOPD by initiation of enzyme replacement therapy within 120 days following diagnosis. Among those diagnosed before age 1 (timely diagnosis), we identified 11 patients with IOPD and 40 patients with LOPD. We identified 40 patients with diagnosis of LOPD between ages 1 and 12 (average age at diagnosis 4.4 years, Exhibit 3). Among the delayed diagnosis cohort, 3 patients had evidence of ERT during follow-up, but none in that cohort initiated treatment within 120 days of diagnosis.

Our definition of classic IOPD requires evidence of receipt of ERT within 120 days of diagnosis. We did not identify any patients diagnosed after age 1 year who also received ERT within 120 days of diagnosis, thus there is no delayed diagnosis of IOPD cohort.

Per patient medical costs for IOPD are shown in Exhibit 9. Annualized medical costs per patient were $176,011 per patient in the year of diagnosis and over $360,000 per patient per year in the post-diagnosis period; these costs were largely driven by OP and Other, which is inclusive costs of infused therapies in an OP setting or in the home, respectively. Medical costs attributed to Pompe diagnosis were $111,584 in the year of diagnosis and $340,682 per patient per year in the post-diagnosis period (data not shown).

Exhibit 9. Annualized Per Patient Direct Medical Costs[a] Relative to Diagnosis of Infantile-Onset Pompe Disease, 2016-2020

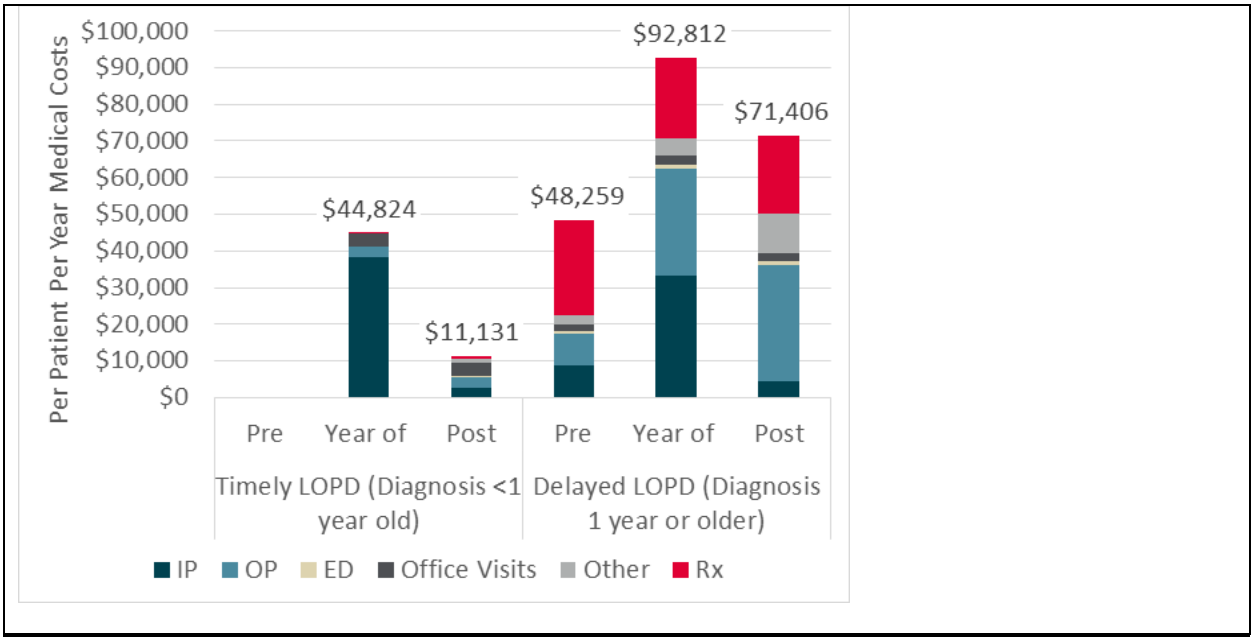


IOPD defined as diagnosis of Pompe before age 1 and evidence of initiation of ERT within 120 days of diagnosis.

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
Because the year of diagnosis is the first year of life, there are no pre-diagnosis costs in the diagnosed <1 year group.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and 2016-2020 T-MSIS files.

Not surprisingly, annualized medical costs per patient costs for LOPD were considerably lower (Exhibit 10). We observed consistently higher medical costs in the pre-diagnosis, year of diagnosis, and post-diagnosis periods for delayed LOPD compared with timely LOPD. Pharmacy and OP costs were greater for delayed compared with timely LOPD. Compared to IOPD, medical costs per patient were much lower in LOPD in general. With timely diagnosis of LOPD, Pompe-specific medical costs were $914 in the year of diagnosis and $1,250 per year in the post-diagnosis period (Appendix A, Exhibit A-3). We only identified 2 LOPD patients initiating ERT during the post-diagnosis period, which likely explains why Pompe-specific costs appear low.

Exhibit 10. Annualized Per Patient Direct Medical Costs[a] Relative to Timing of Diagnosis of Late-Onset Pompe Disease, 2016-2020



[a] CPI adjusted to 2021 USD.
Timely LOPD defined as diagnosis before age 1 and no evidence of initiation of ERT within 120 days of diagnosis; delayed LOPD defined as diagnosis age 1 or older.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
Because the year of diagnosis is the first year of life, there are no pre-diagnosis costs in the diagnosed <1 year group.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and 2016-2020 T-MSIS files.

Caregivers of patients with infantile-onset Pompe disease missed on average 33 days of work related to health care visits in the year of diagnosis (Exhibit 11), which amounted to $7,413. In

the post-diagnosis period, caregivers of patients with infantile-onset Pompe disease missed an average of 25 days of work related to health care visits and $5,597 in lost wages per year.

Exhibit 11. Productivity Loss Relative to Diagnosis Inferred from Utilization of Children with Infantile-Onset Pompe Disease, 2016-2020

	Timely[a]		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	0.0	33.1	25.0
Lost wages[c] per year	$0.00	$7,412.70	$5,597.35

[a] Infant onset Pompe is defined as diagnosis before age 1 year and initiation of ERT with 120 days of diagnosis.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Days of work missed and lost wages for caregivers of patients with late-onset Pompe disease were calculated to be higher among those with delayed diagnosis in the year of and post-diagnosis periods (Exhibit 12). Caregivers of patients with delayed diagnosis of late-onset Pompe had approximately 6-times as many days missed per year in the post-diagnosis period, compared to timely diagnosis.

Exhibit 12. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with Pompe Disease

	Timely LOPD[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	0.0	9.71	2.71		9.4	14.8	16.8
Lost wages[c] per year	$0.00	$2,175.63	$607.85		$2,103.13	$3,322.69	$3,765.10

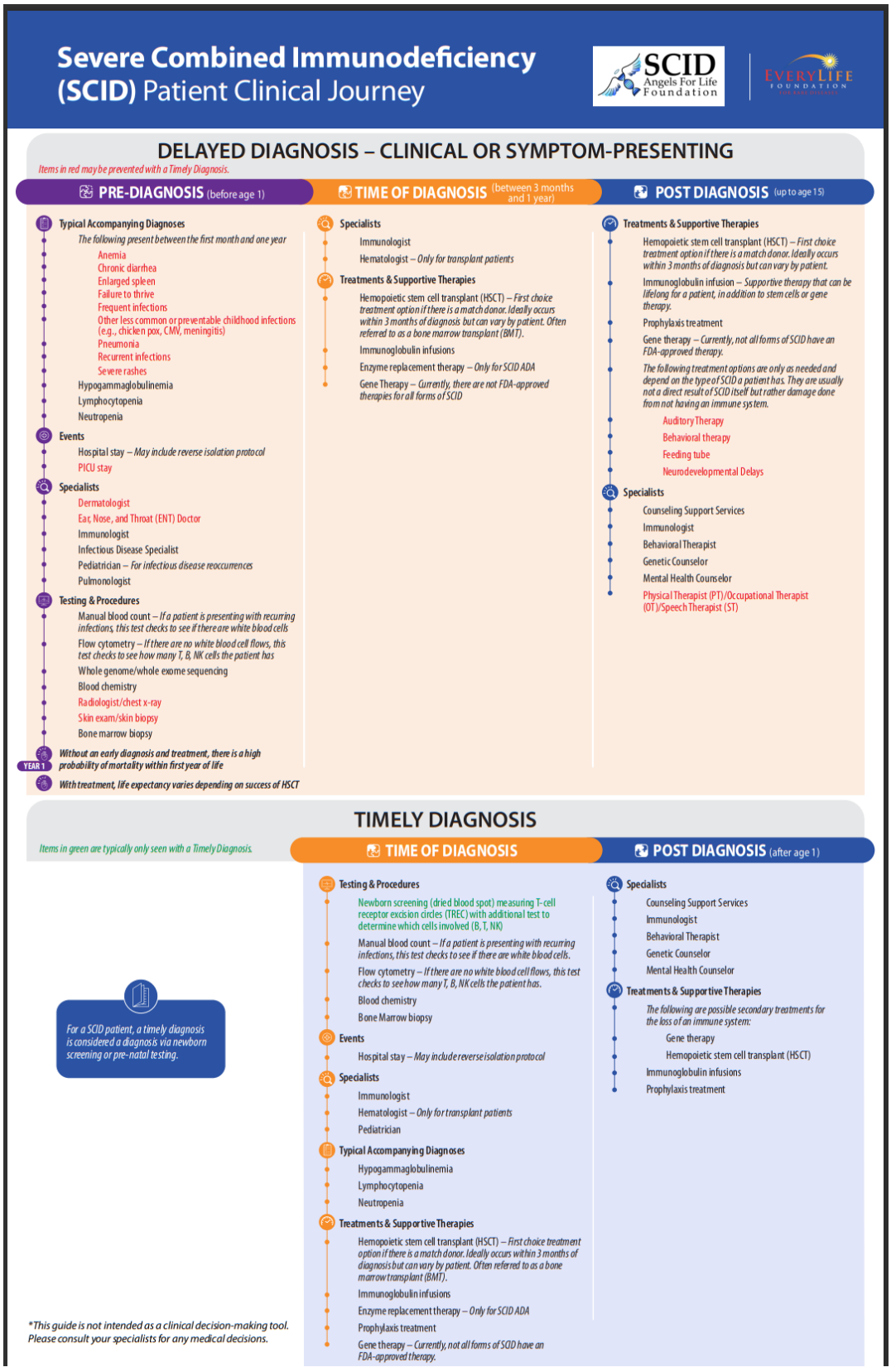
	Timely LOPD[a]		Delayed

[a] Timely diagnosis in late-onset Pompe is defined as before age 1 year with no evidence of ERT; delayed diagnosis in late-onset Pompe is defined as age 1 year or older and before age 12 years.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages are missed days' work (8 hours per day) per patient per year multiplied by mean hourly wage, 2021 USD
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Severe Combined Immunodeficiency

Babies born with Severe Combined Immunodeficiency (SCID) appear normal at birth but cannot fight infection. If SCID is diagnosed early in life, before the onset of infection, a bone marrow transplant can successfully treat the disorder. Without treatment, infants born with SCID will not survive past the first year of life. Therefore, timely diagnosis is critical to ensure that these infants receive appropriate treatment with either ERT or hematopoietic stem cell transplantation (HSCT). NBS for SCID was added to the RUSP in 2010 and by 2018, all 50 states and Puerto Rico had adopted NBS for SCID. Therefore, the majority of infants with SCID are identified by screening rather than clinical presentation. Successful HSCT can essentially cure SCID, thereby prolonging life. Infants and children with SCID need ongoing care and prophylaxis, often requiring supportive therapies like physical therapy, occupational therapy and in some cases, gene therapy.

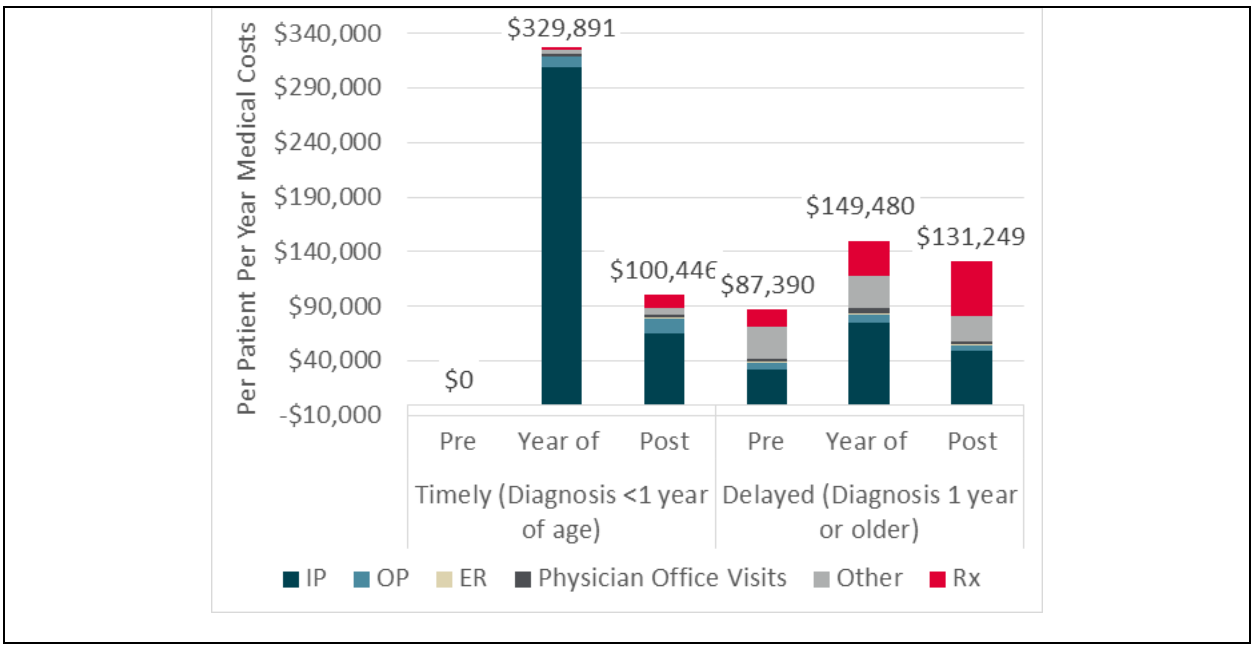
Exhibit 13. Patient Journey Map for SCID



We identified 127 individuals with incident SCID in the commercial claims and Medicaid data, of whom 43% were diagnosed before age 1 and the remaining 57% having delayed diagnosis (age 1 or older). The average post-diagnosis follow-up time was 21.5 months in the timely cohort and 24.1 months in the delayed cohort (Exhibit 3). By definition, everyone in the timely cohort was diagnosed before age 1. The average age in the delayed cohort was 6.3 years (Exhibit 3). The mean annualized direct medical costs were more than 2-times higher in the year of diagnosis compared with delayed diagnosis ($329,891 vs. $149,480). Inpatient costs were the largest contributors to the difference in total costs. In the post-diagnosis period, total medical costs were more than $30,000 higher among those with a delayed diagnosis versus an early diagnosis, largely attributed to Rx costs and IP and Other utilization (Exhibit 15). Costs attributed to SCID diagnosis were considerably higher for those with timely diagnosis compared with delayed diagnosis in both the year of diagnosis ($59,128 and $785, respectively) and post-diagnosis periods ($8,523 and $117, respectively, Appendix A. Exhibit A - 5).

In sensitivity analyses with timely diagnosis defined as age 4 months or younger, the differences in total medical costs between timely and delayed diagnosis were greater. These differences were most pronounced for IP, OP, and physician office visits (Appendix A. Exhibit A - 5).

Exhibit 14. Annualized Per Patient Direct Medical Costs[a] Relative to Timing of Diagnosis of SCID, 2016-2020



[a] CPI adjusted to 2021 USD.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
Because the year of diagnosis is the first year of life, there are no pre-diagnosis costs in the diagnosed <1 year group.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and 2016-2020 T-MSIS files.

Exhibit 15. Annualized Per Patient Healthcare Utilization Counts Relative to Timing of Diagnosis of SCID, 2016-2020

	Timely Diagnosed Before Age 1				Delayed Diagnosed Age 1 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	54	44		73	73	56
IP Acute days	--	25.5	11.4		9.2	14.5	14.8
IP Non-acute days	--	55.7	2.1		9.0	6.5	4.5
OP[b]	--	9.6	31.3		30.3	18.8	22.9
ED	--	1.6	3.5		5.1	3.3	2.9
Office Visits[c]	--	8.4	18.7		30.2	21.8	25.7
Other[d]	--	62.9	87.3		149.6	105.6	138.7

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[b] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[c] Office visits include primary care and specialist.
[d] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

Total days of work missed and lost wages for caregivers of patients with SCID were estimated to be higher among those with timely diagnosis in the year of and similar in the post-diagnosis periods (Exhibit 16).

Exhibit 16. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with SCID, 2016-2020

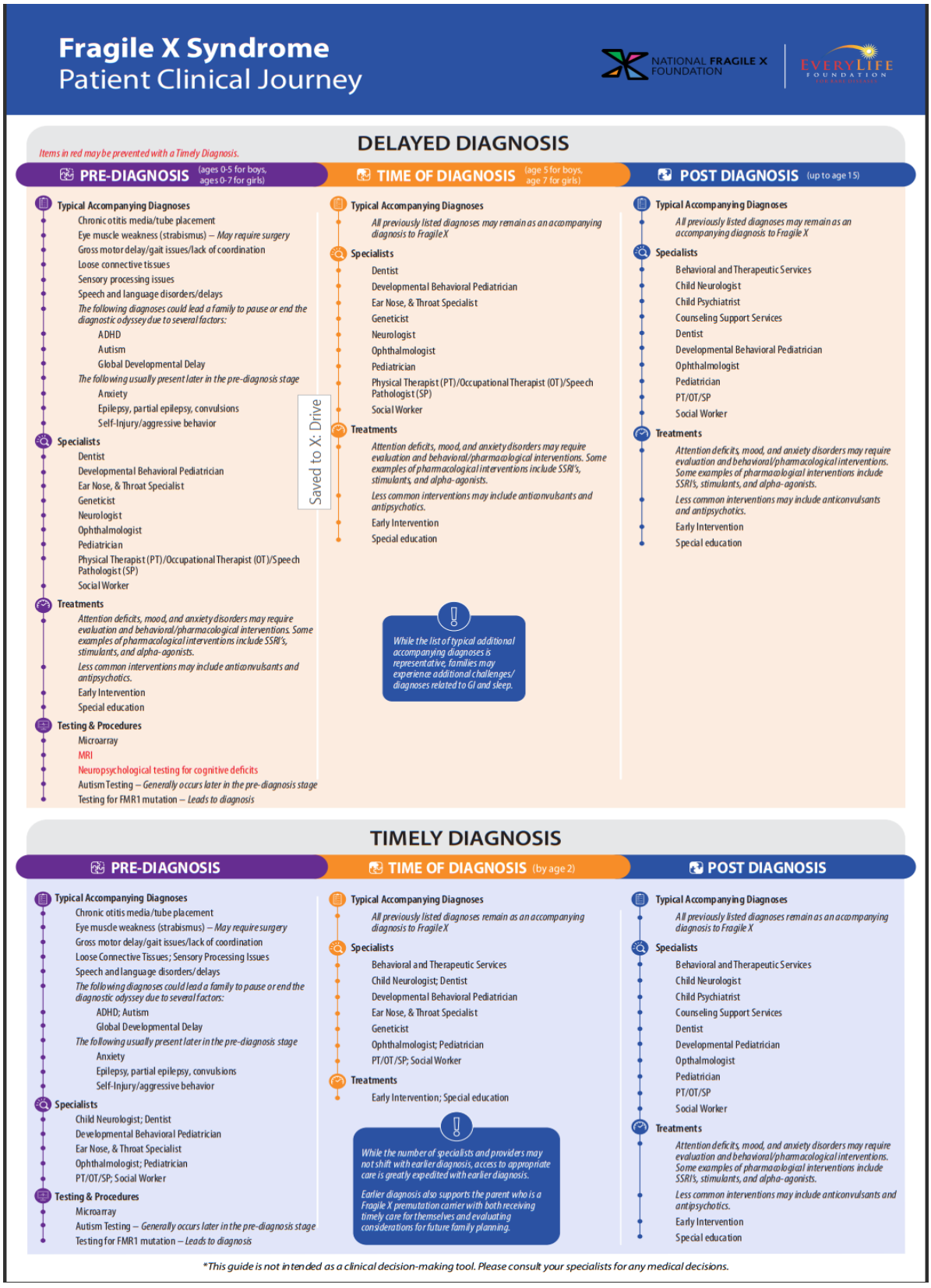
	Timely[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	0.0	89.0	35.6		43.4	37.5	38.7
Lost wages[c] per year	$0.00	$19,943.14	$7,979.03		$9,727.47	$8,410.80	$8,672.17

[a] Timely diagnosis in Pompe is defined as before age 1 year; delayed diagnosis in Pompe is defined as age 1 year or older.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Fragile X Syndrome

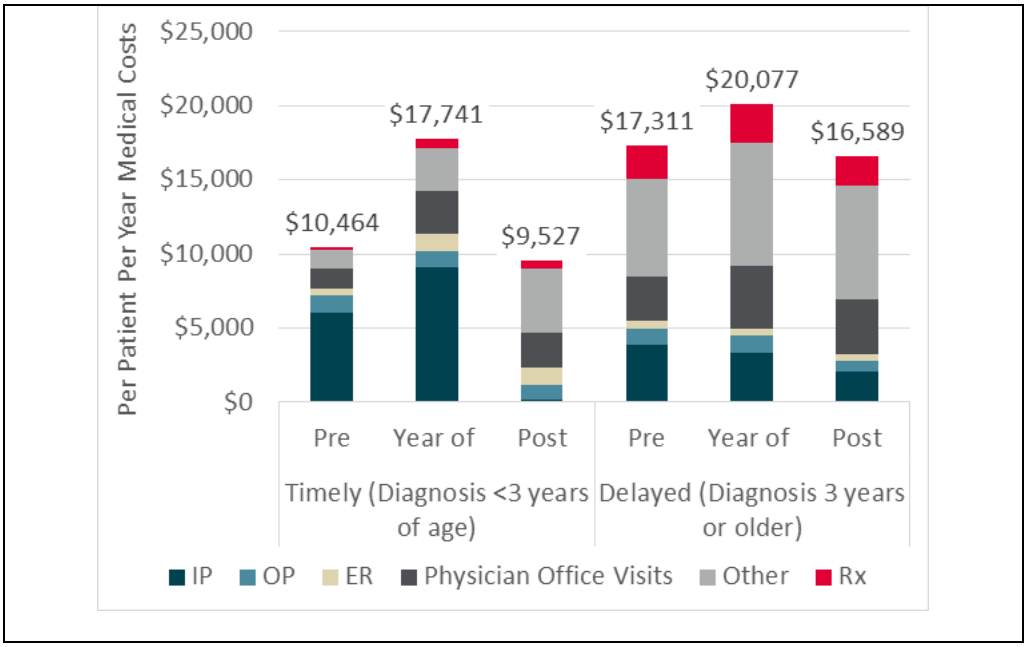
Fragile X syndrome (FXS) is caused by the full mutation of a single gene — *FMR1* — on the X chromosome and is inherited genetically (National Fragile X Foundation). There is no disease-altering treatment approved for FXS, therefore many families rely on therapies, interventions, and medications to treat behavioral symptoms, like anxiety, aggression, ADHD, and medical symptoms, like sleep and seizures. Timely diagnosis can result in positive outcomes for the individual and their family. Earlier initiation of supportive therapies, such as speech, occupational, and physical therapies as well as testing for autism, a common co-occurring condition. Autism can impact a child's long-term outcomes, including school readiness and independence level in the transitions from childhood through adolescence and into adulthood. Delays in diagnosis not only cause delays in accessing supportive therapies and symptom treatment, but may also increase the financial and emotional stress on the family. Because Fragile X-associated conditions are passed down in families (Okoniewski , et al., 2019), once someone is diagnosed with FXS via *FMR1* DNA testing, families may opt to test additional family members for the full mutation, FXS, and/or the Fragile X premutation.

Exhibit 17. Patient Journey Map for Fragile X Syndrome



We identified 347 males with incident FXS in the commercial and Medicaid sample, of whom 22% had timely diagnosis (before age 3) and the remaining 78% had delayed diagnosis (age 3 or older). The average post-diagnosis follow-up was 21.2 months in the timely cohort and 24.4 months in the delayed cohort (Exhibit 3). The average age at diagnosis was 1.0 in the timely cohort and 7.3 in the delayed cohort (Exhibit 3). In general, mean annualized per patient costs were highest in the year of diagnosis with timely and delayed diagnosis (Exhibit 18). Among those with delayed diagnosis, pre- and post-diagnosis annualized costs were only slightly lower while among those with timely diagnosis these differences were larger. Higher costs in the timely diagnosis group were largely driven by IP acute utilization in the pre- and year of diagnosis periods (Exhibit 19). Medical costs attributed to FXS diagnosis were nearly twice as high with delayed diagnosis compared with timely (Appendix A).

Exhibit 18. Annualized Per Patient Direct Medical Costs[a] Relative to Timing of Diagnosis of Fragile X Syndrome in Males ages Birth to 12 Years, 2016-2020



[a] CPI adjusted to 2021 USD.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and 2016-2020 T-MSIS files.

Exhibit 19. Annualized Per Patient Healthcare Utilization Counts Relative to Timing of Diagnosis of Fragile X Syndrome in Males, 2016-2020

	Timely Diagnosed Before Age 3				Delayed Diagnosed Age 3 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	75	50		272	272	220
IP Acute days	4.8	2.9	0.1		1.5	1.1	0.6
IP Non-acute days	1.9	0.7	0.0		2.6	1.4	4.9
OP[b]	5.5	7.5	7.1		8.4	5.1	6.3
ED	1.9	1.8	1.5		2.5	1.1	1.3
Office Visits[c]	10.0	23.6	22.8		47.8	35.4	48.4
Other[d]	11.2	21.3	49.5		90.2	61.6	107.2

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[b] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[c] Office visits include primary care and specialist.
[d] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

The total days missed work for caregivers of patients with FXS were consistently higher for delayed diagnosis than timely diagnosis (Exhibit 20). The caregiver days missed work in the pre-diagnosis and post-diagnosis periods were nearly 2-times higher for the delayed diagnosis compared with the timely diagnosis (21.5 vs. 12.8 and 21.4 vs. 10.1, respectively).

Exhibit 20. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with Fragile X Syndrome

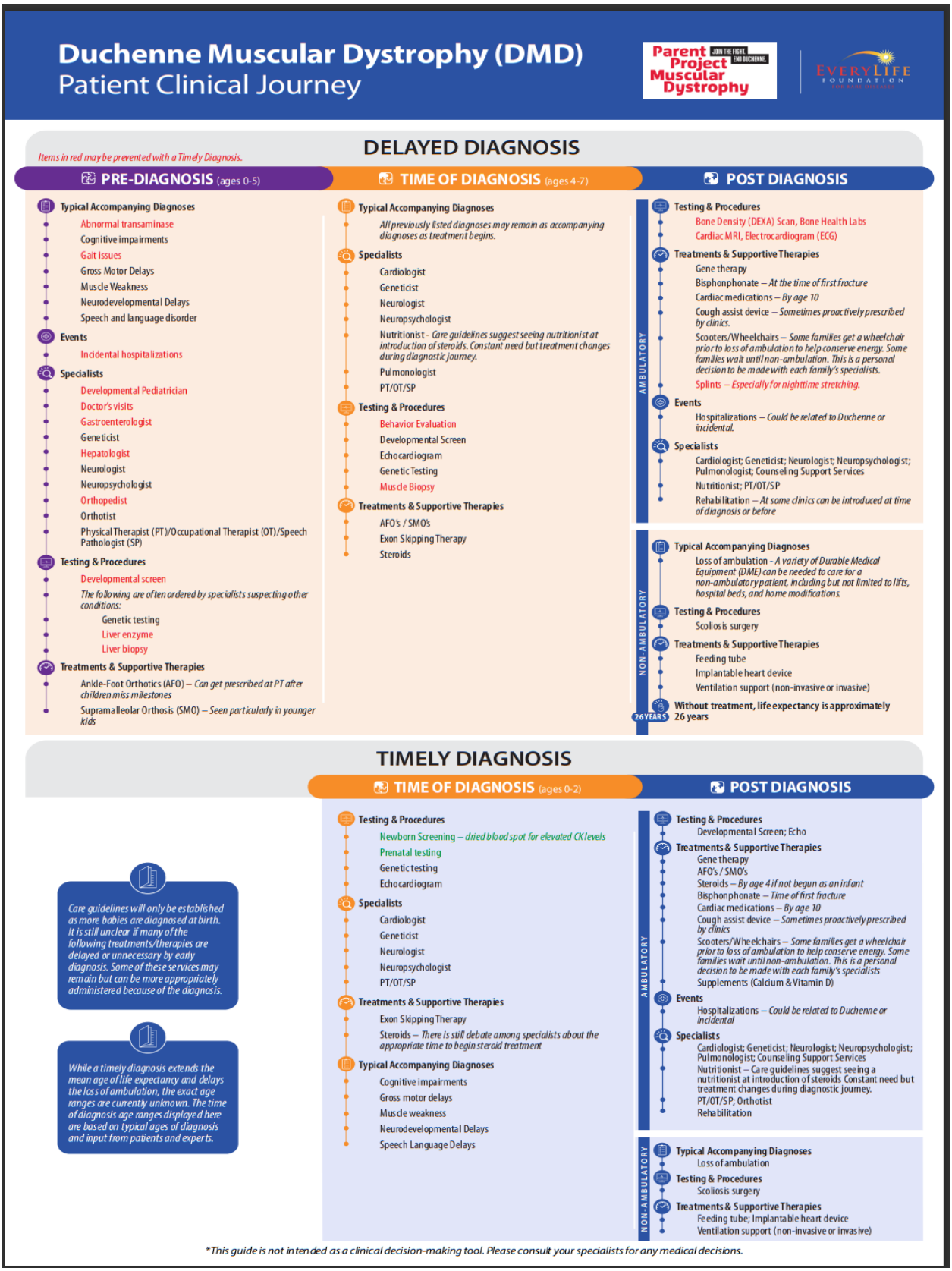
	Timely[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	12.8	14.2	10.1		21.5	14.5	21.4
Lost wages[c] per year	$2,873.03	$3,174.47	$2,263.52		$4,812.80	$3,239.24	$4,794.47

[a] Timely diagnosis in FXS is defined as before age 3 years; delayed diagnosis in FXS is defined as age 3 years or older.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Duchenne Muscular Dystrophy

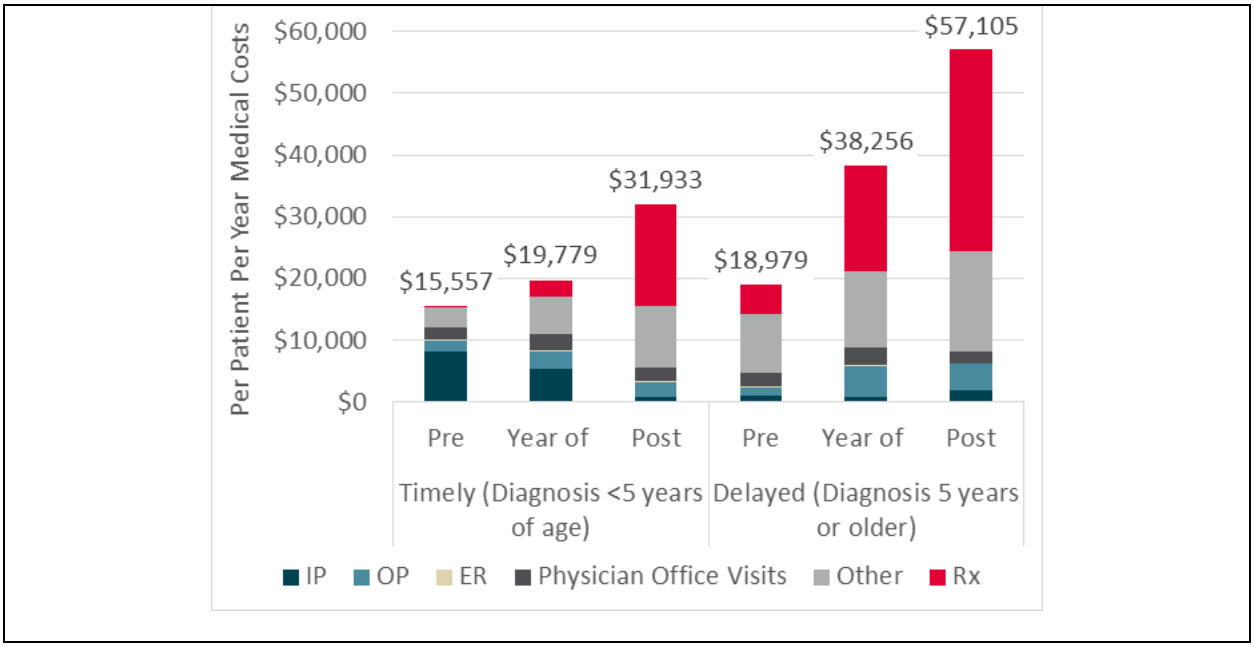
Duchenne muscular dystrophy is an X-linked disorder caused by pathogenic variants in the *DMD* gene and characterized by the progressive loss of muscle. It is a multi-systemic condition, affecting many parts of the body, which results in deterioration of the skeletal, cardiac (heart), and pulmonary (lung) muscles. Diagnosis typically occurs around 5 years of age and with loss of ambulation between age 8 and 14 (Romitti, 2009; Iff, et al., 2022; Ryder, et al., 2017). Because DMD is a progressive disease, timely diagnosis coupled with supportive therapies and treatment can have a tremendous impact on reducing patient burden in terms of prolonging ambulation and postponing or reducing some disease complications (Exhibit 21). It is common for patients with DMD to be treated by cardiology and pulmonary specialists. Early detection and intervention in DMD can slow the progression of symptoms and allow more personalized interventions before the irreversible loss of significant muscle tissue occurs. Newborn screening and early detection in DMD provide the opportunity to receive a diagnosis when the child is still asymptomatic and, more importantly, to initiate treatment that yields an optimal, long-term impact. With timely disease identification patients can maintain ambulation and manage the cardiovascular- and pulmonary-related complications of this disease earlier, thereby delaying or lessening some of these complications. By delaying and reducing complications, timely diagnosis may decrease direct medical and indirect costs.

Exhibit 21. Patient Journey Map for Duchenne Muscular Dystrophy



We identified a total of 737 males in the commercial and Medicaid sample with incident DMD between 2018 and 2020. Of these, 12% had a timely diagnosis (before age 5 years). The average age at diagnosis was 2.6 years in the timely cohort (average post-diagnosis follow-up was 20.4 months) and 9.1 years in the delayed cohort (average post-diagnosis follow-up 20.3 months, Exhibit 3). In general, those with timely diagnosis had lower mean annualized costs in the pre-diagnosis, year of and post-diagnosis periods compared with delayed diagnosis ($3,422, $18,477 and $25,172 lower, respectively, Exhibit 22). These costs appear to be driven by Rx costs and utilization in the Other category.

Exhibit 22. Annualized Per Patient Direct Medical Costs[a] Relative to Timing of Diagnosis with Duchenne Muscular Dystrophy in Males, 2018-2020



[a] CPI adjusted to 2021 USD.
Timely diagnosis in DMD is defined as before age 5 years.
Delayed diagnosis in DMD is defined as at least age 5 and less than age 12
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2018-2020 dNHI commercial claims and T-MSIS files.

We conducted sensitivity analyses restricted to the subset with a second confirmatory diagnosis for DMD with similar results for annualized per patient medical costs and utilization. The IP Acute days in the pre-diagnosis period for timely diagnosis of DMD are higher than expected. In our sensitivity analyses restricted to the subset with a second confirmatory diagnosis we observed similar medical costs and healthcare utilization counts (data not shown). This suggests

that this finding is likely not an artifact but rather due to the relatively small sample size and non-normal distribution of medical costs.

Exhibit 23. Annualized Per Patient Healthcare Utilization Counts Relative to Timing of Diagnosis of Duchenne Muscular Dystrophy in Males, 2018-2020

	Timely Diagnosed Before Age 5				Delayed Diagnosed Age 5 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	85	70		652	652	558
IP Acute days	3.4	2.0	0.5		0.7	0.4	0.6
IP Non-acute days	0.0	0.2	0.0		1.0	0.7	1.0
OP[b]	13.0	10.8	14.1		15.3	9.0	12.1
ED	3.3	1.7	1.9		2.4	1.0	1.2
Office Visits[c]	23.6	19.6	34.4		34.1	19.1	22.9
Other[d]	39.7	27.0	46.7		98.0	52.4	86.6

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[b] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[c] Office visits include primary care and specialist.
[d] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

Total days of work missed for caregivers of patients with DMD were estimated to be highest in the pre-diagnosis and post-diagnosis periods for timely and much higher in the pre-diagnosis period for delayed diagnosis for both timely and delayed diagnosis (Exhibit 24). In the post-diagnosis period, the total days missed of work for caregivers was slightly higher for timely versus delayed diagnosis (17.1 and 13.9, respectively).

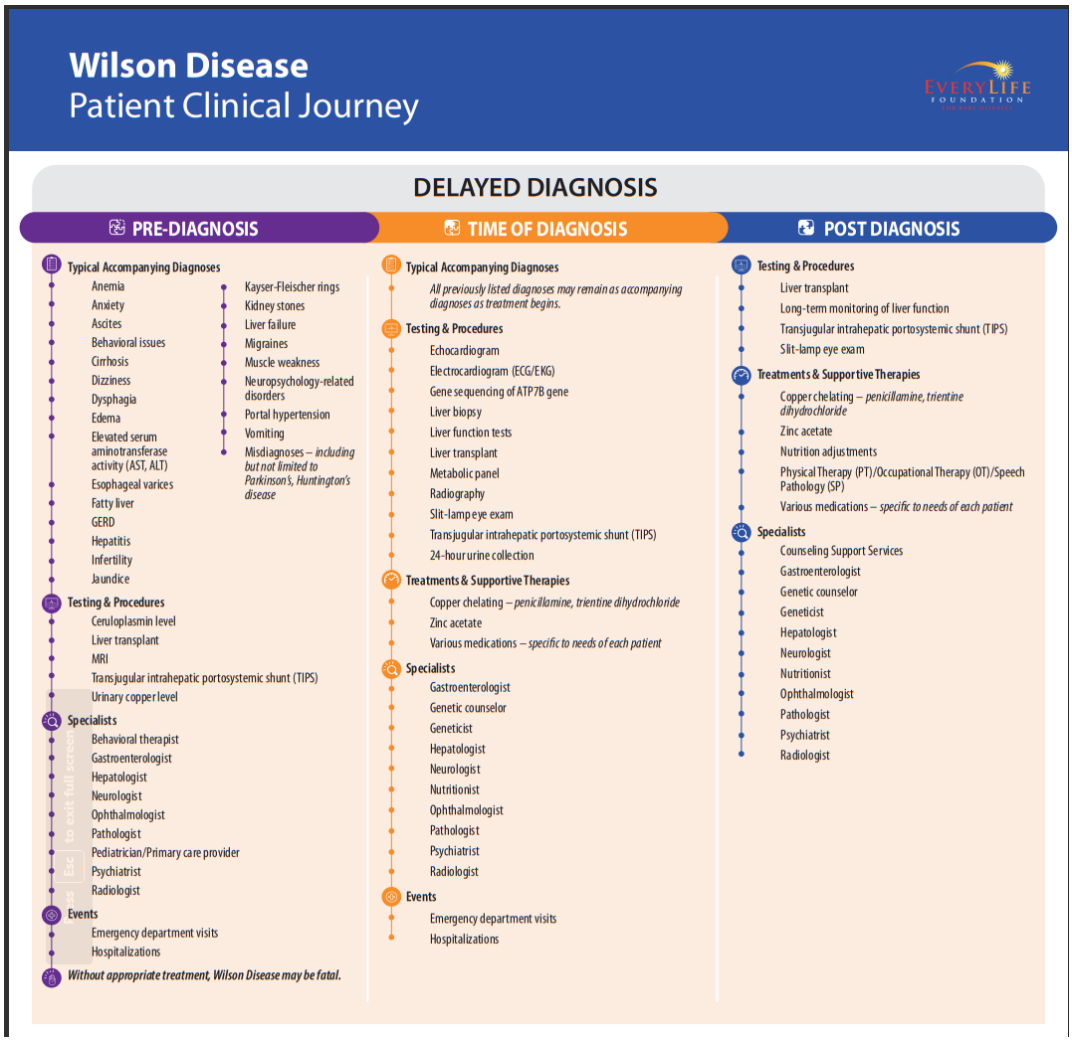
Exhibit 24. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with Duchenne Muscular Dystrophy

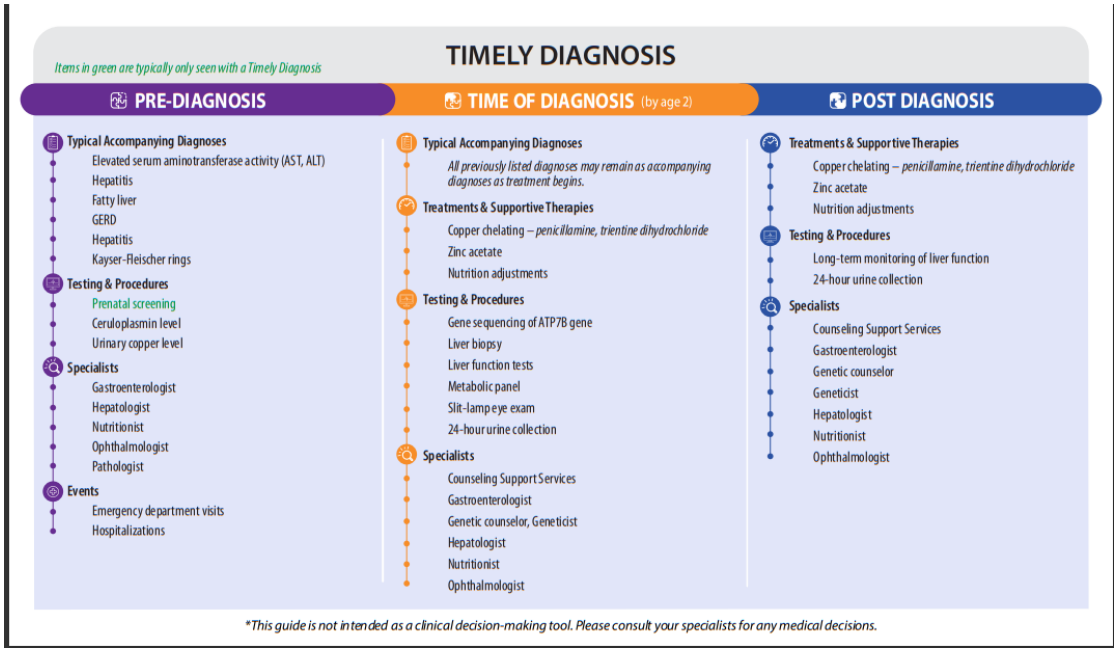
	Timely[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	17.5	13.3	17.1		19.1	10.9	13.9
Lost wages[c] per year	$3,916.45	$2,978.91	$3,831.34		$4,284.16	$2,446.16	$3,121.44

Wilson Disease

Wilson disease is a genetic disorder of copper metabolism. As a genetic disorder, Wilson disease is present at birth, however typically patients are diagnosed between 3 and 40 years of age (Lin, Wang, Ding, Lin, & Zheng, 2013; Machado, et al., 2006). In children, Wilson manifests as impaired liver function, which can go undetected for a long time (Waslhe, 1989). Adults often have neurologic or psychiatric symptoms such as tremor or related to behavior (Oder, et al., 1991). With timely diagnosis, patients can initiate copper chelating treatment before damage to liver and other tissues occur making complications of Wilson disease avoidable.

Exhibit 25. Patient Journey Map in Wilson Disease

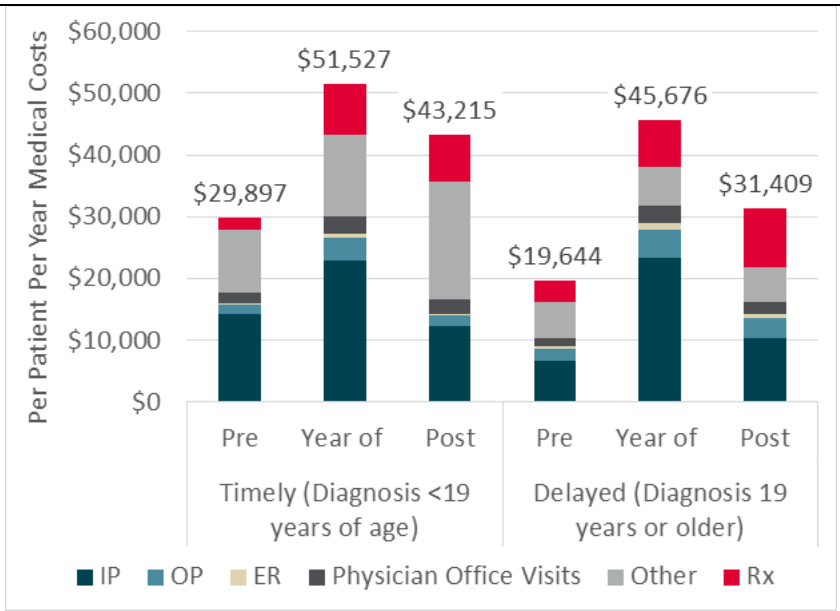




We identified a total of 569 individuals with incident Wilson disease between 2016 and 2020 (Exhibit 3). In total, 29% (N=165) had timely diagnosis (defined as before age 19) and the remaining 71% (N=404) had delayed diagnosis (defined as age 19 or older). Average age at diagnosis was 11.6 years in the timely cohort (average post-diagnosis follow-up 24.9 months) and 39.6 years in the delayed cohort (average post-diagnosis follow-up 20.4 months, Exhibit 3).

In general, annualized per patient medical costs were highest in the year of diagnosis and persisted to be higher in the post-diagnosis years compared with pre-diagnosis costs (Exhibit 26). Inpatient and other utilization appeared to be driving both increases in costs from pre- to post-diagnosis and higher costs for delayed vs timely diagnosis (Exhibit 27). In sensitivity analyses restricted to patients with at least 2 diagnoses, annualized medical costs were generally higher, notably higher IP acute and Rx costs in both the commercial and Medicaid FFS study populations (data not shown). The proportions with neurologic manifestations were similar between timely and delayed (20% and 18%, respectively, data not shown). Medical costs attributed to Wilson disease diagnosis were slightly higher with timely diagnosis compared with delayed (Appendix A. Exhibit A - 8).

Exhibit 26. Annualized Per Patient Medical Costs[a] Relative to Timing of Diagnosis of Wilson Disease, 2016-2020



[a] CPI adjusted to 2021 USD.
Timely diagnosis in WD is defined as before age 19 years.
Delayed diagnosis in WD is defined as age 19 years or older.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files.

Exhibit 27. Annualized Healthcare Utilization Counts Relative to Timing of Diagnosis in Wilson Disease, 2016-2020

	Timely Diagnosed Before Age 19				Delayed Diagnosed Age 19 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N		164	132		404	404	290
IP Acute days	5.3	5.8	3.4		3.9	8.2	4.3
IP Non-acute days	7.4	5.6	7.4		17.5	11.3	13.9
OP[b]	10.2	10.8	15.3		8.5	10.3	7.8
ED	2.9	2.5	2.2		4.5	3.6	2.6
Office Visits[c]	26.3	20.2	33.4		14.4	15.1	14.0
Other[d]	83.0	59.0	103.3		44.8	33.3	40.1

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[b] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[c] Office visits include primary care and specialist.
[d] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

Productivity loss related to days missed of work due to healthcare visits is shown in Exhibit 28. Work days missed and lost wages per patient per year were slightly higher with delayed diagnosis in the pre-diagnosis and year of diagnosis periods and similar in the post-diagnosis period.

Exhibit 28. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Children with Wilson Disease

	Timely[a]				Delayed		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Days missed work[b] per year	25.8	23.1	27.8		31.4	30.3	26.9
Lost wages[c] per year	$5,791.85	$5,170.12	$6,227.86		$7,038.00	$6,784.14	$6,026.94

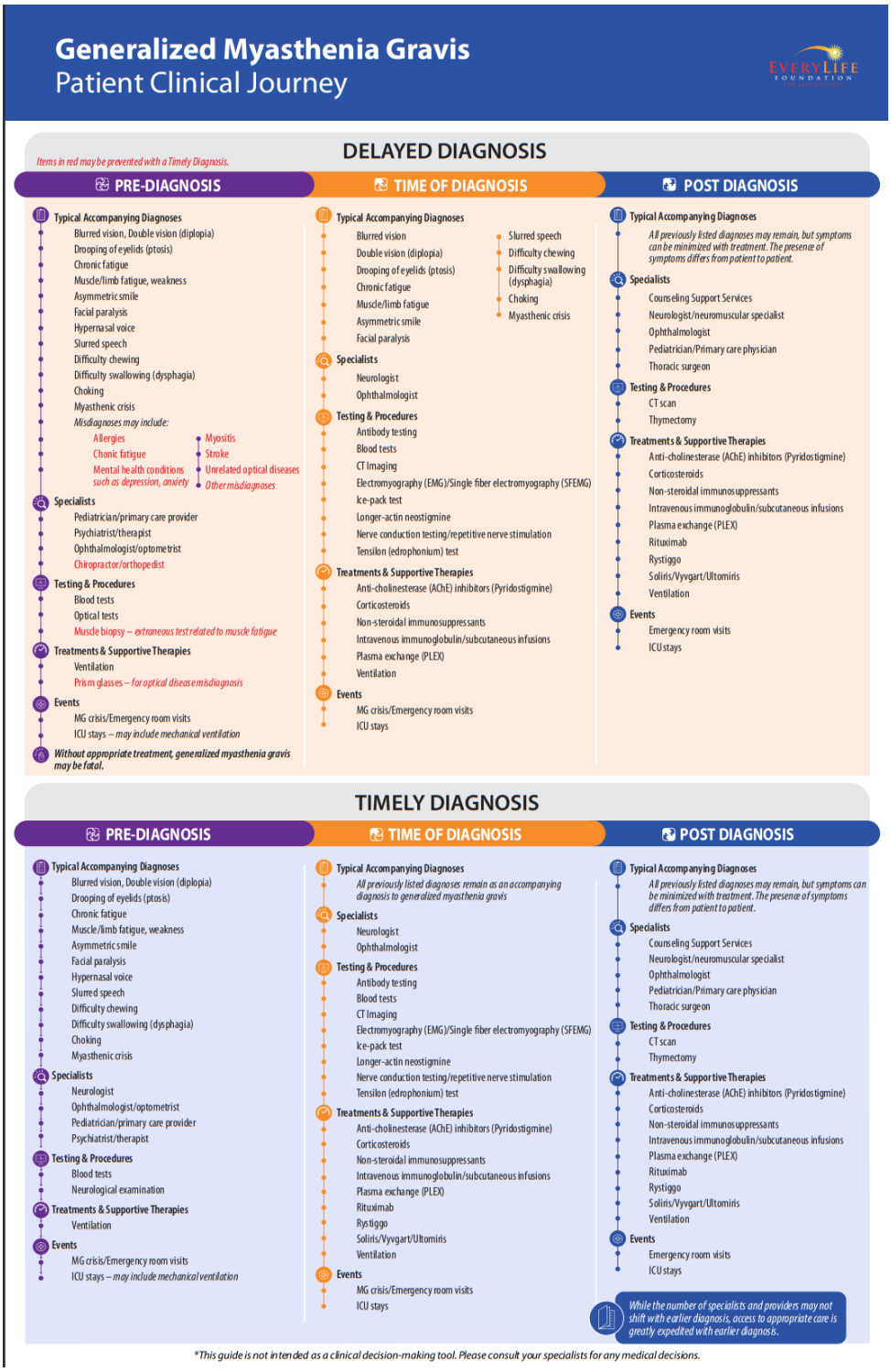
[a] Timely diagnosis in Pompe is defined as before age 19 years; delayed diagnosis in Pompe is defined as age 19 years or older.
[b] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[c] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Generalized Myasthenia Gravis

Myasthenia Gravis is an autoimmune disease that typically starts with weakening of the involuntary muscles that control the eyes. Among those initially presenting with ocular MG, approximately 50% convert to the more severe form, generalized MG (Hendricks, Bhatti, Hodg, & Chen, 2019). The more severe form of the disease involves weakened respiratory muscles

which can result in life-threatening crises requiring a ventilator, affecting approximately 15-20% of patients (Thomas, et al., 1997). Symptom onset is most common in women in their 20s and 30s and in men in their 50s and 60s (National Organization for Rare Diseases, 2022).

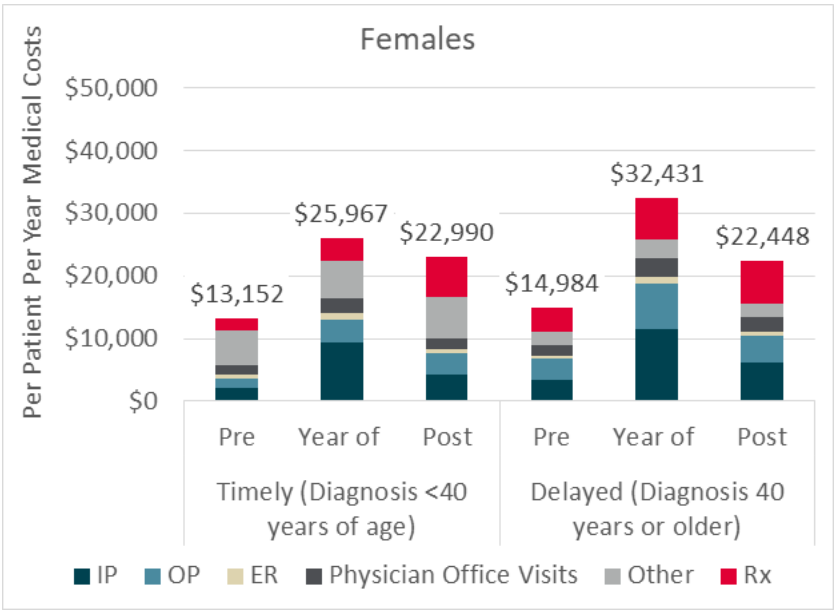
Exhibit 29. Patient Journey Map in gMG

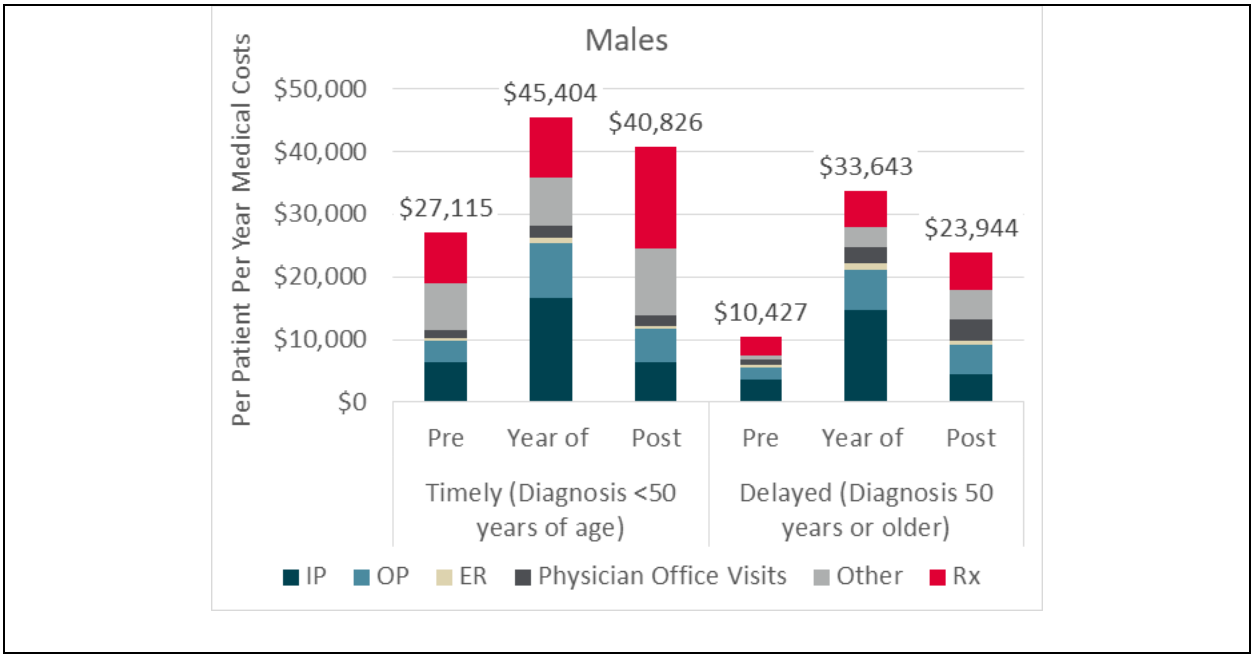


We identified a total of 1,779 females and 1,080 males with a diagnosis of gMG between 2016 and 2020. Of these, approximately 40% of females and 49% of males had timely diagnosis (Exhibit 3). Among females with gMG, the average age at diagnosis was 25.8 in the timely cohort and 52.4 in the delayed cohort (average post-diagnosis follow-up 21.8 months in both timely and delayed, Exhibit 3). Among males with gMG, the average age at diagnosis was 29.6 years in the timely cohort (average post-diagnosis follow-up 22.3 years) and 58.1 years in the delayed cohort (average post-diagnosis follow-up 21.1 months).

In males and females, annualized medical costs per patient were higher in the year of diagnosis and post-diagnosis compared with pre-diagnosis (Exhibit 30). In females, medical costs per year in the pre-diagnosis period were relatively similar between the timely and delayed diagnosis groups. In males with gMG, medical costs per year in the pre-diagnosis period were higher with timely diagnosis compared with delayed.

Exhibit 30. Annualized Per Patient Medical Costs Relative to Timing of Diagnosis with gMG, 2016-2020





[a] CPI adjusted to 2021 USD.
Timely diagnosis in gMG is defined as before age 40 years for females and before age 50 years for males.
Delayed diagnosis for in gMG is defined as age 40 years or older for females and age 50 years or older for males.
IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files.

Exhibit 31. Annualized Per Patient Healthcare Utilization Counts Relative to Timing of Diagnosis with gMG, 2016-2020

	Timely[a]				Delayed[b]		
	Pre[a]	Year of	Post		Pre	Year of	Post
Females							
N	706	706	580		979	979	772
IP Acute days	1.4	3.7	1.8		1.8	4.3	2.6
IP Non-acute days	2.4	1.1	0.8		6.8	5.2	10.5
OP[c]	8.5	7.8	8.9		10.0	9.1	9.8
ED	3.7	3.2	2.9		2.8	2.4	2.5
Office Visits[d]	18.0	15.1	15.2		15.9	18.9	19.1
Other[e]	38.5	25.1	31.9		17.9	18.0	17.2
Males							
N	514	514	390		556	556	403
IP Acute days	2.1	3.9	2.5		1.5	4.7	2.2
IP Non-acute days	14.2	9.2	14.2		7.3	5.3	3.9

	Timely[a]				Delayed[b]		
	Pre[a]	Year of	Post		Pre	Year of	Post
OP[c]	7.1	6.1	6.7		4.7	6.4	6.2
ED	2.2	2.1	2.2		1.8	1.5	1.9
Office Visits[d]	14.9	15.2	19.7		10.5	16.2	16.4
Other[e]	46.8	29.9	50.6		8.1	13.0	14.4

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] Timely diagnosis in gMG is defined as before age 40 years for females and before age 50 years for males. [b] Delayed diagnosis for in gMG is defined as age 40 years or older for females and age 50 years or older for males.
[c] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[d] Office visits include primary care and specialist.
[e] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
Sources: Lewin analyses of 2016-2020 dNHI claims and 2016-2020 T-MSIS files.

In females with gMG, work days missed and lost wages were somewhat similar in the pre-diagnosis and year of diagnosis periods, while nearly twice as high among those with delayed diagnosis compared with timely (Exhibit 32). In males with gMG, work days missed and lost wages per year were lower among those with delayed diagnosis compared with timely.

Exhibit 32. Productivity Loss Relative to Timing of Diagnosis Inferred from Utilization of Males and Females with gMG

	Timely[a]				Delayed[b]		
	Pre-diagnosis	Year of Diagnosis	Post-diagnosis		Pre-diagnosis	Year of Diagnosis	Post-diagnosis
Females							
Days missed work[c] per year	14.5	14.1	12.3		19.0	19.9	24.1
Lost wages[d] per year	$3,239.70	$3,168.19	$2,750.50		$4,252.25	$4,466.50	$5,403.30
Males							
Days missed work[c] per year	24.6	21.0	26.1		14.6	18.0	14.2
Lost wages[d] per year	$5,516.43	$4,703.86	$5,839.16		$3,263.24	$4,037.19	$3,178.02

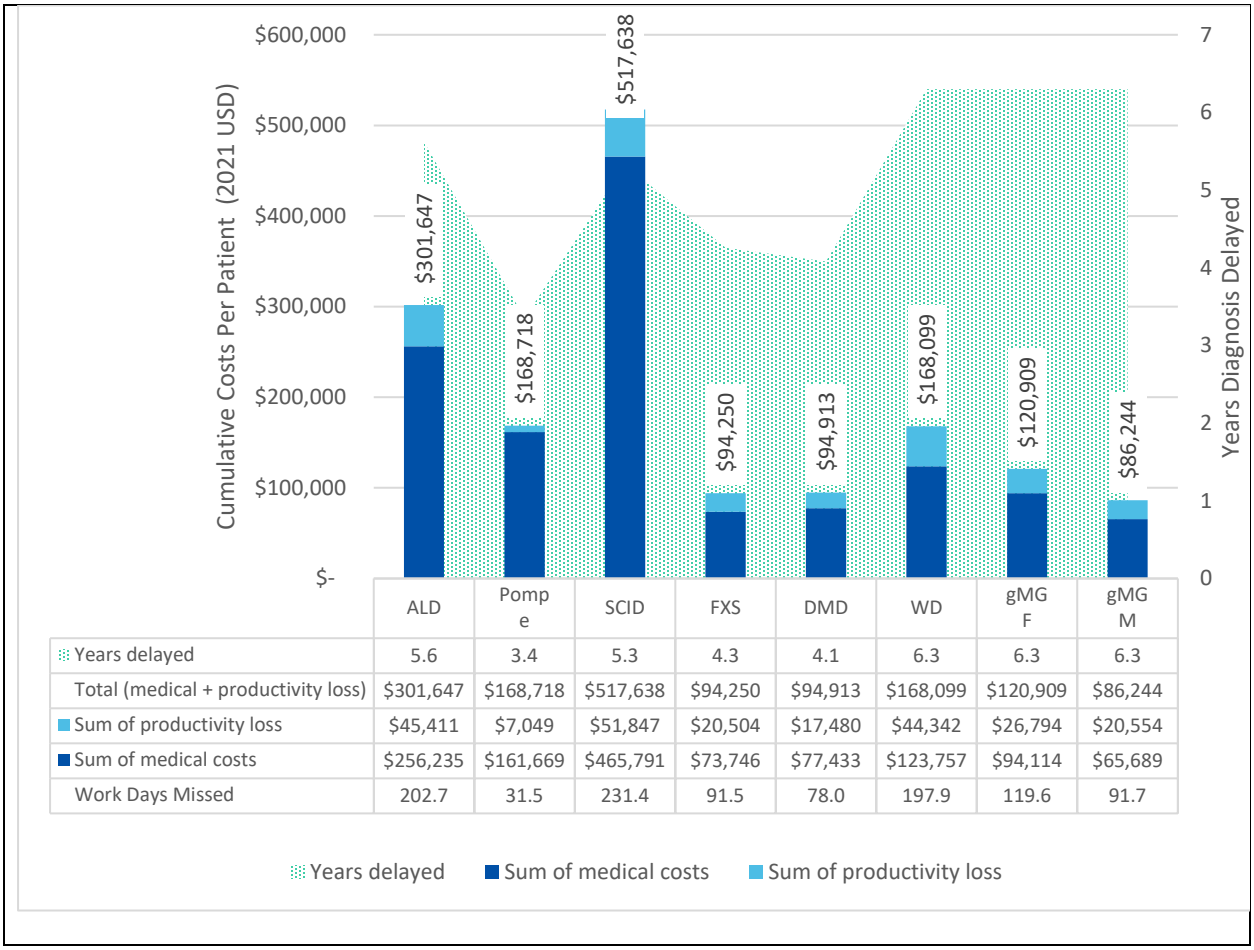
[a] Timely diagnosis in Pompe is defined as before age 1 year; delayed diagnosis in Pompe is defined as age 1 year or older.
[b] Delayed diagnosis for in gMG is defined as age 40 years or older for females and age 50 years or older for males.
[c] Days missed inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work.
[d] Lost wages is calculated as the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Sources: Lewin analyses of 2016-2020 dNHI commercial claims and T-MSIS files.

Costs of Delayed Diagnosis

We calculated the costs of delayed diagnosis in terms of medical costs and productivity losses per patient (Exhibit 33). Missed days' work due to delayed diagnosis were greatest for ALD, SCID, and Wilson Disease (203, 231, and 198 days, respectively and lowest for Pompe (32 days), which also had the shortest delay in diagnosis of 3.4 years. Productivity losses attributable to delay in diagnosis were greatest for ALD, SCID, and Wilson Disease (and $45,411, $51,847, and

$44,342, respectively), diseases that had higher IP utilization relative to other diseases included in this study. Cumulative direct medical costs per patient were highest for ALD, Pompe, and SCID ($256,235, $161,699, and $465,791, respectively) and lowest for gMG in males ($65,689).

Exhibit 33. Costs[a] Attributed to Delayed Diagnosis[b]



	ALD	Pompe	SCID	FXS	DMD	WD	gMGF	gMGM
Years delayed	5.6	3.4	5.3	4.3	4.1	6.3	6.3	6.3
Total (medical + productivity loss)	$301,647	$168,718	$517,638	$94,250	$94,913	$168,099	$120,909	$86,244
Sum of productivity loss	$45,411	$7,049	$51,847	$20,504	$17,480	$44,342	$26,794	$20,554
Sum of medical costs	$256,235	$161,669	$465,791	$73,746	$77,433	$123,757	$94,114	$65,689
Work Days Missed	202.7	31.5	231.4	91.5	78.0	197.9	119.6	91.7

[a] CPI adjusted to 2021 USD.
[b] Delayed diagnosis defined as the length of time from cut point for timely diagnosis to mean age at diagnosis in the delayed group for ALD (6.6 – 1.0 = 5.6), Pompe (4.4 – 1.0 = 3.4), SCID (6.3 – 1.0 = 5.3), FXS (7.3 – 3.0 = 4.3), DMD (9.1 – 5.0 = 4.1) and as the length of diagnostic odyssey reported by RD patients in the RD Impact Survey for Wilson and gMG.
Missed Days' work is the weighted average of commercial and Medicaid FFS pre-diagnosis days missed work (for caregiver or patient) with delayed diagnosis; inferred using algorithm where IP day = 1 day missed work, OP and ER = 0.5 day missed work, office visits = 0.25 day missed work (Mowitz, et al., 2022).
Lost productivity is the missed days' work (8 hours per day) per patient per year multiplied by the mean hourly wage in 2021 USD.
Cumulative pre-diagnosis medical costs are calculated as the per patient per year medical costs with delayed diagnosis multiplied by the number of years between average age with timely and delayed diagnosis.

Survey Analyses

To characterize indirect and non-medical costs in relation to timing of diagnosis, we analyzed data for 1,300 persons with RD (Exhibit 34). Survey respondents were comprised of 745 individuals living with RD (75%) and 555 caregivers and family members responding on behalf

of a person with RD (25%). Among those diagnosed with RD before 19 years old, 82% of survey respondents were caregivers, family members or close friends answering as proxy; among those diagnosed as adults, 9% were answered by proxy.

Exhibit 34. Rare Disease Survey Respondent Characteristics by Age Group

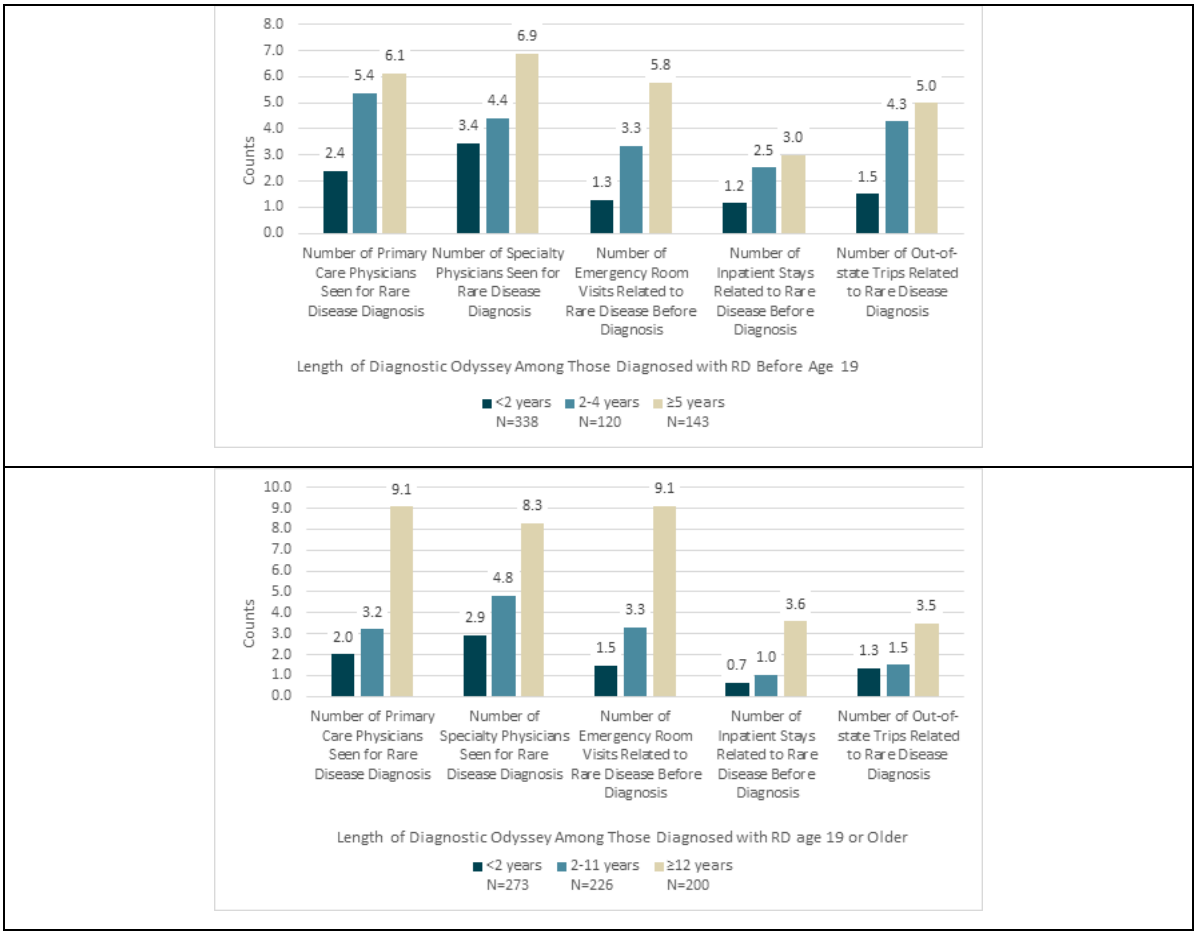
	Diagnosed before age 19	Diagnosed age 19 or Older	
N (%)	601		699
Person living with rare disease	109 (18.1%)		636 (91.0%)
Caregiver, family member or close friend	492 (81.9%)		63 (9.0%)
Male	317 (53.0%)		169 (24.2%)
Age group		Age group	
<5 years	386 (64.2%)	19-39 years	259 (37.1%)
5-9 years	106 (17.6%)	40-54 years	221 (31.6%)
10-14 years	66 (11.0%)	55-65 years	142 (20.3%)
15-18 years	43 (7.2%)	>65 years	77 (11.0%)
Race/ethnicity			
White	512 (85.2%)		626 (89.6%)
Hispanic/Latino	44 (7.32%)		30 (4.3%)
Insurance[a]			
Commercial	459 (76.4%)		456 (65.2%)
Medicaid FFS	275 (45.8%)		107 (15.3%)
Medicare	57 (9.5%)		256 (36.6%)

[a] May sum to >100% because a person can have more than one type of insurance.

Healthcare Events Before Rare Disease Diagnosis

Compared to those with shorter diagnostic odysseys (<2 years), those with longer diagnostic odysseys were more likely to report having seen more primary care physicians and specialty physicians related to their RD diagnosis and have more IP and ED visits before their RD diagnosis (Exhibit 35). Those with longer diagnostic odysseys were approximately 4-times as likely to see 3 or more specialists compared with the shortest diagnostic odyssey (data not shown). Last, compared to those with shorter diagnostic odysseys, those with a longer length of time between symptom onset and diagnosis reported increasingly greaters number of out-of-state trips related to RD diagnosis.

Exhibit 35. Healthcare Events Before Rare Disease Diagnosis by Length of Diagnostic Odyssey Among Children with Rare Disease Diagnosis



Source: Primary data collected via Rare Disease Impact Survey, 2019.

DISCUSSION

The results of this accounting of the diagnostic odyssey in 7 RDs suggest important differences in the economic burden related to timing of RD diagnosis. Analyses revealed striking differences in direct medical costs related to timing of diagnosis in diseases where the diagnostic odyssey can be avoided (ALD, Pompe, SCID). In the cases of ALD and late-onset Pompe, annualized per patient costs were lower in the year of diagnosis among those diagnosed in the first year of life compared with those diagnosed later. In contrast, in SCID, a disease with high mortality if not detected early, average annualized per patient costs in the year of diagnosis were 2-times higher among those diagnosed in the first year of life compared with those diagnosed at age 1 or older. For childhood diseases without routine newborn screening, like FXS and DMD, annualized per patient costs were consistently lower for those with timely diagnosis in the pre-diagnosis, year of, and post-diagnosis periods compared with delayed diagnosis. The economic

burden of delayed diagnosis is substantial, especially in diseases that typically require lengthy hospital stays like SCID or ALD.

The most important benefit of timely diagnosis, whether by routine NBS, comprehensive genetic testing, or well-timed clinical workup, is the opportunity to ensure optimal management and timely treatment initiation for patients. Delays in such care may have long-term impacts on patients' overall health outcomes and survival, and on the quality of life for both the patient and their family. Timely diagnosis also prevents a prolonged diagnostic odyssey and related intangible costs that include the time spent managing financials, time off work for healthcare visits, and in many cases, out-of-state trips to see RD specialists for diagnosis and treatment (Yang, Cintina, & Pariser, 2022). Additionally, the alleviation of anxiety related to the diagnostic odyssey and the negative impact of no diagnosis for patients and families cannot be understated (Bauskis, Strange, Molster, & Fisher, 2022).

NBS makes presymptomatic diagnosis, care, and management possible, and the benefit to affected newborns and families as well as the cost savings is a model for all RDs, regardless of age of onset of observable symptoms (Centers for Disease Control and Prevention, 2012). To be considered for addition to the Recommended Uniform Screening Panel (RUSP), a disease must be assessed by a federal advisory committee to meet specific evidentiary requirements that demonstrate the benefits of screening outweigh the harms (US Department of Health and Human Services). Of the diseases examined, those that have met criteria for addition to the RUSP included Pompe, ALD, and SCID (Health Resources and Service Agency, 2023). As of the time of this study, routine NBS was implemented in 29 states for Pompe, 23 states for ALD, and 50 states for SCID. By quantifying the cumulative burden of the diagnostic odyssey, this study illustrates the potential economic impact of screening and early diagnosis of newborns, particularly when early intervention is essential to preventing long-term harm. While newborn screening is a powerful tool for detection of RDs, it is not a panacea as screening tests have limitations with regard to predictive value. Therefore, strategies to detect RDs should be multifaceted to ensure that delays in diagnosis are mitigated.

Without timely diagnosis, infants with SCID may not survive past their first birthday; however, if detected early SCID is potentially curable with stem cell transplant. Enzyme replacement therapies are also available for some subtypes. Indeed, because the survival rate of children with SCID who are not diagnosed early is so low, it is possible that the lower costs observed in the late diagnosis group (compared to timely diagnosis) reflect only those patients with a less severe subtype of the disease who are able to survive delayed diagnosis. Nevertheless, for all seven diseases included here, among those with delayed diagnosis we found the highest per-patient annualized direct medical costs among those diagnosed with SCID at age one or later, stressing the severity of this disease if undetected.

Both ALD and Pompe were added to the RUSP before the study period. However, unlike SCID, many states had not implemented either or both conditions to their screening panels by 2016,

so we are observing a mix of those born with and without access to NBS in these analyses. In the case of Pompe, NBS identifies both IOPD and LOPD subtypes, and it is not possible to distinguish between these subtypes using ICD-10 diagnosis codes alone. The infantile subtype, which is the most severe, life-threatening form of the disease, requires immediate rescue through enzyme replacement therapy. In addition, a timely diagnosis for LOPD enables monitoring of the disease progression and a more optimized initiation of treatment, when it is appropriate (Stevens, Milani-Nejad, & Mozaffar, 2022). We observed relatively high costs for IOPD, primarily driven by OP and Other utilization categories, which include healthcare settings where infused therapies, such as ERT, would be administered. However, similar to SCID, infants with IOPD do not survive past their first birthday if not detected and treated with potentially curable intervention. These diseases represent a shift from expenditures on diagnostic odysseys and irreversible disease progression to treatment, symptom management, and improved health outcomes.

Although the remaining diseases (Duchenne Muscular Dystrophy and Fragile X Syndrome) examined are not currently included on the RUSP (though Duchenne Muscular Dystrophy is under consideration), our analysis indicates that timely diagnosis is possible through other means. For example, voluntary screening and/or pilot screening projects for both Duchenne Muscular Dystrophy and Fragile X Syndrome have been implemented in some states in recent years. Patients also may be identified by carrier screening, diagnosis of a family member, or through clinical workup. Although neither Fragile X Syndrome nor Duchenne Muscular Dystrophy currently have an available curative therapy, earlier diagnosis can trigger earlier intervention via supportive therapies which may impact school readiness, assist with symptom management, and preserve or improve function and quality of life to the greatest possible extent. In addition, Duchenne Muscular Dystrophy also has multiple FDA approved therapies that may be used to mitigate symptoms and slow disease progression. This includes a recently approved gene therapy that would not be available to children diagnosed after age 5 (US Food and Drug Administration, 2023).

The two diseases included that may have adult-onset (e.g., Wilson and gMG) present a somewhat more complex picture. Wilson disease may present in childhood or adulthood, but often manifests differently, with hepatic manifestation in children and neurological manifestation in adults (Daniel-Robin, Benichou, Leboucher, Blein, & Combal, 2022; Kerkar & Rana, 2022). In adults, neurological symptoms vary greatly and range from tremor and motor issues to psychiatric symptoms and psychosis (Kerkar & Rana, 2022; Daniel-Robin, Benichou, Leboucher, Blein, & Combal, 2022; Machado, et al., 2006), leading to misdiagnosis and delays in diagnosis (Yu, Ren, Zheng, Hong, & Wei, 2022; Rustgi, et al., 2022). If identified early, Wilson can be treated effectively and managed as a chronic disease. Interestingly, we observed higher medical costs per-patient per year among those diagnosed as children (before age 19). This finding may be explained by the costs associated with managing the hepatic manifestation in children (Rustgi, et al., 2022).

Complexities in gMG include known differences in incidence between males and females (Ciafaloni, 2019; Carr, Cardwell, McCarron, & McConville, 2010). Our observations confirm differences in age at diagnosis and also potential differences in length of diagnostic odyssey. Interestingly, we observed higher per-patient annualized direct medical costs for males compared with females with gMG, which may reflect presentation with greater severity among men and could explain a shorter diagnostic odyssey. Furthermore, women with disease onset at younger ages may experience reduced work hours, slower career progression or early retirement – this combined with a prolonged diagnostic odyssey can compound health inequities for gMG patients.

On average, RD patients spend more than six years searching for a diagnoses (Hendriksz, 2013; Benito-Lozano, Lopez-Villalba, Arias-Merino, Posada de le Paz, & Alonso-Ferreira, 2022; Yang, Cintina, & Pariser, 2022). With increased attention to RD collectively as a public health matter, technological advances in genomic sequencing, and the promise of artificial intelligence for identification of rare pathogenic variants in undiagnosed individuals, it may be possible to eliminate or minimize the diagnostic odyssey for many patients with RD. We estimate that the cost per patient of delayed diagnosis in these seven diseases is between $86,000 and $517,000 per patient. Similar calculations could be done for other diseases. The diagnostic odyssey in RD includes many medical visits and tests, and often requiring caregivers to serve as patient navigators and care coordinators in the health system (Baumbusch, Mayer, & Sloan-Yip, 2018). Our conservative estimate of productivity loss for patients and caregivers related to the diagnostic odyssey is driven by IP utilization and does not take consider travel time, which for RD patients and families may be substantial. This is also supported by our survey findings that the numbers of healthcare events and out-of-state trips increase with the length of diagnostic odyssey.

We observed higher healthcare utilization counts per patient in Medicaid FFS enrollees. Possible reasons for this are complex and may be related to both fragmented care and important differences in benefit design between Medicaid FFS and commercial insurance. There are many services covered by Medicaid FFS that are not typically covered under private insurance These include many services that fall into the “other” category such as durable medical goods, transportation, education (e.g., feeding), and home-based services. Medicaid FFS is also mandated to cover all FDA-approved treatments both retail pharmacy and specialty medications; specialty medications are often covered by the medical benefit and may fall under the OP category when delivered in an OP setting or the other category if administered in the home. Additionally, there is some evidence suggesting that adults and children with public insurance have higher IP and ED visits compared with privately insured (Garcia, Bernstein, & Bush, 2010). Children with congenital heart defects and public insurance had more IP and ED visits compared with private insurance and had more severe disease (Lui, et al., 2022). A third explanation for higher utilization observed in Medicaid FFS may be due to care fragmentation, which is more common in patients with public insurance (Walunas, et al., 2017). Children with

public insurance may experience longer time intervals from initial evaluation to seeing a specialist for sleep-disordered breathing (Bhattacharyya & Shapiro, 2014). Fragmented care may be especially salient in a RD population, particularly during the diagnostic odyssey, when many patients seek care in different healthcare systems and often travel out-of-state seeking diagnosis and answers. This fragmented care can cause delays and redundancies when providers operate in separate systems that don't share records, even more true in RD when patients sometimes travel over state lines to seek specialty care in other systems.

Limitations

This retrospective study of patients with ALD, Pompe, SCID, Fragile X Syndrome, Duchenne Muscular Dystrophy, Wilson, and gMG is among the first to report per-patient healthcare resource utilization and costs of the diagnostic odyssey, underscoring the importance of timely diagnosis. However, results of this study are prone to limitations common to the use of administrative claims data. For instance, the presence of a diagnosis code on a medical claim does not guarantee the patient has the condition. Because our case definition requires a minimum of 1 diagnosis, misclassification of disease status cannot be ruled out. To avoid misclassification of disease status, we did not use medical claims from laboratory facilities for identification of patients as these may represent testing to rule out disease. We also conducted sensitivity analyses requiring a confirmatory diagnosis code on a separate date of service and the findings were consistent with the main analysis in direction and magnitude.

Other information not found in administrative claims include details about disease subtype or severity. For instance, the ICD-10 code E74.02 does not distinguish between infantile-onset and late-onset Pompe, thus our study population includes a mix of these subtypes. Similarly, we cannot differentiate between Duchenne Muscular Dystrophy and Becker muscular dystrophy using administrative claims data. As Becker typically has a slightly older age at diagnosis compared with Duchenne Muscular Dystrophy, our average at age diagnosis observed in claims may appear slightly higher. Additionally, we were unable to determine disease severity, which could potentially lead to selection bias in our comparison cohorts where earlier diagnosis might be due to more severe disease. However, this is contradicted by our finding that, in most cases, we observed lower medical costs per patient for the groups diagnosed at younger ages.

In some cases we are unable to distinguish between disease subtypes; for instance, the ICD-10 diagnosis code for Pompe disease does not distinguish between infantile-onset or late-onset Pompe. This and the fact that the newborn screening test for Pompe disease also does not distinguish between infantile- and late-onset subtypes means that more late-onset cases are being identified, thus our study population includes a mix of these subtypes. In the case of Pompe, the subset with infantile-onset will require immediate initiation of treatment with enzyme replacement therapy, a costly, weight-based specialty medicine. The subset with late-onset Pompe will not start treatment right away thereby having considerably lower per patient

costs in the year of diagnosis and early post-diagnosis period. Similarly, in DMD, the ICD-10 code includes Becker Muscular Dystrophy and we are unable to distinguish between the two using administrative claims data; Becker Muscular Dystrophy typically has slightly older age at diagnosis compared with DMD, thus our average at age diagnosis observed in these claims data sources may be slightly higher.

An important limitation of this study of RD is what cannot be ascertained with claims data, such as information about services not covered by insurance or covered through another benefit. This can include services provided by early childhood services. For diseases with infant and early childhood onset, children often receive services, such as physical therapy, occupational therapy, or speech therapy, through early childhood services in their state. As such, it is possible our estimates of healthcare resource utilization for patients with conditions that indicate these services, such as FXS, underestimate the true utilization and costs.

In addition, due to small N we were unable to control for confounding by patient demographics or social determinants of health using administrative claims data. Along the same lines, for a disease with high mortality, like SCID, survival bias must be considered when interpreting results.

Perhaps most important for a study of autosomal recessive RD, such as Pompe and SCID, or an X-linked disorder such as FXS, DMD, or ALD, is the lack of complete information in the claims about siblings who may have been diagnosed or identified as disease carriers. Claims data typically do not include information about genetic testing and family history. Such information can eliminate the diagnostic odyssey altogether.

Survey data is prone to recall bias and misclassification, particularly when proxies are used to complete on the patient's behalf. In addition, the Rare Disease Impact Survey relied on a convenience sample, which may have introduced selection biases. Nevertheless, these survey data allow for close examination of the diagnostic odyssey.

Finally, despite access to two large databases, this study was limited by a small sample size. To preserve sample size, we did not exclude outliers, which may have skewed some distributions of costs. However, these outliers represent the real-world experience of RD patients. Inferring population incidence and prevalence rates in RD is challenging. A recent study found that the prevalence of 12 RDs varied considerably across four health system databases, which may be due to underlying differences in patient populations served and how data are queried (e.g., administrative claims or EHR) – observations that highlight the challenges and lack of infrastructure for sharing RD information (Tisdale, et al., 2021).

Conclusion

Taken together, the findings of this examination of 7 RDs suggest important economic benefits of timely diagnosis in terms of both direct medical costs and lost productivity. Timely diagnosis is especially important when there are potentially disease-altering or life-saving treatments available that can delay or avoid irreversible disease progression and complications. Even in the absence of disease-altering or curative treatments, timely diagnosis can have profound impact when symptoms can be treated and managed, ultimately improving health and reducing the cumulative burden of the diagnostic odyssey on patients and families with rare disease. Lastly, while medical costs are unavoidable in RD, the excess costs attributable to delayed diagnosis represent not only the burden on patients and families of searching for a diagnosis, but also healthcare dollars that could be better spent on treatment and supportive therapies that improve patient quality of life and may even increase workforce productivity.

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APPENDIX A. DIRECT MEDICAL COSTS RESULTS

Exhibit A - 1. Annualized Per Patient Medical Costs Attributed to Adrenoleukodystrophy Diagnosis, 2016-2020.

	Timely Diagnosed Before Age 1				Delayed Diagnosed Age 1 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	29	23		69	69	50
ALD-specific	--	$589	$1,312		--	$17,854	$4,283

[a] Costs attributed to claims with diagnosis code for ALD (E71511, E7152*) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with ALD diagnosis as per definition.
[b] CPI adjusted to 2021 USD.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 2. Annualized Per Patient Medical Costs[a] in Males Diagnosed with Adrenoleukodystrophy Before 4 Months of Age, 2016-2020

	Timely Diagnosed Before 4 Months				Delayed Diagnosed Age 4 Months or Older		
	Pre[b]	Year of	Post		Pre	Year of	Post
N	--	14	12		51	52	37
IP Acute days	--	$35,310	$100		$22,367	$24,844	$20,116
IP Non-acute days	--	$0	$0		$2,372	$1,713	$2,755
OP[c]	--	$821	$1,094		$1,705	$3,215	$3,318
ED	--	$45	$137		$363	$487	$372
Office Visits[d]	--	$1,732	$1,112		$1,758	$1,688	$2,114
Other[e]	--	$2,179	$1,207		$22,464	$29,254	$37,590
Rx		$121	$117		$4,260	$7,251	$8,253
Caregiver[f]		$0	$0		$822	$2,514	$1,655
Total		$40,208	$3,767		$56,111	$70,966	$76,173
ALD-specific Costs[g]		$712	$656		$0	$15,523	$5,486

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] CPI adjusted to 2021 USD.
[b] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[c] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[d] Office visits include primary care and specialist.
[e] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
[f] Caregiver services covered by Medicaid.
[g] Costs attributed to claims with diagnosis code for ALD (E71511, E7152*) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with ALD diagnosis as per definition.
Source: Lewin analyses of 2016-2020 TMSIS Medicaid and CHIP claims.

Exhibit A - 3. Annualized Per Patient Medical Costs[a] Attributed to Late-Onset Pompe Disease Diagnosis, 2016-2020.

	Timely LOPD Diagnosed Before Age 1				Delayed LOPD Diagnosed Age 1 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	40	31		40	40	26
Pompe-specific[b]	--	$914	$1,250		--	$16,781	$31,710

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for Pompe (ICD-10 E7402) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with Pompe diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 4. Annualized Per Patient Medical Costs[a] Attributed to SCID Disease Diagnosis, 2016-2020.

	Timely Diagnosed Before Age 1				Delayed Diagnosed Age 1 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	54	44		73	73	56
SCID-specific[b]	--	$59,128	$8,523			$784	$117

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for SCID (ICD-10 D810, D811, D812 or D8131) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with SCID diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 5. Annualized Per Patient Medical Costs[a] in SCID Before 4 Months of Age, 2016-2020

	Timely Diagnosed Before 4 Months				Delayed Diagnosed Age 4 Months or Older		
	Pre[b]	Year of	Post		Pre	Year of	Post
N	--	33	29		54	56	42
IP Acute days	--	$148,038	$54,940		$13,560	$64,428	$39,564
IP Non-acute days	--	$265,268	$8,682		$440	$7,642	$104
OP[c]	--	$6,508	$8,527		$5,798	$6,514	$5,570
ED	--	$612	$342		$701	$547	$352
Office Visits[d]	--	$2,945	$921		$2,068	$2,367	$2,174
Other[e]	--	$5,702	$6,364		$35,802	$35,065	$26,936
Rx		$47,493	$17,671		$18,445	$22,647	$57,962
Caregiver[f]		$59	$23		$88	$570	$510
Total		$476,625	$97,470		$76,902	$139,780	$133,173

	Timely Diagnosed Before 4 Months				Delayed Diagnosed Age 4 Months or Older		
	Pre[b]	Year of	Post		Pre	Year of	Post
SCID-specific Costs[g]		$29,306	$7,104		$0	$12,521	$151

IP = Inpatient (acute and non-acute) days; OP = Outpatient; ED = Emergency Department visit.
[a] CPI adjusted to 2021 USD.
[b] Because the first year of observation is the year of diagnosis, there are no pre-diagnosis observations in this group.
[c] OP includes outpatient and free-standing surgery centers, rehab, dialysis, and substance abuse.
[d] Office visits include primary care and specialist.
[e] Other category includes lab procedures/testing, education (e.g., diabetes or feeding), home-based care, ambulance, mobile clinics, durable medical equipment and anything else that does not fall into above categories.
[f] Caregiver services covered by Medicaid.
[g] Costs attributed to claims with diagnosis code for SCID (ICD-10 D810, D811, D812 or D8131) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with SCID diagnosis as per definition.
Source: Lewin analyses of 2016-2020 TMSIS Medicaid and CHIP claims.

Exhibit A - 6. Annualized Per Patient Medical Costs[a] Attributed to Fragile X Syndrome Diagnosis, 2016-2020.

	Timely Diagnosed Before Age 3				Delayed Diagnosed Age 3 or Older		
	Pre	Year of	Post		Pre	Year of	Post
N	--	75	50		272	272	220
FXS-specific[b]	--	$8,104.16	$7,245.25		--	$16,902.06	$14,847.94

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for FXS (ICD-10 Q992) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with FXS diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 7. Annualized Per Patient Medical Costs[a] Attributed to Duchenne Muscular Dystrophy Diagnosis, 2018-2020.

	Timely Diagnosed Before Age 5				Delayed Diagnosed Age 5 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	85	70		652	652	558
DMD-specific[b]	--	$13,669	$30,367		--	$35,252	$54,775

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for DMD (ICD-10 G7101) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with DMD diagnosis as per definition.
Source: Lewin analyses of 2018-2020 dNHI claims and T-MSIS files

Exhibit A - 8. Annualized Per Patient Medical Costs[a] Attributed to Wilson Disease Diagnosis, 2016-2020.

	Timely Diagnosed Before Age 19				Delayed Diagnosed Age 19 or Older		
	Pre	Year of	Post		Pre	Year of	Post
N	--	164	132		404	404	290
FXS-specific[b]	--	$2,275	$1,620			$1,451	$657

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for Wilson disease (ICD-10 E8301) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with Wilson disease diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 9. Annualized Per Patient Medical Costs[a] Attributed to Generalized Myasthenia Gravis Diagnosis in Females, 2016-2020.

	Timely Diagnosed Before Age 40				Delayed Diagnosed Age 40 or Older		
	Pre[a]	Year of	Post		Pre	Year of	Post
N	--	706	580		979	979	772
gMG-specific[b]	--	$2,905	$4,229			$2,251	$1,676

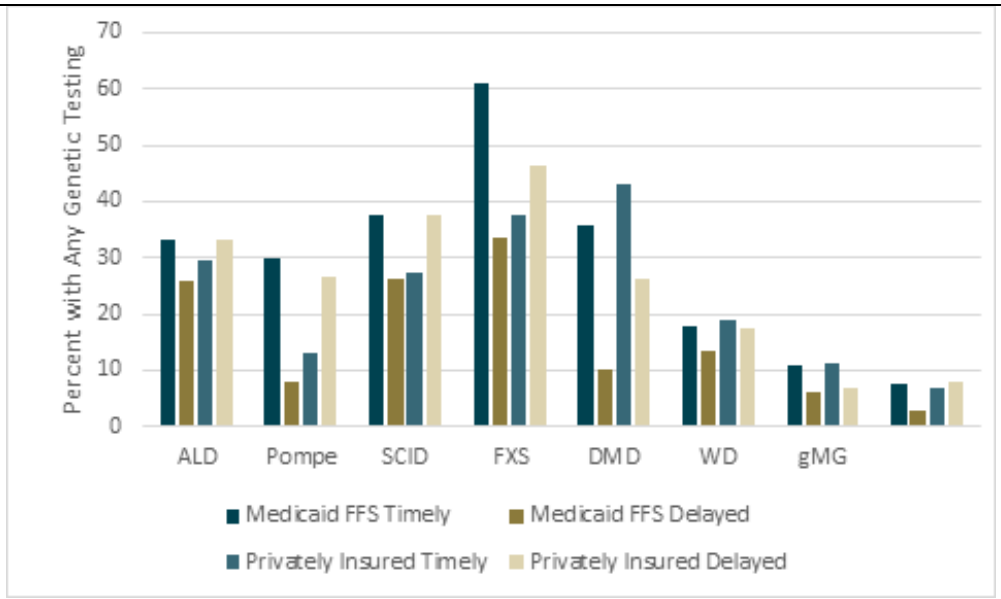
[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for gMG (ICD-10 G7000 or G7001) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with gMG diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 10. Annualized Per Patient Medical Costs[a] Attributed to Generalized Myasthenia Gravis Diagnosis in Males, 2016-2020.

	Timely Diagnosed Before Age 50				Delayed Diagnosed Age 50 or Older		
	Pre	Year of	Post		Pre	Year of	Post
N	--	514	390		556	556	403
gMG-specific[b]	--	$2,100	$4,393			$935	$4,600

[a] CPI adjusted to 2021 USD.
[b] Costs attributed to claims with diagnosis code for gMG (ICD-10 G7000 or G7001) in the year of and post-diagnosis periods; There are no pre-diagnosis costs associated with gMG diagnosis as per definition.
Source: Lewin analyses of 2016-2020 dNHI claims and T-MSIS files

Exhibit A - 11. Utilization of Genetic and Genomic Testing



Genetic and genomic testing include whole genome and exome sequencing, single gene testing, and gene panel testing. Complete list of billing and procedure codes is located in Appendix C. Exhibit C - 3. Genetic Testing Procedure and Billing Codes.

APPENDIX B. RARE DISEASE IMPACT SURVEY

Exhibit B - 1. Rare Disease Impact Survey Sample

	Age <19 years at time of diagnosis		Age ≥19 years at time of diagnosis	
	Frequency	Percent	Frequency	Percent
A person living with rare disease	109	18.1%	636	91.0%
A family caregiver for someone who has a rare disease	480	79.9%	53	7.6%
A paid caregiver for someone who has a rare disease	0	0.0%	1	0.1%
A family member of someone who has a rare disease, but not a direct caregiver	10	1.7%	9	1.3%
A close friend to someone who has a rare disease, but not a caregiver	2	0.3%	0	0.0%
Total	601	100.0%	699	100.0%

Source: Primary data collection through the 2019 Rare Disease Impact Survey **collection**

APPENDIX C. SUPPLEMENTAL METHODS AND CODE LISTS

Exhibit C - 1. Healthcare Utilization Place of Service Logic[a]

	Optum dNHI Commercial Data	T-MSIS Medicaid FFS Data
Inpatient acute	Inpatient hospital Birthing center Residential substance abuse treatment Psychiatric residential treatment center	Inpatient hospital Birthing center Residential substance abuse treatment Psychiatric residential treatment center
Inpatient non-acute	Assisted living facility Skilled nursing facility Nursing facility Custodial care facility Hospice Inpatient psychiatric facility Psychiatric facility – partial hospitalization Intermediate care facility Comprehensive inpatient rehabilitation	Assisted living facility Skilled nursing facility Nursing facility Custodial care facility Hospice Inpatient psychiatric facility Psychiatric facility – partial hospitalization Intermediate care facility Comprehensive inpatient rehabilitation
Outpatient	Off-campus outpatient hospital Urgent care facility Ambulatory surgical center Non-residential substance abuse treatment Comprehensive outpatient rehabilitation End-stage renal disease treatment facility	Off-campus outpatient hospital Urgent care facility Ambulatory surgical center Non-residential substance abuse treatment Comprehensive outpatient rehabilitation End-stage renal disease treatment facility
Emergency department	Emergency room	Emergency room
Physician office visits	Telehealth Office Walk-in retail clinic Independent clinic Federally qualified health center Community mental health center Mass immunization center Public health clinic Rural health clinic	Telehealth Office Walk-in retail clinic Independent clinic Federally qualified health center Community mental health center Mass immunization center Public health clinic Rural health clinic Indian health services freestanding clinic Indian health services provider-based clinic Tribal services
Other	School	School

	Optum dNHI Commercial Data	T-MSIS Medicaid FFS Data
	Home (includes home-based infusion services) Group home Mobile unit Temporary lodging Place of employment Ambulance (land) Ambulance (air or water) Independent laboratory Other place of service not otherwise identified	Home (includes home-based infusion services) Group home Mobile unit Temporary lodging Place of employment Ambulance (land) Ambulance (air or water) Independent laboratory Other place of service not otherwise identified Pharmacy (typically means nutritional supplement) Homeless shelter Prison Military treatment facility Unassigned place of service Home health aide visit Home health visit Case management Personal care services Rehab Self-care/home management (e.g., activities of daily living) Mileage Feeding supplies

[a] Services such as behavioral health counseling, physical therapy, occupational therapy, and speech therapy may fall into OP, office visits, or other depending on where these services are delivered.

Exhibit C - 2. Disease-specific Procedure and Billing Codes

Description	Code Type	Codes
Caregiver billing codes used in Medicaid FFS	HCPCS	S5100 S5101 S5102 S5120 S5121 S5125 S5126 S5130 S5131 S5135 S5136 S5140 S5141 S5150 S5151 S5170 S5175 S9125 T1005 T1019 T1020 T1021 T1022 99502 99504 99509
HSCT-related procedure and billing codes	CPT	28206 36561 38204-38215 38220-38222 38230 38232

Description	Code Type	Codes
		38240-38244 81370-81383
	HCPCS	S2149 S2142 S2159
Enzyme replacement therapy	HCPCS	J0221 C9085 J3590
Exon-skipping therapy (for Duchenne)	HCPCS	J1428 J1428 C9484 C9071 C9075 J1426 J1427 J1429

Exhibit C - 3. Genetic Testing Procedure and Billing Codes

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81161	DMD (dystrophin) deletion and duplication analysis	1							1	
81171	FMR gene analysis	1						1		
81172	FXS	1						1		
81173	Androgen receptor gene analysis	1								
81174	Androgen receptor gene analysis	1								
81175	Additional sex combs like 1, transcriptional regulator (ASXL1) full gene sequence analysis	1								
81176	Additional sex combs like 1, transcriptional regulator (ASXL1) targeted sequence analysis	1								
81177	ATN1 gene analysis	1								
81178	ATXN1 gene analysis	1								
81179	ATXN2 gene analysis	1								
81180	ATXN3 gene analysis	1								
81181	ATXN7 gene analysis	1								
81187	CNBP gene analysis (myotonic dystrophy type 2)	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81188	CSTB gene analysis (Unverricht-Lundborg disease)	1								
81189	CSTB gene analysis (Unverricht-Lundborg disease)	1								
81190	CSTB gene analysis (Unverricht-Lundborg disease)	1								
81200	Aspartoacylase (ASPA) gene analysis for detection of common variant	1								
81201	Adenomatous polyposis coli (APC) full gene sequence analysis	1								
81202	Adenomatous polyposis coli (APC) gene analysis for known familial variants	1								
81203	Adenomatous polyposis coli (APC) gene analysis for deletion variant	1								
81204	Androgen receptor gene analysis	1								
81205	Branched-chain keto acid dehydrogenase E1, beta polypeptide (BCKDHB) gene analysis for detection of co	1								
81209	Bloom syndrome, RecQ helicase-like (BLM) gene analysis for detection of 2281del6ins7 variant	1								
81218	CCAAT/enhancer binding protein [C/EBP], alpha (CEBPA) full gene sequence analysis	1								
81219	Calreticulin (CALR) gene analysis for detection of common variant on exon 9	1								
81220	Cystic fibrosis transmembrane conductance regulator (CFTR) gene analysis for detection of common varia	1								
81221	Cystic fibrosis transmembrane conductance regulator (CFTR) gene analysis for detection of known familial	1								
81222	Cystic fibrosis transmembrane conductance regulator (CFTR) gene analysis for detection of deletion variant	1								
81223	Cystic fibrosis transmembrane conductance regulator (CFTR) full sequence gene analysis	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81224	Cystic fibrosis transmembrane conductance regulator (CFTR) gene analysis with intron 8 poly-T analysis	1								
81228	Cytogenetic constitutional microarray analysis	1								
81229	Cytogenetic constitutional microarray analysis	1						1		
81234	DMPK gene analysis	1								
81238	F9 (coagulation factor IX) (e.g., hemophilia B), full gene sequence	1								
81239	DMPK gene analysis	1								
81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant	1								
81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant	1								
81242	Fanconi anemia, complementation group C (FANCC) gene analysis for detection of common variant	1								
81243	Fragile X mental retardation 1 (FMR1) gene analysis for detection of abnormal allele	1						1		
81244	Fragile X mental retardation 1 (FMR1) gene analysis for characterization of allele	1						1		
81247	G6PD (glucose-6-phosphate dehydrogenase) gene analysis for detection of A variant	1								
81248	Glucose-6-phosphate dehydrogenase (G6PD) gene analysis for detection of known familial variant	1								
81249	Glucose-6-phosphate dehydrogenase (G6PD) full gene sequence analysis	1								
81250	Glucose-6-phosphatase, catalytic subunit (G6PC) gene analysis for detection of common variant	1								
81251	Glucosidase, beta, acid (GBA) gene analysis for detection of common variant	1								
81252	Gap junction protein, beta 2, 26kDa; connexin 26 (GJB6) full gene sequence analysis	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81253	Gap junction protein, beta 2, 26kDa; connexin 26 (GJB6) for detection of known familial variants	1								
81254	Gap junction protein, beta 6, 30kDa, connexin 30 (GJB6) gene analysis for detection of 232kb [del(GJB6-D1	1								
81255	Hexosaminidase A (alpha polypeptide) (HEXA) gene analysis for detection of common variant	1								
81256	Hemochromatosis (HFE) gene analysis for detection of C282Y and H63D variants	1								
81257	Alpha globin 1 and alpha globin 2 (HBA1/HBA2) gene analysis for detection of common deletion	1								
81258	Alpha globin 1 and alpha globin 2 (HBA1/HBA2) gene analysis for detection of known familial variant	1								
81259	Alpha globin 1 and alpha globin 2 (HBA1/HBA2) gene analysis of full gene sequence	1								
81260	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP)	1								
81265	Comparative analysis using Short Tandem Repeat (STR) marker	1								
81266	Comparative analysis using Short Tandem Repeat (STR) marker	1								
81269	Alpha globin 1 and alpha globin 2 (HBA1/HBA2) gene analysis for detection of duplication and deletion var	1								
81271	Huntington disease	1								
81274	Huntington disease	1								
81284	Friedreich ataxia gene analysis	1								
81285	Friedreich ataxia gene analysis	1								
81286	Friedreich ataxia gene analysis	1								
81289	Friedreich ataxia gene analysis	1								
81290	Mucolipidosis, type IV (MCOLN1) gene analysis for detection of common variant	1								
81291	MTHFR gene analysis	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81298	MutS homolog 6 (E. coli) (MSH6) full gene sequence analysis	1								
81299	MutS homolog 6 (E. coli) (MSH6) gene analysis for detection of known familial variant	1								
81300	MutS homolog 6 (E. coli) (MSH6) gene analysis for detection of deletion variant	1								
81302	Methyl CpG binding protein 2 (MECP2) full gene sequence analysis	1								
81303	Methyl CpG binding protein 2 (MECP2) gene analysis for detection of known familial variant	1								
81304	Methyl CpG binding protein 2 (MECP2) gene analysis for detection of deletion variant	1								
81317	Postmeiotic segregation increased 2 (S. cerevisiae) (PMS2) full gene sequence analysis	1								
81318	Postmeiotic segregation increased 2 gene analysis for detection of known familial variant	1								
81319	Postmeiotic segregation increased 2 (PMS2) gene analysis for detection of deletion variant	1								
81321	Phosphatase and tensin homolog (PTEN) full gene sequence analysis	1								
81322	Phosphatase and tensin homolog (PTEN) gene analysis for known familial variant	1								
81323	Phosphatase and tensin homolog (PTEN) gene analysis for deletion and duplication variants	1								
81324	Peripheral myelin protein 22 (PMP22) gene analysis for deletion and duplication variants	1								
81325	Peripheral myelin protein 22 (PMP22) full gene sequence analysis	1								
81326	Peripheral myelin protein 22 (PMP22) gene analysis for known familial variant	1								
81329	SMN1 Gene analysis	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81330	Sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1) gene analysis for detection of common variant	1								
81331	SNRPN/UBE3A Prader-Willi or Angelman syndrome	1								
81332	Serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1 (SERPINA1) gene analysis	1								
81333	TGFBI corneal dystrophy gene analysis	1								
81334	Runt related transcription factor 1 (RUNX1) gene analysis of exons 3-8	1								
81336	SMA gene analysis	1								
81337	SMA gene analysis	1								
81349	genome-wide analysis for chromosomal abnormalities	1		1						
81361	Hemoglobin, subunit beta (HBB) gene analysis for detection of HbC variant	1								
81362	Hemoglobin, subunit beta (HBB) gene analysis for detection of known familial variant	1								
81363	Hemoglobin, subunit beta (HBB) gene analysis for detection of deletion and duplication variants	1								
81364	HBB (hemoglobin, subunit beta) full gene sequence analysis	1								
81400	Level 1 molecular pathology procedure	1								
81401	Level 2 molecular pathology procedure	1								
81402	Level 3 molecular pathology procedure	1								
81403	Level 4 molecular pathology procedure	1				1				1
81404	Level 5 molecular pathology procedure	1								
81405	Level 6 molecular pathology procedure	1			1					1
81406	Level 7 molecular pathology procedure	1				1				1
81407	Level 8 molecular pathology procedure	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81408	Level 9 molecular pathology procedure	1								
81410	Aortic dilation gene deletion analysis for detection of FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SL	1								
81411	Aortic dilation gene deletion analysis for detection of TGFBR1, TGFBR2, MYH11, and COL3A1 variants	1								
81412	Ashkenazi Jewish associated disorders genomic sequence analysis panel	1								
81413	Cardiac ion channelopathies duplication/deletion gene analysis panel with sequencing of 10 or more gene	1								
81414	Cardiac ion channelopathies duplication/deletion gene analysis panel with analysis of at least genes	1								
81415	Exome sequence analysis	1	1							
81416	Exome sequence analysis	1	1							
81417	Exome sequence analysis	1	1							
81425	Genome sequence analysis	1		1						
81426	Genome sequence analysis	1		1						
81427	Genome sequence analysis	1		1						
81430	Hearing loss genomic sequence analysis panel including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, M	1								
81431	Hearing loss gene analysis for detection of deletion and duplication variants including STRC and DFNB1 del	1								
81434	Retinal disorders (ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1) genomic s	1								
81437	Neuroendocrine tumor disorders (MAX, SDHB, SDHC, SDHD, TMEM127) genomic sequence analysis	1								
81438	Neuroendocrine tumor disorders (SDHB, SDHC, SDHD, VHL) gene analysis for detection of duplication and d	1								
81439	Hereditary cardiomyopathy genomic sequence analysis	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
81440	Mitochondrially encoded genomic sequence panel for detection of BCS1L, C10orf2, COQ2, COX10, DGUOK	1								
81442	Noonan spectrum disorders genomic sequence analysis panel including BRAF, CBL, HRAS, KRAS, MAP2K1,	1								
81443	Genetic testing for severe inherited conditions gene sequence panel	1								
81448	Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), genomic sequence panel	1								
81448	Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), genomic sequence anal	1								
81460	Mitochondrially encoded genomic sequence analysis with detection of heteroplasmy	1								
81465	Mitochondrially encoded genomic sequence analysis for detection of deletion and heteroplasmy variants	1								
81470	X-linked intellectual disability (XLID) genomic sequence analysis panel including ARX, ATRX, CDKL5, FGD1,	1								
81471	X-linked intellectual disability (XLID) gene analysis for detection of deletion and duplication variants	1								
81479	Molecular pathology procedure	1								
88245	Chromosome analysis for breakage syndrome	1								
88248	Chromosome analysis for breakage syndrome	1								
88249	Chromosome analysis for breakage syndrome using clastogen stress	1								
88261	Chromosome analysis	1								
88262	Chromosome analysis	1								
88263	Chromosome analysis for mosaicism	1								
88264	Chromosome analysis	1								
88271	Molecular cytogenetics using DNA probe	1								
88272	Molecular cytogenetics using chromosomal in situ hybridization	1								

CPT	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
88273	Molecular cytogenetics using chromosomal in situ hybridization	1								
88274	Molecular cytogenetics using interphase in situ hybridization	1								
88275	Molecular cytogenetics using interphase in situ hybridization	1								
88280	Chromosome analysis	1								
88283	Chromosome analysis using specialized banding technique	1								
88285	Chromosome analysis	1								
88289	High resolution chromosome analysis	1								
88291	Interpretation and report of cytogenetic and molecular cytogenetic studies	1								
88299	Cytogenetic study	1								

HCPCS	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
0004M	scoliosis DNA analysis of 53 SNOs	1								
0007M	neuroendocrine tumors	1		1						
0012U	Next-generation sequencing of whole genome for detection of gene rearrangement associated with germ	1		1						
0014U	hematology gene rearrangement detection by whole genome next generation sequencing	1								
0036U	Exome sequence analysis	1	1							
0094U	whole genome rapid sequence analysis	1		1						
0212U	Rare diseases whole genome and mitochondrial sequence analysis	1		1						
0213U	Rare diseases whole genome and mitochondrial sequence analysis	1		1						
0214U	rare disease whole exome and mitochondrial sequence analysis	1	1							

HCPCS	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
0215U	rare disease whole exome and mitochondrial sequence analysis	1	1							
0216U	inherited ataxias genomic DNA sequence analysis	1								
0217U	inherited ataxias genomic DNA sequence analysis	1								
0218U	dystropin gene sequence	1							1	
0230U	Androgen receptor gene analysis	1								
0231U	spinocerebellar ataxia gene sequence analysis	1								
0232U	CSTB gene sequence analysis (myoclonic epilepsy, Unverricht-Lundborg disease0	1								
0233U	Friedrich ataxia gene analysis	1								
0235U	Cowden syndrome gene analysis	1								
0236U	SMN1 and SMN2 gene sequence analysis for SMA	1								
0260U	rare diseases identification of copy number variations, inversions, insertions, translocations	1								
0254U	rare diseases identification of copy number variations, inversions, insertions, translocations	1								
0265U	rare other heritable siders, whole genome	1		1						
0267U	rare other heritable siders, whole genome	1		1						
0335U	rare diseases whole genome sequence analysis	1		1						
0336U	rare diseases whole genome sequence analysis	1		1						
0037U	targeted genomic sequence analysis	1								
0171U	targeted genomic sequence analysis panel	1								
81479x1	molecular testing	1				1				
G0452	Molecular pathology procedure; physician interpretation and report	1								

HCPCS	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
G9843	Ras (KRAS or NRAS) gene mutation	1								
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)	1								
S3828	Complete gene sequence analysis; MLH1 gene	1								
S3829	Complete gene sequence analysis; MSH2 gene	1								
S3833	Complete APC gene sequence analysis for susceptibility to familial adenomatous polyposis (FAP) and attenuated fap	1								
S3834	Single-mutation analysis (in individual with a known APC mutation in the family) for susceptibility to familial adenomatous polyposis (FAP) and attenuated FAP	1								
S3835	Complete gene sequence analysis for cystic fibrosis genetic testing	1								
S3837	Complete gene sequence analysis for hemochromatosis genetic testing	1								
S3841	Genetic testing for retinoblastoma	1								
S3842	Genetic testing for Von Hippel-Lindau disease	1								
S3843	DNA analysis of the F5 gene for susceptibility to factor V Leiden thrombophilia	1								
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness	1								
S3845	Genetic testing for alpha-thalassemia	1								
S3846	Genetic testing for hemoglobin E beta-thalassemia	1								
S3847	Genetic testing for Tay-Sachs disease	1								
S3848	Genetic testing for Gaucher disease	1								

HCPCS	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
S3849	Genetic testing for Niemann-Pick disease	1								
S3850	Genetic testing for sickle cell anemia	1								
S3851	Genetic testing for Canavan disease	1								
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease	1								
S3853	Genetic testing for myotonic muscular dystrophy	1								
S3855	Genetic testing for detection of mutations in the presenilin - 1 gene	1								
S3860	Genetic testing, comprehensive cardiac ion channel analysis, for variants in 5 major cardiac ion channel genes for individuals with high index of suspicion for familial long QT syndrome (	1								
S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected	1								
S3862	Genetic testing, family-specific ion channel analysis, for blood-relatives of individuals (index case) who have previously tested positive for a genetic variant of a cardiac ion channel syndrome	1								
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy	1								
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with	1								
S3870	Comparative genomic hybridization (CGH) microarray testing for	1								

HCPCS	Description	Genetic Test (any)	WES	WGS	ALD	Pompe	SCID	FXS	DMD	Wilson
	developmental delay, autism spectrum disor									