

The National Economic Burden of Rare Disease Study



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PREPARED FOR:



PREPARED BY:



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Background

Researchers estimate there are more than 7,000 rare diseases (RDs) affecting about 30 million Americans.¹ According to the National Human Genome Research Institute, while the exact cause for many rare diseases remains unknown, for a large number of RDs the origin can be traced to mutations in a single gene. These genetic causes range from mutations in single genes, contributions from multiple genetic factors, and/or a combination of genetic and environmental factors. Individuals with RDs have higher medical needs, often miss work, retire early, and require the assistance of a caregiver.^{2,3} As such, the direct and indirect economic burden of RD is likely to be significant, for the patient, the unpaid family caregivers, and from the societal perspective. That is, in addition to the direct medical costs associated with managing the disease, there are also indirect costs associated with productivity losses due to the disease and non-medical costs associated with necessary modification of home or vehicles.

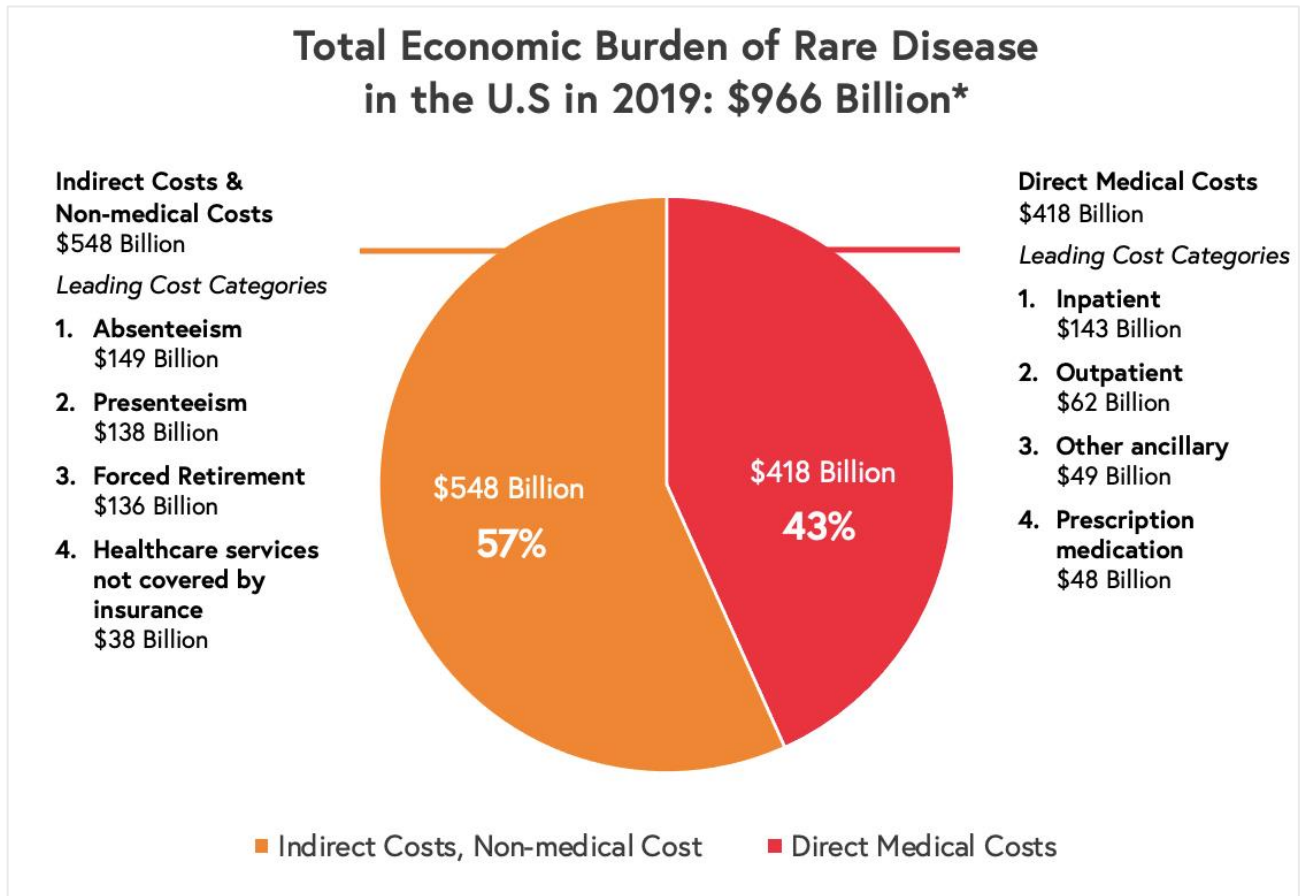
As part of its mission to empower the rare disease patient community to advocate for impactful, science-driven legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments and cures, the EveryLife Foundation undertook an initiative to understand the economic burden of RD by commissioning the Lewin Group to estimate the economic impact of RD in the U.S. in 2019. This study aims to provide the most comprehensive assessment of the total burden of RD to date, including filling the knowledge gap in some of the less well-understood cost components (such as productivity loss in both the labor market as well as in social life) and caregiver economic burden.

Study Highlights

This study provides a comprehensive assessment of the economic burden of RD in the U.S. in 2019. The estimated total economic burden of 379 RDs with a prevalence of 15.5 million people in 2019 was \$966 billion, including a direct medical cost of \$418 billion and an additional \$548 billion in indirect and non-medical cost. **Exhibit 1** shows the estimated total economic burden of RD in the U.S. in 2019 by cost components. The direct medical cost of RD represents more than one-third of the total burden (43%), followed by absenteeism losses (15%), and loss due to presenteeism (25%). Overall, labor market productivity losses due to RD, including absenteeism, presenteeism, and earnings losses from forced retirement, represent roughly the same proportion of the total burden as direct medical costs (44%). Non-medical costs represent about 12% of the total burden.

Another highlight of the study is the National Economic Burden of Rare Disease Study (hereafter, the RD Impact Survey). This primary survey was specifically designed and administered for this study to deepen the understanding of the full spectrum of RD impact. The survey was able to collect detailed data on a broad set of indirect and non-medical costs of RD that were previously unavailable, especially the impact of RD on unpaid caregivers. This survey was one of the largest surveys conducted so far covering multiple RD communities and received 1,399 fully completed responses from communities representing about 400 rare diseases.

Exhibit 1: Total Economic Burden of Rare Disease in the U.S. in 2019: \$966 Billion



Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; direct medical cost estimates obtained using 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims; indirect and non-medical costs estimated using Lewin’s analyses of the RD Impact Survey data.

Abbreviations: dNHI: Optum de-identified Normative Health Information system; Medicare SAF: Medicare Standard Analytical File 5% sample.

Methods Used for Estimation of Direct and Indirect Components of Economic Burden

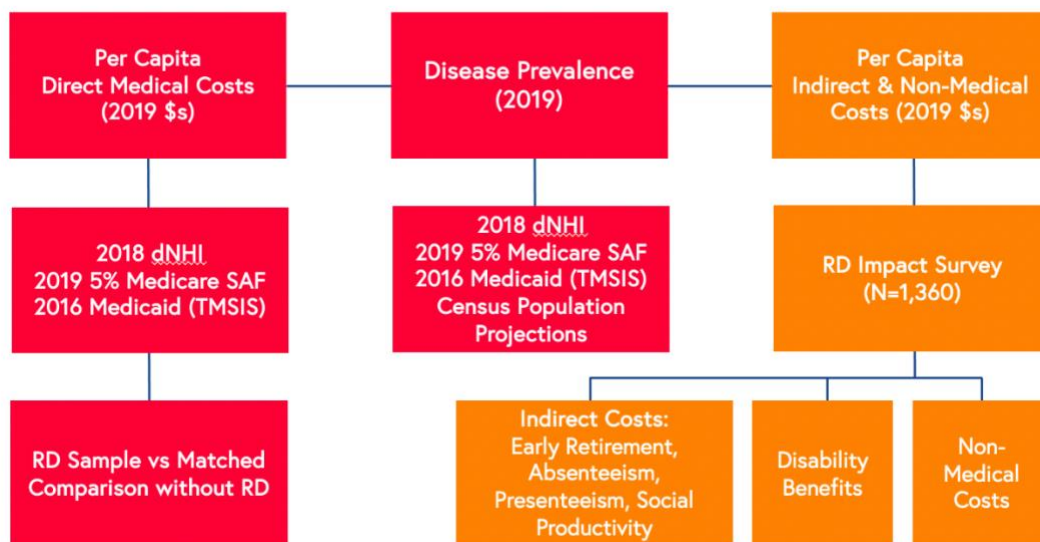
To estimate the economic burden of RD in 2019, we took a prevalence-based approach, by which we combined the prevalence of RD with per-capita cost to derive the national economic burden by patient age and specific RD. Due to a relatively small sample size, we were not able to further break down the burden by patient gender or race/ethnicity.

To estimate prevalence and the direct medical cost of RDs, we used claims data from three sources: Medicare Standard Analytical File (SAF, Medicare 5% claims data), Transformed Medicaid Statistical Information System (TMSIS), and Optum de-identified Normative Health Information (dNHI, a large, geographically diverse claims database for the privately insured). Separately, we designed and implemented a primary survey – the RD Impact Survey – to estimate other indirect and non-medical cost components, including:

1. Loss in labor market earnings for persons with RD and their unpaid caregivers due to reduced employment;
2. Reduced labor market productivity, including absenteeism and presenteeism, for persons with RD and their family caregivers;
3. Productivity loss from reduced participation in social activities for persons with RD and their family caregivers;
4. Cost for the government to provide supplemental disability income such as Supplemental Security Income (SSI) and Social Security Disability Insurance (SSDI); and
5. Non-medical cost of RD such as the cost of hiring a professional non-medical caretaker to assist with daily living, cost associated with special education, home modification costs and increased transportation costs.

Exhibit 2 below describes the cost calculation steps and data source for each cost component.

Exhibit 2: Flow Chart of Cost Calculation and Data Sources



Abbreviations: dNHI: Optum de-identified Normative Health Information system; Medicare SAF: Medicare Standard Analytical File 5% sample; TMSIS: Transformed Medicaid Statistical Information System.

Given the nature and the large number of rare diseases, there is not a single comprehensive data source sufficient to estimate the prevalence of all RDs. Many national survey data such as the National Health Interview Survey (NHIS) and the Medical Expenditure Panel Survey (MEPS) do not contain questions or diagnosis codes that would enable the identification of individual RDs. Although data sources such as the Europe-based Orphanet⁴ contain prevalence estimates for many RDs, these data may or may not apply to the U.S. population and, furthermore, do not always contain certain details such as the age-specific prevalence.

Our estimates of the RD prevalence and direct medical costs were based on U.S.-specific claims databases, including the Medicare SAF 5% sample claims, Medicaid TMSIS, and the Optum dNHI database for the privately insured population. In each of the data sources, we identified patients with nearly 400 RDs using the International Classification of Disease 10th Edition (ICD-10) codes and categorized them into 16 RD groups for adults and 7 RD groups for children (<18 years), to both increase the sample size and to be consistent with the disease groupings used in the survey study (see below).

The direct medical cost of the RD estimate needs to consider not only the cost of treating the disease itself, but also the impact on overall health and well-being. Therefore, we estimated the direct medical costs of RD by comparing the healthcare expenditure incurred by the samples with RD with that incurred by non-RD comparison samples that are matched on age, gender, race/ethnicity, and insurance (matching is done with a 10:1 ratio). We attributed the differences between the medical costs of each RD group and the comparison group to the specific RD group. Due to the fact that many patients have

multiple RDs, we used the group average across all RDs to compare with the comparison group and to derive the average RD-attributable cost.

We estimated the direct medical costs of RD by types of healthcare service including acute and non-acute inpatient stay; outpatient care; physician office visit; durable medical equipment (DME); other ancillary, outpatient-based drug administration; retail prescription drug use; and caregiver payments (by Medicaid). Medical cost variables included primary payer paid amount, patient out-of-pocket expenses (e.g., copay, co-insurance, deductibles), and any third-party paid amount. All costs estimates were expressed in 2019 dollars. Since the Medicare 5% sample claims data do not include pharmacy claims, we used commercial per-person prescription cost to impute the Medicare per-person prescription cost for each age group and disease group.

We estimated the indirect and non-medical costs of RD in 2019 using the RD Impact Survey. The survey included 39 questions on several key domains, including: 1) health status, disease history, and severity of RD; 2) demographics, socio-economic characteristics, and insurance coverage of the person with RD; 3) informal caregiver profile and caregiver roles and responsibilities; 4) employment status, productivity, and annual earnings of the person with RD and caregivers; 5) non-medical costs, and 6) disability benefits. Most of the questions were close-ended and written at an appropriate literacy level (approximately 8th grade reading level). Given that respondents were members of the RD patient and caregiver community, we minimized the use of skip patterns to reduce survey response burden. Additionally, in instances in which the health of the person with the RD prevented accurate self-reporting, or if the person was a minor, we allowed the family member most familiar with the health of the person with the RD to respond to the survey.

We created a pilot version of the survey to assess the difficulty of answering the key questions and how each question could be improved. We sent this draft version to 25 members of the various RD communities. Based on the feedback received from the 15 complete responses and the patterns of attrition from the incomplete responses, we optimized the survey questions, changed order of questions, and skip logic of questions, and clarified or reduced the difficulty of certain questions. The resulting final survey was approved by the New England IRB and programmed into the Qualtrics online survey platform. The survey did not include any personally identifiable information to ensure respondent confidentiality and privacy.

Despite the intention to use a stratified, random sampling approach, an examination of the possible sources for a sampling frame indicated that obtaining the contact information of the entire U.S. RD population was infeasible. Therefore, we took convenience samples and disseminated the survey to the RD communities via partner networks. More than 200 partner patient advocacy organizations participated in the study by helping disseminate the survey to their members or affiliated patient communities.

The partner organizations distributed the survey following informational rare disease community webinars and email communication of the upcoming survey, including its importance to the RD

community and logistics of responding to the survey. The survey was open for 4 weeks. Two rounds of follow-up reminders were sent to non-respondents before the established closing date.

A total of 3,484 households responded to the survey. Among them, 1,409 (40.4%) completed the survey. Ten respondents did not have, or know anyone with, a RD and were excluded from analysis. Further, 39 responses were dropped because the name of the disease entered was either an invalid entry or it was not a RD, resulting in a final analysis sample of 1,360. **Exhibit A-1 (Appendix A)** provides the breakdown of responses by self-description and shows that 57% of respondents were people with a RD; 41% of responses were from a family caregiver. About 28% of respondents with a RD were children (<18 years); the rest were adults, with those above age 65 representing 14% of responses. People with RDs were predominantly white (87%), followed by multi-racial individuals (4%). About 2% (N=33) of respondents preferred not to reveal their race/ethnicity. Additional breakdowns by disease duration and by number of healthcare events prior to the RD diagnosis are shown in **Exhibit A-2** and **Exhibit A-3**, respectively.

The survey included a question about the specific RD the respondent had and provided a selection of 156 diseases to choose from. We also included an open-ended option “Other” that allowed respondents to write in the name of their specific diseases. About 40% of respondents opted for a write-in response; the total number of RDs mentioned was 581. After cleaning the disease list (e.g., removing misspellings and alternative names of the diseases), there were 426 unique diseases mentioned. Next, we removed diseases that were not deemed as rare (e.g., cancer), represented a protein, or were just not valid answers (e.g., disease1). The remaining list contained 379 RDs. **Exhibit B-1 in Appendix B** contains mapping of the 379 RDs into 16 larger RD groups to improve sample size. For children, we had to further aggregate individual RDs into 7 RD groups as the sample size was too small to report estimates individually for all 16 RD groups.

Mapping of diseases was done in several steps. First, we went through all the diseases and identified the codes assigned to each disease. We then began working with the team at NCATS, who then helped us further map the ICD-10 codes and add decision tree logic to the most granular (i.e., “leaf nodes”). Additionally, we ran the data against the Orphanet codes to see whether there was agreement – and whether we could identify any codes in Orphanet that were unidentifiable using the ICD. To ensure calculation of direct medical costs and the indirect and non-medical cost burden for the same age-RD strata, we calculated direct costs for the same disease groups as were identified for the indirect cost analysis.

Study Findings

An estimated 15.5 million individuals in the U.S. have any of the 379 RDs included in this study in 2019.

Exhibit 3 shows the estimated RD prevalence:

- RD is much more prevalent in the ≥ 65 population than in the younger population (prevalence of 11.3% versus 4.6% for working-age adults and 1.8% among children).
- While prevalence is lower among the commercially and Medicaid covered populations because of their younger age, these two groups combined represent 56% of people with RD.

Exhibit 3. Rare Disease Prevalence for 379 RDs Included in the Study by Age and Insurance Coverage (in 2019)

	No. of Persons Estimated to Have RD	Population	Prevalence
Age			
<18	1,322,886	71,580,109	1.8%
18-64	8,371,639	182,528,781	4.6%
≥ 65	5,850,660	51,822,242	11.3%
Insurance			
Commercial	7,124,610	188,738,510	3.8%
Medicaid	1,582,062	57,833,466	2.7%
Medicare	6,838,513	59,359,156	11.5%
Total	15,545,185	305,931,132	5.1%

Source: Lewin analyses of 2018 dNHI claims, 2019 Medicare claims, and 2016 Medicaid claims, and Census population projection for 2019.

The overall economic burden of RD is \$966 billion, of which 43% are direct medical costs (\$418 billion) and 57% are indirect costs and non-medical costs (\$548 billion, of which \$437 billion are indirect costs associated with productivity losses and \$111 billion are non-medical costs).

The total excess medical cost associated with the 379 RDs is an estimated \$418 billion in 2019, with a per-person excess cost of \$26,887, meaning that an average person with RD has an annual medical cost that is \$26,887 more than a comparison person without RD. **Exhibit 4** shows the estimated direct medical cost of RD.

- The working-age population with commercial health coverage bears the majority of the medical cost of RD (51%). The Medicare population with RD accounts for about 39% of total excess costs, and the Medicaid population with RD accounts for the remaining 10% of the total excess costs.
- On average, the per-person excess direct medical cost of RD is \$26,887 more than that for comparison individuals without RD. Per-person direct medical cost of RD decreases with age, with children on average having an annual excess cost of \$32,037 when they have RD; \$29,647 for working-age adults with RD, and \$21,772 for RD patients age 65 and older. Across different insurance coverages, the highest per-person excess costs are for the privately insured (\$29,910), followed by persons with RD who are on Medicaid (\$27,573); the lowest per-person excess costs are for the Medicare beneficiary population with RD (\$23,579).
- Hospital inpatient care and outpatient care are the two largest cost categories, representing 34% and 15% of the total direct cost, respectively. Durable medical equipment (DME) and caregiver costs represent the two smallest categories. Caregiver costs were only covered by Medicaid; however, we estimated them as an average value for the entire RD population, to be consistent with other cost categories.

Exhibit 4. Direct Medical Cost of Rare Diseases by Age, Insurance Coverage, and Type of Service (in 2019)

	Total Excess Medical Cost due to RD		Per Capita (\$)
	(in \$ Millions)	Percentage of the Total	
Age			
<18	\$42,381	10.2%	\$32,037
18-64	\$248,198	59.8%	\$29,647
≥65	\$127,380	30.7%	\$21,772
Insurance			
Medicaid	\$43,621	10.5%	\$27,573
Commercial	\$213,094	51.4%	\$29,910
Medicare	\$161,243	38.9%	\$23,579
Type of service			
Inpatient	\$143,000	34.2%	\$9,199
Outpatient	\$62,032	14.8%	\$3,990
Other ancillary	\$48,974	11.7%	\$3,150
Prescription medication	\$47,963	11.5%	\$3,085
Outpatient prescription administration	\$47,567	11.4%	\$3,060
Physician	\$31,372	7.5%	\$2,018
Non-acute inpatient	\$30,759	7.4%	\$1,979
Durable medical equipment (DME)	\$4,401	1.1%	\$283
Caregiver	\$1,890	0.5%	\$122
Overall	\$417,959	100%	\$26,887

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; direct medical cost estimates were obtained using 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims. Other ancillary services for example include telehealth, ambulance transportation via land, air or water, mobile unit services, etc.

Exhibit 5 shows the average annual direct medical cost by age and RD group. Per-person excess costs are higher for children than for adults: \$32,037 versus \$26,408. The highest per-person excess medical

cost is for “Lysosomal storage diseases” regardless of the age group: \$132,757 for children and \$54,996 for adults. The second most expensive rare disease group among children based on per-person excess costs is “Other endocrine or metabolic disorders” (\$72,285); whereas among adults it is “Diseases of the blood and blood-forming organs” (\$52,201).

Exhibit 5. Average Direct Medical Costs by Age Group and Group of Rare Diseases (in 2019)

Rare Disease Group	Mean Excess Cost due to RD (\$)	
	Age <18	Age 18+
Chromosomal abnormalities, not elsewhere classified	\$40,877	\$27,198
Congenital malformations and deformations of the musculoskeletal system	-	\$21,570
Congenital malformations, deformations and chromosomal abnormalities	\$38,483	\$29,898
Diseases of the blood and blood-forming organs	-	\$52,201
Diseases of the circulatory system	-	\$42,871
Diseases of the digestive system	-	\$36,017
Diseases of the eye and adnexa	-	\$12,612
Diseases of the musculoskeletal system and connective tissue	\$21,041	\$21,389
Diseases of the nervous system	\$41,880	\$29,220
Diseases of the respiratory system	-	\$48,422
Diseases of the skin and subcutaneous tissue	-	\$20,870
Immunodeficiency	-	\$24,965
Lysosomal storage diseases	\$132,757	\$54,996
Neoplasms	-	\$48,060
Other	-	\$19,936
Other endocrine or metabolic disorders	\$72,285	\$39,432
Combined Diseases*	\$46,750	Not Applicable
Any Rare Disease	\$32,037	\$26,408

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; direct medical cost estimates obtained using 2018

dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims.* Due to small sample sizes among children, rare disease groups which are not individually displayed are combined in one group – Combined Diseases.

Exhibit C-1 (Appendix C) provides an additional breakdown of direct medical costs by insurance and RD group, in addition to showing the per-person total cost of the entire RD group, as compared to the matched comparison group without RD.

The estimated total indirect and non-medical cost of RD is \$548 billion in 2019, with \$343 billion to persons with RD and another \$205 billion to unpaid caregivers. **Exhibit 6** shows the estimated indirect and non-medical cost of RD separately for children (age <18 years) and for adults (age ≥18 years):

- The estimated total indirect and non-medical cost of RD is \$64 billion for children (age <18) and \$484 billion for adults (age ≥18).
- Total indirect cost and non-medical costs associated with RD are \$548 billion. The cost of absenteeism to both persons with RD and their caregivers is nearly \$149 billion (27% of the \$548 billion), followed by presenteeism cost (\$138 billion, 25%), and losses due to forced retirement (\$136 billion, 25%). For adults, the costs of absenteeism for the caregivers are about half of those for the person with RD (\$89 billion versus \$45 billion). However, when the costs to caregivers for children with RD are taken into account, the costs of absenteeism for the caregivers surpass those for the person with RD (\$89 billion versus \$60 billion); losses associated with presenteeism are slightly smaller for caregivers compared to the person with RD (\$63 billion across all caregivers for children and adults with RD versus \$75 billion for RD).
- The total non-medical cost is \$111 billion. Healthcare services not covered by insurance (e.g., experimental, alternative, or non-traditional treatments; over-the-counter drug therapies; dental surgeries; medical food) represent the largest share (34%), followed by costs of necessary specialized equipment for home or motor vehicle (21%), and transportation cost (18%).

Exhibit 6. Total Indirect and Non-Medical Costs by Cost Component (in \$ Millions)
(in 2019)

	Age <18			Age ≥18		
	RD	PC	SC	RD	PC	SC
Indirect Productivity Loss						
Forced retirement	NA	\$850	\$1,083	\$88,877	\$38,462	\$6,823
Absenteeism	NA	\$10,265	\$14,497	\$59,853	\$50,176	\$14,024
Presenteeism	NA	\$10,176	\$7,232	\$74,741	\$40,453	\$5,367
Social productivity loss in volunteer work	\$494	\$550	\$424	\$8,226	\$4,035	\$89
Non-Medical Costs						
Healthcare services not covered by insurance	\$2,172	NA	NA	\$35,750	NA	NA
Paid daily care	\$1,482	NA	NA	\$7,477	NA	NA
Other costs: necessary home modification	\$1,682	NA	NA	\$8,709	NA	NA
Other costs: necessary special equipment at home or on a personal or family vehicle	\$1,865	NA	NA	\$21,677	NA	NA
Other costs: transportation costs	\$1,305	NA	NA	\$19,127	NA	NA
Other costs: home schooling	\$454	NA	NA	NA	NA	NA
Other costs: missed schooling	\$2,298	NA	NA	NA	NA	NA
Other: special education	\$7,199	NA	NA	NA	NA	NA
Overall in \$ Millions	\$18,951	\$21,840	\$23,237	\$324,437	\$133,125	\$26,303
Grand Total in \$ Millions (to society)	\$64,028			\$483,865		

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; indirect and non-medical costs estimated using Lewin's analyses of the RD Impact Survey data. RD: Person with a rare disease; PC: Primary caregiver; SC: Secondary caregiver.

- **Exhibit 7** shows per capita indirect and non-medical costs separately for children and for adults. The average indirect and non-medical cost per child with RD (i.e., age <18) is \$14,326 for person with RD only and \$48,400 for person with RD combined with caregiver economic burden. Per

capita indirect and non-medical costs among adults are \$22,812 per adult person with RD and \$34,022 when person with RD is combined with caregiver burden.

Exhibit 7. Per Capita Indirect and Non-Medical Costs by Cost Component (in 2019)

	Age <18			Age ≥18		
	Rare Disease	PC	SC	Rare Disease	PC	SC
Indirect Productivity Loss						
Loss due to forced retirement	NA	\$642	\$818	\$6,249	\$2,704	\$480
Absenteeism	NA	\$7,759	\$10,959	\$4,208	\$3,528	\$986
Presenteeism	NA	\$7,692	\$5,467	\$5,255	\$2,844	\$377
Social productivity loss in volunteer work	\$373	\$416	\$321	\$578	\$284	\$6
Non-Medical Costs						
Healthcare services not covered by insurance	\$1,642	NA	NA	\$2,514	NA	NA
Paid daily care	\$1,121	NA	NA	\$526	NA	NA
Other costs: necessary home modification	\$1,271	NA	NA	\$612	NA	NA
Other costs: necessary special equipment at home or on a personal or family vehicle	\$1,409	NA	NA	\$1,524	NA	NA
Other costs: transportation costs	\$986	NA	NA	\$1,345	NA	NA
Other costs: home schooling	\$344	NA	NA	NA	NA	NA
Other costs: missed schooling	\$1,737	NA	NA	NA	NA	NA
Other: special education	\$5,442	NA	NA	NA	NA	NA
Overall in Millions	\$14,326	\$16,509	\$17,565	\$22,812	\$9,360	\$1,849
Grand Total in Millions	\$48,400			\$34,022		

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; indirect and non-medical costs estimated using Lewin's analyses of the RD Impact Survey data. RD: Person with a rare disease; PC: Primary caregiver; SC: Secondary caregiver.

- Financial assistance from disability income, although considered a transfer cost, is substantial at approximately \$115 billion, and \$134 billion if financial assistance from charitable organizations is included (**Exhibit 8**).

Exhibit 8. Transfer Payments Associated with Rare Disease to the Persons with RD (in 2019)

	Age <18		Age ≥18	
	Financial Assistance (in \$ Millions)	Per Capita (\$)	Financial Assistance (in \$ Millions)	Per Capita (\$)
Financial assistance from charitable programs	\$319	\$241	\$19,381	\$1,363
Supplemental security income (SSI)	\$452	\$342	\$16,770	\$1,179
Social security disability insurance (SSDI)	NA	NA	\$46,896	\$3,297
Other disability benefits	\$924	\$698	\$49,532	\$3,483
Total	\$1,694	\$1,281	\$132, 578	\$9,322

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; financial assistance is estimated using the Lewin’s analyses of the RD Impact Survey data.

Discussion

This new study provides a comprehensive evaluation of the current economic impact of RD in the U.S. Using diverse and best available primary and secondary data sources, we estimated the overall economic burden of RD at more than \$966 billion in 2019, including \$418 billion in direct medical cost and \$548 billion in indirect and non-medical costs absorbed directly by families living with rare diseases. This estimate is based on a subset of 379 RDs rather than the nearly 7,000 rare diseases that are identified worldwide. Therefore, our economic impact estimate represents a lower bound estimate and is not generalizable to all rare diseases.

The previous burden estimates are generally limited to a specific rare disease or a small group of rare diseases. A systematic literature review of cost of illness studies conducted for a set 10 selected rare diseases revealed that cost evidence on rare diseases is very scarce, especially in the U.S. With the exception of cystic fibrosis and hemophilia, which are relatively well studied, information on cost of illness information for other conditions (e.g., Duchenne muscular dystrophy, fragile X syndrome, juvenile idiopathic arthritis, mucopolysaccharidosis, scleroderma, Prader-Willi syndrome, histiocytosis, epidermolysis bullosa) was very limited. Angelis et al (2015) also found total annual costs (including indirect costs) for only five rare diseases.⁵

In addition to the limited number of comprehensive studies that target multiple rare diseases, studies that target a specific disease produce cost estimates with very wide ranges. For example, a review of the costs of systemic lupus erythematosus showed that mean annual direct per patient costs estimates range from \$2,214 to \$16,875 and mean annual indirect cost estimates range from \$2,239 to \$35,540 (in 2010 values).⁶

Kawalec and Malinowski (2015), in their systematic review of the indirect costs related to psoriatic arthritis, showed even a wider variation in indirect cost estimates depending on the chosen calculation approach. For example, per person indirect cost ranges from \$1,694 to \$12,318 based on the friction cost approach and from \$1,751 to \$50,270 using the human capital approach.⁷ These cost estimates are in 2013 dollars. In our study, psoriatic arthritis is included in the “Diseases of the skin and subcutaneous tissue” group, with estimated indirect costs of \$22,066 per adult with such conditions.

Our findings show that RD significantly affects individuals living with rare diseases as well as their unpaid caregivers, employers, and payers. Study findings demonstrate that diagnosis, care navigation, and treatment of rare disease include significant costs to individual households and the health system. As most individuals living with rare diseases are between the ages of 18 and 65, commercial payers bear the largest share of medical cost. Significant productivity losses associated with absenteeism and presenteeism are experienced by employers. These productivity losses include \$135 billion from adults with RD whose disease progression and diagnoses require time away from the workplace and \$152 billion from their caregivers. Additionally, government supplemental income programs, which are based

on disability eligibility, provide disability support (\$115 billion) to persons with RD whose ability to participate in labor market or volunteer activities is significantly affected by RD.

As shown in **Exhibit 9**, the RD direct medical cost and indirect and non-medical costs estimated in this study are higher than the burden estimates for many of the most costly chronic diseases described by the Centers for Disease Prevention and Control (CDC). For example, for more than 24.7 million Americans who have diabetes, the total estimated cost of diagnosed diabetes in 2017 was \$327 billion (combining direct medical costs and lost productivity). This cost represents about one-third of the rare disease burden estimated for about 15 million individuals with any of the 379 rare diseases included in this study (out of a total of 25-30 million people estimated to have a rare disease).⁸ Notably, these studies are not easily comparable to ours, as they are based on different data, or include various burden components. Therefore, any comparison between the findings of this new study and any previous literature should consider these differences.

Exhibit 9. Burden Estimates of Chronic Diseases

Condition	Source	Burden estimates
Diabetes	American Diabetes Association (2017) ⁹	\$327 billion (2017)
Cancer	National Cancer Institute (2011) ¹⁰	Projected \$174 billion in 2020
Heart disease and stroke	Benjamin et al (2018) ¹¹	\$214 billion (2018)
Obesity	Finkelstein et al (2009) ¹²	\$147 billion (2008)
Arthritis	CDC (2013) ¹³	\$304 billion (2013)
Alzheimer's disease	Hurd et al (2013) ¹⁴	Between \$159 billion and \$215 billion (2010)

Source: Centers for Disease Prevention and Control (CDC). Health and Economic Costs of Chronic Diseases. <https://www.cdc.gov/chronicdisease/about/costs/index.htm#ref4>

There are several limitations to our study. A key limitation is that RD prevalence estimates and estimates of the direct medical costs relied on one diagnosis code, which may include cases that are false positives (i.e., persons who have a singular diagnosis code but were later ruled out as having a rare disease). We choose this approach to be able to capture as many rare diseases as possible, and this analytical decision may have led to an overestimate of the prevalence, and/or an underestimate of the direct medical costs (as patients with one diagnosis code may not be as severe as those with multiple diagnosis codes of rare disease in a given year).

Additionally, despite our best efforts and with multiple rounds of expert reviews, not every RD could be matched to a definitive ICD-10 code. Therefore, for some rare diseases, we matched to the closest ICD-10 code, which might have captured a broader group of people than intended. Conversely, in some

instances the absence of a specific ICD-10 code for a specific rare disease required that it be mapped to a disease category that was not rare, thus eliminating it from inclusion in the direct cost analysis. If future studies on the economic burden of rare disease are to build on this study, attention should be paid to the availability of ICD codes for rare diseases for a more complete understanding.

Another limitation of the study is that the indirect and non-medical costs were estimated based on a primary survey with the self-reported data. Since it is a convenience sample rather than a random sample, there may be selection biases in the event that people who are more severely affected by a rare disease might be more likely to respond to the survey than those whose rare disease is less severe.

It should be noted that the direct medical and indirect and non-medical costs reflected a one-year time period (2019). Survey respondents were asked to provide financial details about costs incurred during the calendar year 2019, which may not reflect costs incurred typically (i.e., due to a home renovation for accessibility or a year in medical care necessitated time lost from work or significant medical expenses and travel). Additionally, rare disease costs associated with living with a rare disease are accumulated over decades and exponentially increase the financial impact to the individual and family living with the rare disease.

Finally, due to small sample sizes, we could not break down burden estimates by desired population strata, such as by sex or by race/ethnicity. For indirect and non-medical cost estimates by disease group, due to extremely small sample sizes, oftentimes we had to use a higher group aggregation to estimate cost components for disease groups with ultra-small sample size.

Despite these limitations, this study is the largest and most comprehensive effort so far in the U.S. to measure the societal impact of many rare diseases at once (i.e., the majority of previous studies focused on the burden of a specific rare disease), encompassing various cost components (such as cost of social productivity loss and cost of special education), and including estimates of indirect productivity loss for family caregivers whose lives are significantly affected by rare disease.

Conclusion

Together, the 379 rare diseases included in this study represent an economic burden that far surpasses some of the costliest chronic diseases studied in the U.S., both due to a high prevalence (i.e., more than 15 million individuals with these rare diseases) and a higher per-person cost. The findings of this study highlight the scale of the rare disease burden and call for immediate attention from the scientific communities, policy leaders, and other key stakeholders such as health care providers and employers, to think innovatively and collectively, to identify new ways to help improve the care and treatment of rare disease. These findings demonstrate that the rare disease community has a significant unmet need with tremendous public health impact, one that requires urgent support to advance research and development of resources for prevention, management, and ultimately, cures of these often devastating diseases. All these steps may lead to significant societal benefit.

Appendix A

Exhibit A-1. Analysis Sample

Which of the following best describes you (the person who is responding to the survey)?	Frequency	Percent	Cumulative
A person living with a rare disease	802	56.9	56.9
A family caregiver for someone who has a rare disease	572	40.6	97.5
A paid caregiver for someone who has a rare disease	1	0.1	97.6
A family member of someone who has a rare disease, but not a direct caregiver (e.g., family member who is not responsible for organizing/providing day-to-day care)	21	1.5	99.1
A close friend to someone who has a rare disease, but not a caregiver	3	0.2	99.3
Sub-total	1,399	99.3	99.3
Do not have a rare disease and do not know anyone with a rare disease	10	0.7	100.0
Total number of respondents	1,409	100	100

Source: Primary data collected through the RD Impact Survey.

Exhibit A-2. Disease Duration for Persons with RD

	Duration Since the 1st Symptom		Duration Since Diagnosis	
	Frequency	Percent	Frequency	Percent
Less than 5 years	265	19.5	513	37.7
5-9 years	273	20.1	322	23.7
10-14 years	250	18.4	214	15.7
15 -19 years	146	10.7	106	7.8
20 years or more	426	31.3	205	15.1
Total	1,360	100	1,360	100
Mean		16.5		10.2

Source: Primary data collected through the RD Impact Survey.

Exhibit A-3. The Number of Rare Disease-Related Healthcare Events the Affected Person had Before Receiving a Formal Diagnosis of the Rare Disease

	Mean	Std
Number of primary care physicians (e.g., family doctors, internists, pediatricians) seen for rare disease diagnosis	4.2	9.0
Number of specialty physicians (e.g., genetic counselors, geneticists) seen for rare disease diagnosis	4.8	7.6
Number of emergency room visits related to rare disease before diagnosis	3.7	11.0
Number of hospital admissions related to rare disease before diagnosis	1.7	6.4
Number of out-of-state trips related to rare disease diagnosis	2.4	8.6
Total (sum of the above events)	16.9	28.0

Source: Primary data collected through the RD Impact Survey. Sample size 1,360.

Appendix B

Exhibit B-1. Mapping of Rare Diseases Into 16 Rare Disease Groupings

Rare Disease	Rare Disease Grouping
<p>15Q11.2 Microdeletion 15Q24 Microdeletion Syndrome 22Q11 Chromosome Duplication Syndrome 22Q13, Phelan-Mcdermid Syndrome 2Q37 Deletion Syndrome 7Q11.23 Duplication Syndrome Angelman Syndrome Chromosome 19 Microdeletion Syndrome Chromosome 21Q Deletion Ddx3X Syndrome Fragile X Syndrome Jacobsen Syndrome Mef2C Deletion Partial Trisomy 16Q Phelan-Mcdermid Syndrome Satb2-Associated Syndrome Syngap1 Syndrome Tetrasomy X Turner Syndrome Williams Syndrome</p>	<p>Chromosomal abnormalities, not elsewhere classified</p>
<p>Ehlers Danlos Syndrome Hypermobile Ehlers-Danlos Syndrome Hypochondroplasia Klippel Feil Syndrome Mccune-Albright Syndrome Osteogenesis Imperfecta Polyostotic Fibrous Dysplasia Short Rib Polydactyly Syndrome Type 2</p>	<p>Congenital malformations and deformations of the musculoskeletal system</p>
<p>Aarschot-Scott Syndrome Absence Corpus Callosum Adnp Syndrome Agenesis Of The Corpus Callosum Alagille Syndrome Alport Syndrome</p>	<p>Congenital malformations, deformations and chromosomal abnormalities</p>

Rare Disease	Rare Disease Grouping
<p>Aplasia Cutis Congenita Arnold Chiari Syndrome Arteriovenous Malformation Autosomal Recessive Alport Syndrome Blue Rubber Bleb Nevus Syndrome Cardiofaciocutaneous Syndrome Ccm3 Gene Mutation Chiari Malformation Choanal Atresia Cloves Syndrome Constitutional Mismatch Repair Deficiency (Cmmrd) Dandy Walker Syndrome Dlg4 Epidermolysis Bullosa Floating Harbor Syndrome Foxg1 Syndrome Hereditary Lymphedema Heterotaxy Syndrome Hypohidrotic Ectodermal Dysplasia Hypoplasia Of The Corpus Callosum Hypoplastic Left Heart Syndrome Ichthyosis Isolated Congenital Asplenia Li Fraumeni Syndrome Loeys-Dietz Syndrome Marfan Syndrome Mastocytosis Mayer-Rokitansky-Kuster-Hauser Syndrome Neurofibromatosis Type 1 Noonan Syndrome Pachygyria Peters Anomaly Pfeiffer Syndrome Pppd Prader-Willi Syndrome Primary Ciliary Dyskinesia Primary Congenital Lymphedema Pseudobulbar Affect Rieger Syndrome Shones Complex Slc1A4 Deficiency Snyder-Robinson Syndrome Sticklers Syndrome</p>	

Rare Disease	Rare Disease Grouping
<p>Sturge-Weber Syndrome Tethered Cord Syndrome Tuberous Sclerosis Complex Unilateral Microphthalmia Vacterl Syndrome Von Hippel Lindau Disease X-Linked Hypohidrotic Ectodermal Dysplasias</p>	
<p>Cnot3 Mutation Congenital Dyserythropoietic Anemia Erdheim Chester Disease Hemophilia Idiopathic Thrombocytopenia Purpura Severe Chronic Neutropenia - Autoimmune Sickle Cell Disease Thalassemia Unspecified Severe Chronic Neutropenia Warm Hemolytic Anemia</p>	<p>Diseases of the blood and blood-forming organs</p>
<p>Arterial Fibromuscular Dysplasia Cadasil Catecholaminergic Polymorphic Ventricular Tachycardia Fibromuscular Dysplasia Generalized Lymphatic Anomaly Idiopathic Pulmonary Hypertension Long Qt Syndrome Median Arcuate Ligament Syndrome Moyamoya Non-Genetic Ascending/Descending Aortic Dissection Postural Orthostatic Tachycardia Syndrome Pots Primary Lymphedema Prolong Qt Pulmonary Hypertension</p>	<p>Diseases of the circulatory system</p>
<p>Achalasia Amalogenesis Imperfecta Autoimmune Pancreatitis Chronic Intestinal Pseudo-Obstruction Eosinophilic Esophagitis Lymphocytic Colitis Mesenteric Panniculitis</p>	<p>Diseases of the digestive system</p>

Rare Disease	Rare Disease Grouping
<p>Microvillus Inclusion Disease Primary Biliary Cholangitis Psuedo Obstruction Sclerosing Mesenteritis Short Bowel Syndrome Short Gut</p>	
<p>Acoustic Neuroma Bilateral Vestibular Disorder Bilateral Vestibular Hypofunction Bilateral Vestibular Loss With Oscillopsia Bosch Boonstra Optric Atrophy Syndrome 5Q 15-21 Microdeletions Central Vestibular Disorder Chronic Vestibular Neuritis Duane Syndrome Hyperacusis With Pain Kearns-Sayres Syndrome Leber Congenital Amaurosis Mal De Debarquement Meniere's Disease Osteopetrosis Otosclerosis Semi-Circular Canal Disorder Superior Semicircular Canal Disorder Vestibular Disorder Visual Vestibular Mismatch</p>	<p>Diseases of the eye and adnexa</p>
<p>Anca Vasculitis Ankylosing Spondylitis Autoimmune Vasculitis Behcet Disease Behcet's Disease Chronic Recurrent Multifocal Osteomyelitis Dermatomyositis Diffuse Systemic Scleroderma Diffused Systematic Sclerosis Fibrodysplasia Ossificans Progressiva Ghorom-Stout Disease Gorham-Stout Disease Granulomatosis With Polyangiitis Hypocomplementemic Urticarial Vasculitis Hypodermitis Sclerodermiformis Or Lipodermata Sclerosis</p>	<p>Diseases of the musculoskeletal system and connective tissue</p>

Rare Disease	Rare Disease Grouping
<p>Juvenile Dermatomyositis Limited Cutaneous Systematic Sclerosis Limited Scleroderma Limited Systemic Sclerosis Micro Angiitis Vasculitis P-Anca Microscopic Polyangiitis Myositis Polymyositis Progressive Familial Intrahepatic Cholestasis Progressive Systemic Sclerosis Sapho Scleroderma Shrinking Lung Disease/Syndrome Sjogrens Syndrome Systemic Diffuse Scleroderma Systemic Juvenile Idiopathic Arthritis Systemic Scleroderma Systemic Sclerosis Takayasu Arteritis Tarlov Cyst Disease Thrombotic Thrombocytopenia Purpura Urticarial Vasculitis Vasculitis</p>	
<p>Aicardi Gouteres Syndrome Alper's Syndrome Alternating Hemiplegia Of Childhood Amyotrophic Lateral Sclerosis Arachnoiditis Atp6V1A Gene Mutation Autoimmune Autonomic Ganglionopathy Autoimmune Encephalitis Becker Muscular Dystrophy Cacna1S Cataplexy Cdk15 Deficiency Disorder Centronuclear Myopathy Charcot-Marie-Tooth Chronic Immune Demyelinating Polyneuropathy Collagen 6 Congenital Muscular Dystrophy Communicating Hydrocephalus Complex Regional Pain Syndrome Congenital Titinopathy</p>	<p>Diseases of the nervous system</p>

Rare Disease	Rare Disease Grouping
<p>Corticobasal Syndrome Also Referred To Corticobasal Degeneration Dravet Syndrome Duchenne Muscular Dystrophy Dysautonomia Dystonia 27 Facioscapulohumeral Muscular Dystrophy Familial Dysautonomia Friedreich Ataxia Giant Axonal Neuropathy Gnao1 Gene Mutation Guillain-Barre Syndrome Hereditary Inclusion Body Myopathy Hereditary Spastic Paraplegia Huntington Disease Hypokalemic Periodic Paralysis Idiopathic Hypersomnia Inclusion Body Myositis Kennedy's Disease Kleine Levin Syndrome Lama li Muscular Dystrophy (Merosin Deficient) Lama2 Congenital Muscular Dystrophy Landau-Kleffner Syndrome Lennox-Gastaut Syndrome Limb Girdle Muscular Dystrophy Multifocal Motor Neuropathy Multiple System Atrophy Muscular Dystrophy Myasthenia Gravis Myotonic Muscular Dystrophy Myotubular Myopathy Narcolepsy Nemaline Myopathy Neurodegeneration With Brain Iron Accumulation Neuromyelitis Optica Non 24 Ohtahara Syndrome Olivopontocerebellar Atrophy Primary Hypersomnia Primary Lateral Sclerosis Ryanodine Cardiac Dystrophy Schwartz Jampal Syndrome Scn8A Sepn1 Related Myopathy (Subtype Of Congenital Muscular Dystrophy)</p>	

Rare Disease	Rare Disease Grouping
<p>Small Fiber Polyneuropathy Spinal Cerebellar Atrophy Spinal Muscular Atrophy Spinocerebellar Ataxia Stxbp1 Encephalopathy With Epilepsy Syringomyelia Titinopathy Transverse Myelitis Trigeminal Neuralgia Trpv4 Tubulinopathy Tuba1A Ullrich Congenital Muscular Dystrophy Vcp Disease West Syndrome X-Linked Myotubular Myopathy</p>	
<p>Copa Syndrome Idiopathic Pulmonary Fibrosis Non-Specific Interstitial Pneumonia</p>	<p>Diseases of the respiratory system</p>
<p>Bullous Pemphigoid Dermatitis Herpetiformis Lichen Planopilaris Mucous Membrane Pemphigoid Ocular Cicatricial Pemphigoid Paraneoplastic Pemphigus Pemphigus Vulgaris Pityriasis Rubra Pilaris Prurigo Nodularis Psoriatic Arthritis</p>	<p>Diseases of the skin and subcutaneous tissue</p>
<p>22Q11.2 Deletion Syndrome Burning Mouth Syndrome Cardiac Sarcoidosis Chronic Sarcoidosis Common Variable Immune Deficiency Hereditary Angioedema Mast Cell Activation Syndrome Pulmonary Sarcoidosis Ryr1 Gene Mutation Sarcoidosis Secondary Reynauds</p>	<p>Immunodeficiency</p>

Rare Disease	Rare Disease Grouping
<p>Severe Combined Immunodeficiency Disorder Specific Antibody Deficiency</p>	
<p>Alexander Disease Adult Onset Batten Disease Canavan Disease Ddost-Cdg Fabry Gaucher's Gm1 Gangliosidosis Hunter Syndrome Hurler Syndrome Late Onset Tay-Sachs Lysosomal Storage Diseases Mucopolysaccharidosis Type 1 Mucopolysaccharidosis Type 2 Mucopolysaccharidosis Type 4A Multiple Sulfatase Deficiency Niemann-Pick Type C Pompe Pseudo Hurler Polydystrophy Sanfilippo Syndrome Undiagnosed Leukodystrophy</p>	<p>Lysosomal storage diseases</p>
<p>Chronic Myelogenous Leukemia With P230 Breakpoint Cns Lymphoma Cutaneous T-Cell Lymphoma Desmoid Tumor Desmoid Type Aggressive Fibromatosis Kaposiform Lymphangiomatosis Leiomyosarcoma Lymphangiomatosis Mastocytosis Mesenchymal Chondrosarcoma Metastatic Leiomyosarcoma Multiple Myeloma Neuroendocrine Tumors Paraganglioma Pheochromocytoma Polycythemia Vera Recurrent Respiratory Papillomatosis</p>	<p>Neoplasms</p>

Rare Disease	Rare Disease Grouping
<p>Sacral Chordoma Synovial Sarcoma Thymoma Waldenstroms Macroglobulinemia</p>	
<p>Cyclic Vomiting Syndrome Diaphragmatic Endometriosis Endosalpingiosis</p> <p>Focal Segmental Glomerulosclerosis (FSGS) Minimal Change Disease Mycobacterium Avium Complex Nontuberculous Mycobacteria Nontuberculous Mycobacterial Infection Ramsey Hunt Syndrome</p>	Other
<p>Acromegaly Addisons Disease Adiposis Dolorosa Adrenal Insufficiency Adrenoleukodystrophy Adult Polyglucosan Body Disease Alpha-1 Antitrypsin Deficiency Amyloidosis Ataxia Barth Syndrome Congenital Adrenal Hyperplasia Creatine Transporter Deficiency Cushing's Disease Cystic Fibrosis Cystinuria Familial Chylomicronemia Syndrome Familial Hypercholesterolemia Familial Partial Lipodystrophy Fcs Familial Chylomicronemia Syndrome Glycogen Storage Disease Hermansky Pudlak Syndrome Homozygous Familial Hypercholesterolemia Hyperinsulinism Hyperammonemia Syndrome Hypoparathyroidism Hypophosphatemic Ricketts Lchad Deficiency Lipodystrophy</p>	Other endocrine or metabolic disorders

Rare Disease	Rare Disease Grouping
<p>Lipomatosis Dolorosa Type 2 Lipoprotein Lipase Deficiency Methylmalonic Acidemia Mitochondrial Disease Mitochondrial Metabolism Disorder Neonatal Onset Multisystem Inflammatory Disease Organic Acidemias Peroxisomal Biogenesis Disorder Phenylketonuria Porphyria Primary Adrenal Insufficiency Primary Hyperoxaluria Type 1 Pten Hamartoma Tumor Syndrome Tyrosinemia Urea Cycle Disorder Wilson Disease Wolfram-Like Syndrome X-Linked Hypophosphatemia Zellwegers Spectrum Disorder</p>	

Appendix C

Exhibit C-1. Medical Per Capita Direct Costs for Rare Disease Group vs Comparison Group, by Disease Group and Insurance

Rare Disease Group	dNHI		Medicaid		Medicare	
	Age <18	Age 18-64	Age <18	Age 18-64	Age 18-64	Age 65+
Chromosomal abnormalities, not elsewhere classified	\$50,842	\$31,642	\$35,504	\$45,151	\$17,311	\$40,078
Congenital malformations and deformations of the musculoskeletal system	NA	\$31,074	NA	\$25,751	\$24,116	\$23,383
Congenital malformations, deformations and chromosomal abnormalities	\$47,558	\$38,599	\$33,810	\$44,965	\$30,363	\$26,183
Diseases of the blood and blood-forming organs	NA	\$71,452	NA	\$40,344	\$63,001	\$39,806
Diseases of the circulatory system	NA	\$68,691	NA	\$37,866	\$67,092	\$37,161
Diseases of the digestive system	NA	\$42,737	NA	\$34,120	\$26,295	\$57,985
Diseases of the eye and adnexa	NA	\$18,851	NA	\$27,620	\$25,297	\$15,162
Diseases of the musculoskeletal system and connective tissue	\$24,708	\$28,887	\$18,810	\$21,876	\$38,005	\$22,320
Diseases of the nervous system	\$49,314	\$38,497	\$38,257	\$41,414	\$37,665	\$29,213
Diseases of the respiratory system	NA	\$107,582	NA	\$34,639	\$75,395	\$34,262
Diseases of the skin and subcutaneous tissue	NA	\$31,310	NA	\$23,349	\$36,274	\$16,920
Immunodeficiency	NA	\$33,958	NA	\$25,272	\$38,033	\$23,451

Lysosomal storage diseases	\$206,988	\$71,885	\$80,989	\$67,717	\$62,935	\$43,517
Neoplasms	NA	\$75,542	NA	\$34,925	\$58,545	\$33,567
Other	NA	\$27,908	NA	\$10,793	\$46,038	\$25,292
Other endocrine or metabolic disorders	\$91,549	\$51,669	\$50,046	\$46,323	\$67,522	\$34,357
Combined Diseases*	\$60,701	NA	\$28,734	NA	NA	NA
Any Rare Disease	\$38,731	\$35,583	\$28,417	\$32,433	\$40,493	\$26,008
Comparison Group (Non-Rare Disease)	\$2,636	\$6,413	\$1,877	\$4,292	\$6,213	\$4,236

Source: Lewin analyses of RD prevalence calculated from the 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims combined with the Census population projection for 2019; direct medical cost estimates obtained using 2018 dNHI claims, 2019 Medicare SAF 5% sample claims, and 2016 Medicaid claims. *Due to small sample sizes among children, rare disease groups which are not individually displayed are combined in one group – Combined Diseases.

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