July 2020

Rare Diseases in the United States: Establishing prevalence, the insurance experience, and orphan drug expenditures in Medicare Part D

Tai Pasquini
University of Massachusetts Amherst

Rare Diseases in the United States: Establishing prevalence, the insurance experience, and orphan drug expenditures in Medicare Part D

A Dissertation Presented

by

TAI SPARGO PASQUINI

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirement for the degree of

DOCTOR OF PHILOSOPHY

May 2020

Public Health

Health Policy and Management

Rare Diseases in the United States: Establishing prevalence, the insurance experience, and orphan drug expenditures in Medicare Part D

A Dissertation Presented

by

TAI SPARGO PASQUINI

Approved as to style and content by:

_____

Michael E. Begay, Chair

_____

Sarah Goff, Member

_____

Jennifer Whitehill, Member

_____

Gerald Friedman, Outside Member

_____

Elizabeth R. Bertone-Johnson, Department Chair

Department of Health Promotion and Policy

DEDICATION

To my grandfather, Stanley Niegelsky, and the millions of other individuals that have been impacted by rare diseases.

ACKNOWLEDGEMENTS

I would like to thank my dissertation committee for their guidance and support through this process. Many members of this team stepped in at unconventional points in the process and I am appreciative of their willingness to do so. I am very grateful for the opportunities I was given to explore and fine tune my ideas, especially over a cup of tea or an engaging lunch. I will always value the opportunity to explore new topics and methods as a research assistant for Gerald Friedman.

I would like to thank my friends and colleagues at UMass who have been integral in helping me navigate the exhilarating and terrifying world of graduate school. I am very grateful to the many moments Paula Stamps stepped in to give reassuring advice. Thank you to Serena Houghton and Alex Bogden for their willingness to be a sounding board as I worked through my statistics. I would like to thank my research assistant Joyce Libbin for her energy and willingness to learn new skills.

A special thanks to the rare disease community for inspiring me to take this journey. Especially to my former colleagues at NORD, Mary Dunkle and Marsha Lanes for providing guidance as I looked for the best way to complete this work. I would like to thank Cure SMA and Chloe's Fight Rare Disease Foundation for their assistance in patient recruitment.

To my loving family who has been unwavering in their support. I never would have had the courage to take this leap without the encouragement and unconditional love from my parents Karen and Owen Spargo. Finally, I am especially grateful for my husband Joe Pasquini who was always willing to make dinner, reminded me to go outside and get fresh air, and provided the best pep talks on the hardest days.

ABSTRACT

RARE DISEASES IN THE UNITED STATES: ESTABLISHING PREAVELENCE, THE INSURANCE EXPERINECE, AND ORPHAN DRUG EXPENDITURES IN MEDICARE PART D

MAY 2020

TAI SPARGO PASQUINI, B.A., AMERICAN UNIVERSITY

M.P.A., AMERICAN UNIVERSITY

Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Michael E. Begay

In the United States, there are an estimated 30 million people living with one or more rare diseases. Each rare disease impacts fewer than 200,000 people. Small patient populations create research and medical challenges. Patients and the healthcare system experience high costs. To adequately address patient needs and prepare our healthcare system, it is critical that we conduct research that contextualizes the U.S. rare disease experience.

This dissertation includes three related studies that look at the U.S. rare disease experience. The first paper investigates the availability and data quality of rare disease prevalence estimates and the healthcare infrastructure that could be utilized to establish future estimates. The paper found that prevalence estimates rarely follow best practices in data quality. U.S. healthcare infrastructure is ill-equipped to track rare diseases and produce future prevalence estimates. This could impact our ability to realize and equitably administer healthcare innovations, including precision medicine.

The second paper looked at the caregiver experience navigating health insurance using a grounded theory qualitative approach. The paper found that rare disease caregivers feel it is imperative to learn how to navigate insurance, especially since health setbacks are costly and disruptive. Insurance companies are rarely knowledgeable about the disease and interactions are time intensive. Parents are required to meticulously track benefits to balance long-term medical needs and financial stability.

The third paper investigated orphan drug expenditures in Medicare Part D from 2013 to 2017. The study found that orphan only drugs represent 8.67% and partial orphan drugs represent 6.74% of total aggregate costs. In 2017, the average cost per beneficiary for orphan drugs was $92,753 and $3,920 for common drugs. Almost half of orphan drug costs are attributed to beneficiaries under age 65.

Together, these studies point to the need to invest in our healthcare system and explore programs that can address issues of access for patients. Currently, our system is not equipped to address patient needs and current funding increases are not sustainable. Policy considerations, such as a rare disease national plan, could help ensure rare disease patient needs are addressed in a methodical way.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

CHAPTER 1

INTRODUCTION

In the United States, there are an estimated 30 million people living with one or more rare diseases.[1] Rare diseases are defined in the U.S. as a condition impacting fewer than 200,000 people.[2,3] There are an estimated 6,500-7,000 rare diseases.[3] The small patient population for each disease creates challenges for research; including for basic epidemiological data, natural history studies, and clinical trials for the development of treatments.[4–9] The lack of research and awareness also means that many medical professionals and health insurance companies are unfamiliar with the disease and patients may struggle to find basic information about their condition.[4,10] This can lead patients and their caregivers to feel isolated or unsupported in their attempts to find information or resources.[6] Additionally, many patients face financial challenges when seeking care.[11–15] "Financial toxicity" is a term identified in the cancer literature to describe the impact of economic stress that can impact a patient's overall well-being, however, this phenomenon is not unique to the cancer community.[11–14]

An orphan drug is a treatment that has an indication for a disease with an estimated population of less than 200,000 people in the U.S. or where it is unlikely the manufacturer will be able to recoup the costs of manufacturing the drug.[2] Orphan drug designation occur as part of the Food and Drug Administration's (FDA) drug approval process.[16] Roughly 300 rare diseases (less than 5%) have an FDA approved orphan drug.[17] The Orphan Drug Act of 1983 established economic incentives to encourage the research and development of orphan drugs, including 7-year market exclusivity and fee-waivers.[2] In 2017, the invoice prices of orphan drugs indicated that the median annual

cost was over $46,800 per year and the mean was $87,319.[18] The average sales for the 50 highest cost orphan drugs was $639.5 million in 2017.[18] The high cost of orphan drugs in the U.S. has resulted in criticisms related to the incentive structures and other pharmaceutical company efforts to maximize their profits.[19–24]

Challenges faced by rare disease patients are largely universal and are often approached as an international public health challenge. Although rare diseases are clinically heterogenous, challenges such as diagnosis, finding knowledgeable medical providers, and accessing treatments and services are often similar across different disease states.[4,6] Approaching rare diseases on a global scale allows for international collaboration and knowledge sharing that is critical when resources are limited. There have been concerted international efforts to bring consistency to the nomenclature of rare diseases,[25–27] increase the visibility of rare diseases in healthcare infrastructure,[28,29] establish estimated prevalence,[30] and establish national priorities for rare diseases.[31] However, there are gaps in the regarding how international efforts are being implemented, how patients are being impacted, and what infrastructure exists to support these efforts in the United States.

Although there is a considerable body of research on healthcare access for other patient populations, few studies focus on rare disease patients as a group or the U.S. capacity to provide access to care. This dissertation research is comprised of three papers that look at different topics related to rare diseases and components of the U.S. healthcare system. The first paper explores the data quality of available prevalence estimates and the infrastructure that exists to establish future prevalence estimates for a sample of rare diseases. Prevalence is a fundamental component of understanding a disease,

appropriately planning for health expenditures, and educating key stakeholders about the disease. The second paper is a qualitative study with caregivers whose children are living with metachromatic leukodystrophy (MLD) or spinal muscular atrophy (SMA) that used a grounded theory approach to describe caregivers' perceptions of the health insurance experience. The third paper investigates the expenditures of orphan drugs in Medicare Part D from 2013 to 2017.

Together, this research provides an assessment of U.S. specific infrastructure, insurance access, and public program spending trends for rare diseases and orphan drugs. Individuals living with rare diseases are estimated to represent 10% of the U.S. population, but much of our understanding about the rare disease experience comes from international studies or studies that focus on an individual rare disease. This research will contribute to our knowledge of the patient experience and how policymakers should invest in our healthcare system infrastructure to better prepare for current and future health needs.

References

1. National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

2. *Orphan Drug Act*. Vol USC 21 I Subchapter D Part 316; 1983. https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21. Accessed January 13, 2017.

3. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. NIH.gov. https://rarediseases.info.nih.gov/. Accessed January 13, 2017.

4. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

5. Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive Care Needs of Parents With a Child With a Rare Disease: A Qualitative Descriptive Study. *J Pediatr Nurs*. 2016;31(3):e207-218. doi:10.1016/j.pedn.2015.10.022

6. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88. doi:10.1186/s12875-016-0488-x

7. Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. *Adv Exp Med Biol*. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

8. Groft SC, Posada de la Paz M. Preparing for the future of rare diseases. *Adv Exp Med Biol*. 2017;1031:641-648. doi:10.1007/978-3-319-67144-4_34

9. *Report of The National Commission on Orphan Diseases*. U.S. Department of Health and Human Services Public Health Service Office of the Assistant Secretary for health; 1989. https://rarediseases.info.nih.gov/files/report_of_the_national_commission_on_orphan_diseases_february_1989.pdf. Accessed March 31, 2017.

10. R de Vrueh, ERF Baekelandt, JMH de Haan. *Priority Medicines for Europe and the World "A Public Health Approach to Innovation."* World Health Organization; 2013. https://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf. Accessed July 2, 2019.

11. Barbaret C, Brosse C, Rhondali W, et al. Financial distress in patients with advanced cancer. *PloS One*. 2017;12(5):e0176470. doi:10.1371/journal.pone.0176470

12. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin*. 2018;68(2):153-165. doi:10.3322/caac.21443

13. Zafar SY. Financial toxicity of cancer care: It's time to intervene. *J Natl Cancer Inst*. 2016;108(5). doi:10.1093/jnci/djv370

14. Meeker CR, Geynisman DM, Egleston BL, et al. Relationships among financial distress, emotional distress, and overall distress in insured patients with cancer. *J Oncol Pract*. 2016;12(7):e755-764. doi:10.1200/JOP.2016.011049

15. Shen C, Zhao B, Liu L, Shih Y-CT. Financial burden for patients with chronic myeloid leukemia enrolled in Medicare Part D taking targeted oral anticancer medications. *J Oncol Pract*. January 2017:JOP2016014639. doi:10.1200/JOP.2016.014639

16. Commissioner of the Food and Drug Administration. Designating an Orphan Product: Drug and Biological Products - Frequently Asked Questions (FAQ). https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm. Accessed July 23, 2018.

17. U.S. Food & Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed March 31, 2017.

18. Aitken M, Kleinrock M. *Orphan Drugs in the United States Growth Trends in Rare Disease Treatments*. Parsippany, NJ: IQVIA Institute; 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf. Accessed November 20, 2018.

19. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis*. 2011;6:42. doi:10.1186/1750-1172-6-42

20. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. *Orphanet J Rare Dis*. 2008;3:33. doi:10.1186/1750-1172-3-33

21. Wellman-Labadie O, Zhou Y. The U.S. Orphan Drug Act: rare disease research stimulator or commercial opportunity? *Health Policy*. 2010;95(2-3):216-228. doi:10.1016/j.healthpol.2009.12.001

22. Picavet E, Dooms M, Cassiman D, Simoens S. Drugs for rare diseases: influence of orphan designation status on price. *Appl Health Econ Health Policy*. 2011;9(4):275-279. doi:10.2165/11590170-000000000-00000

23. Picavet E, Morel T, Cassiman D, Simoens S. Shining a light in the black box of orphan drug pricing. *Orphanet J Rare Dis*. 2014;9:62. doi:10.1186/1750-1172-9-62

24. Hemphill TA. Extraordinary pricing of orphan drugs: Is it a socially responsible strategy for the U.S. pharmaceutical industry? *J Bus Ethics*. 2010;94(2):225-242.

25. About Monarch. https://monarchinitiative.org/page/about. Accessed July 15, 2019.

26. Cutillo CM, Austin CP, Groft SC. A global approach to rare diseases research and orphan products development: The International Rare Diseases Research Consortium (IRDiRC). *Adv Exp Med Biol*. 2017;1031:349-369. doi:10.1007/978-3-319-67144-4_20

27. International Rare Diseases Research Consortium. International Consortium of Human Phenotype Terminologies (ICHPT). IRDiRC. http://www.irdirc.org/activities/task-forces/international-consortium-of-human-phenotype-terminologies/. Published December 1, 2017. Accessed March 7, 2019.

28. Aymé S, Bellet B, Rath A. Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding. *Orphanet J Rare Dis*. 2015;10(1):35. doi:10.1186/s13023-015-0251-8

29. Fung KW, Richesson R, Bodenreider O. Coverage of rare disease names in standard terminologies and implications for patients, providers, and research. *AMIA Annu Symp Proc AMIA Symp*. 2014;2014:564-572.

30. *Prevalence and Incidence of Rare Diseases: Bibliographic Data*. European Commission; 2017. https://ec.europa.eu/health/rare_diseases/orphanet/report_en. Accessed April 19, 2017.

31. Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. *Intractable Rare Dis Res*. 2018;7(4):213-222. doi:10.5582/irdr.2018.01085

CHAPTER 2

RARE DISEASE PREVALENCE QUALITY AND INFRASTRUCTURE IN THE UNITED STATES

Background

Rare diseases

In the United States, the Orphan Drug Act (ODA) and the National Institutes of Health (NIH) define rare diseases as conditions with less than 200,000 active cases.[1,2] In the European Union, a disease affecting fewer than 5 in 10,000 people is considered rare.[3] The Genetic and Rare Diseases Information Center (GARD) at NIH currently lists over 6,500 rare diseases.[1] Rare diseases impact a variety of body systems and the clinical manifestations of rare diseases are heterogenous. Disease onset can occur at any age and conditions can be either acute or chronic, but many are debilitating. Although little is known about the causes of most rare diseases, an estimated 80% are thought to have a genetic component.[4] Exposure to environmental toxins, infections, adverse reactions to therapies, or immune responses are other known factors of onset, but for some conditions the cause is never identified.[1,4] Due to the limited research, knowledge, and treatment options, many rare conditions are fatal.[4,5] It is often difficult for patients to receive an accurate diagnosis or to find other individuals with the condition.[5–7] Research for rare diseases can be difficult based on the small and dispersed patient population.

Rare cancers share the same definition and many of the same challenges.[8] One study found that 60 of 71 forms of cancer are considered rare in adults.[9] Additionally, in another study of cancerous tumors between 22-25% have been estimated to be rare.[11] Rare cancers have been reported to have a five-year survival rate of 47% compared to a

five-year survival rate of 65% for common cancers.[8] Rare cancers are often divided into more specific subtypes based on genetic characteristics, meaning that even common cancers are becoming increasingly rare.[8] Despite limited research overall, rare cancers may benefit from efforts to research common cancers.[8,10]

Importance of estimating the prevalence of rare diseases

Estimating the burden of disease is a critical public health function. For most rare diseases, basic information such as the natural history of the disease and epidemiological data is limited or missing.[5,6] Very little is known about the exact prevalence of most rare diseases, both in the U.S. and globally.[5] A commonly referred to figure estimates between 25 to 30 million Americans are living with one or more rare diseases,[11] but this is a difficult claim to substantiate as the original source and methodology of this estimation is difficult to identify.

Knowing prevalence of a disease provides a baseline to track inequities in the impacted population or identify changes in disease burden that may be based on environmental exposures, social determinants of health, or structural barriers to care. In rare cancers, there is evidence that the distribution, incidence rates, and types can vary by region,[12] but, without epidemiological data, the cause for these differences cannot be explored. Researchers at the World Health Organization also hypothesized that epidemiological data contributed to the increased number of treatments and resulting health benefits for rare cancers and inborn errors of metabolism.[5] Understanding trends in morbidities and mortality is necessary to inform a logical approach for disease response and planning.

Healthcare allocation decisions rely on strong epidemiological and actuarial data related to the expected healthcare needs and expenditures of the population an entity or provider serves. Understanding needs across a population can help identify the specialists that will be needed by patients and gaps in services. Estimating the financial impact is also important to plan for individual out-of-pocket expenditures and the costs associated with disease management. These costs are often high and a source of stress for patients and families.[13,14] "Financial toxicity" is a growing concept in the research literature that describes the personal and treatment related financial burden faced by patients, particularly patients with cancer.[15,16]

Identifying patients with rare diseases can help inform policies to address the financial burden to individuals and the healthcare system. Patient identification is important for ensuring a patient base for future clinical trial research.[17] It is critical to develop evidence-based research on the natural history of a disease and the anticipated disease progression. Knowing the number of people impacted by a disease can help inform decisions about clinical trial designs and the best way to gather scientific evidence for developing treatment protocols. Treatments may only be effective in a portion of patients, understanding the total number of people impacted by a condition allows a more thoughtful evaluation of clinical effectiveness.

Prevalence in orphan drug research and development

The Orphan Drug Act (ODA) incentivizes research and development of rare disease products through fee waivers and seven-year marketing exclusivity.[2] These benefits are based on the estimated prevalence of the targeted disease. Companies developing a product submit an application to the Food and Drug Administration (FDA)

to establish eligibility for obtaining an orphan designation.[18] Drugs are eligible for an orphan designation if they are intended to treat a disease that affects fewer than 200,000 people in the U.S. and there is no expectation of recovering the research, development, and marketing costs from U.S. sales of the drug. This process can occur at any point in the drug development process, anytime between laboratory drug discovery and clinical trials.[18] Once the safety and efficacy of the drug has been established through clinical trials, the FDA determines the final indications for the drug's marketing approval.[18] Between January 1983 and August 2018, 503 drugs were approved with an orphan indication for drug approval.

Despite the small market for orphan drugs, the pharmaceutical industry has demonstrated the potential for large profits.[19,20] Of the estimated 6,500 rare diseases only about 300 diseases currently have a FDA approved treatment, leaving many patients desperate for successful treatments.[21] Some of the criticisms of the ODA include the allegation that incentives are exploited to develop drugs that may fall outside of the intended scope of the law.[19] Of all orphan designation applications received between 2008 and 2017, 71% were for drugs intended to treat diseases impacting fewer than 100,000 people[18] and the average estimated patient population per orphan therapy was 5,730.[22] Rare cancers have been estimated to represent roughly 30% of orphan drug approvals and up to 43% of orphan indications, which is a higher percentage than drugs to treat any other category of orphan drug therapeutic use.[5,18,22,23]

As part of the orphan drug application process the FDA requires prevalence data with references to the estimates' sources; outdated or international sources need to be justified and contextualized for the relevance to the U.S.[18,24] The pharmaceutical

companies provide these estimates and the FDA validates them. However, in a 2018 Government Accountability Office (GAO) report, the independent verification of population estimates were not conducted for 23 of 148 review templates and for 15 of the applications for drugs that were ultimately approved.[18] Skipping this verification was cited by GAO as one of the concerns related to the review process, but does not acknowledge the difficulty in finding and verifying these numbers.

Measures for establishing disease prevalence

There are many ways to describe the number of people living with a particular disease and different stakeholders have varying priorities that may lead to the use of different metrics. Prevalence refers to the number or proportion of people who have a particular condition in a population at a particular time.[25] This can refer to a point prevalence, the number of cases at a specified point in time; or period prevalence, the number of cases over a specified period of time.[25] These estimates may account for changes based on mortality and newly identified cases. Incidence describes the proportion of new cases in a time interval.[25] Incidence can be expressed as a cumulative rate, the total number of new cases, the number of new cases per unit of a population, or as a measurement of risk. This paper will refer to prevalence, as this is the measurement used for rare diseases in the U.S. and was identified as the preferred epidemiological metric in rare disease definitions internationally.[26] For some rare diseases the total number of identified patients is so small that the estimated disease prevalence is described as the number of estimated cases.[27]

Many study factors can impact these estimates including the sample population, the time frame of interest, the data collection methods, the study design, the tools utilized,

and the methodologies used for data analysis.[25] Prevalence data can come from a variety of sources including the medical literature, "umbrella" organizations that represent a group of related rare diseases, disease specific organizations, government, industry, medical records, medical institutions, insurance claims data, and health foundations.[28]

When attempting to estimate the number of individuals impacted by a rare condition, it is first necessary to determine if a sample would be adequate, or if the disease population is so small that a sample is unable to accurately establish population level prevalence.[29] For example, in one study that reviewed laboratory samples from 1,825 patients who had two indicator symptoms for lysosomal acid lipase deficiency, none of the patients in the study were found to have the disease.[30] Rare diseases estimates may require infrastructure that has been established to collect prevalence data for the disease of interest as other methods may not capture cases of the disease.

Registries

A registry is a tool to collect and store data. Commonly identified goals include to identify a list of patients, to perform natural history studies, and to support research objectives such as for product and treatment evaluation.[31–33] Rare disease registries have been developed by patient organizations, government entities, and industry. Medical centers or designated disease programs within hospitals or treatment centers are also natural settings to establish disease registries.[34]

Disease registries are well established as a data source for providing population estimates for diseases.[31,32,35,36] High-quality data relies on well-defined diagnostic criteria.[29,37] This can be complicated when multiple sites or investigators are involved or if there are subsets of the disease of interest.[29] Registries often require participants to opt-

in. Some diseases may be covered under multiple registries, which increases duplication and can divide resources. Privacy laws limit the opportunity to cross-check redundancy across different systems.[37,38] It is also important to make the distinction between duplicate records and individuals who may appear multiple times because they have multiple qualifying conditions to be added to the registry.[39]

If a registry is not compulsory for all patients, there may be a selection bias in the type of patients who decides to participate or who are referred to the registry.[29] Patients who have more mild forms of a disease or whose care can be managed by their own physician are less likely to be referred to specialty centers or seek out additional care. Patients may be limited in their ability to travel to specialty medical centers and it is not feasible to have multiple geographically diverse centers for diseases with a small population.[40] Age of diagnosis could also impact where a patient seeks care.[41] Participation may also be influenced by a patient's perception of his or her benefit, such as the availability of therapies or cultural feelings of trust in the medical system.[29]

There are a few registries in the U.S. that may provide an opportunity to estimate prevalence for the included rare diseases. The Rare Disease Clinical Research Network (RDCRN), a network of rare disease centers of excellence within NIH, oversees a voluntary patient contact registry.[42] The Surveillance, Epidemiology, and End Results Program (SEER) at the National Cancer Institute at NIH tracks cancer rates through registries in a sample of states which provides coverage for 34.6% of the population.[43] The Centers for Disease Control and Prevention (CDC) funds a program to collect information about rare bleeding disorders and patient demographic information through a network of nationwide Hemophilia Treatment Centers.[44,45]

Data within a registry often requires further investigation before prevalence can be reported. One study was conducted to assess the quality of data and provide prevalence estimates for diseases in RARECARE, a European based rare cancer registry.[46] The study found differences in the level of uniformity and accuracy of the classification across the different types of rare cancers.[46] Without clear diagnostic criteria, it is often difficult to consistently code and track cases of diseases. Statistical analysis to validate estimates often requires comparisons from other data sources, which may or may not be available for rare diseases, which makes it challenging to validate disease estimates.[37,39]

Surveillance and required reporting

Surveillance is the ongoing collection, analysis, and interpretation of data to help prevent disease and injury and to provide scientific evidence for program and policy decisions.[47,48] This can include passive surveillance of all clinical interactions at certain institutions, syndromic surveillance based on clinical features, and sentinel surveillance where certain institutions or groups agree to report all cases of a defined condition, often these are for disease outbreaks or bioterrorism.[47] There are tradeoffs between the sensitivity of detecting an event and the simplicity, timeliness, and cost of inclusion.[48] The ability to control or prevent the disease is often seen as the most compelling reason to invest in a surveillance system, but other justifications include tracking medical costs or mortality rates associated with the condition.[47,48] The costs of establishment, infrastructure, and maintenance of surveillance systems can be high, but the benefits include the potential for long-term cost savings especially if successful interventions are

established. Data collected through surveillance are less likely than other methods of disease identification to disproportionally include more severe forms of the condition.[49]

There are international examples of required rare disease reporting. For example, Italy established a country-wide network of accredited centers to serve rare disease patients and mandated that new cases be reported to the National Registry of Rare Diseases, which now provides country specific incidence measures for rare diseases based on population level data.[50] Rare diseases are not systematically required to be reported in the U.S., but some conditions may be captured in other official public health surveillance systems. For example, the National Notifiable Disease Surveillance System (NNDSS) at the CDC collects information on a set of infectious diseases across the entire U.S.[51] Concerns about morbidity and mortality in children, has led to targeted pediatric surveillance efforts for some rare diseases.[52] Currently, 43 states have birth defects tracking programs, 14 of which are funded by the CDC.[53] The Recommended Uniform Screening Panel is a list of disorders that have been identified by the Secretary of the Department of Health and Human Services for inclusion in state newborn screening programs.[54] However, states decide what is included on newborn screening panels, which creates differences across jurisdictions.[49]

Disease terminologies and coding systems

Genetic and rare diseases are generally underrepresented in coding systems.[55] Both registries and surveillance systems are dependent on clear and consistent disease identification and coding to maximize the potential for discovery and clinical use.[56] These systems are used by a variety of audiences and were established for different purposes including electronic health records and insurance claims. There have been

efforts to increase rare disease visibility in health information systems and to increase interoperability between databases.[57–60] Classification systems need to account for descriptive and genetic information, especially as new conditions are observed. One of the challenges is mapping the terminologies across the existing resources and coding platforms that are used to identify and describe rare diseases. A study that looked at consistency in coding case reports for a sample of rare diseases found that professional coding companies were in agreement on the core concepts 33% of the time.[61]

International Classification of Diseases (ICD) codes are used to code diagnoses, symptoms, and procedures.[62] Globally they are used to track disease statistics and trends. In the U.S. they are primarily used for billing purposes. The U.S. first adopted the ICD-9 codes for use in 1977 and adopted the updated ICD-10 codes on January 1, 1999.[63,64] ICD codes are used in studies that rely on hospital discharge data, insurance claims, and mortality records.[65] Most rare diseases are absent from the ICD-10 codes and diseases that do exist are often misclassified.[66]

One study found that of the 6,519 rare diseases listed by NIH, 11% were broadly included in ICD-9 and 21% in ICD-10.[57] The study also found that only 25% of the ICD-10 codes were for only one disease, limiting the level of specificity that can be garnered from the data. There are many examples of rare diseases that do not have any ICD code. If a disease does not have a specific ICD code, researchers must investigate medical records or use proxy indicator variables to create algorithms to identify the disease of interest from claims data. This requires dedicated resources to validate information for each condition of interest.

Studies to assess the accuracy of ICD code or administrative data in identifying cases of rare diseases have had mixed results.[65,67–73] The clarity of the case definition and the number of clinical visits by the patient increased the accuracy identifying disease cases. Studies that used only ICD codes to assess true cases of rare diseases found between 15% and 65% accuracy in identifying cases.[65,68,69,74] Differences in the accuracy and completeness of capturing cases of a disease between data sets highlights the necessity of cross-validating cases. For example, in a validation study to see if muscular dystrophy cases were accurately identified in claims and hospital discharge data, 74.02% of cases in the claims data were not included in the hospital discharge records.[65] Reference data sets or records to validate cases are not always available for rare diseases.

The European Commission called for an investment in increasing rare disease representation, which will be reflected in the ICD-11 revisions that are being developed by the World Health Organization; currently over 5,000 rare diseases are listed in this new system.[62,66] The roll out and implementation of ICD-11 in the U.S. is unknown. The complexities of accurate coding, especially for diseases that clinicians are unfamiliar with, will continue to be a barrier for finding and identifying disease cases.

Challenges in estimations for rare diseases

Accurate estimates are often impacted by diagnosis related challenges, with many rare disease organizations and patients claiming that the actual prevalence is greater than the currently identified population.[6] The small patient population also makes it more difficult to establish tracking systems as the population is likely geographically disbursed and difficult to identify. This increases the need for collaboration, but there is evidence that some centers are hesitant to join multi-site trials due to fears of low patient accrual,

increased regulatory burden, or unclear benefits.[17] Rare diseases are competing for limited funding, which can mean an investment in the infrastructure to establish biobanks and registries may be hard to justify.[12,38]

In Europe there has been an investment in establishing prevalence and encouraging country specific rare disease plans.[27,75] A preliminary report was released to provide initial data on rare disease prevalence for a sample of conditions.[76] Some therapeutic categories such as pediatric oncology and rare blood disorders are also creating frameworks to address healthcare challenges.[38,41] In the U.S., leaders at NIH and FDA have outlined priorities to address core rare disease challenges faced by patients with rare diseases.[28] This includes increasing current knowledge of rare diseases, additional partnerships with patient organizations, and the need to track genetic variability and environmental factors for use in future research.[28,77]

Policymakers, patients, medical professionals, researchers, and industry all have an interest in understanding the impact of a disease. Understanding prevalence impacts healthcare allocation decisions and industry incentives. The GAO has indicated the need for increased investment in verification of prevalence data in FDA drug application reviews. Researchers rely on epidemiological data to make decisions related to the robustness of data for natural history and treatment protocols. Previous rare disease prevalence studies have evaluated a single disease[78,79] or coding systems[62,80] without considering other types of infrastructure. It is important to evaluate rare diseases at a systems level and determine if disease characteristics impact the availability of prevalence estimates or the available infrastructure. To date, there have been no studies to

quantify the scope of our knowledge for U.S. based prevalence estimates or the potential to leverage current infrastructure to provide prevalence estimates in the future.

Methods

Objectives

This study seeks to explore two inter-related questions; what is the quality of the existing prevalence estimates for a sample of rare diseases in the United States and what infrastructure is in place that may be used to ascertain prevalence estimates in the future. The research questions for this study are:

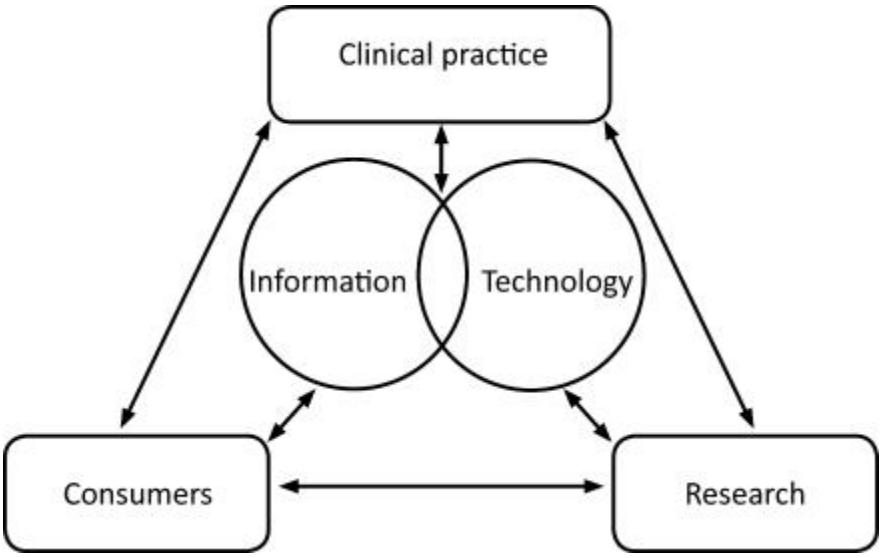
1. What is the availability and data quality for prevalence estimates for a sample of rare diseases in the United States?
2. What infrastructure is available that has the potential to facilitate generating valid prevalence estimates for a sample of rare diseases in the United States?
3. Is there a difference in the availability, information quality, or infrastructure for estimates of rare disease prevalence in the United States for diseases that:
    a. have an orphan drug approval compared to those that do not have an orphan drug approval?
    b. are rare cancer compared to diseases that are not cancer?

Conceptual model

Cleveland's model of the healthcare environment is the conceptual framework utilized for this study.[81] (Figure 1) The model underscores the importance of information and technology for three key arenas in healthcare; clinical practice, healthcare consumers, and research. The model was originally developed to inform the needs of health information education, but provides a framework for understanding the interplay between

information and technology advancement in the broader healthcare environment. Technological advancement and additional healthcare information simultaneously drive innovation and must be responsive to healthcare practice and research needs. The model is impacted by both internal and external factors including the structure of the healthcare system and the values and goals of healthcare delivery.[81]

Figure 1: Cleveland's model of the healthcare environment



This study is driven by the informational importance of rare disease prevalence data. This information is critical for establishing information about patients (consumers) and for creating clinical practice guidelines. Clinical practice is informed by natural history of disease progression, which is predicated on understanding the population impacted by a disease. Epidemiological, healthcare utilization, and product development research all require an understanding of the total population impacted. Technological solutions such as registries provide data for determining prevalence. However, the data available for prevalence on many health information websites underscore the deficiencies of our current infrastructure to collect, process, and report reliable information.

Rare disease sample

To generate a sample of rare diseases, three lists of rare diseases were accessed from the GARD website; a list of rare cancers, [82] a list of diseases with FDA orphan drugs,[83] and the full list of diseases in the GARD database.[84] (Figure 2) Data were obtained from GARD, the leading U.S.-based government agency for rare disease information. The rare cancer and orphan drug lists were combined and redistributed into three groups; rare cancers with an orphan drug (group 1), rare cancers without an orphan drug (group 2), and non-cancer diseases with an orphan drug (group 3). Group 4, non-cancer diseases without an orphan drug, was created by taking the full list and removing duplicate conditions from any of the other lists. Microsoft Excel was used to categorize each list and obtain a sample of 20 diseases per group for a purposeful stratified sample of 80 rare diseases total. (Table 1)

Figure 2: Flowchart for sample diseases by group

The full GARD list includes diseases that are not rare, but are included based on patient inquiries for information on those conditions. Additionally, disease synonyms are also included as separate entries on the list which accounts for the large number of duplicate and not rare conditions.

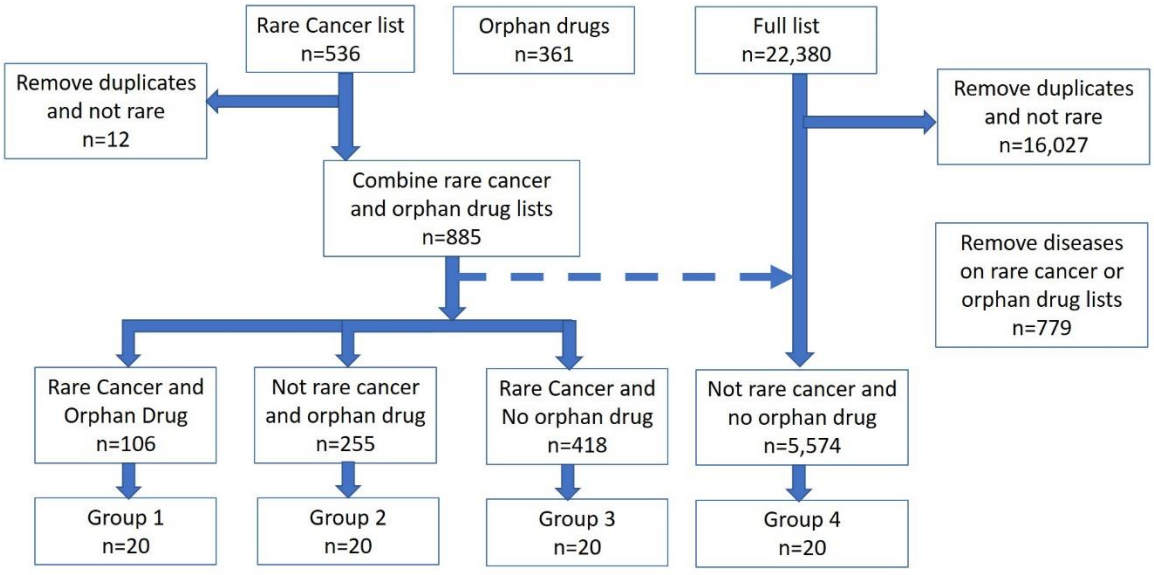


Table 1: Diseases included in the sample

	Orphan drug	No orphan drug
	Group 1	***Group 3***
Cancer	Acral lentiginous melanoma	Acute panmyelosis with myelofibrosis
	Acute lymphoblastic leukemia	Adrenal medulla cancer
	Anaplastic thyroid cancer	Ameloblastic carcinoma
	Chronic lymphocytic leukemia	Autoimmune lymphoproliferative syndrome
	Clear cell renal cell carcinoma	Basal cell carcinoma, multiple
	Ewing sarcoma	Familial pancreatic cancer
	Familial prostate cancer	Familial Wilms tumor 2
	Follicular lymphoma	Gangliocytoma
	Hairy cell leukemia	Glassy cell carcinoma of the cervix
	Kaposi sarcoma	Goblet cell carcinoid
	Malignant mesothelioma	Infantile myofibromatosis
	Melanoma astrocytoma syndrome	Juvenile myelomonocytic leukemia
	Neuroblastoma	Multiple endocrine neoplasia type 2B
	Oslam syndrome	Multiple familial trichoepithelioma
	Papillary thyroid carcinoma	N syndrome
	Renal cell carcinoma 4	Nevoid basal cell carcinoma syndrome
	Soft tissue sarcoma childhood	Nijmegen breakage syndrome
	Subependymal giant cell astrocytoma	Oropharyngeal cancer
	Testicular cancer	Ovarian carcinosarcoma
	Thyroid cancer, follicular	Von Hippel-Lindau disease
	Group 2	***Group 4***
	Cholesteryl ester storage disease	Achard Thiers syndrome
	CINCA	Baritosis
	Cystinosis	Cercarial Dermatitis
	Factor VII deficiency	Chorioretinitis

Not cancer	Herpes simplex encephalitis	Dubowitz syndrome
	Hyperkalemic periodic paralysis	Farber's disease
	Keratoconus	Graham-Little-Piccardi-Lassueur syndrome
	Methylmalonic acidemia with homocystinuria	Houlston Ironton Temple syndrome
	Homocystinuria type cblD	Hutterite cerebroosteonephrodysplasia syndrome
	Mild phenylketonuria	Hypomandibular faciocranial dysostosis
	Mucopolysaccharidosis type VI	Isochromosome Yp
	Myasthenia gravis	Limb body wall complex
	Narcolepsy	Manitoba oculotrichoanal syndrome
	Orotic aciduria type 1	Mastocytic enterocolitis
	Prader-Willi syndrome	Osteogenesis imperfecta type IV
	Transverse myelitis	Primary pigmented nodular adrenocortical disease
	Tuberous sclerosis, type 2	Seow Najjar syndrome
	Ventricular fibrillation, idiopathic	Spastic paraplegia 14
	Wilson disease	Thickened earlobes with conductive deafness from incus-stapes abnormalities
	Zygomycosis	Tremor hereditary essential, 2

The FDA orphan drug designations and approvals database was used to collect the total number of orphan drug approvals per disease.[21] Diseases with an approved orphan product are more likely to be the focus of research studies and have a more clearly defined patient population due to the clinical trial process. If a disease did not have an orphan drug approval, but had an orphan drug designation, that was noted. There is a substantial interest in cancer research and care infrastructure.[85] Rare cancers may benefit

from more accessible treatment centers for both patient information and the collection of data. Diseases with orphan drugs and rare cancers have the potential for additional information and interest, purposeful sampling was employed to investigate these differences.[86] The sample size allowed for a feasible investigation into data source quality and infrastructure for rare disease prevalence.

Data sources and searches for evaluating quality of existing prevalence estimates

The Cleveland model of the healthcare environment[81] demonstrates the interplay between information and the consumers, clinicians, and researchers who utilize and generate the data. The data sources for existing prevalence estimates were evaluated based on the standards outlined by Silberg, Lundberg, and Musacchio.[87] This framework provides principles to evaluate the credibility and usefulness of health data. The four areas are authorship, attribution, disclosure, and currency. Authorship refers to disclosing the affiliations and credentials of authors and contributors. Attribution is clearly displaying references and sources for all content. Disclosure is the ownership of the website, including any commercial funding and conflicts of interest. Currency is the date that content was posted and updated; for the purpose of this study it will be referred to as date. Disclosure was evaluated at the website level and the other areas were assessed at the article or webpage level for individual disease listings.

Eight rare disease, genetic disease, or health information websites were identified prior to conducting the study as resources that researchers, patients, or medical professionals in the U.S. might access for rare disease information. GARD, Orphanet, and NORD are established rare disease specific resources. Genetics Home Reference, GeneReviews, and OMIM provide information on genetic based conditions, which

represent an estimated 80% of rare diseases. Medscape is a popular source for disease information and is routinely included as a data source in previous studies that evaluated internet based health information.[78,88] SEER provides a query function on their website to provide cancer statistics based on collected registry information. Descriptions of these data sources and the sources' disclosure information are listed in Table 2. These sites were used to determine if information about the disease was available and if a prevalence estimate was available.

Table 2: Data sources for prevalence searches for data quality information and infrastructure assessment

Searches were conducted for two purposes: to evaluate data quality of existing prevalence estimates and to determine the infrastructure for future estimates. This chart provides the data source, a short description from the source's website, the financial disclosure for their funding, and if it was used for data quality or infrastructure.

Data source	**Description**	**Disclosure**	**Used for**	
			Data quality	***Infrastructure***
Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences (NCATS)	Provides the public with access to current, reliable, and easy-to-understand information about rare or genetic diseases	Funded by two parts of the National Institutes of Health: NCATS and the National Human Genome Research Institute (NHGRI)	X	
Orphanet	Portal for rare diseases that includes an encyclopedia of rare diseases and associated genes	Funded by Inserm, the French Directorate General for Health, and the European Commission through OrphaNetWork, a Direct Grant of the 3rd Health Programme of the European Union	X	
Genetics Home Reference, U.S. National Library of Medicine	A consumer health website from the National Library of Medicine, which provides information for the general public about the effects of genetic variation on human health	Funded by the U.S. Government	X	
GeneReviews, National Center for Biotechnology Information	Provides clinically relevant and medically actionable information for inherited conditions	Funded by the government through the National Institutes of Health and chapters are owned by the University of Washington	X	

Rare Disease Database, National Organization for Rare Disorders (NORD)	Provides brief introductions for patients and caregivers to specific rare diseases	Primary sources of funding are grants, contracts, contributions, and an annual fund-raising event; enhancements to the Rare Disease Database were made possible through a grant from the Anthem Foundation	X	
Online Mendelian Inheritance in Man (OMIM)	Documents genetic defects by identified human genes when available or genetic phenotypes as a proxy	Funded by a grant from the National Human Genome Research Institute and individual donors; Initial development was supported by Johns Hopkins Medicine and a grant from the Maryland Department of Health and Mental Hygiene	X	
Medscape	Website providing physicians and healthcare professionals medical news, point-of-care drug and disease information, and relevant professional education and CME	Revenue is generated through the sale of various types of advertising and sponsorship products which include: pharmaceutical, biotechnology and medical device companies; hospitals and other healthcare services companies; health insurance providers; companies whose products or services relate to health, wellness, diet, fitness, lifestyle, safety and illness prevention; and various other businesses, organizations and governmental entities. Advertisements are guided by posted policies.	X	
Surveillance, Epidemiology, and End Results Program (SEER), National Cancer Institute	Provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population.	Supported by the Surveillance Research Program in National Cancer Institute's Division of Cancer Control and Population Sciences	X	X

Clinicaltrials.gov	ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.	Funded through the Department of Health and Human Services		X
ICD-10 and ICD-11	Foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. ICD defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive, hierarchical fashion	Developed and distributed by World Health Organization (WHO) globally and adapted in the United States by the Centers for Medicare and Medicaid Services (CMS) and the National Center for Health Statistics (NCHS)		X
National Notifiable Disease Surveillance System (NNDSS)	Helps public health monitor, control, and prevent a sample of diseases including infectious diseases such as Zika and foodborne outbreaks, and noninfectious conditions such as lead poisoning	Funded by the U.S. Government		X
Recommended Uniform Screening Panel	List of disorders that the Secretary of the Department of Health and Human Services recommends for states to screen as part of their state universal newborn screening programs	Funded by the U.S. Government		X

Google Disease Disease + Organization Disease + Registry Disease + Medical Center	Search engine	Publicly traded company, funded through ad revenues	X	X
Pubmed Disease Disease + [Incidence OR Prevalence]	The National Library of Medicine's full-text repository of life sciences journal literature	U.S government agencies and private investors		X

Searches were conducted using both the primary disease name and any additional synonym names listed in GARD. Google searches were conducted for the disease name and the disease name and "organization", "registry", or "medical center". If any of the searches resulted in a resource that listed the disease on the website or in the mission statement, it was recorded. Some medical centers publish disease encyclopedias from third party providers; these sources were not included to limit the over representation of available data sources. Organizations, registries, and medical centers were included if they were physically located in the U.S. or had a global organizational reach. It was noted if the disease was listed under a broader umbrella disease or a more specific sub-type of the condition. Two name variables were created; if the disease was listed under a broader name on any of the health information websites and if the disease was listed under a more specific name on any of the health information websites.

The data availability variables included if the disease was listed on each of the health information website. Prevalence variables included if an estimate was available and the quality estimates of authorship, attribution, and date. The total number of available prevalence estimates and the total number of available prevalence estimates with all three quality factors were also reported. Initial disease searches were conducted between June 4 and August 21, 2018.

Infrastructure for establishing disease prevalence estimates

Building off Cleveland's model of the healthcare environment, infrastructure can be described as the interplay between information and technology. Prevalence information can only be collected or evaluated if technologies and systems are in place. Seven data sources were identified as indicators of prevalence infrastructure. In this

paper, prevalence infrastructure refers to the organizations, technology, or data sources that provide capacity to provide prevalence estimates. The availability of an ICD code was evaluated for the current ICD-10[63] system and the working list for ICD-11.[89] Disease inclusion in the ICD system was coded as not available or a specific disease code exists. Two registries were included in the sample the National Notifiable Disease Surveillance System (NNDSS) and SEER, a national cancer registry. The Recommended Uniform Screening Panel was also reviewed to see if any of the diseases in the sample are recommended for newborn screening.

For searches conducted on Clinicaltrials.gov the total number of search results and the number of trials that were considered active were recorded. [90] A trial was considered active if it was currently listed as not yet recruiting, recruiting, enrolling by invitation, or active not recruiting. Clinical trials indicate the current level of governmental and industry investment and interest in a particular disease and the opportunity to collect prevalence information.

A Pubmed search was conducted for each disease using the primary and any secondary disease names. An additional search using the disease names and "incidence" or "prevalence" was also conducted. The number of results were recorded. The purpose of conducting these searches was to see the depth of published knowledge on the disease and to provide an indication of the academic and clinical interest in the disease as is represented by the research and clinical practice components of the model of the healthcare environment. The individual studies were not evaluated as the goal was not to determine a specific prevalence for each disease, but to assess what information is currently accessible and the potential for future validation of prevalence estimates. The

web sources included in the study routinely synthesize and report the key information from academic studies as part of disease listings. Reporting the number of PubMed results provides an indication of the any recent findings that may inform reported disease estimates in the future. Finally, during the previously described google searches, the total number of organizations, disease specific organizations, registries, and medical centers were recorded. If a disease had an organization that designated medical centers that was also recorded.

Data analysis

Data analysis was conducted in Stata version 13.1. Descriptive statistics were calculated and recorded for data quality and infrastructure variables. This included frequency counts for categorical data and the mean, standard deviation for continuous variables. Means, standard deviation, and p-values were reported. None of the variables were found to be normally distributed, so non-parametric statistics were used. Results were considered statistically significant at p=.05.

Chi-squared tests were conducted to compare the statistical significance of the availability of the disease appearing on each health website by group. Simple logistic regression was conducted on both name variables; disease listed under a broader name and disease listed under a more specific name. Simple logistic regression was also conducted for the availability of a prevalence estimate in each health information website. (Table 5) The dependent variables were orphan drug, rare cancer, and an interaction variable for rare cancer and orphan drugs. Shapiro-Wilk tests were conducted to determine if the residuals were normally distributed. F-tests were conducted to make

additional comparisons by group. The logistic regression results are presented in the appendix.

$$y = \beta_0 + \beta_1 rarecancer + \beta_2 orphandrug + \beta_3 rarecancer * orphandrug + \varepsilon$$

Simple linear regression and follow-up Shapiro-Wilk and F-tests were conducted at the disease level for the average number of prevalence estimates available and the average number of quality prevalence estimates. Simple linear regression and the follow-up tests were also conducted to investigate the impact of having an orphan drug and being a rare cancer for each of the quality indicators (author, date, and attribution) and for having all quality estimates. Means, standard deviation, and p-values were reported. (Table 5)

Chi-squared analysis was conducted to compare the number of quality estimates by group according to the sector of the location for the estimate. The different sectors were government funded, industry or private funding, medical center or professional society, and organization. (Table 6)

Simple logistic regression was conducted for each independent infrastructure variable with the dependent variables rare cancer, orphan drug, and the interaction variable. These variables included if each disease had an organization, a disease specific organization, a registry, a medical center, an organization that designates medical centers, an ICD-10 specific code, and an ICD-11 specific code. (Table 7) Follow-up Shapiro-Wilks and F-tests were conducted and the individual linear regression results are presented in the appendix.

Simple linear regression for continuous infrastructure variables and follow-up tests were conducted for the number of organizations, the number of medical centers, the

number of clinical trials, the number of active clinical trials, the number of PubMed disease results, and the number of PubMed incidence or prevalence results.

Results

Disease sample characteristics

Of the 80 sample diseases, 70 included information about therapeutic category in GARD. (Table 3) Additional information about disease characteristics were not captured. Most diseases (38%) had one therapeutic category listed and 15 diseases (18.8%) had two. Ten of the diseases (12.5%) did not have any information listed about their therapeutic category. Von Hippel-Lindau disease (group 3) had the most identified with 8 listed. The therapeutic category with the most disease representation in the sample were congenital and genetic diseases (39%), with nervous system (20%), blood diseases (13%), and eye diseases (13%).

Table 3: Therapeutic categories for sample diseases

Category	Total
Rare Cancer	40
Congenital and Genetic Diseases	32
Nervous System Diseases	16
Blood Diseases	10
Eye diseases	10
Not Listed	10
Metabolic disorders	9
Skin Diseases	7
Digestive Diseases	6
Endocrine Diseases	6
Immune System Diseases	4
Kidney and Urinary Diseases	4
Musculoskeletal Diseases	4
Newborn screening	4
Reproductive Diseases	4
Hereditary Cancer Syndromes	3
Mouth Diseases	2
Viral infections	2

Autoimmune / Autoinflammatory diseases	1
Ear, Nose, and Throat Diseases	1
Fungal infections	1
Parasitic diseases	1

Of the diseases in the sample that had at least one approved orphan drug, 65% had more than one drug approval. There was a statistically significant difference (p=.036) in the average number of orphan drugs if the disease was a rare cancer (mean=2.9) compared to the number of orphan drugs if a disease was not cancer (mean=1.25). Acute lymphoblastic leukemia (ALL) (group 1), had the greatest number of orphan drug approvals with 13. Four diseases had an orphan drug designation, but the drugs had not been approved by the FDA. Of these, 3 were rare cancers.

Available prevalence estimates and data quality

Four of the diseases were only identified on the GARD list and could not be found in any other data source, these diseases were all in group 4. This difference was found to be statistically significant by group (p=.006), orphan drug, and rare cancer status (both p=.04). Orphanet included the greatest number of the diseases (78%) followed by OMIM (71%), Medscape (53%), NORD (39%), Genetic Home Reference (36%), and Gene Reviews (19%).

Of the diseases included in the sample, 13 (16.25%) were listed under a more specific name and 27 (33.8%) were listed under a broader disease name on at least one of the health information websites. For example, in GARD the disease chosen for the sample was “transverse myelitis”, but in Orphanet a more specific name included two additional subtypes and a listing for acute transverse myelitis. Spastic paraplegia 14 was listed under the broader “spastic paraplegia” everywhere except GARD. One disease per

group was listed by both a broader and more specific disease name in different sources. OMIM had the most diseases (9) listed under a more specific disease name and Medscape listed the most diseases under a broader disease name (13). Orphan drug and rare cancer were not statistically significant factors for being listed under another name. (Table 4)

Table 4: Disease name conventions and data websites with prevalence estimates by group

The coefficients, standard error, and statistical significance for individual logistic regression results can be found in Appendix A-B.

	Group 1 (OD, RC) n=20	**Group 2 (OD, no RC) n=20**	**Group 3 (no OD, RC) n=20**	**Group 4 (no OD, no RC) n=20**	**Total n=80**	**Factors and differences in groups that are statistically significant**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Broader name	7 (35)	9 (45)	7 (35)	4 (20)	27 (33.8)	None
More specific name	6 (30)	5 (25)	1 (5)	1 (5)	13 (16.3)	None
GARD	2 (10)	2 (10)	3(15)	1 (5)	8 (10)	None
NORD	4 (20)	10 (50)	5 (25)	1 (5)	20 (25)	Group 3 vs. Group 4
Orphanet	8 (40)	12 (60)	10 (50)	8 (40)	38 (47.5)	None
Genetics home reference	2 (10)	10 (50)	5 (25)	2 (10)	19 (23.8)	Group 3 vs. Group 4; Group 1 vs. Group 2; Group 1 vs. Group 3
GeneReviews	0 (0)	4 (20)	4 (20)	1 (5)	9 (11.3)	None
Medscape	12 (60)	9 (45)	4 (20)	3 (15)	28 (35)	Group 3 vs. Group 4; Group 1 vs. Group 2
OMIM	3(15)	8 (40)	2 (10)	0 (0)	13 (16.3)	None

Orphanet included prevalence estimates for the diseases studied more frequently than any other source (47.5%) followed by Medscape (35%) and NORD (25%). (Table 4) GARD only listed prevalence estimates for 10% of the diseases. The difference in the

number of prevalence estimates available was statistically significant by orphan drug status for NORD, Genetics Home Reference, and Medscape. Rare cancer status was not a statistically significant predictor of having a prevalence estimate listed on any of the sites. OMIM provided information about known case studies for an additional 24 conditions. Of the diseases, 75% had a prevalence estimate listed in at least one of the data sources. Of the diseases that had an estimate, 46.78% of the diseases had the same estimate listed in multiple places.

There were a total of 443 prevalence estimates for diseases in the sample, 361 for rare cancers and 262 estimates for diseases with an orphan drug. Diseases with an orphan drug had an average of 9.03 available prevalence estimates and 2.05 estimates with all three quality factors, while diseases without an orphan drug had an average of 2.05 disease estimates and .575 quality estimates. Rare cancers had an average of 6.55 prevalence estimates and 1.73 quality estimates, compared to non-cancers which had 4.53 average estimates and .9 quality estimates. Diseases with an orphan drug that were cancer had an average of 9.8 estimates compared to diseases without a drug that were not rare cancer that had an average of .8 estimates. (Table 5) Having an orphan drug was a statistically significant factor for both having a prevalence estimate and having a quality prevalence estimate.

Of the 443 total prevalence estimates available for any of the sample diseases, only 106 (23.93%) had all three quality indicators. (Table 5) Of the estimates, 47.4% had attribution, 45.4% had date, and 32.7% listed authorship. Of the estimates that had attribution, 30.5% of them only included the name of the original source for the content and not specific data source, dates, or authorship for the source content. For the author,

9.7% of estimates provided an organizational editorial board for the author, but did not identify a specific person who was responsible for the content. Including a date was statistically significant by rare cancer status. Within the estimates, there was no statistically significant difference in having all three quality factors by orphan drug or rare cancer status.

Table 5: Prevalence estimates with data quality factors

The coefficients, standard error, and statistical significance for individual logistic or linear regression results can be found in Appendix C-D.

	Group 1 (OD, RC)	Group 2 (OD, no RC)	Group 3 (no OD, RC)	Group 4 (no OD, no RC)	Total	Factors and differences in groups that are statistically significant
By disease	**n=20**	**n=20**	**n=20**	**n=20**	**n=80**	
	m (std)	**m (std)**	**m (std)**	**m (std)**	**m (std)**	
Average number of estimates	9.8 (9.82)	8.25 (8.95)	3.3 (4.27)	.8 (1.01)	5.54 (7.78)	Group 3 vs. Group 4; Group 1 vs. Group 2 (therefore orphan drug)
Average estimates with all quality factors	2.5 (2.59)	1.6 (1.50)	.95 (1.50)	.2 (.52)	1.31 (1.87)	Group 3 vs. Group 4; Group 1 vs. Group 2 (therefore orphan drug)
By estimate	**n=196**	**n=165**	**n=66**	**n=16**	**n=443**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Author	61 (31.12)	45 (27.27)	31 (46.97)	8 (50)	145 (32.73)	None
Date	85 (43.37)	60 (36.36)	45 (68.18)	11 (68.75)	201 (45.37)	Group 2 vs. Group 4; Group 1 vs. Group 3 (therefore cancer)
Attribution	99 (50.51)	67 (40.61)	37 (56.06)	7 (43.75)	210 (47.40)	None
All quality factors	50 (25.51)	32 (19.39)	20 (30.30)	4 (25)	106 (23.93)	None

Of the estimates, 39.3% were listed on a medical center's website and 31.4% were listed on government funded sites or data sources (including Orphanet). (Table 6) Orphanet was the source with the single highest number of estimates, 38. Estimates posted on industry or privately funded sites had the highest percentage of including all three quality factors (64.3%). Government funded websites had the highest number of quality estimates, but this represented only 38.9% of the estimates available on these sites. Only one estimate (.57%) listed on a medical center website included all three quality factors.

Table 6: Sector for estimates by orphan drug, rare cancer, and data quality status

	Group 1 (OD, RC) n=196	Group 2 (OD, no RC) n=165	Group 3 (no OD, RC) n=66	Group 4 (no OD, no RC) n=16	Total n=443	Total with quality n=106
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Government funded	52 (26.53)	40 (24.24)	34 (51.52)	13 (81.25)	139 (31.38)	54 (38.9)
Industry or private funding	14 (7.14)	22 (13.33)	5 (7.58)	1 (6.25)	42 (9.48)	27 (64.3)
Medical center or professional society	97 (49.49)	63 (38.18)	13 (19.70)	1 (6.25)	174 (39.28)	1 (.57)
Organization	33 (16.84)	40 (24.24)	14 (21.21)	1 (6.25)	88 (19.86)	24 (27.27)

Infrastructure for prevalence estimates

Having an orphan drug was a statistically significant predictor of having an organization, medical center, registry, ICD-10, and ICD-11 specific code. (Table 6) A total of 50 (62.5%) diseases had at least one patient organization. On average there were 3.1 organizations per disease. (Table 7) Neuroblastoma (group 1, cancer and has an orphan drug) had the most organizational representation with 19 organizations. Being a rare cancer was a statistically significant factor in the likelihood of the disease having an

organization. Only four the diseases in group 4, not cancer and no orphan drug, had organizational representation. Disease specific registries were available for 19 diseases. Medical centers were identified for 56 (70%) of the diseases. Testicular cancer (group 1) had the most identified medical centers with 96. Seven of the diseases had an organization that designates medical centers of excellence for the disease of interest. Only 19 diseases (23.75%) had an ICD-10 specific code and 43 diseases had an ICD-11 specific code (54%).

The total number of diseases listed in the SEER Coding and Staging Manual was not statistically significant by orphan drug status (p=.677). None of the diseases in the sample were included in the NNDSS system. One disease, methylmalonic acidemia with homocystinuria (group 2), was listed as a secondary condition in the Recommended Uniform Screening Panel (RUSP) for newborn screening.

Table 7: Prevalence infrastructure by group

The coefficients, standard error, and statistical significance for individual logistic regression results can be found in Appendix E.

	Group 1 (OD, RC)	**Group 2 (OD, no RC)**	**Group 3 (no OD, RC)**	**Group 4 (no OD, no RC)**	**Total**	**Factors and differences in groups that are statistically significant**
	n=20	**n=20**	**n=20**	**n=20**	**n=80**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Organization exists for disease	17 (85)	17 (85)	12 (60)	4 (20)	50 (63)	Group 2 vs. Group 4; Group 3 vs. Group 4
A disease specific organization exists	6 (30)	10 (50)	5 (25)	2 (10)	23 (29)	Group 3 vs. Group 4
A registry exists	4 (20)	11 (55)	3 (15)	1 (5)	19 (24)	Group 3 vs. Group 4; Group 1 vs. Group 3

A medical center exists	17 (85)	17 (85)	14 (70)	8 (40)	56 (70)	Group 3 vs. Group 4
ICD-10 Specific	7 (35)	8 (40)	3 (15)	1 (5)	19 (23.75)	Group 3 vs. Group 4
ICD-11 Specific	14 (70)	14 (70)	5 (25)	3 (15)	36 (45)	Group 3 vs. Group 4; Group 1 vs. Group 2

Table 8: Continuous prevalence infrastructure components by group

The coefficients, standard error, and statistical significance for individual linear regression results can be found in Appendix F.

	Group 1 (OD, RC) n=20	**Group 2 (OD, no RC) n=20**	**Group 3 (no OD, RC) n=20**	**Group 4 (no OD, no RC) n=20**	**Total n=80**	**Factors and differences in groups that are statistically significant**
	m (std)	**m (std)**	**m (std)**	**m (std)**	**m (std)**	
Number of organizations	5.5 (4.81)	4.45 (4.31)	2.1 (2.65)	0.25 (.55)	3.075 (4.0)	Group 3 vs. Group 4; Group 1 vs. Group 2
Number of medical centers	30.95 (25.20)	16.85 (23.91)	8.65 (13.61)	1.5 (3.68)	14.49 (21.4)	Group 3 vs. Group 4; Group 1 vs. Group 2; Group 1 vs. Group 3
Number of clinical trials	341.35 (518.49)	26.45 (39.33)	41.9 (115.73)	.9 (1.77)	102.65 (296.1)	Group 1 vs. Group 3; Group 1 vs. Group 2
Number of active clinical trials	102.85 (151.56)	8.45 (12.68)	11.4 (29.52)	.25 (.55)	30.74 (86.9)	Group 1 vs. Group 3; Group 1 vs. Group 2
PubMed disease results	7834.15 (9905.07)	2479.25 (3876.32)	1046.2 (1451.33)	425.1 (834.99)	2946.18 (6042.4)	Group 1 vs. Group 3; Group 1 vs. Group 2
PubMed incidence or prevalence results	626.65 (680.34)	142.15 (192.39)	126.75 (289.28)	41.7 (120.18)	234.31 (444.1)	Group 1 vs. Group 3; Group 1 vs. Group 2

The average number of PubMed search results per disease were 7,834 for Group 1 compared to 425 for group 4. Nueroblastoma (group 1) had the highest number of total

PubMed results with 38,880 and Acute lymphoblastic leukemia (ALL) (group 1) had the highest number of search results for incidence or prevalence data in PubMed (2,510). There was a statistically significant difference in the number of PubMed results when comparing Group 1 with either Group 3 or Group 2. One disease, Hutterite cerebroosteonephrodysplasia syndrome (group 4), had no results and 7 diseases did not have any search results for incidence or prevalence data in PubMed.

There were clinical trials registered for 71.25% of the diseases and active clinical trials for 60% of the diseases. (Table 7) The average number of active clinical trials for diseases with an orphan drug were 55.65 compared to 5.83 for diseases without an orphan drug, there were statistically significant differences between diseases in Group 1 and those in Group 3 or Group 2. (Table 8) Only 4 diseases in Group 4 had active clinical trials, while there were 19 (95%) in Group 1.

Discussion

The Cleveland model of the healthcare environment details the relationship between patients, clinical practice, and research to both inform and utilize information and technology.[81] For rare diseases this interplay provides context for the availability of prevalence information and the related challenges of rare disease knowledge and data quality. However, the data quality of that information is not meeting core standards of data information.[87] Overall, few rare diseases report the data sources used to establish prevalence. Diseases that have an orphan drug are statistically more likely to have infrastructure in the form of organizations, identified medical centers, registries, or ICD-11 specific codes to establish prevalence estimates in the future. An orphan drug approval can serve as a catalyst for increased medical knowledge and prevalence infrastructure.

Rare cancer was not seen to be a statistically significant factor in information availability, quality, or infrastructure. Our methods to establish prevalence through registries, claims data, or other methods require a substantial investment of resources and are not always reliable without a substantial sample size, a clear disease definition, and a significant investment of resources,[33,35,70–73,91] qualities many rare diseases do not exhibit.

Limitations

It is possible that the total prevalence of a disease is a confounding factor for the availability of information. For example, the identification of 500 cases of an emerging disease might result in more attention and opportunities for further investigation compared to a disease with only 50 identified cases. This study was meant to assess what we know about the prevalence of rare diseases or how we can ascertain this information, but the number of people impacted is likely a contributing factor to what is known. It would have been difficult to control for prevalence, based on the limited available information. This both contributes to the problem and highlights the need for the study.

It was not possible to complete searches for all 6,500 rare diseases; a sample of 80 rare diseases was chosen to allow for representation and analysis that would allow for informed comparisons by group, rare cancer, and orphan drug status. The sample did not control for disease diversity beyond the status of having an orphan drug or being a rare cancer. The overall heterogeneity of rare diseases made it difficult to account for the many potential factors that could be relevant in available prevalence information.

Age of onset and therapeutic category are two areas that could be confounding factors within the results. If some therapeutic categories have more rare diseases, the specialists and researchers in those areas may have developed increased strategies for

diagnosis, tracking, and patient support. Age of onset could impact prevalence estimates or infrastructure due to an increased concern about pediatric conditions and the loss of life due to early mortality. Therefore, diseases with pediatric onset may have a disproportionate level of infrastructure compared to later onset diseases. Ethical considerations for testing therapies for childhood diseases may mean that there are fewer orphan drugs for childhood diseases. Information about the breakdown of therapeutic categories for all rare diseases or differences based on age of onset are not available and could not be controlled for the purpose of this study.

The disease sample disproportionately included melanomas; 3% of rare cancers on the GARD list and 12% of cancers with an orphan drug are melanomas. In this study, 25% of rare cancers with an orphan drug are melanomas. Despite these sample limitations, the sample size is believed to be adequate to assess the current state of available infrastructure and to guide for future investigations or policy considerations.

The identification of the GARD list of rare diseases to generate the sample was based on GARD's status as one of the authoritative resources and leaders for rare disease information in the U.S. The list included diseases that were difficult to identify in other sources as the listing sometimes only included the name without a disease description. For example, one of the sample diseases was Renal cell carcinoma 4. There was no description of the disease listed in the GARD database, therefore it was difficult to determine if this was Stage 4 or Type 4. The GARD list also may have had duplication beyond what was indicated. In a few cases, other data sources indicated that a disease synonym existed, but in GARD that term had its own listing, indicating a unique condition. It is possible that the listed term was outdated and the records were describing

the same condition or that there is not scientific consensus on the disease definition. This could result in misclassification of the overall availability of information for the disease. This inconsistency is a valuable finding in understanding how we should approach the dissemination of rare disease information in the future and the challenges individuals face when searching for high-quality information.

There is also the potential of disease misclassification into the wrong group. For example, on the GARD website, "melanoma astrocytoma syndrome" is listed as having an approved drug, Aldesleukin[92]. However, the website for this condition states that it is "indicated for the treatment of adults with metastatic renal cell carcinoma (mRCC) or metastatic melanoma (mM)" and neither the prescribing information nor the drug website specifically mention "melanoma astrocytoma syndrome". It is possible that the drug treats all forms of melanoma, that it is used off-label, or that this syndrome is not well defined. Either way, the current information brings up questions related to how we name, classify, and describe diseases.

Some of the diseases included on the list were "familial" versions of other conditions, such as "familial pancreatic cancer". The distinction of a familial form of the condition has clinical importance for the risk of inheritance of the disease, but is difficult to differentiate in most data sources and requires family history in addition to an individual's medical records.[93,94] Familial diseases were considered distinct forms of the disease for the purpose of this study, but there are inconsistencies related to the importance of that distinction across data sources and in practice.

Systematized Nomenclature of Medicine- Clinical Terminology (SNOMED) is the clinical healthcare terminology system used in many electronic health records.[57]

SNOMED can capture clinical observations and was established to integrate with ICD-10 codes as part of the electronic health record systems.[95] SNOMED nomenclature and use happens largely behind the scenes in most electronic health records systems. Despite SNOMED being included in other studies to evaluate coding language for rare diseases, it was not included in this study as it is not extensively used for research purposes in the U.S. as most methodologies rely on ICD codes.[80]

The number of PubMed search results could be skewed by additional factors such as diseases that had an animal form. It is also possible that a study had the primary goal of estimating the total number of people impacted by the disease, but it did not appear in the "incidence or prevalence" search. PubMed searches were meant to serve as indicator variables for the extent of scientific interest and current investment in the disease and the impact is likely minimal.

U.S. based clinical trials are required to be submitted and listed on ClinicialTrials.gov if the study purpose is to evaluate a drug, biologic or device.[96] Researchers can voluntarily submit their study if they are investigating other methods, but investigators conducting observational studies are not required to do so. Therefore, it is likely that diseases that have an orphan product approval in the U.S. would have had a study that was required to be posted on the site. The use of actively recruiting or on-going studies is a more accurate indicator of current or future research investment.

Data quality was assessed using a widely cited set of principles.[87] Some of the disease estimates were identified as having attribution, but the listed information only provided an organization source, such as the American Cancer Society or Orphanet. The same disease estimate in those data sources may not have included attribution or the

listed author was only at the organizational level, such as a medical advisory board for the organization. This would make it difficult to trace the data estimate to the original source. The author or attributed sources were often trusted organizations who would have access to expert reviewers, but it may misrepresent the reader's ability to accurately identify how estimates were determined. Authors were listed at an organizational level for 9% of the estimates and 30% for the attribution of estimates. The majority of these estimates were missing one of the other two data quality measures, limiting the overall impact of misclassification of the estimate as high-quality data.

Identifying specific rare diseases in data sources

Identifying a disease across case studies and in medical terminologies is critical to advancing research. The importance of consistent identification and naming conventions for rare diseases has led to the establishment of collaborations such as the Monarch Initiative and IRDiRC to map terminologies across resource sites and to accelerate translational research.[60,97,98] Some data sources, such as Orphanet, provide the known linked identifiers from a variety of places, including OMIM, ICD-10, and GARD. However, other resources are more isolated in the information that they provide, which makes it more difficult to track diseases with less information across data sources. Although NIH collaborates on many of the international initiatives, the data resource list does not currently reflect some of the on-going international efforts to improve naming conventions, such as providing the identifier for other sources.

Personalized medicine and a trend towards common diseases being subcategorized into distinct disorders are also impacting the healthcare landscape.[17,28,38] The increase in genetic testing is changing the information that is available to patients[99]

and the types of treatments that are in development.[17] In 2010, an estimated 10% of FDA approved drugs contained pharmacogenomic information.[77] Targeted drugs have the potential to result in fewer adverse events and decrease healthcare costs.[100–102] This approach requires clinically validated biomarkers and evidence that the resulting treatment is effective, safe, and more cost-effective than drugs already on the market. Understanding the relationship between prevalence, personalized medicine, and drug incentives will be necessary to prepare for costs and potential inequities in our healthcare system. As our ability to pinpoint genetic variations of diseases increases, we will need to find ways to provide information on these differences to clinicians and patients. Our infrastructure to identify and treat these patients may not be ready for these types of advances. This may to lead to increased inequities based on patient characteristics and the ability to access to elite providers.

Beyond genetic variation, multiple diseases in the sample were listed under a broader umbrella term in both NORD (6.25%) and Medscape (23.75%). Grouping diseases under umbrella terms is useful for pooling resources and sharing medical advances; rare diseases have even been credited with providing medical insights for related common conditions.[91,103] However, evidence indicates that small differences in cancer type and location can impact prognosis[17] and the increasing use of genetic data for biologics[101] necessitates specificity. Understanding the differences between diseases within an umbrella grouping can impact treatment effectiveness and health outcomes. There is also a statistically significant difference in the likelihood of being listed under a more specific name according to the presence of an orphan drug, which may indicate some of the ways drug companies access the incentives of the ODA.

The importance of this consistency and ability to follow the depth of current medical knowledge may not be necessary to the average medical consumer. However, many rare disease patients and caregivers express the need to become experts in their disease due to the limited information and knowledge among many health experts.[7,104,105] Many rare disease patient organizations, which are often founded by caregivers, become the driving force behind research and product innovation.[106–110] Finding ways to link data across information sources becomes necessary to ensure that clinicians writing case studies, researchers conducting studies, and patients establishing organizations can work together to identify advances.

Prevalence data quality

Statistical analysis for prevalence requires knowledge about the anticipated size of the population, for small populations these variations can impact the accuracy of prevalence calculations.[25,37] The need for baseline information and an ability to identify the source of these estimates is a necessity for data integrity. Data sources, even trusted sources such as medical centers and government websites do not always provide the information needed for individuals to assess the quality or relevance of the data. In the Google searches for centers and organizations estimates for diseases were often posted without any reference to the data source for the estimate. Often, these estimates were consistent across multiple sites, without attribution.

Industry had the most complete data quality information (64% of estimates) compared to any other source. This may be attributed to the fact that they are less likely to have implicit trust from consumers. It should be concerning that only 1 estimate available on a medical center website had all three data quality factors. Health websites

should provide the information necessary for individuals to find the original source of the information to allow them to critically assess the information and current scientific knowledge.

The primary audience of interest for health websites informs the content and depth of technical language. The funding source may also impact the type of content displayed and the date of updates. NORD, Genetic Home Reference, and Medscape were the sites with a statistically significant difference in posted information by orphan drug status. OMIM only had two prevalence estimates for diseases without an orphan drug. The listings in OMIM are often the synthesis of other published studies to identify and link information about genes and disease phenotypes, which could explain why diseases with less published data from other sources are unlikely to appear in this data source. Some of the entries in NORD's Rare Disease Database are provided through educational grants from pharmaceutical companies or disease specific organizations.[11] Similarly, Medscape receives grants and advertising revenue.[111] Both organizations have editorial and conflict of interest policies on the content of articles, but the decision related to which content is produced, is likely impacted by the availability of resources and easily identifiable disease experts.

Keratoconus (Group 2) had the highest number of consistent estimates (19). Of these, only 1 referenced the source of these estimates, a study published in 1986 that found a total of 64 residents of Olmsted County, Minnesota were diagnosed between 1935 and 1982.[112] Would we still consider these results generalizable to a modern US population? More recent studies have been conducted internationally and indicated that the impacted population may be larger than previously estimated.[113] In the U.S., no

additional prevalence studies have been conducted. The most recent orphan drug designation was filed in 2017, indicating that pharmaceutical companies may still be able to benefit from current prevalence estimates. However, by not investing in new estimates we might be missing other key data trends such as disparities in who is impacted by the condition or inequities in who is being diagnosed or treated. This condition has an effective treatment, but for other conditions outdated statistics may represent missed opportunities.

Infrastructure for prevalence estimates

The findings related to ICD-10 codes are consistent with similar investigations in the literature.[62,66] It is well documented that ICD-10 codes do not accurately capture rare diseases. A disease with an approved orphan drug would necessitate a billing code for submitting claims to the insurance company, therefore, it is not surprising that there was a statistically significant difference based on orphan drug status for ICD-10 and ICD-11.

Rare disease patient organizations have a well-documented history of driving change in the rare disease space and collaborating with the other stakeholders. However, if a disease does not generate interest or support from beyond the identified population, the organization may not be financially sustainable. Which may indicate why the presence of an orphan drug impacts the likelihood that an organization for the disease exists. Rare cancer status was a statistically significant indicator of having an available patient organization, but not for the number of organizations. Many of the cancers included in the study were found to be naturally grouped with other diseases or listed under broader disease groupings. It is possible that rare cancers, despite being classified as rare diseases, are viewed differently by patients, families, and the infrastructure that

supports them. There may be a closer alignment to cancer, rare or common, then to rare diseases. Many top selling orphan drugs are oncology drugs,[19] and this study found a relationship between rare cancer and a higher number of available orphan drugs. Decisions to reinforce infrastructure and stimulate the investment in rare diseases, should consider the goals and recognize the disparities in what is available based on disease and therapeutic category.

Registries, organizations, and medical centers for rare cancers often did not include the specific subtypes of the cancer included in the study. Oncologists may be capturing this information, but it is not being reported in scientific and patient resources. It is also possible that the federal investment in cancer infrastructure through SEER changes the need for smaller registries to be established and maintained for individual cancers. Registry data does not always include the detailed site and histology information for rare cancers.[46] Indicating a need for a better way to capture this information in the future.

Having an orphan drug is a statistically significant factor for more infrastructure. However, it is difficult to determine the direction of the relationship between pharmaceutical interest and infrastructure. Four diseases had an orphan designation without an FDA approval for any orphan drug. There was a statistically significant difference ($p=.0002$) between the average number of prevalence estimates available for diseases with an orphan designation (7.5) compared to diseases that did not have an orphan drug designation (1.44). These diseases were not statistically more likely to have an organization and only one of the four had an ICD-10 code. This could support a theory that a disease needs some research or investment prior to attracting pharmaceutical

investment and the additional infrastructure follows, potentially with pharmaceutical support.

Policy implications

Rare disease patient organizations are an increasingly integral force in driving research.[35,106,108,109] Establishing systems that can provide higher quality raw data could help drive other research goals; establishing natural history progression, investigating disease risk, identifying treatment protocols, and developing treatments. The pace of scientific advancement, especially in genetics, provides hope to many patients.[56,102,114] There are international efforts underway to leverage these technologies by mapping disease terminologies across data sources[97,98] and establishing prevalence estimates.[76] To realize these benefits in the U.S., especially with the geographic diversity and inequitable access to high quality healthcare, supportive infrastructure must be established to support these efforts in a systematic way instead of a disease-by-disease approach.

When discussing the U.S. definition for rare diseases, it is important to acknowledge that the current definition is a static prevalence. As the U.S. population grows, the threshold for attaining rarity will become less inclusive over time, rather than staying proportional to the population. In 1983, the year the Orphan Drug Act was passed, the population of the U.S. was 233.8 million[115], in 2019 the estimated population was roughly 328.6 million[116]. In 1983, to be considered a rare disease it needed to impact .086% of the population, whereas in 2018 a disease would need to impact .061% of the population. Although this difference is currently minimal, over time, we must decide if this metric needs to be reconsidered and if the definition itself can help us meet policy and population health goals.

As is outlined in the healthcare infrastructure model, the technological needs and information are both being generated and demanded by consumers, researchers, and clinicians simultaneously. This can occur as new conditions are being identified and information is being collected across platforms. Disease experts and clinicians, guided by patients, should drive infrastructure needs, instead of pharmaceutical companies. It is not possible to ascertain the direction of the relationship between a disease having an orphan drug and additional infrastructure. It is difficult to determine if a disease requires infrastructure prior to attracting pharmaceutical interest or if a disease gains infrastructure support based on pharmaceutical investment.

The heterogeneity of rare diseases and the size of the U.S. makes it unlikely that a one-size fits all approach would adequately account for the diverse needs associated with capturing, tracking, and estimating prevalence. Most rare diseases are unlikely to meet the criteria needed to justify establishing a surveillance system.[47] Under our current system, organizations or medical centers are the most likely champions to represent a rare disease and invest in registries or other disease specific structures. Ultimately, pharmaceutical companies have an interest in prevalence, but not until they have a product in development. Leveraging long-term pharmaceutical interest in prevalence estimates may provide an opportunity to utilize some of the application fees for the FDA approval process to establish a fund to conduct and validate rare disease prevalence studies.

Entities that maintain their own tracking infrastructure such as registries should investigate data sharing agreements with entities tracking the same diseases.[39,58] Of diseases that had at least one patient organization, 82% had more than one organization.

This represents a splintering of resources and knowledge that could complicate the ability to validate estimates. Medical centers may be able to attract patients if they establish disease centers of excellence within their facility. Patient organizations have begun to identify and designate these entities to provide patients with recommendations for where to find disease experts. Patients who are not satisfied with care at their local medical facilities may seek a specialized medical center. These centers will not be able to develop in all geographic regions.

Clinicians are on the front line of disease tracking. Even if a patient seeks out a patient organization and decides to independently join a registry, that would be based on a diagnosis they received from a physician. Physicians are trained to look for the most likely solution to a problem, "when you hear hoofbeats, think of horses not zebras". If a condition is only documented as impacting a handful of patients, it may be more difficult for a medical professional to consider the possibility of the rare "zebra", leaving patients without a diagnosis or appropriate care. Diagnosis is a well-documented challenge for rare disease patients, which may result in multiple interactions with the healthcare system in multiple locations before an accurate diagnosis is achieved.[28] Disease experts may be outside of an individual's geographic region[65] and understanding care patterns is crucial when assessing the limitations of using clinical data, especially if it is limited to one site or database.[73] Research is also reliant on collecting substantial evidence prior to developing treatment guidelines, but understanding what is substantial must be based on the estimated population. Payers may be reluctant to authorize experimental procedures without clear medical guidelines, especially if the evidence is less robust then for a common condition.

Researchers who investigate estimates are reliant on ICD codes to indicate a specific condition or to sort through case notes and indicator codes to validate the diagnosis. Studies have found that different individuals code and interpret medical conditions differently.[61] It is important to work with clinicians to understand how we can better interpret clinical notes to further validate diseases, especially ones that do not have a specific ICD code. This will become more critical as genetic data becomes more prominent in medical practice, a shift that many physicians feel ill-equipped to handle.[117] Rare diseases do not provide a compelling case of the ability of our current infrastructure to track and disseminate this information to a broad clinical base.

Data quality will increase if there is greater collaboration between clinicians and those working to provide these estimates; researchers, registries, and organizations.[46] Maintaining high-quality biologic samples and biobanks with appropriate informed consent from patients can provide a base of samples for future investment and validation. Centralized infrastructure for labs could provide greater consistency with the identification and diagnosis of rare conditions.[46] Establishing rare disease centers of excellence, such as through expanding the Rare Disease Clinical Research Network[42] would provide more opportunities to collect prevalence data and increase our ability to track natural history data.

The U.S. should continue to collaborate with international efforts to address rare diseases as a global public health challenge. The importance of including the patient voice in drug development and state-based coalitions is well established.[106] To identify the appropriate next steps and ensure that rare diseases are being addressed holistically within our healthcare system, a national rare disease plan should be created. There has

been successful patient advocacy representation in the efforts to advance the science behind rare diseases, but national plans can address aspects of care including coordination of care, patient engagement, and early access drug programs.[75] A national plan would help identify and create a roadmap to prioritize investments that would benefit the rare disease community, such as adopting the finalized ICD-11 codes.

Despite a number of systems to identify high-quality medical or health information,[118] many sites do not follow core standards for high-quality health information. Even trusted sources such as government websites should commit to data quality standards to ensure consumers can identify the source of information. Rare disease studies may be limited in scope and it is important for individuals to evaluate the quality of the information source. Identifying the source of previous estimates may help establish new networks for collaboration. Patient advocates or emerging researchers may want to contact the authors of previous studies to establish partnerships at clinical sites or to establish data sharing agreements with registries.

Any new policies around infrastructure and tracking must also consider the ethical components of patient identification. HIPPA protections limit the ability to share data across platforms or with unauthorized entities. Although it is critical to avoid duplication of data for diseases that may have multiple registries, these needs must still protect patients and gather consent. Despite current protections for individuals with preexisting conditions under the Patient Protection and Affordable Care Act's (ACA),[119] there is political pressure to dismantle this law. It would be naïve to ignore these concerns without ensuring the societal interest in patient identification is not at the expense of individual harm.

Conclusion

Current infrastructure to provide prevalence estimates would require collaboration with medical centers, organizations, registries, and researchers conducting insurance claims studies using ICD-10 codes. For the majority of rare diseases, this would require establishing a clearer disease definition and validating the name of the disease across data sites. Data quality for existing rare diseases is often inadequate according to key data quality metrics. Rare cancers are not more likely to have better quality data or infrastructure compared to other rare diseases. Diseases with an orphan drug have more sources of disease information, but this may not result in higher quality prevalence estimates overall. Diseases with an orphan drug do have more available infrastructure, but the direction of this relationship between information and pharmaceutical investment cannot be determined. Establishing data infrastructure and investing in the verification of prevalence data is important for clinicians, patients, and researchers. The U.S. should continue to collaborate internationally on initiatives to support rare disease research and find ways to invest in systems and policies that will support better data quality.

References

1. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. NIH.gov. https://rarediseases.info.nih.gov/. Accessed January 13, 2017.

2. *Orphan Drug Act*. Vol USC 21 I Subchapter D Part 316; 1983. https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21. Accessed January 13, 2017.

3. European Commission. Rare diseases. Public Health - European Commission. https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en. Published November 25, 2016. Accessed March 5, 2019.

4. Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, Field MJ, Boat TF. *Profile of Rare Diseases*. National Academies Press (US); 2010. https://www.ncbi.nlm.nih.gov/books/NBK56184/. Accessed March 31, 2017.

5. R de Vrueh, ERF Baekelandt, JMH de Haan. *Priority medicines for Europe and the world "A public health approach to innovation."* World Health Organizatoin; 2013. https://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf. Accessed July 2, 2019.

6. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

7. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88. doi:10.1186/s12875-016-0488-x

8. Geissler, Oliver, Weinman. *Mapping out the Similarities and Differences between Rare Cancers and Rare Diseases*. European Organisation for Rare Diseases; 2015. https://www.eurordis.org/sites/default/files/rare-cancers-2015-2016.pdf. Accessed July 8, 2019.

9. Greenlee RT, Goodman MT, Lynch CF, Platz CE, Havener LA, Howe HL. The occurrence of rare cancers in U.S. adults, 1995-2004. *Public Health Rep Wash DC 1974*. 2010;125(1):28-43. doi:10.1177/003335491012500106

10. Gatta G, Trama A, Capocaccia R, RARECARENet Working Group. Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. September 2017. doi:10.1016/j.ejso.2017.08.018

11. National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

12. Pillai RK, Jayasree K. Rare cancers: Challenges & issues. *Indian J Med Res*. 2017;145(1):17-27. doi:10.4103/ijmr.IJMR_915_14

13. Cohen S. *Differentials in the Concentration of Health Expenditures across Population Subgroups in the U.S., 2013*. Rockville, MD: Agency for Healthcare Research and Quality; 2015. https://meps.ahrq.gov/data_files/publications/st480/stat480.shtml. Accessed September 22, 2017.

14. Gallo AM, Hadley EK, Angst DB, Knafl KA, Smith CAM. Parents' concerns about issues related to their children's genetic conditions. *J Spec Pediatr Nurs*. 2008;13(1):4-14. doi:10.1111/j.1744-6155.2008.00129.x

15. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin*. 2018;68(2):153-165. doi:10.3322/caac.21443

16. Zafar SY. Financial toxicity of cancer care: it's time to intervene. *J Natl Cancer Inst*. 2016;108(5). doi:10.1093/jnci/djv370

17. Schott AF, Welch JJ, Verschraegen CF, Kurzrock R. The National Clinical Trials Network: conducting successful clinical trials of new therapies for rare cancers. *Semin Oncol*. 2015;42(5):731-739. doi:10.1053/j.seminoncol.2015.07.010

18. U. S. Government Accountability Office. *Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue*.; 2018. https://www.gao.gov/products/GAO-19-83?utm_source=onepager&utm_medium=email&utm_campaign=email_HC. Accessed May 3, 2019.

19. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis*. 2011;6:42. doi:10.1186/1750-1172-6-42

20. Alhawwashi S, Seoane-Vazquez E, Eguale T, Rodriguez-Monguio R. Prices of drugs for chronic use with orphan designation in the United States (1983–2014). *Value Health*. 2016;19(3):A4. doi:10.1016/j.jval.2016.03.040

21. U.S. Food & Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed March 31, 2017.

22. Aitken M, Kleinrock M. *Orphan Drugs in the United States Growth Trends in Rare Disease Treatments*. Parsippany, NJ: IQVIA Institute; 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf. Accessed November 20, 2018.

23. Stockklausner C, Lampert A, Hoffmann GF, Ries M. Novel Treatments for Rare Cancers: The U.S. Orphan Drug Act Is Delivering—A Cross-Sectional Analysis. *The Oncologist*. 2016;21(4):487-493. doi:10.1634/theoncologist.2015-0397

24. U.S. Food & Drug Administration. *Rare Diseases: Common Issues in Drug Development Guidance for Industry*. Food and Drug Administration; 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf. Accessed January 13, 2017.

25. Centers for Disease Control and Prevention. *Morbidity Frequency Measures*. Principles of Epidemiology in Public Health Practice, Third Edition An Introduction to Applied Epidemiology and Biostatistics; 2012. https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section2.html. Accessed March 15, 2019.

26. Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. 2015;18(6):906-914. doi:10.1016/j.jval.2015.05.008

27. Orphanet Report Series. *Prevalence and Incidence of Rare Diseases: Bibliographic Data*; 2019. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. Accessed March 11, 2019.

28. Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. *Adv Exp Med Biol*. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

29. Fine JD. Epidermolysis bullosa. Application of epidemiologic principles to the study of a group of rare diseases via a disease registry. *Dermatol Clin*. 1995;13(3):659-670.

30. Reynolds TM, Mewies C, Hamilton J, Wierzbicki AS, PATHFINDER Project Collaboration group. Identification of rare diseases by screening a population selected on the basis of routine pathology results-the PATHFINDER project: lysosomal acid lipase/cholesteryl ester storage disease substudy. *J Clin Pathol*. 2018;71(7):608-613. doi:10.1136/jclinpath-2017-204727

31. Gliklich RE, Leavy MB, Karl J, Campion DM, Levy D, Berliner E. A framework for creating standardized outcome measures for patient registries. *J Comp Eff Res*. 2014;3(5):473-480. doi:10.2217/cer.14.38

32. Ayme S, Kole A, Rodwell C. *Patient Registries in the Field of Rare Diseases*. Rare Disease Task Force Report; 2011. http://www.eucerd.eu/EUCERD/upload/file/RDTFReportRegistriesJuly2011.pdf. Accessed April 12, 2017.

33. Daneshvari S, Youssof S, Kroth PJ. The NIH Office of Rare Diseases Research Patient Registry Standard: A Report from the University of New Mexico's Oculopharyngeal Muscular Dystrophy Patient Registry. *AMIA Annu Symp Proc*. 2013;2013:269-277.

34. Yeoh ZW, Navaratnam V, Bhatt R, McCafferty I, Hubbard RB, Johnson SR. Natural history of angiomyolipoma in lymphangioleiomyomatosis: implications for screening and surveillance. *Orphanet J Rare Dis*. 2014;9:151. doi:10.1186/s13023-014-0151-3

35. Woodward L, Johnson S, Walle JV, et al. An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry. *Orphanet J Rare Dis*. 2016;11(1):154. doi:10.1186/s13023-016-0537-5

36. Baggi F, Mantegazza R, Antozzi C, Sanders D. Patient registries: useful tools for clinical research in myasthenia gravis. *Ann N Y Acad Sci*. 2012;1274:107-113. doi:10.1111/j.1749-6632.2012.06771.x

37. Papoz L, Balkau B, Lellouch J. Case counting in epidemiology: limitations of methods based on multiple data sources. *Int J Epidemiol*. 1996;25(3):474-478.

38. Kotecha RS, Kees UR, Cole CH, Gottardo NG. Rare childhood cancers--an increasing entity requiring the need for global consensus and collaboration. *Cancer Med*. 2015;4(6):819-824. doi:10.1002/cam4.426

39. Kodra Y, Posada de la Paz M, Coi A, et al. Data Quality in Rare Diseases Registries. *Adv Exp Med Biol*. 2017;1031:149-164. doi:10.1007/978-3-319-67144-4_8

40. Hennekam RCM. Care for patients with ultra-rare disorders. *Eur J Med Genet*. 2011;54(3):220-224. doi:10.1016/j.ejmg.2010.12.001

41. Grosse SD, James AH, Lloyd-Puryear MA, Atrash HK. A public health framework for rare blood disorders. *Am J Prev Med*. 2011;41(6 Suppl 4):S319-323. doi:10.1016/j.amepre.2011.09.010

42. Rare Diseases Clinical Research Network. RDCRN Contact Registry. https://www.rarediseasesnetwork.org/registry. Accessed March 8, 2019.

43. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. About the SEER Program. SEER. https://seer.cancer.gov/about/overview.html. Accessed March 8, 2019.

44. Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. *Am J Prev Med*. 2010;38(4 Suppl):S475-481. doi:10.1016/j.amepre.2009.12.023

45. Centers for Disease Control and Prevention. About Community Counts. Community Counts. https://www.cdc.gov/ncbddd/hemophilia/communitycounts/about.html. Published August 8, 2018. Accessed March 8, 2019.

46. Trama A, Marcos-Gragera R, Sánchez Pérez MJ, et al. Data quality in rare cancers registration: the report of the RARECARE data quality study. *Tumori*. 2017;103(1):22-32. doi:10.5301/tj.5000559

47. Nsubuga P, White ME, Thacker SB, et al. Public Health Surveillance: A Tool for Targeting and Monitoring Interventions. In: Jamison DT, Breman JG, Measham AR, et al., eds. *Disease Control Priorities in Developing Countries*. 2nd ed. Washington (DC): World Bank; 2006. http://www.ncbi.nlm.nih.gov/books/NBK11770/.

48. German RR, Lee LM, Horan JM, et al. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. *MMWR*. 2001;50(RR-13):1-35-7.

49. Jackson JM, Crider KS, Olney RS. Population-based surveillance for rare congenital and inherited disorders: models and challenges. *Adv Exp Med Biol*. 2010;686:133-150. doi:10.1007/978-90-481-9485-8_9

50. Taruscio D, Vittozzi L, Rocchetti A, Torreri P, Ferrari L. The Occurrence of 275 Rare Diseases and 47 Rare Disease Groups in Italy. Results from the National Registry of Rare Diseases. *Int J Environ Res Public Health*. 2018;15(7). doi:10.3390/ijerph15071470

51. Centers for Disease Control and Prevention. 2017 Nationally Notifiable Conditions. National Notifiable Diseases Surveillance System (NNDSS). https://wwwn.cdc.gov/nndss/conditions/search/. Accessed April 19, 2017.

52. Elliott EJ, Nicoll A, Lynn R, Marchessault V, Hirasing R, Ridley G. Rare disease surveillance: An international perspective. *Paediatr Child Health*. 2001;6(5):251-260.

53. Centers for Disease Control and Prevention. Birth Defects State-based Tracking. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/birthdefects/states/index.html. Published November 30, 2017. Accessed January 10, 2018.

54. U.S. Health Resources & Services Administration. Recommended Uniform Screening Panel. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed March 4, 2019.

55. Schieppati A, Henter J-I, Daina E, Aperia A. Why rare diseases are an important medical and social issue. *Lancet Lond Engl*. 2008;371(9629):2039-2041. doi:10.1016/S0140-6736(08)60872-7

56. Baynam G, Bowman F, Lister K, et al. Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework. *Adv Exp Med Biol*. 2017;1031:55-94. doi:10.1007/978-3-319-67144-4_4

57. Fung KW, Richesson R, Bodenreider O. Coverage of rare disease names in standard terminologies and implications for patients, providers, and research. *AMIA Annu Symp Proc*. 2014;2014:564-572.

58. EURORDIS, NORD, CORD. *EURORDIS-NORD-CORD Joint Declaration of 10 Key Principles of Rare Disease Patient Registries.* 2012. http://download.eurordis.org/documents/pdf/EURORDIS_NORD_CORD_JointDec_Registries_FINAL.pdf. Accessed April 12, 2017.

59. European Union Committee of Experts on Rare Diseases. Smmary of the EUCERD/Eurogentest Workshop on Cross-Referencing of Terminologies. In: Paris, France; 2012. http://www.eucerd.eu/wp-content/uploads//2015/03/EGTEUCERD_Terminologies_270912_WP5.pdf. Accessed March 7, 2019.

60. International Rare Diseases Research Consortium. International Consortium of Human Phenotype Terminologies (ICHPT). IRDiRC. http://www.irdirc.org/activities/task-forces/international-consortium-of-human-phenotype-terminologies/. Published December 1, 2017. Accessed March 7, 2019.

61. Andrews JE, Richesson RL, Krischer J. Variation of SNOMED CT coding of clinical research concepts among coding experts. *J Am Med Inform Assoc*. 2007;14(4):497-506. doi:10.1197/jamia.M2372

62. Aymé S, Bellet B, Rath A. Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding. *Orphanet J Rare Dis*. 2015;10(1):35. doi:10.1186/s13023-015-0251-8

63. Centers for Medicare & Medicaid Services. 2016-ICD-10-CM-and-GEMs. https://www.cms.gov/Medicare/Coding/ICD10/2016-ICD-10-CM-and-GEMs.html. Published October 8, 2015. Accessed July 18, 2018.

64. ICD - ICD-10-CM - International Classification of Diseases, Tenth Revision, Clinical Modification. https://www.cdc.gov/nchs/icd/icd10cm.htm. Published July 1, 2019. Accessed July 9, 2019.

65. Smith MG, Royer J, Mann JR, McDermott S. Using Administrative Data to Ascertain True Cases of Muscular Dystrophy: Rare Disease Surveillance. *JMIR Public Health Surveill*. 2017;3(1):e2. doi:10.2196/publichealth.6720

66. Rodwell C, Aymé S. Rare disease policies to improve care for patients in Europe. *Biochim Biophys Acta*. 2015;1852(10 Pt B):2329-2335. doi:10.1016/j.bbadis.2015.02.008

67. Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Inform Assoc*. 2013;20(e2):e349-354. doi:10.1136/amiajnl-2013-001827

68. Leake J, Albani S, Kao A, et al. Acute Disseminated Encephalomyelitis in Childhood: Epidemiologic, Clinical and Laboratory Features. *Pediatr Infect Dis J*. 2004;23(8):756-764. doi:10.1097/01.inf.0000133048.75452.dd

69. Ruiz E, Ramalle-Gómara E, Quiñones C, Rabasa P, Pisón C. Validation of diagnosis of aplastic anaemia in La Rioja (Spain) by International Classification of Diseases codes for case ascertainment for the Spanish National Rare Diseases Registry. *Eur J Haematol*. 2015;94(5):400-403. doi:10.1111/ejh.12432

70. Munshi N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. *Leuk Lymphoma*. 2015;56(5):1252-1260. doi:10.3109/10428194.2014.953145

71. Williams SE, Carnahan R, Krishnaswami S, McPheeters ML. A systematic review of validated methods for identifying transverse myelitis using administrative or claims data. *Vaccine*. 2013;31 Suppl 10:K83-87. doi:10.1016/j.vaccine.2013.03.074

72. Lee CD, Williams SE, Sathe NA, McPheeters ML. A systematic review of validated methods to capture several rare conditions using administrative or claims data. *Vaccine*. 2013;31:K21-K27. doi:10.1016/j.vaccine.2013.03.044

73. Kaye WE, Sanchez M, Wu J. Feasibility of creating a National ALS Registry using administrative data in the United States. *Amyotroph Lateral Scler Front Degener*. 2014;15(5-6):433-439. doi:10.3109/21678421.2014.887119

74. Dal J, Skou N, Nielsen EH, Jørgensen JOL, Pedersen L. Acromegaly according to the Danish National Registry of Patients: how valid are ICD diagnoses and how do patterns of registration affect the accuracy of registry data? *Clin Epidemiol*. 2014;6:295-299. doi:10.2147/CLEP.S63758

75. Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet J Rare Dis*. 2017;12(1):63. doi:10.1186/s13023-017-0618-0

76. *Prevalence and Incidence of Rare Diseases: Bibliographic Data*. European Commission; 2017. https://ec.europa.eu/health/rare_diseases/orphanet/report_en. Accessed April 19, 2017.

77. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010; 363(4):301-304. doi:10.1056/NEJMp1006304

78. Priyanka P, Hadi YB, Reynolds GJ. Analysis of the Patient Information Quality and Readability on Esophagogastroduodenoscopy (EGD) on the Internet. *Can J Gastroenterol Hepatol*. 2018;2018:2849390. doi:10.1155/2018/2849390

79. San Giorgi MRM, de Groot OSD, Dikkers FG. Quality and readability assessment of websites related to recurrent respiratory papillomatosis. *The Laryngoscope*. 2017;127(10):2293-2297. doi:10.1002/lary.26521

80. Pasceri E. Analyzing rare diseases terms in biomedical terminologies. *JLIS.it*. 2012;3(1). doi:10.4403/jlis.it-4783

81. Cleveland AD. Miles to go before we sleep: education, technology, and the changing paradigms in health information. *J Med Libr Assoc*. 2011;99(1):61-69. doi:10.3163/1536-5050.99.1.011

82. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Rare Cancers. https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers. Accessed July 19, 2018.

83. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. List of FDA Orphan Drugs. https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs. Accessed July 19, 2018.

84. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Diseases. https://rarediseases.info.nih.gov/diseases/browse-by-first-letter. Accessed July 19, 2018.

85. Comprehensive Cancer Information. National Cancer Institute. https://www.cancer.gov/. Published January 1, 1980. Accessed August 5, 2019.

86. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Adm Policy Ment Health*. 2015;42(5):533-544. doi:10.1007/s10488-013-0528-y

87. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveant lector et viewor--Let the reader and viewer beware. *JAMA*. 1997;277(15):1244-1245.

88. Kang R, Lipner S. Assessment of internet sources on subungual melanoma. *Melanoma Res*. August 2018. doi:10.1097/CMR.0000000000000508

89. World Health Organization. ICD-11 - Mortality and morbidity statistics. https://icd.who.int/dev11/l-m/en. Accessed July 18, 2018.

90. U.S. National Library of Medicine. ClinicalTrials.gov. ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed July 18, 2018.

91. Bellgard MI, Napier KR, Bittles AH, et al. Design of a framework for the deployment of collaborative independent rare disease-centric registries: Gaucher disease registry model. *Blood Cells Mol Dis*. January 2017. doi:10.1016/j.bcmd.2017.01.013

92. Prometheus Laboratories Inc. Proleukin®(aldesleukin)Immunotherapy for mM and mRCC. https://www.proleukin.com/. Published October 2017. Accessed April 18, 2019.

93. Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. *Cancer Lett*. 2016;381(1):269-277. doi:10.1016/j.canlet.2016.07.022

94. Hemminki K, Li X, Sundquist K, Sundquist J. Familial risks for common diseases: etiologic clues and guidance to gene identification. *Mutat Res*. 2008;658(3):247-258. doi:10.1016/j.mrrev.2008.01.002

95. U.S. National Library of Medicine. SNOMED CT to ICD-10-CM Map. https://www.nlm.nih.gov/research/umls/mapping_projects/snomedct_to_icd10cm.html. Accessed August 16, 2018.

96. ClinicalTrials.gov Background - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/about-site/background. Accessed August 6, 2019.

97. About Monarch. https://monarchinitiative.org/page/about. Accessed July 15, 2019.

98. Cutillo CM, Austin CP, Groft SC. A Global Approach to Rare Diseases Research and Orphan Products Development: The International Rare Diseases Research Consortium (IRDiRC). *Adv Exp Med Biol*. 2017;1031:349-369. doi:10.1007/978-3-319-67144-4_20

99. Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic Test Availability And Spending: Where Are We Now? Where Are We Going? *Health Aff Proj Hope*. 2018;37(5):710-716. doi:10.1377/hlthaff.2017.1427

100. Tambuyzer E. Towards a framework for personalized healthcare: lessons learned from the field of rare diseases. *Pers Med*. 2010;7(5):569-586. doi:10.2217/pme.10.52

101. Dolled-Filhart MP, Lordemann A, Dahl W, Haraksingh RR, Ou-Yang C-W, Lin JC-H. Personalizing rare disease research: how genomics is revolutionizing the diagnosis and treatment of rare disease. *Pers Med*. 2012;9(8):805-819. doi:10.2217/pme.12.97

102. Lee S, Choi M. Ultra-rare Disease and Genomics-Driven Precision Medicine. *Genomics Inform*. 2016;14(2):42-45. doi:10.5808/GI.2016.14.2.42

103. Aflaki E, Westbroek W, Sidransky E. The Complicated Relationship between Gaucher Disease and Parkinsonism: Insights from a Rare Disease. *Neuron*. 2017;93(4):737-746. doi:10.1016/j.neuron.2017.01.018

104. Curtis K, Foster K, Mitchell R, Van C. Models of Care Delivery for Families of Critically Ill Children: An Integrative Review of International Literature. *J Pediatr Nurs*. 2016;31(3):330-341. doi:10.1016/j.pedn.2015.11.009

105. Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive Care Needs of Parents With a Child With a Rare Disease: A Qualitative Descriptive Study. *J Pediatr Nurs*. 2016;31(3):e207-218. doi:10.1016/j.pedn.2015.10.022

106. Koay PP, Sharp RR. The role of patient advocacy organizations in shaping genomic science. *Annu Rev Genomics Hum Genet*. 2013;14:579-595. doi:10.1146/annurev-genom-091212-153525

107. Terry SF, Terry PF, Rauen KA, Uitto J, Bercovitch LG. Advocacy groups as research organizations: the PXE International example. *Nat Rev Genet*. 2007;8(2):157-64. doi: 10.1038/nrg1991.

108. Aymé S, Kole A, Groft S. Empowerment of patients: lessons from the rare diseases community. *Lancet.* 2008; 371(9629):2048-51. doi: 10.1016/S0140-6736(08)60875-2.

109. Wood J, Sames L, Moore A, Ekins S. Multifaceted roles of ultra-rare and rare disease patients/parents in drug discovery. *Drug Discov Today*. 2013;18(21-22):1043-1051. doi:10.1016/j.drudis.2013.08.006

110. Forsythe LP, Szydlowski V, Murad MH, Ip S, Wang Z, Elraiyah TA, Fleurence R, Hickam DH. A systematic review of approaches for engaging patients for research on rare diseases. *J Gen Intern Med*. 2014;29 Suppl 3:S788-800. doi: 10.1007/s11606-014-2895-9.

111. Diseases & Conditions - Medscape Reference. https://emedicine.medscape.com/. Accessed April 19, 2019.

112. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. *Am J Ophthalmol*. 1986;101(3):267-273.

113. How many people have keratoconus? *NKCF.org*. January 2018. https://www.nkcf.org/how-many-have-kc/. Accessed August 19, 2019.

114. Valdez R, Grosse SD, Khoury MJ. The need for a next-generation public health response to rare diseases. *Genet Med*. 2016;19(5):489-490. doi:10.1038/gim.2016.166

115. Population Estimates Program, Population Division. *Historical National Population Estimates: July 1, 1900 to July 1, 1999*. U.S. Census Bureau; 2000. https://www.census.gov/population/estimates/nation/popclockest.txt. Accessed April 17, 2019.

116. United States Census Bureau. U.S. and World Population Clock. https://www.census.gov/popclock/. Accessed March 15, 2019.

117. Owusu Obeng A, Fei K, Levy KD, et al. Physician-Reported Benefits and Barriers to Clinical Implementation of Genomic Medicine: A Multi-Site IGNITE-Network Survey. *J Pers Med*. 2018;8(3). doi:10.3390/jpm8030024

118. Jadad AR, Gagliardi A. Rating health information on the internet: Navigating to knowledge or to Babel? *JAMA*. 1998;279(8):611-614. doi:10.1001/jama.279.8.611

119. 42 U.S.C. *Patient Protection and Affordable Care Act*; 2010. https://www.hhs.gov/healthcare/about-the-law/read-the-law/index.html. Accessed January 9, 2017.

CHAPTER 3

THE HEALTH INSURANCE EXPERIENCE AS DESCRIBED BY RARE DISEASE CAREGIVERS

Background

Rare diseases are defined in the United States as conditions with less than 200,000 cases.[1,2] The National Institutes of Health currently lists over 6,500 identified rare diseases. A commonly cited estimate indicates between 25 to 30 million Americans are living with a rare disease.[3] Rare disease patients experience barriers to optimal health outcomes due to an inability to receive a timely diagnosis, insufficient treatments, lack of knowledge among some healthcare providers, and limited knowledge or research about the condition.[4–10] Patients and their caregivers often feel isolated and helpless.[8,11] In one study, parents expressed concerns about the ability to access needed genetic information,[12] which is often key for a diagnosis.

Although not all rare diseases are chronic, the literature around the chronic disease community can provide insight for the rare disease experience, which is often similar. Care coordination is critical for individuals with chronic care needs and parents often must take responsibility for coordinating the care team and being the expert in their child's care.[6,7,13] Care access points for medical equipment and therapy are often unclear, especially when services are provided at a community level.[14] A tool was created as the result of a qualitative study[6] and online survey[7] to measure the supportive care needs of rare disease caregivers. The tool was developed to be used in both a clinical setting and in the development of policies and programs to support caregivers. The key domains of

necessary support included understanding the disease, working with health professionals, emotional issues, and financial needs.[15] In the development of this tool and in other broader studies on rare disease experiences, caregivers expressed fear around the uncertainty of the health of their family member, their financial ability to respond to health needs, and future life decisions.[6–8]

Achieving positive health outcomes is dependent on healthcare access.[16,17] Access depends on a variety of well-established factors including geographic, demographic, structural, and financial.[17,18] Health insurance is a critical factor for needed healthcare utilization, but in the U.S. insurance access and quality are highly variable.[19,20] In 2016, 49% of the U.S. population received coverage through employer sponsored insurance, 35% were on public insurance, 7% through non-group insurance, and 9% were uninsured.[21] According to the National Health Interview Survey working-age individuals with disabilities are more likely have coverage through Medicaid, Medicare, or military benefits and less likely to be uninsured than nondisabled individuals.[22] Supplemental programs such as early intervention (EI), which provides services for children at risk for development delays are often critical for accessing needed services, such as therapy.[23] However, changes in eligibility status for Medicaid and EI have resulted in geographic variations of care and quality outcomes.[20] Individuals residing in Medicaid expansion states were more likely to have coverage.[24]

Respondents to the Health Reform Monitoring Survey, a nationally representative sample of U.S. adults, found that even with health insurance, 17.9% of families and 23.3% of individuals reported having problems paying for medical bills in 2016.[25] In a recent Gallup poll, 77% of respondents reported they are concerned or extremely

concerned about healthcare costs and an estimated 15 million individuals deferred or skipped recommended medicines due to costs.[26]

Maintaining consistent health insurance coverage is a high priority for individuals with high healthcare costs. One study of the commercial health insurance marketplace found that families that include an individual living with a rare disease have longer retention with their health insurance plan ($p<.0001$) than families without at least one rare disease child.[27] In the 10-year study period, people on plans where the employers' bear the burden for enrollee's health claims had an average enrollment for 84 months for rare diseases families and 72.6 months for all other families. This is consistent with other studies that found that rare disease caregivers are more likely to consider health insurance needs when making employment decisions.[6,12]

Individuals with complex health conditions, such as rare diseases, often require more health care services. It is estimated that 10% of patients account for 65% of all U.S. health care expenditures and 1% accounted for 21.5% of all health care expenditures.[28] Attempts to limit healthcare costs have included initiatives to change behaviors or shift costs at the individual and systems level, including through managed care plans, investment in wellness programs, cost sharing, and the reduction of benefits.[29–31] In a study of parents with children with genetic conditions, 68% expressed concern about the financial strain associated with getting health care and covering daily care expenses for their child.[12]

Roughly 300 rare diseases have a Food and Drug Administration (FDA) approved orphan drug.[32] There has been much criticism of the financial incentives and price of orphan drugs.[33–36] A study of orphan drugs on the Health Insurance Exchange Plans,

which were established by the Patient Protection and Affordable Care Act (ACA), found that coverage varied within and across states from 2-82% depending on the drug.[37] Many of the drugs included cost sharing or utilization management provisions, including up to 50% coinsurance until patients met the out-of-pocket maximums for the plan.[37] There is a complicated balance between decreasing healthcare costs and meeting patient needs. To date, there have been no published studies that describe the rare disease health insurance experience in the U.S. through the perspective of the caregiver. The aim of the study was to qualitatively describe the rare disease caregivers' experience with health insurance for their child living with a rare disease.

Methods

Study Design

In-depth interviews were conducted with caregivers of individuals living with rare diseases. A qualitative study approach was identified to allow the subjects to guide the development of the themes and variables of influence to formulate an understanding of this experience.[38] Grounded theory principles were used to conceptualize the study design and analysis.[39] Two different conceptual categories were identified, a disease that has an FDA approved orphan drug and a disease without an orphan drug, to explore the properties that shape the patient and caregiver experience.

Sampling and Recruitment

Two diseases were chosen for inclusion in the study: metachromatic leukodystrophy (MLD) and spinal muscular atrophy (SMA). The heterogeneity of rare diseases makes it difficult to identify a "typical" disease. MLD and SMA were identified for inclusion in the study with the assistance of a rare disease genetic counselor. Both

diseases have an identified genetic mutation, have varying degrees of severity within the disease, and the age of onset can vary based on the form of the disease.[40,41] It is estimated that SMA affects 1 per 8,000 to 10,000 people worldwide.[40] MLD is estimated to affect 1 in 40,000 to 160,000 people worldwide.[41] Both diseases have a patient organization that could assist with study recruitment.

SMA and MLD both impact motor function. SMA is caused by the loss of motor neurons that impact muscle movement, especially proximal muscles.[40,42] Some forms of the disease also impact the ability to breathe and eat. Diagnosis is confirmed through genetic testing and SMA is one of the core conditions on the recommended uniform newborn screening panels.[43] In 2016, nusinersen was approved by the FDA to treat SMA.[44] Clinical trial results found that the nusinersen group had a higher percentage of a motor-milestone response (37 of 73 participants), compared to the control group (0 of 37). The nusinersen group also had a higher likelihood of overall survival (hazard ratio for death, .37; P=.004).[45] Other disease management focuses on symptoms or management of specific health issues.[46]

MLD leads to the destruction of white matter in the brain which causes progressive deterioration of motor skills and intellectual functions.[41,47] Additional symptoms can include loss of feeling in extremities, paralysis, blindness, hearing loss, seizures, and the inability to speak; over time an individual loses awareness of their surroundings. Diagnosis is made through a medical evaluation and lab tests. A newborn screening pilot study is currently underway in Washington State.[48] Stem cell transplantation may be appropriate for some patients and other treatments focus on symptom management or supportive treatments.[47]

Individuals were eligible to participate in this study if they were at least 18 years of age, a legal resident of the U.S., and the medical or legal guardian of a living individual diagnosed with SMA or MLD. Recruitment messages were provided to patient organizations that represent one of the diseases and sent through their email and Facebook pages in September 2018-January 2019. Messages reached roughly 7,200 SMA and 600 MLD families. Snowball sampling techniques were used to recruit additional MLD participants. Interested participants were sent to a study recruitment screening questionnaire to establish their eligibility and provide contact information. Individuals provided initial informed consent and then the primary researcher contacted individuals through email to set-up a time for the interview. Additional informed consent was provided verbally prior to beginning the call.

Ethical human subjects approval was obtained from the University of Massachusetts Amherst Institutional Review Board. All participants received an informed consent information sheet and provided verbal informed consent prior to the start of the phone interviews. Data collection methods and research procedures were clearly documented and findings were considered to be an accurate and truthful reflection of the experiences of parents with a child with a rare disease.

Data Collection

Thirty-two individuals completed the screening questionnaire and 15 completed an interview. The other individuals did not respond to the emails to set-up a time to complete the interview or became unresponsive while trying to set-up a call. Calls were made to an individual's phone using Skype, a conferencing software, as in-person interviews were not feasible due to travel and time restraints. Interviews were conducted

by the primary researcher who has extensive professional experience with the rare disease community. Calls lasted an average of 29 minutes. An interview script (Appendix G) was developed prior to the interviews based on the key areas of interest for the study and the prior literature. As the interviews progressed, relevant follow-up and probing questions were used to gain additional insight. Interviews were then transcribed by a professional transcription service. Transcripts were read and compared to the original recordings by the primary researcher to ensure accuracy. Recruitment ended when the researcher believed data saturation had been reached; no new themes were emerging from the data and no new codes were needed for additional interviews.[49]

Data Analysis

Interview transcripts were analyzed using NVivo 12 software using both open and axial coding.[50] Broad a priori codes such as "cost sharing" and "navigation" based on the categories of questions were created prior to the interviews. Coding was completed by the primary investigator in sections, refined, and organized into thematic categories. A codebook was created and discussed with a research assistant hired to work on the project. The research assistant independently coded one of the transcripts and then side-by-side comparison was performed and there was discussion for any differences in the codes. This process was completed for a 2nd transcription and only minor differences arose, about 15% difference. The research assistant completed two final transcriptions and the side-by-side comparison showed near identical coding, roughly 5%, the differences were based on the inclusion of a few contextual words or phrases before or after the statements of interest. The researcher also utilized peer debriefing to discuss the codes with another researcher prior to constructing the proposed model.

Results

Participant Characteristics

A total of 15 parents (14 mothers and 1 father) participated in the study. Four parents had children with MLD and 11 parents had at least one child living with SMA. The median age of participants was 37. The median age of their children was 6 (birth years 1997 to 2017). Six of the participants were diagnosed the same year they were born, the longest time to diagnosis was 4 years. Individuals lived in the South (6), North (3), Mid-West (5), and West (1). For patient privacy, only the child's initials are reported and quotes include the state of residence and child's diagnosis.

Every child had healthcare through at least one parent's employer, eight participants were the primary policy holders. Eight patients were also double or triple-covered through a public insurance program such as Medicaid (6) or the Children's Health Insurance Plan (2). Two were on a Medical Assistance Program through their state or county, three were currently receiving additional services through their Early Intervention Programs, and four had participated in EI until their child aged out. One child was on Medicare. Most individuals did not differentiate between their public and private insurance experience and some commented that they were not aware of the specifics between the plans or what was covered under what plan mechanism.

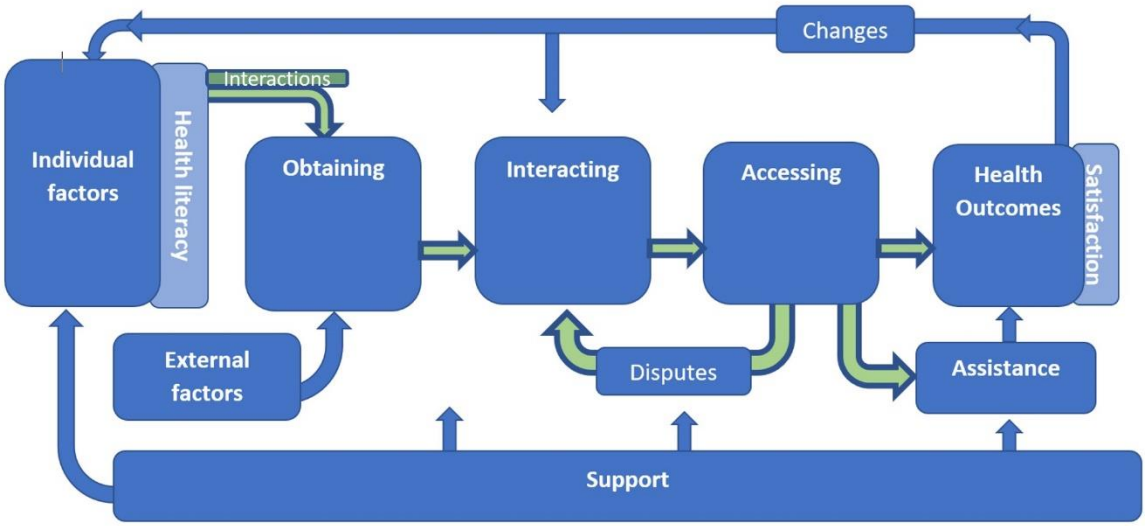
Model

The *Rare Disease Caregiver Health Insurance Experience Model* (Figure 3) was created by the principle investigator to contextualize the experience as described by rare disease caregivers. The model was then shared and furthered refined through collaboration with other members of the research team. Critical **individual factors**

include demographics, location, employment, and the patient diagnosis. Emotional factors such as uncertainty, urgency, and responsibility also impacted decisions and involvement. **Health literacy** was a product of individual factors and evolves over time as an individual navigates the system and identifies strategies to successfully engage insurance companies. Established **external factors** of accessibility, availability, acceptability, and healthcare quality impacts an individual's opportunity to obtain insurance. Politics was added to reflect the importance caregivers placed on the impact of political decisions, such as protections for preexisting conditions. An individual's potential **involvement** in the insurance process was signified by the lines with a heavy border. Emotional and knowledge **support** was provided by external forces throughout the process.

Obtaining, interacting, and accessing coverage decisions are where individuals encounter obstacles. **Obtaining** insurance can be complicated by the options available and whether an individual qualifies. **Interacting** with the insurance company requires complex documentation, redundancy in reauthorizations, time, and can result in incomplete information or being bounced to multiple sources in the company. **Accessing** can result in approval of claims, coverage questions between multiple insurers, and costs to the patient. Individuals may dispute these claims, requiring further interaction. Coverage decisions may require the individual to access outside financial **assistance**. The result of this access can impact the **health outcomes** for the child, either improvements or medical setbacks, which can **change** the way an individual interacts with the system. The results of this process and the child's health impacts overall satisfaction.

Figure 3: Rare disease caregiver health insurance experience model



Health Literacy

Individuals showed high health literacy by identifying clear strategies related to how they navigate healthcare. Some people had confusion around the health insurance documentation, such as the benefit descriptions and explanation of claims. Most had identified strategies to get the information they needed, but most still found it challenging to navigate on their own, even if they were part of the health system.

> *I mean, I am far more comfortable than the average person. I'm a physician myself. Although, I have still found it to be overly complicated and difficult, despite the years of, you know, training in the system. (SMA, TN)*

There was a strong sense that navigating insurance correctly was a necessity. Some people wanted more help in finding information, while others did not believe clearer answers existed or that insurance was willing to provide them. Individuals spoke about the iterative process of learning the system and piecing together information over time.

> *You know, we have talked to a lot of organizations and individuals over the course of her 11 months of life, but I think it has really fallen to us to educate ourselves. So, I mean, we've probably talked to 50+ people from advocacy groups, to disability coalition, to lawyers, to case workers, to social workers to, you know, political advocates, and I think each person has provided us with a little piece of information, but it's kind of remained up to us to sort of figure out overall how to navigate the system. (SMA, TN)*

Involvement and Support

Parents felt obligated to research their needs, chase down answers, and secure the authorizations directly from the insurance plan. People described keeping detailed notes of everything they were told by insurance agents. Often, they were reliant on medical professionals or other advocates to write letters for medical necessity or to get them started in the right direction for securing approvals of healthcare services. Sometimes this help came from within the community of families living with the disease, such as an SMA specific health insurance Facebook page. In some cases individuals would passively wait for claims to move through the system and "resolve themselves", but most individuals indicated they needed to be vocal and involved for success.

> *Yeah, so I kind of go into mama bear advocate mode. [laughter] And I don't like going to that place, because it usually means I have to be very assertive. I always try to be super polite, so I hate having to be aggressive with them. But it usually means I have to do a lot of follow-up calls or I have to do a lot of follow-up paperwork. (SMA, CA)*

Many individuals tried to pre-plan their short and long-term care health needs and work with insurance to see what might be covered in a specified timeframe. The purpose was to get needs met quickly and anticipate potential denials or reauthorization periods to limit disruptions in care. Caseworkers within the insurance company were sometimes provided proactively, while other individuals requested one. Caseworker quality was described as highly variable but improved if the caseworker stayed with the family over time. Individuals felt that caseworkers had the potential to help navigate the terminology, documentation, or indicate areas for saving money. Some individuals felt this was successful to help them plan, but many others felt that insurance would not provide clear answers or the answers they were given changed.

> *So, and we did have a case manager with my husband's insurance, I don't know if we triggered some sort of, you know, like, high cost flag or something. [laughter]… And I never found that person terrible useful. You know, like, I had these conversations and I explained our situation, and she just really couldn't provide me assistance in any sort of useful way. So, I liked the idea, but it didn't turn out to be what I hoped. (SMA, IL)*

> *You know, it's not something you'd notice the next day, like, some service kind of message or something like that, it's just we would be missing out, and we wouldn't know what we're missing out on or what's available down the line. (SMA, NY)*

Emotional, logistical, and knowledge-based support was proactively sought by parents or provided at many points in the process of navigating insurance. Disease specific organizations, disability organizations, or social services agencies were often seen as a valuable starting point for support and knowledge. Providers were also seen as supportive knowledgeable resources. Conversely, providers could be a barrier if they did not believe that a test or treatment was necessary. Benefits managers or members of the leadership team, such as Presidents, at the place of employment provided guidance and intervened to get benefits on behalf of some of the families. Most individuals spoke about the importance of peer support to find others who understood their experience and could provide valuable insight on navigating insurance. Often this came from connections made through organizations or social media, especially Facebook.

> *There was at least one time I remember specifically, where I was receiving incorrect information from our insurance company. I went online. I was put on hold, because they were trying to figure things out, and I went online, and I said, "Hey, who here has this insurance company and was told that?" And literally 30 seconds later, another mom wrote in to say, "We do. This is what I was told, and this is what you need to tell them." So by the time I got off hold, they were like, "Here." I told them, "Here, this is what it is. No." I was like telling the insurance company, "This is why. It really is." (SMA, TX)*

Obtaining Insurance

All individuals stated their child had consistent insurance coverage. Some participants had difficulty obtaining secondary insurance or described the process as daunting and time consuming. Individuals described both positive and negative aspects of state specific eligibility criteria or benefits. Secondary insurance, such as Medicaid, was seen as critical to unlocking access to some forms of care, including nursing services and therapy. Only MLD caregivers discussed their lack of a diagnosis as a barrier to being able to qualify for secondary medical insurance, but individuals from both disease groups discussed challenges.

> *Almost every single state in this country has a waiver that allowed medically disabled children to get on the state Medicaid system, so that they can get access to all of those services, regardless of parental income, and our state does not have that, so that has been incredibly difficult for us, and has been a major barrier in getting her care, you know, nursing, and some of the equipment that is only covered by Medicaid, it's not covered by private insurance. (SMA, TN)*

Employment was a major factor in obtaining insurance and many people felt limited in their coverage based on the options available to them through their employer. The scope of benefits was also attributed to the size of the employer, especially in covering unique services or treatments.

> *That might work for, like, a Walmart, where it's spread over 50,000 employees, but the [organization] that I work at has 300 employees, so if you added a rider saying, "Nursing for SMA is now covered," and everyone's premiums go up $5, they all know I am the one using that. (SMA, NY)*

Their child's health insurance needs were cited as a determining factor when considering employment decisions and contributed to job loss fears. One individual spoke about fears of repercussions for being "too costly", despite the legal ramifications of discrimination.

> *Insurance will always be a determining factor of taking on a new job, because if their insurance doesn't cover what this insurance does, then, you know. (SMA, MD)*

Interacting

The time needed to interact with insurance and processing claims was one of the most prominent obstacles. One source of delays in approvals or claims was related to the interplay between multiple insurers or providers incorrectly submitting claims to the wrong insurer. Getting through the automated systems and first tier customer service representatives to get accurate information was especially complicated with the realities of life.

> *And so, especially if you're trying to manage – you have other children and you work and you're trying to keep a household and what not, it's hard to sit on the phone for 30 minutes waiting for someone to help you, and then, you may get redirected five times. (SMA, CA)*

Many of the SMA parents discussed the wait time associated with the FDA's approval of nusinersen and the additional time to get access to the drug through insurance. The sense of urgency for the health benefits of nusinersen were palpable, one individual even structured her birthing plan around getting her child a Social Security number, which is necessary for health insurance enrollment paperwork, to access the nusinersen as soon as possible. Individuals in this study whose children received nusinersen within a few days of being born, stated their children were essentially asymptomatic and did not require any specialized care beyond nusinersen.

> *A lot of it came down to the cost because it's so costly per injection. U of M wasn't just going to give her the treatment and figure out the billing later and insurance was going to take their sweet time looking at it, so like we're just kind of stuck somewhere in the middle. And 30 days is a long time when your child is waiting for a life-saving medication. (SMA, MI)*

Some people believed that they could interpret their benefits themselves, but most felt they needed help to decode the information. When individuals tried to contact the insurance company, they often had to talk to multiple people before finding someone who

could provide an answer and many cited times when they felt that they received different answers from different people. The lack of transparency in tracking claims and the inconsistency in approvals was a large obstacle. Correctly submitting documentation was described as a team effort. Providers submitting claims to the wrong insurer or incorrectly submitting claims using the wrong code could result in claims sitting in limbo for months or denials. Certain treatments, referrals, and equipment required reauthorizations, the repetition to continually prove the same medical necessity or on-going care needs was seen as time-consuming and as a disruption in successful care routines.

> *At least the specialists that she will need for the rest of her life, it would be very nice if we didn't have to get referrals all the time and then sort of deal with, "Oh, you know, this appointment wasn't covered under the years' worth of referrals that we sent in that time." (MLD, NY)*

> *For example with M's Synagis injection last year, we waited like 2 months for insurance to approve it, and I got a letter like two days after Christmas they approved it, and then the new year started so we had to get a new approval… She doesn't have something that's just going to get better or go away. She's always going to have it; so I just don't know why we have to keep running through the same circles for the same thing. (SMA, MI)*

The insurance companies' comprehension and understanding of the medical situation seemed inadequate to most participants. This was related to both a misunderstanding of the medical needs and the complete picture of other care needs, such as equipment or services to help with day-to-day living. Due to the lack of knowledge of the disease, parents wanted insurance to try to understand their case history or defer to the medical professionals related to their care needs when making coverage decisions.

> *So, for example, she has to be on continuous pulse oximetry monitoring, which we were denied multiple times, getting that piece of equipment, until our doctor wrote for oxygen, and she doesn't actually need oxygen. In fact, that's kind of contraindicated actually in SMA, because the problem is not oxygen delivery, it's muscle weakness. But the insurance company would not allow us to have a pulse*

oximeter to monitor her oxygen level, you know, in her blood, and her adequacy of ventilation until she was written for oxygen (SMA, TN)

For her, you might need a drug that is proven for cystic fibrosis, but we know for a fact that she has some of the same lung issues, but we may not be able to get the insurance to cover that equipment or that drug because we don't have the background that says, "Oh yeah, they will work for MLD too." (MLD, MN)

People wanted to be treated with a sense of respect and felt that they were being treated as if they were trying to "game" the system, when individuals just wanted to provide appropriate care for their child. When they did not feel heard, respected, or if there were inconsistencies in what they were told, it often eroded trust and further establish a need for the parents to be vigilant and fight. Many people used what they learned as part of the run-around to devise strategies to get faster or more accurate answers in the future.

The left hand doesn't know what the right hand is doing, and that makes it really tricky to navigate, because, you know, it puts more pressure on the parents or the caregiver to do their due diligence, where I feel like it shouldn't necessarily be all on us to do it. (SMA, TX)

Accessing

Individuals experienced the greatest barriers to coverage for equipment, nursing care, therapy, and out-of-network providers. Individuals who were aware of tiered-financing schemes indicated their providers were always on the highest tier where they would need to pay the most out-of-pocket. Seeking out of network care was discouraged by insurance, but many caregivers expressed the frustration of not being able to see out-of-network disease specialists or go to the specialty centers where children could benefit from targeted knowledgeable care.

We live on Long Island in New York, and he wanted – it was recommended that we go to Columbia Children's Hospital, where they have an SMA clinic, but originally, we were denied coverage there because it was out of network, and basically I said, "Why?" They said I have a pulmonologist center up closer to

home… they weren't going to cover us going to Columbia, where we would argue that there's not any other SMA specialists out here. (SMA, NY)

Nursing care was a critical support for families. Finding the mechanism to get nursing care was often described as a time-consuming challenge, especially if people could not qualify for Medicaid. Nursing companies were often critical in helping caregivers navigate the coverage. A good nurse was described as being invaluable to a family and often went above and beyond in providing guidance and support, but there was high turnover.

We only had one hour of a consultation nurse. That nurse stayed for three hours, stayed two hours on her own time, because she felt that we were in kind of a dire situation and didn't have any of the home care set up, because we, you know, didn't know how to set up our home. Nobody took us—nobody met us at home. So he went home without insurance covering private-duty nursing, and we had no nursing coverage, and we were expected to stay awake all night while my son returned from the hospital, and that did not end well. (SMA, MD)

Therapy was described as expensive and critical to helping the child achieve the best mobility and health outcomes. Many companies had caps on what is covered by insurance, but the terms of coverage were often unclear. Multiple people spoke about trying to get clarity on the number of allotted hours only to be quoted wrong information and losing access mid-year.

If you're making, like, huge gains, which is good, but it, would be, something, like, $28,000, which I couldn't afford. Because, it says here, physical, speech, occupational therapy, "Subject to specialist's office, visit copay," which is $0, "And 90 visits per calendar year." So, for me, I should be able to go to wherever we want for 90 visits a year, but I don't really know where I can go, and for what. (SMA, NY)

Every year, we run out of PT hours, and we run out in October, so we have a hard limit on our insurance, and every year, a nurse case manager that's on our case tells us, "Oh, if you get a doctor's prescription, you can increase it." We say every year, "No, we can't," and then we spend another 90 minutes on the phone between our physical therapy gym and the insurance company. (SMA, MD)

The out-of-pocket costs were described by some as reasonable when considering

the scope and total cost of their care needs. There was a split between individuals who just referred to "bills" and those who can recite their entire paradigm of premiums, deductibles, copays, and coinsurance. Some of these fees were covered as a perk of employment or through secondary insurance programs. Some individuals had out-of-pocket maximums for the year. Those who had deductibles spoke about how quickly they met them.

> *And then we have like a per-person ones, like M's is 500 and she meets that within like 30 seconds in the new year so. (SMA, CA)*

The cost of equipment, drugs, therapy, and out-of-network services were described as the most expensive parts of care. These types of services often had cost-sharing mechanisms, but the patient's portion was still quite large.

> *So, you know, 20% – or, I guess it's 10% drug. But anyway, you know, a 10% copay on a $150,000 per year bill is, like, prohibitive for most people. (SMA, TN)*

Different values contributed to different expectations about what should and should not be covered, especially around equipment and quality of life supportive technologies, such as powerchairs and adaptive beds. Some individuals were narrowly focused on specific medical costs, while others looked at the full paradigm of care and support. Many expressed that if a doctor indicated that something was medically necessary, families should have an affordable way to access it.

> *Again, I know there are like private groups that you can go on funding and you can do social funding, but things that like are clearly medical necessities in order to be able to navigate the home and reach the home and go to the doctor's appointments, for example, seem like they should have better coverage. (MLD, MA)*

Insurance was described as one piece in the larger financial structure, but timely complete information was necessary for long-term planning. Almost all of the SMA individuals received nusinersen with assistance from the clinical trial or the drug

company's copay assistance program. Early intervention was described as a key safety net program for individuals to get started, but there was concern about what would happen when the child aged out after 3 and this assistance ended. The expectation is that schools will provide services and equipment. The variability of school resources, knowledge, and capacity to support students was identified by the parents. An individual often needed to decide when to utilize outside sources of assistance, such as grants or fundraisers.

> *And I really think that when you look at someone's care needs you know insurance is one part of it but it's really like trying to understand all of the benefits including insurance that they are entitled to and how all of those pieces need to work together. (SMA. MN)*

A few individuals spoke about how they have not accessed any other sources of financial assistance due to time, a sense of greater future need, eligibility, or they felt that others required the assistance more. Many people reflected on how they did their best to contribute their fair share and to cut costs by repurposing supplies or using equipment shares, but they wanted insurance to understand the importance of the needs they did submit.

> *Now, I am trying to get some equipment for her mattress and I am just trying to get it paid for with the proper paperwork signed and everything to get it through and it is almost like I feel if I did the financial analysis on how much it costs to take care of a wound, they would certainly rather pay for the mattress, it is 300 bucks instead of the $3000 that it is going to cost if I have to put her in the hospital time and time again. (MLD, MN)*

A few individuals spoke about shifting formularies, gatekeeping requirements, networked providers, and benefits that sometimes changed how the individual could access care. Sometimes these changes would be related to eligibility shifts, such as a provider who was included in Early Intervention, but out-of-network when the child aged-out. Other insurance changes would not be communicated to families directly and

might only be uncovered when individuals received a bill or were outside of their plan's scope of coverage.

> *The state of Illinois doesn't really care that she's out of network, but then, when S turned three, we have to deal with the insurance and her billing and stuff directly. (SMA, IL)*

Many people discussed the concern about the health consequences of the delays or denials of the insurance company, especially the potential for worst health outcomes or lost opportunities, such as clinical trial participation. People spoke about how the coverage they could access would impact their life decisions, such as having more children. Many expressed a sense that things were not fully in their control and they only had so much bandwidth to continually fight. The political climate and fears of losing protections for preexisting conditions weighed heavily on many. Only a few people spoke directly about their own mental health.

Satisfaction and Health Outcomes

When asked if individuals were satisfied with their insurance, many said yes, despite describing challenging experiences. One respondent stated, "That's kind of a trick question." Those who were most satisfied had decent benefits or had overcome a large obstacle with coverage. Some people were very distrustful, but most expressed a sense that they wanted to work better with the companies to find the best way to balance their child's needs, doctor's recommendation's, and cost-savings.

> *It can be a nightmare if the right people aren't in place to monitor it… Yeah, so because everything is pretty covered for her, and we, again, knock on wood, are pretty healthy, there's not a lot of – I don't feel that I am having to follow up with insurance companies or, you know, ask for things to get taken care of. (MLD, TX)*

> *It shouldn't be about, "Oh, sorry, you can't have this because it's too expensive." Well, but that's what the patient needs. So, if that's what the patient needs, find a way to make it more affordable so that they can have it. (SMA, CA)*

A few reflected on the importance of taking care of each other and how their experience has impacted their individual value sets. Individuals also looked at their own privilege related to education, support, and the severity of their child's condition when reflecting on their experience compared to others. This sometimes resulted in not accessing certain financial resources or finding ways to give back to others in the community in whatever way they could.

> *And it's like basically, I think you know could be a part-time job for someone. And so, for people who perhaps are not native English speakers or who don't have a level of education that allows them to sort of navigate through these systems or don't have the time to be on the phone for you know 10 hours a week on hold or whatever, I think really is a disservice and kind of a shame. (SMA, MN)*

When looking at what changes caregivers most wanted to see, many people spoke about making the process more user friendly, decreasing the time it took to interact and get approval answers, and reducing the need for reauthorizations for on-going needs. Communication was a consistent theme including a desire for a clear line of direct communication, greater transparency, and a shift to more consumer-focused care. People wanted to be treated humanely and with an understanding that they are just trying to take care of their child.

> *It goes back to walking around with, you know, in somebody else's shoes and trying to figure it out. It is not like we are trying to take advantage of anybody when we have kids with rare genetic illnesses. It is very difficult. (MLD, MN)*

> *I guess I just wish, like, the answers were easier to find, and they were more black and white, like, as if it was more like a puzzle, and felt like, "You know, isn't this the point of having a job and health insurance, so that when you have something you need, like, you'll get it?" (SMA, VA)*

> *I mean, I hate it, but it has to be done, because we can't afford to not have it be done right, so we just have to continue to keep this documentation of every call and every time and what they said, because I feel like I'm more organized than they are, and I feel that I have to be, because my daughter's definitely worth it, so this is where we have to be. (SMA, TX)*

Discussion

The purpose of including MLD and SMA was to explore the potential differences in the presence of an orphan drug for patients accessing medical care. However, these preliminary results indicate limited differences in the caregiver experience based on the availability of an orphan drug. This is consistent with previous findings that rare disease care needs are largely similar despite disease differences.[6] SMA patients with early access to nusinersen, did not experience many further healthcare coverage needs, which was different from their peers whose children still required complex care needs. Both SMA and MLD parents had to fight with insurers to gain access to services and products seen as medical necessities. The MLD care needs are less established, which often required additional justification to ensure insurance coverage.

Parents and medical professionals often were looking at long-term needs and outcomes, while insurance was more focused on more immediate utilization controls aimed at reducing access to expensive drugs and services. This applied to the medical pay-off of certain equipment in preventing hospitalizations or medical complications and the approach for finding an MLD diagnosis; test-by-test vs whole genome sequencing which could provide a broader scope of genetic data. This is consistent with studies that indicate that diagnosis can take years.[8] The negotiation between insurance company and patient interests will likely create inequities based on an individual's health literacy and overall access to knowledgeable providers. As a society, we must decide how we believe these negotiations should go and what entities we believe should be driving decisions.

Managed care models of insurance rely on patients using in-network care. However, rare disease diagnosis may rely on numerous visits to specialists in multiple

locations[9] and may only have a handful of experts or specialty centers, which are often organized regionally or nationally.[10] Patients may need to seek care outside of the insurer's negotiated networks of providers. We must find a way to balance these competing needs to allow individuals to access disease experts, without unduly burdening patients with greater out of pocket costs. Private insurance companies are often only temporary stewards of an individual's health as individuals are assumed to change plans every few years. Long-term savings, such as through supportive technologies, may not be as important as the year-end bottom line. However, with complex conditions small setbacks can become incredibly costly and disruptive to the health of the child and the life of the family.

Currently, there are assumptions related to the care paradigm that most people will navigate, including logical places to gain access to certain services based on demographic factors. However, if a state has exclusions to secondary insurance or if an individual has more complex needs then can be addressed at the site (such as a school), the system is not equipped to adjust. Complex care cases have few options for recourse within the system and may toil in limbo or fall through the cracks, unless caregivers can devote the time and energy to fight for needed services.

A few individuals interviewed commented on structural changes or unique providers that were seen as beneficial. One had a complex care provider through the hospital that was able to serve as the gatekeeper and primary navigator for other points of care but was equipped with the specific knowledge of complex care needs and available resources. Another individual spoke about the integrated financing and delivery system

for the Medicaid program in their state, which from their perspective made the process when accessing services more seamless.

Based on the interviews, policy changes or insurance company initiatives that could improve the experience of rare disease patients include establishing time limits for processing coverage decisions and increasing the transparency in the claims and preauthorization process. Allowing options for universal authorizations for certain domains of care or changing the frequency of the reauthorizations would also decrease the burden on families and medical providers to continually prove medical necessity. More research into the natural history of rare diseases and establishing medically recognized treatment guidelines would improve evidence-based care for patients, especially if insurance was required to provide coverage for the services necessary to follow those guidelines.

Training insurance specialists that are familiar with complex and chronic care needs, are trained to review medical records, and can interface with this population in a respectful way, would also increase the overall experience for patients. It is unrealistic to expect insurance companies to become experts in every rare disease, but there should be a framework for assessing claims to make coverage decisions without unduly delaying progress or harming patients. Individuals who felt that there was someone at their insurance company who could intelligently answer questions, had far fewer complaints than those who did not.

Our healthcare delivery system is moving towards centers of excellence or a centralized hub model of for specialist care, but our payment systems often require in-network care. In many cases, there are limited options to choose more flexible plans.

Individuals with compelling needs to see an out-of-network specialist should have an opportunity to seek waivers from out-of-network care cost restraints or to seek expert opinions in a cost-effective way. This goal would be easier to achieve if health insurance companies were incentivized to invest in an individual's long-term health outcomes. As the U.S. investigates single-payer healthcare options, which would likely integrate payment and delivery networks, we need to identify appropriate ways to make allocation decisions for the long-term health of an individual. Successful policy changes must include the patient voice to ensure that solutions for a sustainable healthcare system are flexible for adapting to evolving patient needs.

Limitations

The estimated MLD population is smaller, recruitment was more challenging as the disease organization infrastructure is less developed. Every MLD caregiver who participated offered to help recruit. This likely means that the MLD participants joined due to personal outreach and snowball sampling, where most of the SMA participants self-selected due to general recruitment messages. The SMA group also did not include any individuals who are not currently using nusinersen, the overall proportion of individuals on the drug cannot be determined, which makes it difficult to assess the impact of this representation. There is a limit on the amount of time caregivers can give and it is possible that we are missing the perspective of individuals who are in even more dire financial situations. Insurance status was self-reported and cannot be validated, but is likely accurate due to the level of involvement most caregivers had in their child's insurance.

Although, there was some geographic diversity, some states included multiple participants including Minnesota and New York. The study also put a large importance on equipment and therapy as these are key features in diseases with mobility issues, other rare diseases are likely to have slightly different needs, which may result in other unexplored challenges. However, we believe that the themes and the model provide a medically agnostic starting point to the overall caregiver experience. Finally, as a qualitative study the results could be subject to other interpretations, but this was limited due to the use of double-coding and peer-debriefing.

Conclusion

This study adds to the scholarly research and literature and has the potential to improve practice and policy. There are possible policy initiatives that could impact our payment and delivery systems that could greatly improve patient experience and outcomes. However, it is critical that the patient voice is represented in efforts to establish a framework for assessing and approving care needs. Parents with a child living with a rare disease are required to meticulously track insurance in order to maximize benefits. They are often asked to navigate difficult decisions to balance medical needs and financial stability. Individuals are often grateful for a supportive network of peers and providers, but the final responsibility falls to them.

References

1. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. NIH.gov. https://rarediseases.info.nih.gov/. Accessed January 13, 2017.

2. *Orphan Drug Act*. Vol USC 21 I Subchapter D Part 316. 1983. https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21. Accessed January 13, 2017.

3. National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

4. Mooney J, Poland F, Spalding N, Scott DGI, Watts RA. "In one ear and out the other - it"s a lot to take in': a qualitative study exploring the informational needs of patients with ANCA-associated vasculitis. *Musculoskeletal Care*. 2013;11(1):51-59. doi:10.1002/msc.1030

5. Babac A, Frank M, Pauer F, et al. Telephone health services in the field of rare diseases: a qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany. *BMC Health Serv Res*. 2018;18(1):99. doi:10.1186/s12913-018-2872-9

6. Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive Care Needs of Parents With a Child With a Rare Disease: A Qualitative Descriptive Study. *J Pediatr Nurs*. 2016;31(3):e207-218. doi:10.1016/j.pedn.2015.10.022

7. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88. doi:10.1186/s12875-016-0488-x

8. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

9. *Report of The National Commission on Orphan Diseases*. U.S. Department of Health and Human Services Public Health Service Office of the Assistant Secretary for health; 1989. https://rarediseases.info.nih.gov/files/report_of_the_national_commission_on_orphan_diseases_february_1989.pdf. Accessed March 31, 2017.

10. Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. *Adv Exp Med Biol*. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

11. Pelentsov LJ, Laws TA, Esterman AJ. The supportive care needs of parents caring for a child with a rare disease: A scoping review. *Disabil Health J*. 2015;8(4):475-491. doi:10.1016/j.dhjo.2015.03.009

12. Gallo AM, Hadley EK, Angst DB, Knafl KA, Smith CAM. Parents' concerns about issues related to their children's genetic conditions. *J Spec Pediatr Nurs*. 2008;13(1):4-14. doi:10.1111/j.1744-6155.2008.00129.x

13. Curtis K, Foster K, Mitchell R, Van C. Models of Care Delivery for Families of Critically Ill Children: An Integrative Review of International Literature. *J Pediatr Nurs*. 2016;31(3):330-341. doi:10.1016/j.pedn.2015.11.009

14. American Academy of Pediatrics Council on Children with Disabilities. Care coordination in the medical home: integrating health and related systems of care for children with special health care needs. *Pediatrics*. 2005;116(5):1238-1244. doi:10.1542/peds.2005-2070

15. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. Development of the parental needs scale for rare diseases: a tool for measuring the supportive care needs of parents caring for a child with a rare disease. *J Multidiscip Healthc*. 2016;9:425-433. doi:10.2147/JMDH.S113898

16. Uninsurance I of M (US) C on the C of. *Why Health Insurance Matters*. National Academies Press (US); 2001. https://www.ncbi.nlm.nih.gov/books/NBK223643/. Accessed September 22, 2017.

17. Levesque J-F, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health*. 2013;12:18. doi:10.1186/1475-9276-12-18

18. Aday LA, Andersen R. A framework for the study of access to medical care. *Health Serv Res*. 1974;9(3):208-220.

19. Andrulis DP. Access to care is the centerpiece in the elimination of socioeconomic disparities in health. *Ann Intern Med*. 1998;129(5):412-416.

20. Committee on Geographic Variation in Health Care Spending and Promotion of High-Value Care, Board on Health Care Services, Institute of Medicine. *Variation in Health Care Spending: Target Decision Making, Not Geography*. (Newhouse JP, Garber AM, Graham RP, McCoy MA, Mancher M, Kibria A, eds.). Washington (DC): National Academies Press (US); 2013. http://www.ncbi.nlm.nih.gov/books/NBK201647/.

21. Health Insurance Coverage of the Total Population. *Henry J Kais Fam Found*. September 2017. http://www.kff.org/other/state-indicator/total-population/. Accessed September 22, 2017.

22. Kennedy J, Wood EG, Frieden L. Disparities in Insurance Coverage, Health Services Use, and Access Following Implementation of the Affordable Care Act: A Comparison

of Disabled and Nondisabled Working-Age Adults. *Inq J Med Care Organ Provis Financ*. 2017;54:46958017734031. doi:10.1177/0046958017734031

23. What is “Early Intervention”? Centers for Disease Control. https://www.cdc.gov/ncbddd/actearly/parents/states.html. Accessed December 21, 2018.

24. Vistnes JP, Lipton BJ. The Uninsured in America: Estimates of the Percentage of Non-Elderly Adults Uninsured throughout Each Calendar Year, by Selected Population Subgroups and State Medicaid Expansion Status: 2013 and 2014. In: *Statistical Brief (Medical Expenditure Panel Survey (US))*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2001. http://www.ncbi.nlm.nih.gov/books/NBK447195/.

25. Long SK, Bart L, Karpman M, Shartzer A, Zuckerman S. Sustained Gains In Coverage, Access, And Affordability Under The ACA: A 2017 Update. *Health Aff Proj Hope*. 2017;36(9):1656-1662. doi:10.1377/hlthaff.2017.0798

26. Inc G. The U.S. Healthcare Cost Crisis. Gallup.com. https://news.gallup.com/poll/248123/westhealth-gallup-us-healthcare-cost-crisis-report.aspx. Accessed April 25, 2019.

27. Kuester MK, Jackson EA, Runyan BM, Pezalla EJ, Nussbaum SR. The Effect of a Pediatric Rare Disease on Subscriber Retention Rates for Commercial Health Insurers in the United States. *J Manag Care Spec Pharm*. September 2018:1-9. doi:10.18553/jmcp.2018.18205

28. Cohen S. *Differentials in the Concentration of Health Expenditures across Population Subgroups in the U.S., 2013*. Rockville, MD: Agency for Healthcare Research and Quality; 2015. https://meps.ahrq.gov/data_files/publications/st480/stat480.shtml. Accessed September 22, 2017.

29. Mays GP, Claxton G, White J. Managed care rebound? Recent changes in health plans’ cost containment strategies. *Health Aff Proj Hope*. 2004;Suppl Web Exclusives:W4-427-436. doi:10.1377/hlthaff.w4.427

30. Obama B. United States Health Care Reform: Progress to Date and Next Steps. *JAMA*. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

31. Orszag PR. US Health Care Reform: Cost Containment and Improvement in Quality. *JAMA*. 2016;316(5):493-495. doi:10.1001/jama.2016.9876

32. U.S. Food & Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed March 31, 2017.

33. Alhawwashi S, Seoane-Vazquez E, Eguale T, Rodriguez-Monguio R. Prices of Drugs For Chronic Use With Orphan Designation In The United States (1983–2014). *Value Health*. 2016;19(3):A4. doi:10.1016/j.jval.2016.03.040

34. American Health Insurance Plans (AHIP). *Orphan Drug Utilization and Pricing Patterns (2012-2014)*. Washington, DC; 2016. https://www.ahip.org/wp-content/uploads/2016/10/OrphanDrug_DataBrief_10.21.16.pdf. Accessed September 22, 2017.

35. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis*. 2011;6:42. doi:10.1186/1750-1172-6-42

36. Divino V, DeKoven M, Kleinrock M, Wade RL, Kaura S. Orphan drug expenditures in the United States: a historical and prospective analysis, 2007-18. *Health Aff Proj Hope*. 2016;35(9):1588-1594. doi:10.1377/hlthaff.2016.0030

37. Robinson SW, Brantley K, Liow C, Teagarden JR. An early examination of access to select orphan drugs treating rare diseases in health insurance exchange plans. *J Manag Care Spec Pharm*. 2014;20(10):997-1004. doi:10.18553/jmcp.2014.20.10.997

38. Creswell JW. *Research Design: Qualitative, Quantitative, and Mixed Methods Approaches*. Thousand Oaks, California: Sage Publications, 2003.

39. Glaser BG, Strauss AL. *The Discovery of Grounded Theory : Strategies for Qualitative Research*. Hawthorne, New York: Aldine de Gruyter, 1967.

40. Genetics Home Reference, U.S. National Library of Medicine. Spinal muscular atrophy. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy. Accessed February 7, 2019.

41. Genetics Home Reference, U.S. National Library of Medicine. Metachromatic leukodystrophy. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/metachromatic-leukodystrophy. Accessed February 7, 2019.

42. Russman B. *Spinal Muscular Atrophy*. National Organization for Rare Disorders; 2012. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. Accessed March 4, 2019.

43. U.S. Health Resources & Services Administration. Recommended Uniform Screening Panel. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed March 4, 2019.

44. Office of the Commissioner. Press Announcements - FDA approves first drug for spinal muscular atrophy.https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm. Published December 23, 2016. Accessed February 7, 2019.

45. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1723-1732. doi:10.1056/NEJMoa1702752

46. Russman B. Spinal Muscular Atrophy. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. Published 2004. Updated 2012. Accessed April 30, 2019.

47. Adang L, Rosenzweig J. Metachromatic Leukodystrophy. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/metachromatic-leukodystrophy/. Published 1986. Updated 2019. Accessed March 4, 2019.

48. Schielen PCJI, Kemper EA, Gelb MH. Newborn Screening for Lysosomal Storage Diseases: A Concise Review of the Literature on Screening Methods, Therapeutic Possibilities and Regional Programs. *Int J Neonatal Screen*. 2017;3(2). doi:10.3390/ijns3020006

49. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. *Field methods.* doi/abs/10.1177/1525822X05279903. 2006.

50. Strauss AL, Corbin JM. *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory*. Thousand Oaks, California: Sage Publications, 1998.

CHAPTER 4

MEDICARE PART D ORPHAN DRUG EXPENDITURES FROM 2013 TO 2017

Background

Rare diseases

In the United States, a rare disease is a condition that impacts less than 200,000 people.[1,2] An estimated 30 million Americans are impacted by one or more of the roughly 6,500 identified rare diseases.[3] The diseases are clinically heterogenous and an estimated 60% are genetic in origin. Many of the conditions have insufficient research resulting in undefined clinical guidelines, limited treatment options, and inadequate knowledge among some healthcare providers.[4–10] Individuals living with rare diseases often feel isolated and can face challenges finding an accurate diagnosis and treatment plan.[8,11]

Orphan drug coverage and expenditures

Orphan drugs are products designated for the treatment of rare diseases. The 1983 Orphan Drug Act (ODA) provides economic incentives for the research and development of orphan products including 7-year marketing exclusivity, fee-waivers, and grant opportunities.[2] Companies developing a product submit an application to the Food and Drug Administration (FDA) to establish eligibility for obtaining an orphan designation.[12] Drugs are eligible if they are intended to treat a disease that affects fewer than 200,000 people in the U.S. and there is no expectation of recovering the research, development, and marketing costs from U.S. sales of the drug. This process can occur at any point between laboratory drug discovery and clinical trials in the drug development process.[12]

Once there is evidence related to the safety and efficacy of the drug, the company submits a marketing application to the FDA. The FDA approves the drug's indications, the identified uses for the drug. Indications are based on the clinical trial information and the marketing application materials. The indication is often narrower than the orphan designation and may only include a subtype of the disease or a specified patient population.[12] Between January 1983 and August 2018, 503 drugs were approved with an orphan indication. Of those drugs, 394 (78%) were only approved for the orphan indication, while 109 (22%) also had a non-orphan indication.[13]

There has been criticism related to the price of orphan drugs.[14–18] Using 2017 invoice prices, the median annual cost for an orphan drug was $46,800 per year and the mean was $87,319.[13] Of the 374 orphan drugs that were on the market in 2017, 301 (80.4%) had an annual cost of over $6,000 and 73 (19.5%) of the drugs had an annual cost per patient of less than $6,000.[13] Of those, 109 (29.1%) were oncology products with an annual cost of over $6,000 which represented 40.8% of all orphan sales.[13] There are 5 orphan drugs (1.3%) that are priced over $500,000 per year, which contributed to 1.8% of total orphan drug spending.[13] The average sales for the 50 highest-selling orphan products was $639.5 million and the next 50 highest selling products averaged $139.5 million in 2017.[13] These costs may not reflect what an individual or a payer actually spends based on the availability of medication assistance programs or coupon programs.

Patients are experiencing high healthcare costs, for drugs and other medical costs. A nationally representative sample of U.S. adults found that 17.9% of families and 23.3% of individuals reported having problems paying for medical bills in 2016.[19] A Gallup poll found that 77% of respondents reported they were concerned or extremely concerned

about healthcare costs and an estimated 15 million individuals deferred or skipped recommended medicines due to costs.[20] Studies that focused on families living with rare diseases or genetic conditions also report concerns related to financial stress.[7,21] In oncology, the term "financial toxicity" has been used in the healthcare literature to describe the impact of the financial burden of treatment on a patient's overall wellbeing.[22–25] Having insurance can help decrease costs associated with drugs, but there is a high degree of variability in orphan drug coverage across insurance plans. Insurance access to orphan drugs through Health Insurance Exchange plans established through the Patient Protection and Affordable Care Act (ACA) found that insurance coverage varied within and across states from 2-82% coverage depending on the drug.[26]

In the research literature, orphan drugs are sometimes considered a subsection of specialty pharmaceuticals. Specialty pharmaceuticals tend to include biologic and injectable agents and are often used for complex conditions, including cancer and some conditions that are considered rare.[27] However, there is not an agreed upon definition for specialty drugs. One definition is based entirely on the cost of the drug; for 2019 one definition is a drug that costs at least $670 per month.[28] Another definition requires that a drug meet a certain number of cost, delivery, and medical factors to be considered a specialty drug.[13,29] Specialty drugs often require prior authorization or impose quantity limits.[30] Information about specialty drugs can help inform orphan drug research.

Three studies have looked at the total orphan drug expenditures in the United States. In 2017, total drug sales in the U.S. based on corporate sales data were $451 billion for pharmacies, clinics, hospitals, and healthcare providers; with $43 billion (9.5%) attributed to orphan drugs and another $157 billion (34.8%) attributed to non-

orphan specialty drugs.[13] A 2017 study found that orphan drug spending was $36 billion (7.9%) of the total $450 billion drug sales in 2016.[13] The study also found that orphan drugs contributed $14.6 billion of growth in spending from 2011 to 2016 while non-orphan specialty drugs saw $74.6 billion in growth in the same time period.[13] In 2013, orphan drug spending totaled $30 billion (8.9%) of total pharmaceutical expenditures in the U.S.[31] Oncology drugs represented $12.22 billion (40.7%) of the total orphan drug expenditures.

Internationally, orphan drug expenditures represent less than 6% of total pharmaceutical expenditures. In 2007, a study of 5 European countries found that the percentage of orphan drug spending as a percentage of total drug spending was 1.7% in France, 2.1% in Germany, 1.0% in the UK, 1.5% in Italy and 2.0% in Spain.[32] More recent studies found that the orphan drug percentage of total pharmaceutical spending was 5.6% in Canada in 2013[33], 2.7% in Sweden in 2013,[34] 3.2% in France in 2013,[34] 1.9% in Belgium in 2008,[35] 4.2% in the Netherlands in 2012[36], and 3.3% in Europe in 2010.[37]

Medicare Part D

Medicare Part D is a prescription drug coverage plan that was implemented in 2006 and is administered by the Centers for Medicare and Medicaid Services (CMS).[38] The program provides pharmaceutical coverage for individuals enrolled in Medicare. Medicare is a health insurance program that was established in 1966 for the elderly and was expanded to individuals with permanent disabilities in 1972. In 2018, 43 million people were enrolled in Medicare Part D.[28] The majority of individuals (58%) are enrolled in a stand-alone prescription drug plan (PDP), while the remaining 42% are in

Medicare Advantage prescription drug plans (MA-PD). The Low-Income Subsidy (LIS) program provides premium and cost-sharing assistance for roughly 12 million (39%) of Part D enrollees.[28] Dual eligible individuals who receive benefits through Medicaid and Medicare, are required to participate in Part D.

The majority of individuals enrolled in Medicare Part D are over the age of 65, but 8.6 million people (14.4%) are under the age of 65 and qualify due to a long-term disability.[39] An individual who has received Social Security Disability Insurance benefits, based on a long-term physical or mental impairment that will last for more than 24 months, can become eligible for Medicare. If an individual has end-stage renal disease or amyotrophic lateral sclerosis, the individual can begin receiving benefits without the waiting period.[28] The Compassionate Allowances program identified a list of conditions that have already been evaluated to qualify as a serious disability, many of these conditions are rare diseases.[40] The program was established to reduce the wait time for individuals with serious conditions to receive Social Security benefits.[40]

Compared to beneficiaries over the age of 65, younger Medicare beneficiaries are more likely to be male (55% versus 44%), have lower incomes, and are more likely to be Hispanic or black.[41] In 2012, 65% of younger beneficiaries had a cognitive or mental impairment, compared to 29% of beneficiaries over 65.[41] A similar proportion of beneficiaries from both age groups reported having five or more chronic conditions, 31% for under 65 and 28% for over 65.[41] Nearly 35% of younger beneficiaries are dual eligible for Medicare and Medicaid, compared to 10% of beneficiaries over 65. [41] Seventy-five percent of Medicare beneficiaries under the age of 65 are enrolled in a Part

D plan and 55% qualify for the Part D LIS. Sixty-three percent of older beneficiaries are enrolled in a Part D plan and only 16% qualify for the LIS subsidies.[41]

Medicare Part D has been credited with a decrease in total out-of-pocket expenditures for beneficiaries.[42–46] After Part D implementation, there was evidence of a shift in drug expenditures from private insurance and Medicaid to the Medicare program.[43,46] Some studies also showed a decrease in hospital admissions for individuals who were enrolled in Part D plans.[47,48] Medicare beneficiaries can be subjected to high out-of-pocket expenditures through cost-sharing mechanisms and can find it difficult to identify the right plan for their needs.[49]

Part D cost sharing mechanisms

In 2019, there were 901 unique Medicare Part D prescription drug plans offered across the country, with at least 22 plans available in each state.[50] The average premium for Medicare PDPs in 2018 was $41 per month and the average MA-PD was $34.[28] Deductibles were included in 45% of plans.[28] Most of the plans included a formulary that lists the covered drugs under the plan. Formularies were required to include at least two drugs in each prescription class or category, the included drugs can change during a plan year.[51] Cost-sharing differs across plans and drug types, with higher-cost sharing for brand drugs and drugs that were off-formulary.[30] There can be considerable variation across plans, one study found that cost-sharing for a 30-day supply of 10 brand drugs could be between 2 to 14 times higher on a particular PDP compared to another.[30] Copayment and coinsurance rates in drug plans were established based on a tiered system, with different costs for drugs in different tiers, with higher payments for drugs on higher tiers.[52]

Once an individual on Medicare Part D has spent a certain amount of money, most plans require that the individual enter a coverage gap or "donut hole".[53] While in this gap, individuals pay a larger share towards drugs until the end of the plan year or until the catastrophic coverage amount is reached. In 2019, the coverage gap begins after an individual and the plan spend $3,820 on covered drugs.[53] While in the gap, an individual pays 25% of the plan's costs for brand name drugs and 37% for generic drugs. In 2019, an individual leaves the coverage gap and operates under "catastrophic coverage" after the person has spent $5,100 out-of-pocket.[54] For the rest of the year, drugs are subject to 5% coinsurance. The ACA legislated the closure of the coverage gap and in 2020 an individual will be responsible for 25% of the costs for brand name or generic drugs while in the gap.[55]

Part D access to drugs

A 2010 study of Medicare Part D coverage of 99 orphan drugs found that each orphan drug was covered by 87% of MA-PDPs and 84% of PDPs.[56] Four drugs were not listed on any PDPs, but all other drugs were covered by at least 50% of national plans.[56] There is higher coverage for national plans (86%) compared to plans that are only offered in certain states (77%). Within nonnational plans, 23% of drugs have low or no coverage.[56] Of the covered drugs, 19 (20%) were covered by less than 50% of the nonnational plans. Of the covered drugs, 84 (88%) were on tier 4 or higher on at least one PDP and 28 (29%) were placed on tier 4 or higher by at least 75% of plans.[56]

Drug approval can occur through traditional channels or accelerated approval pathways.[57] A study of FDA approved therapies that used novel approval pathways identified 144 therapeutics, of which 45 (31%) were approved with an orphan

designation.[58] Overall, 129 (90%) of the drugs in the study were covered by at least one Medicare plan, 93 (65%) drugs were covered by at least half of the plans, and 22 (15%) were covered by all of the plans within one year of approval.[58] Three years after the approval of the drug, 140 (97%) were covered by one plan, 112 (78%) were covered by at least half, and 40 (28%) were covered by all of the plans. The median proportion of plans covering the orphan drugs in the study was 62% (IQR=43-92) at one year post-approval and 79% (IQR=66-100) at year three.[58]

Part D expenditures

The average per capita spending for Part D drugs for a beneficiary under the age of 65 is $3,817 compared to $1,159 for an individual over the age of 65.[41] A study comparing the spending patterns for people who had LIS discounts and those that did not found that individuals who received the LIS discounts had total Part D expenditures of $1,887 compared to $1,341 for individuals that did not have LIS or another form of gap coverage.[59] Additionally, the individuals with LIS paid an average of $148 out-of-pocket compared to $570 out-of-pocket for individuals without supplements. Of the total expenditures, for individuals with LIS 27.6% occurred after the individual reached the coverage gap and for individuals without supplements to help with drug costs, 16.9% of expenditures occurred after the gap.[59] Prior authorization was required for coverage on at least one Medicare Part D PDP plan for 80 (84%) orphan drugs and 33 (35%) orphan drugs were required to have prior authorization by at least half of the PDPs.[56]

No study has investigated all orphan drug expenditures in Medicare Part D, but studies have looked at expenditures and out-of-pocket costs for categories of drugs that include some orphan products or drugs that have similar cost attributes, such as specialty

drugs. Multiple studies have been conducted to look at specialty drug spending trends. In a study of specialty drug spending in 2007-2011 for a 20% random sample of all 65+ Medicare beneficiaries, specialty drugs accounted for $7.6 billion in total pharmacy spending in 2007 and $10.2 billion in 2011.[27] Per beneficiary spending increased from $2,641 to $8,976 in the study period. This represented 6.7% of total drug spending per beneficiary in 2007 and 9.1% of spending in 2011.[27]

A study of Medicare beneficiaries from 2007 to 2011 found that spending on specialty drugs per beneficiary increased in almost all therapeutic areas and significantly increased in oral cancer agents ($17.5 in 2007 to $40.99 in 2011) and immunomodulators ($15.6 in 2007 to $32.29 in 2011).[27] In 2010, the out-of-pocket burden for specialty drugs decreased by 26%, which the authors theorize is related to a reduction in the cost-sharing burden while in the donut hole.[27] A Congressional Budget Office (CBO) report on specialty drug spending in Medicare Part D using beneficiary level claims data found a 31% average annual increase in aggregate specialty drug spending from $8.7 billion in 2010 to $32.8 billion in 2015.[29] The top 50 selling brand-name specialty drugs in 2015 had a weighted average retail price of $4,380, with a range of $250 to $43,000.[29] The average net price for brand name specialty drugs grew at an average annual rate of 22% from $1,310 in 2010 to $3,590 in 2015 and a net per capita spending from $330 to $830 in the same time frame.[29]

Two studies looked at a sample of specialty drugs to determine the expected out-of-pocket costs for individuals on Medicare Part D. One looked at 12 specialty drugs in 2016[30] and the other looked at 30 drugs in 2019.[60] In 2016, the expected out-of-pocket costs for were at least $4,000 and up to $12,000 for one drug[30] and in the 2019 study the

range was from $2,622 to $16,551 with an average of $8,109 across specialty drugs. Both studies found that a significant portion of spending occurred after the individual had met the catastrophic cap. In 2016, one-third of the total out-of-pocket spending occurred after the individual met the catastrophic cap and for 7 of the drugs, more than half occurred after the catastrophic threshold.[30] In the 2019 study, the range of out-of-pocket spending above the catastrophic cap varied by drug from 13 to 86%. For 19 of the drugs, more than half of spending occurred after the cap.[60] For the cancer drugs included in the study, enrollees paid at least 70% of total OOP after the cap.[60]

Out-of-pocket costs can vary between PDPs from 2 to 14 times higher for brand drugs based on cost-sharing, tier placement, and the use of copays versus coinsurance.[30] Specialty drugs incur the highest costs when the drug is off formulary, 50% of the 12 specialty drugs in the 2016 study were not included on all formularies.[30] Two of the drugs included in the 2019 study were not included on any of the plans. For drugs that were not covered by some or all plans, the median annual cost when it was not included on the formulary ranged from $26,209 to $145,769. The median out-of-pocket costs for the 12 specialty drugs that were on some but not all plans, found that the drug was at least 10 times higher than the median cost if it was covered.[60]

This is consistent with another study of specialty drugs for 6 uncommon cancers, which found that 99.21% of non-LIS individuals and 99.72% of LIS individuals in the sample reached the coverage gap and 94.4% non-LIS and 97.96% of LIS reached their catastrophic coverage.[44] In this study the annual spending on specialty cancer drugs was $44,764 for non-LIS individuals and $44,272 for LIS individuals. Out-of-pocket

spending was $4,870 overall and $2,689 while in the gap for non-LIS individuals and $44 overall and $41 in the gap for LIS individuals.[44]

Oral cancer drugs are a specific form of specialty drug that are associated with high drug costs. One study found that the median cost for a 30-day supply of these types of drugs was $10,060 with a range of $5,123 to $16,093 and median out-of-pocket costs for a median duration course ranged from $6,456 to $12,160.[61] With these expenses, most beneficiaries on oral cancer drugs left the donut hole after 1.6 fills of the product.[61] Chronic myeloid leukemia (CML) is a rare cancer. A study that looked at CML patients who were taking targeted oral anticancer medication found that 81% of patients reached the catastrophic phase of coverage within the year and a majority of patients reached this point within the first month.[62] The median costs for the first fill of the prescription was $3.7 for individuals with heavy subsidies, $6.9 for individuals with moderate subsidies, and $2,309.4 for individuals without subsidies.[62] CML patients with subsidized Part D plans (68%) paid less than $2 for a 30-day supply, but 40% of individuals without subsidies paid out-of-pocket costs over $900.[62] Another study looking at newly diagnosed CML patients found that individuals who did not have LIS coverage faced mean out-of-pocket costs of $2,600 for the first 30-days of their treatment and were less likely to fill the initial prescription.[63] For those that did fill the prescription, those with LIS subsidies initiated the prescription in 23.7 days on average and those without LIS subsidies took 50.9 days.[63]

To date, no studies have investigated the total Medicare Part D expenditures for all orphan drugs. Previous studies related to Part D expenditures have focused on specialty drugs, but the definition has been inconsistent or does not include all approved

orphan indications. Studies on orphan drug expenditures in the United States have not provided aggregate or beneficiary level costs for Medicare Part D.

Objectives

Medicare Part D is a critical program for drug access for both individuals over the age of 65 and for individuals with qualifying disabilities. The primary purpose of this study is to determine how orphan drug expenditures in Medicare Part D compare to overall Medicare Part D drug expenditures. This research will fill the gap related to orphan drug costs and characteristics in this program. The specific questions this paper proposes are:

1. How do orphan drug expenditures in Medicare Part D compare to overall Medicare Part D pharmaceutical expenditures?
2. How do orphan drug expenditures for individuals over the age of 65 in Medicare Part D compare to orphan drug expenditures for individuals under the age of 65?
3. How do orphan drug expenditures in Medicare Part D for:
    A. rare cancer drugs compare to orphan drug expenditures for drugs that do not treat a rare cancer?
    B. a drug with a single orphan indication compare to expenditures for drugs approved for multiple orphan indications?

Data and Methods

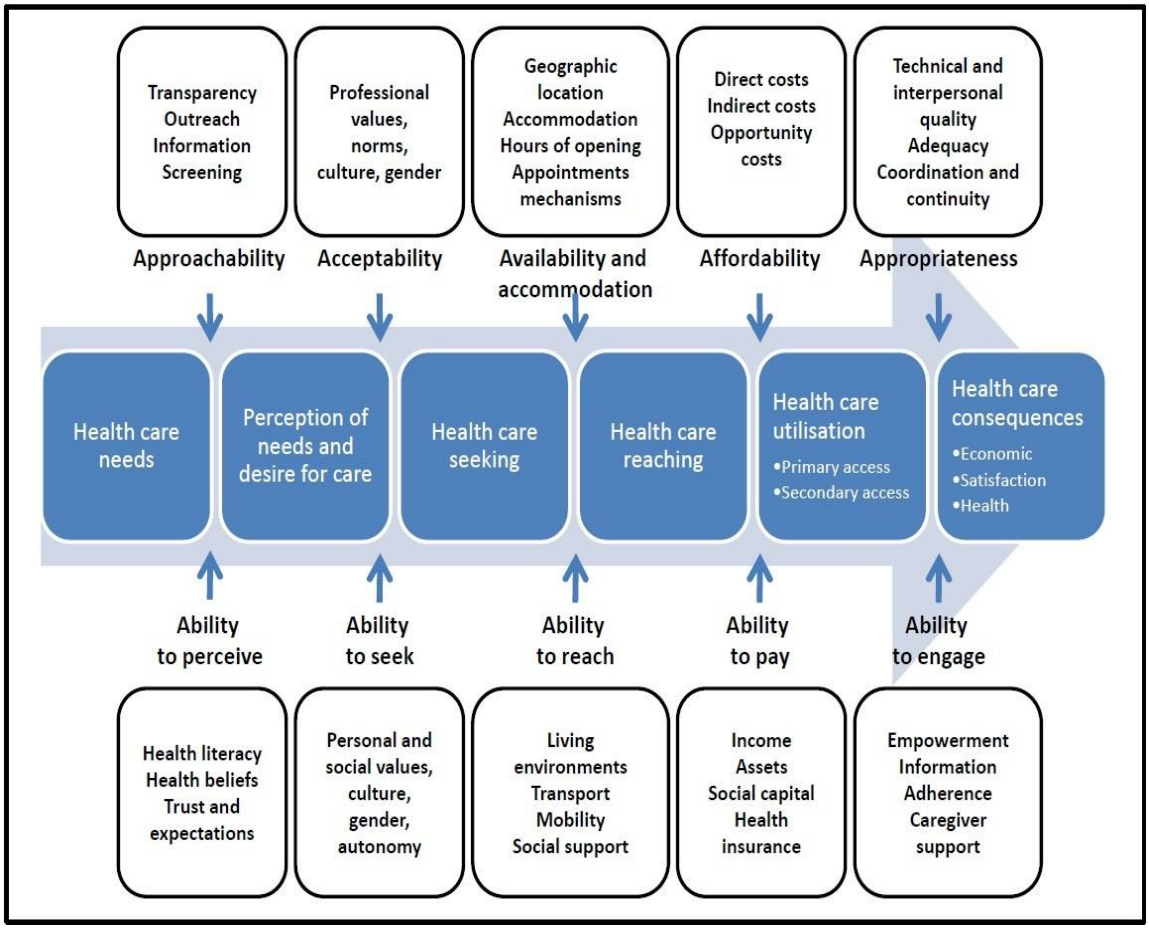
Conceptual model

Levesque, Harris, and Russell's patient centered healthcare access model provides a conceptual basis for this research.[64] (Figure 4) The model utilizes individual and supply-side factors to inform the dimensions of accessibility of healthcare services. The model was chosen based on the patient centric orientation of the model for both

systematic and individual components of access. The model is informed by a patient's navigation of the healthcare system. Rare disease patients often face additional challenges while interacting with the healthcare system, but the model accounts for the key moments and forces that impact both the process and outcomes.

Figure 4: Patient centered health care model

Model by Levesque, Harris and Russell



This paper is informed by the supply side factors that can result in the goal of access and positive health outcomes. Medicare Part D provides a mechanism for elderly and disabled individuals to access drugs in a cost-effective manner, which is reflected in the approachability and affordability domains of the model. Approachability describes the opportunity to identify, utilize, and benefit from health services.[64] Programmatic

factors such as eligibility, cost-sharing requirements, available subsidies, and drug coverage mechanisms, such as formularies, directly impact access and cost differences for individual patients. Health literacy can impact an individual's ability to choose the best plan. However, the approachability of the system is influenced by the quality and availability of decision-making tools.

Drug prices can impact both the acceptability and availability of drugs offered through Medicare Part D. Acceptability refers to the cultural and social forces that impact both the individual's ability to engage in services and the way society judges the appropriateness of an individual seeking that type of care.[64] The acceptability of using an orphan drug is impacted by the drug approval, drug marketing processes, and provider perceptions of new drugs. Availability through Part D is officially dependent on drug approval, but off-label use may present inequitable variations in access for different patients. The number of prescribers who are writing prescriptions for orphan drugs can help inform the availability and accommodation of an individual's ability to find a medical professional who is knowledgeable in the condition and can provide a prescription for an appropriate treatment. The supply-side factors in this model can help frame the importance of the cost, prescriber, and beneficiary data as it relates to orphan drugs. It can also inform decisions about how to ensure adequate access to treatments.

Data Source

Drug cost data was accessed from CMS Medicare Part D Prescriber Public Use Files for the national prescription drug data from 2013-2017.[65] The data is collected through CMS's Chronic Conditions Data Warehouse and provides drug event records submitted through both MA-PDs and PDP plans. Data is sorted on the drug level and

includes the number of claims, beneficiaries, prescribers, total drug costs, and specific information for beneficiaries over the age of 65. The aggregate costs paid by beneficiaries with and without low income subsidies was available for 2016 and 2017.

Data on orphan drug characteristics were obtained from the IQVIA Institute for Human Data Science information was deidentified at the drug level.[66] Data was from 2016 national sales data and included total aggregate sales costs. A drug was considered an "orphan only" drug if it only had approved indicated orphan uses and a "partial orphan" drug if it had both orphan and common indications. The data also indicated if the drug had a single or multiple orphan indications. If the drug was a partial orphan, the order of approval was provided. These characteristics were verified through the FDA Orphan Drug Designations and Approvals database.[67] Drug data included the costs and approval order for all orphan only and partial orphan drugs.

Data preparation

Data is suppressed in the National drug files if the records are derived from 10 or fewer claims. To ensure that the missing data would not significantly impact results, totals from the national drug file spreadsheets were compared to the grand total aggregate costs. Missing data accounted for .002% or less for cost data in each year and .014% or less for cost data for age specific data. Any drug record with suppressed data was coded to indicate if the suppression was due to fewer than 10 claims for beneficiaries over age 65 or under age 65. Proportional variables for the number of claims per prescribers, the number of claims per beneficiaries, the costs per claim, and the costs per beneficiary were created. Proportional variables were created to compare the share of claims, beneficiaries,

and costs associated with individuals under the age of 65 compared to all claims, beneficiaries, and costs.

Any drug that received an orphan indication from 1983 to December 2016 was coded as "orphan only" or "partial orphan" if they had indications for rare and common uses. A variable was created to identify orphan drugs that had an indication for a rare cancer based on the listed indications in FDA's database. Variables to identify if a drug had single or multiple orphan indications and the order of the approved partial indications (orphan first, common first, or concurrent) were also created.

A variable for approval order for partial indications was created in the sales data. For each partial orphan drug, the orphan spending was divided by total spending to calculate the total proportional orphan spending. Quintiles and quartiles were created based on total spending for the drugs. The average proportional spending was calculated for all partial orphans by quartile, by quintiles, and by approval order group.

The list of orphan drugs was then compared to the Medicare Part D drug data and each drug was coded according to orphan only, partial orphan, or common only. None of the orphan only drugs had claims prior to the approved marketing date. Partial orphan drugs were only included as contributing to partial orphan spending after the earliest orphan marketing approval date. Any previous orphan associated spending would be considered "off-label" and beyond the scope of this study.

Data analysis

Data analysis was conducted in Stata version 13.1. Descriptive statistics were calculated and recorded for all variables. This included frequency counts for categorical data and the mean, standard deviation, and range for continuous variables. Variables were

tested to see if they were normally distributed and all variables were found to be non-parametric. Variables were then compared by drug type for each year. Kruskal Wallis tests were conducted to compare the statistical significance of the differences in values across continuous variables by orphan drug status. Means, standard deviation, and p-values were reported. Unless otherwise noted, results were considered statistically significant at p=.05.

Sign tests were conducted to compare the differences between costs for individuals under and over the age of 65. Sign tests were also conducted to investigate the difference in costs paid by individuals with LIS and those with no subsidies. This was chosen over the Wilcoxon signed-rank test as the alternate hypotheses provide a direction for the differences between variables.[68]

In group analysis was completed for orphan drug specific variables. Kruskal Wallis tests were conducted to determine any differences in costs by approval order, rare cancer status, and for drugs with multiple orphan indications compared to drugs with single indications. Chi-squared tests were completed to investigate the statistical significance of suppression by age and drug type and age and rare cancer status.

The proportional share of orphan spending was not normally distributed. Kruskal Wallis tests were conducted on the weighted proportional differences for the quartiles, quintiles, and approval order groups. There was no statistical difference between groups for quartiles (p=.8786) or quintiles (p=.3762), the estimated costs for partial orphan spending were not calculated by these factors. There was a statistical difference (p=.020) in the proportion of orphan spending by approval order.

The mean proportional weight for all partial orphan drugs (0.23941) was applied to each partial orphan drugs' total costs to create a new variable with the estimated orphan contribution to cost. The median proportional weight (0.08365) was also applied to costs for partial orphans. Proportional weighting by approval order group for orphan first (0.3808), common first (0.236), and concurrent approvals (0.2716) was also generated. Inverse variables for the estimated common costs for each of these three treatments were also calculated.

The three weighting applications were then used to calculate estimated means, ranges, and the aggregate sums of the estimated orphan and common spending by year. Pair-wise sign tests were conducted to compare the difference in estimated orphan spending by the three weighted estimate treatments. The partial estimates of orphan and common spending were added to the known common and orphan drug spending for each year and estimated totals by each model were reported.

Results

There were a total of 17,022 drug records in Medicare Part D from 2013-2017. There were 305 unique orphan drugs with claims in this time frame. On average for all years, there were 25,283 prescribers, 423,566 claims, and 112,896 beneficiaries per drug per year. The differences in the average number of claims, beneficiaries, and prescribers by drug type were all statistically significant (p=.0001) for each year. (Table 9)

Table 9: Beneficiary, cost, claim, and prescriber data by year 2013-2017

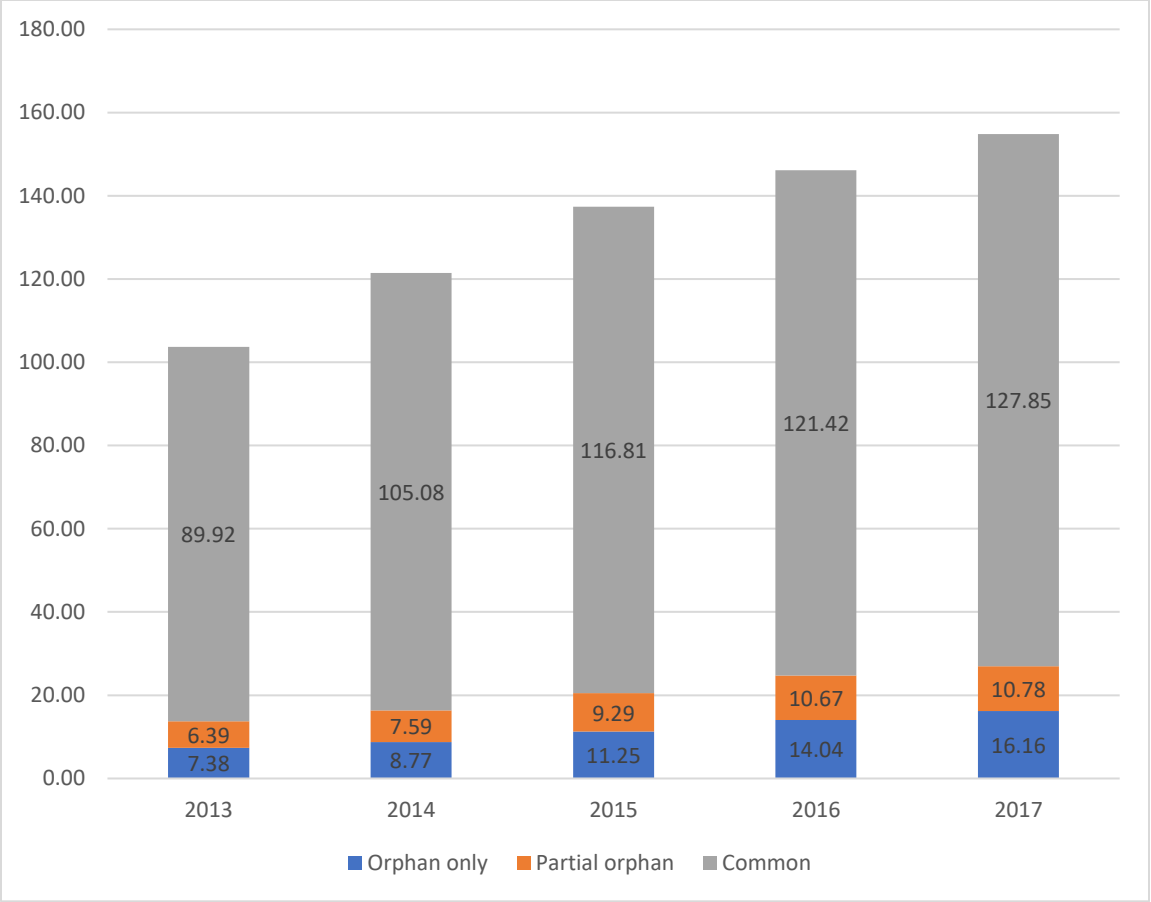
Results are statistically significant at (p<.0001) by drug type for each year.

	2013	2014	2015	2016	2017	Total	% for <65
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Beneficiaries							31.11

Orphan only	7,565 (55,474)	4,357 (22,868)	2,975 (9,338)	2,476 (7,194)	2,433 (7,406)	3,825 (26,156)	25.43
Partial orphan	27,325 (86,124)	28,100 (89,722)	24,990 (81,473)	40,785 (192,757)	22,339 (77,788)	28,752 (115,014)	20.32
Common	108,620 (491,524)	117,546 (528,441)	122,135 (555,641)	125,951 (577,168)	130,291 (600,331)	120,835 (551,563)	30.58
Claims							34.08
Orphan only	28,603 (170,993)	20,794 (94,254)	16,233 (61,045)	15,175 (58,964)	15,197 (64,456)	18,748 (95,328)	43.98
Partial orphan	113,377 (370,661)	104,725 (341,059)	105,385 (357,472)	159,044 (744,976)	85,521 (321,482)	113,597 (456,920)	36.92
Common	421,549 (2,198,313)	450,049 (2,318,808)	458,932 (2,383,625)	470,576 (2,459,113)	472,778 (2,472,927)	454,595 (2,367,592)	33.42
Costs (in millions)							35.00
Orphan only	46.686 (159.696)	51.292 (172.124)	59.547 (198.763)	70.554 (239.534)	79.625 (288.569)	62.615 (220.752)	45.36
Partial orphan	89.942 (204.844)	106.943 (252.081)	125.502 (302.734)	138.552 (360.473)	134.772 (347.672)	119.883 (300.640)	38.77
Common	27.943 (132.028)	33.680 (159.129)	37.297 (198.223)	38.954 (174.973)	40.690 (172.985)	35.672 (168.734)	34.29
Prescribers							N/A
Orphan only	2,949 (17,231)	2,044 (9,654)	1,514 (4,446)	1,230 (2,582)	1,187 (2,574)	1,733 (8,739)	
Partial orphan	8,807 (27,985)	9,153 (28,485)	7,695 (22,029)	9,036 (32,138)	7,156 (21,030)	8,339 (26,467)	
Common	25,272 (67,448)	26,635 (70,105)	27,107 (71,935)	27,631.20 (73,744)	28,272.49 (75,614)	26,975 (71,802)	

By drug type, total aggregate costs were $57.606 billion (8.67%) for orphan only drugs, $44.716 billion (6.74%) for partial orphan drugs, and $561.084 billion (84.58%) for common drugs. (Figure 5) The average total costs per year by drug type was statistically significant (p=.0001). In each year, partial orphan drugs had higher average costs than orphan only or common drugs. In 2017, orphan only drugs averaged $74.6 million, partial orphan drugs averaged $134.8 million, and common drugs averaged $40.7 million in mean costs.

Figure 5: Aggregate total costs in billions of dollars by drug type from 2013 to 2017

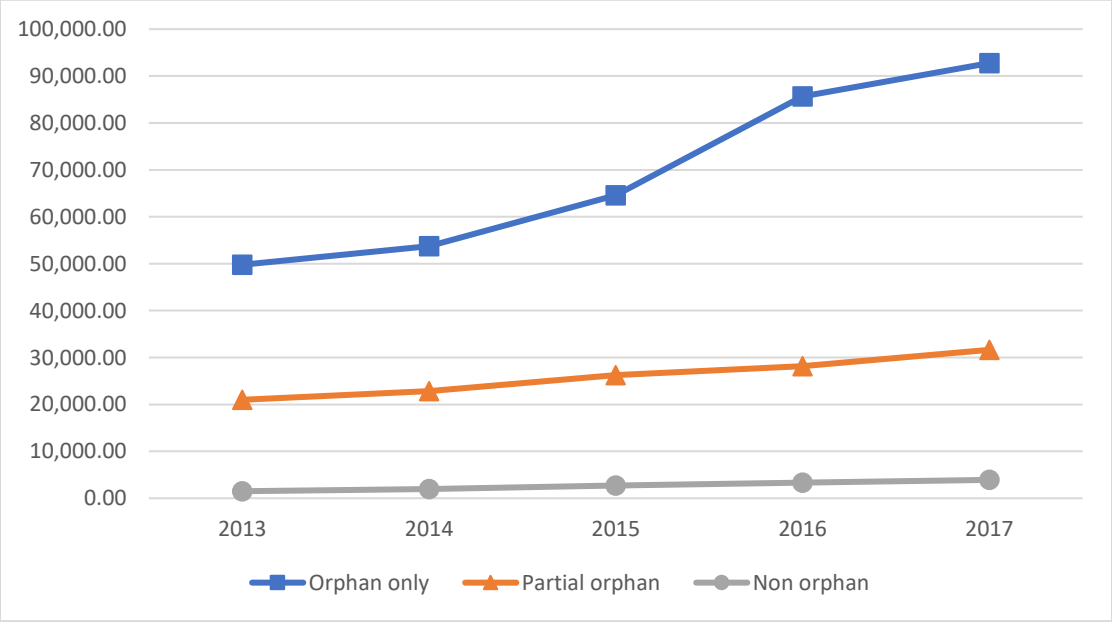


There was a statistically significant difference in the costs per beneficiaries by drug type in each year (p=.0001). (Figure 6) Orphan only drugs had the highest average cost per beneficiary in each year. In the timeframe, the average cost per beneficiary for orphan drugs increased from $49,776 in 2013 to $92,753 in 2017. In the same timeframe, the average cost per beneficiary for common only drugs rose from $1,505 in 2013 to $3,920 in 2017.

The lowest cost orphan only drug was $122 in 2017 for Cetylev, a drug to prevent or lessen hepatic injury. The drug with the maximum cost per beneficiary was $1,306,221 for Strensiq a drug approved for hypophaosphatasia, a rare metabolic disease. It should also be noted that this drug is indicated for infantile and juvenile use and does not currently have an approved indication for adult use. There were 30 beneficiaries in 2016

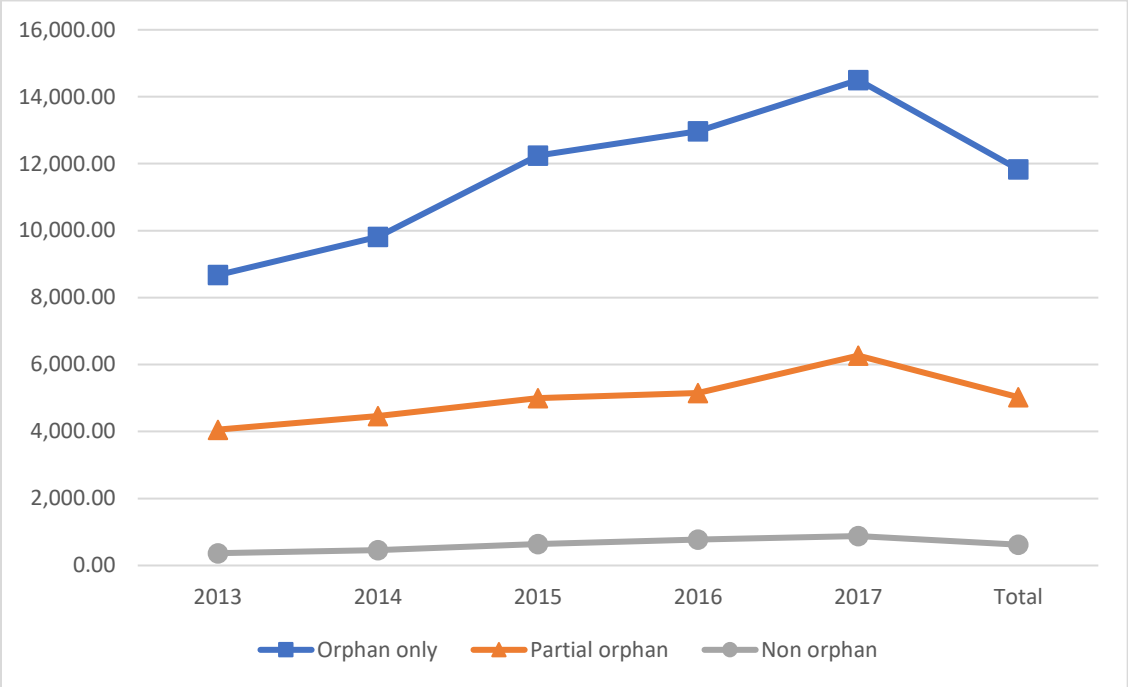
and 40 beneficiaries in 2017 who submitted claims for Strensiq. Vimizim, another single orphan only indicated drug for mucopolysaccharidosis Type IV, a lysosomal storage disorder, is the only other drug to have per beneficiary costs over one million dollars. The common drug with the highest cost per beneficiary was $533,197 per beneficiary for Chenodal in 2017, which is indicated to dissolve gallstones. This drug had only 31 beneficiaries listed and of to the total $16 million in expenditures, $13 million is associated with beneficiaries under the age of 65. The number of beneficiaries under the age of 65 is suppressed, but this does indicate very high costs for a small number of beneficiaries.

Figure 6: Average costs per beneficiary by drug type from 2013 to 2017



Orphan only drugs had the highest average costs per claim across the timeframe and the difference by drug type was statistically significant and increased over time. (Figure 7) In 2017, the average cost per claim was $14,500.87 for orphan only drugs and $878 for common drugs.

Figure 7: Average costs per claim by drug type from 2013 to 2017



There was a statistically significant difference in the number of beneficiaries per prescriber across drug type by year. (Figure 8) For all years combined the average number of beneficiaries per prescribers was 1.31 for orphan only drugs, 1.72 for partial orphan drugs, and 1.69 for common drugs. There was a statistically significant difference in the number of claims per beneficiaries by drug type and year. (Figure 9) On average, there were 5.29 for orphan only, 4.91 for partial orphans, and 3.49 for common only drug claims per beneficiary.

Figure 8: Average beneficiaries per prescriber by drug type from 2013 to 2017

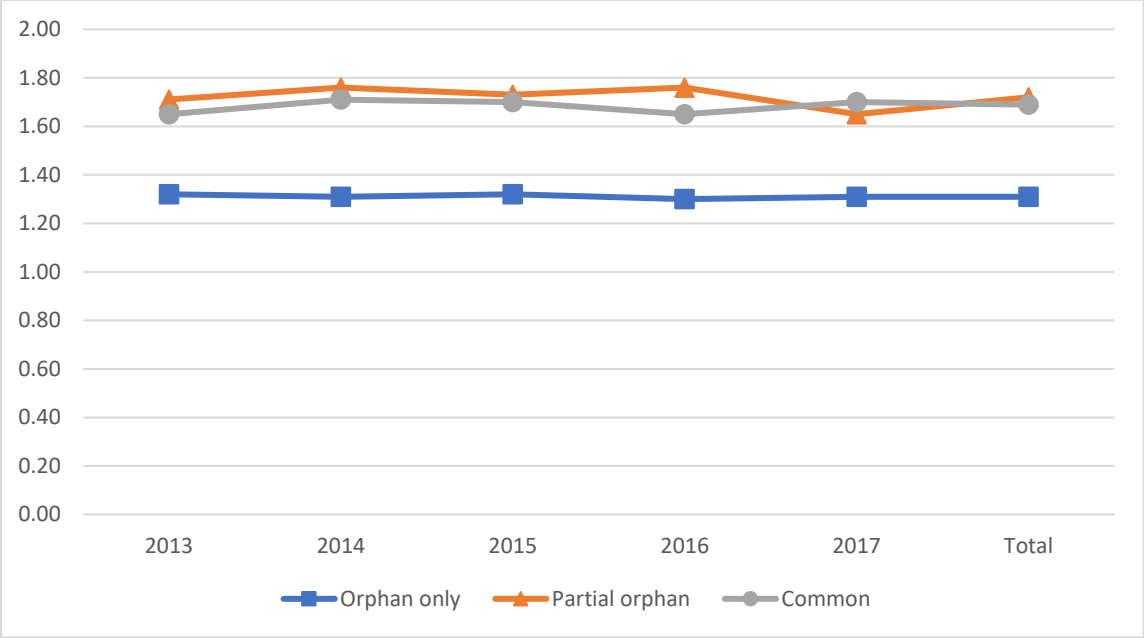
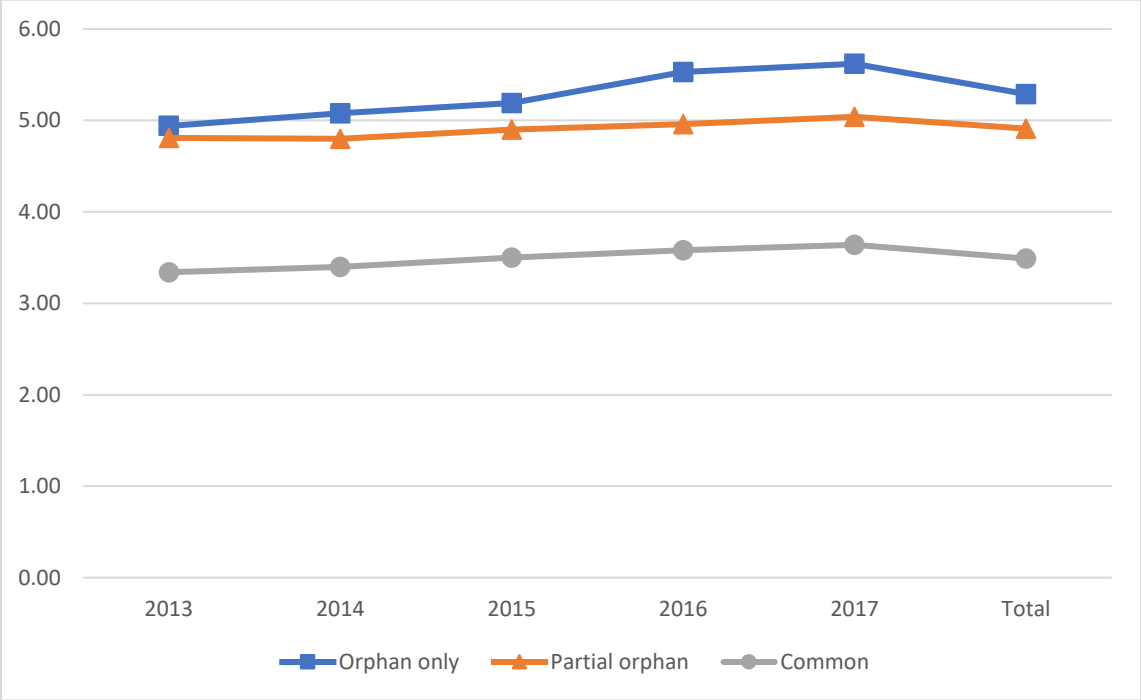


Figure 9: Average claims per beneficiaries by drug type from 2013 to 2017



There was statistically significant difference in the aggregate total costs paid by individuals with LIS compared to individuals who do not have any subsidies ($p<.0001$). (Table 9) There was also a statistically significant difference in the aggregate subsidies

paid according to orphan drug status in both 2016 and 2017. However, we are unable to determine the total number of claims for individuals with and without these subsidies.

Table 10: Average aggregate total cost sharing by drug type with low-income subsidies and without subsidies

	With low income subsidies (LIS)			Without cost sharing subsidies		
	Mean (SD)	**Maximum**	**p-value**	**Mean (SD)**	**Maximum**	**p-value**
2016 by drug type			0.0001			0.0001
Orphan only	60,981 (233208)	2,391,922		2,875,377 (10977383)	124,581,608	
Partial orphan	274,101 (1185265)	9,839,207		7,584,638 (30820336)	263,742,128	
Common	304,062 (1272528)	19,964,674		4,373,747 (17202718)	264,950,880	
2017 by drug type			0.0001			0.0004
Orphan only	62,545 (258323)	2,833,621		3,076,643 (12570954)	143,904,384	
Partial orphan	176,186 (514023)	3,643,136		4,831,917 (10108338)	56,076,244	
Non orphan	304,705 (127259)	18,169,668		4,491,525 (18116438)	410,296,864	

There were 449 orphan drugs in the national sales data set, 110 did not have any sales data for 2016. Of the remaining drugs, 255 were orphan only drugs with 100% orphan spending and 84 were partial orphan drugs. Of those, three drugs had only orphan spending and one drug had only common spending. The total aggregate spending in the national sales data had higher overall spending and a higher percentage of partial spending then was seen in the Part D data.

Of the weighted models, the mean proportional weighting resulted in the highest aggregate ($10.7 billion total) and mean costs ($28.7 million) and the median weighted model had the lowest aggregate ($3.7 billion total) and mean costs ($10.02 million). (Table 10) The weighted model based on approval order estimated $7.6 billion in total

aggregate costs in the study period and $20.3 million in mean costs. These estimates were compared to the known costs for each year. (Figure 10)

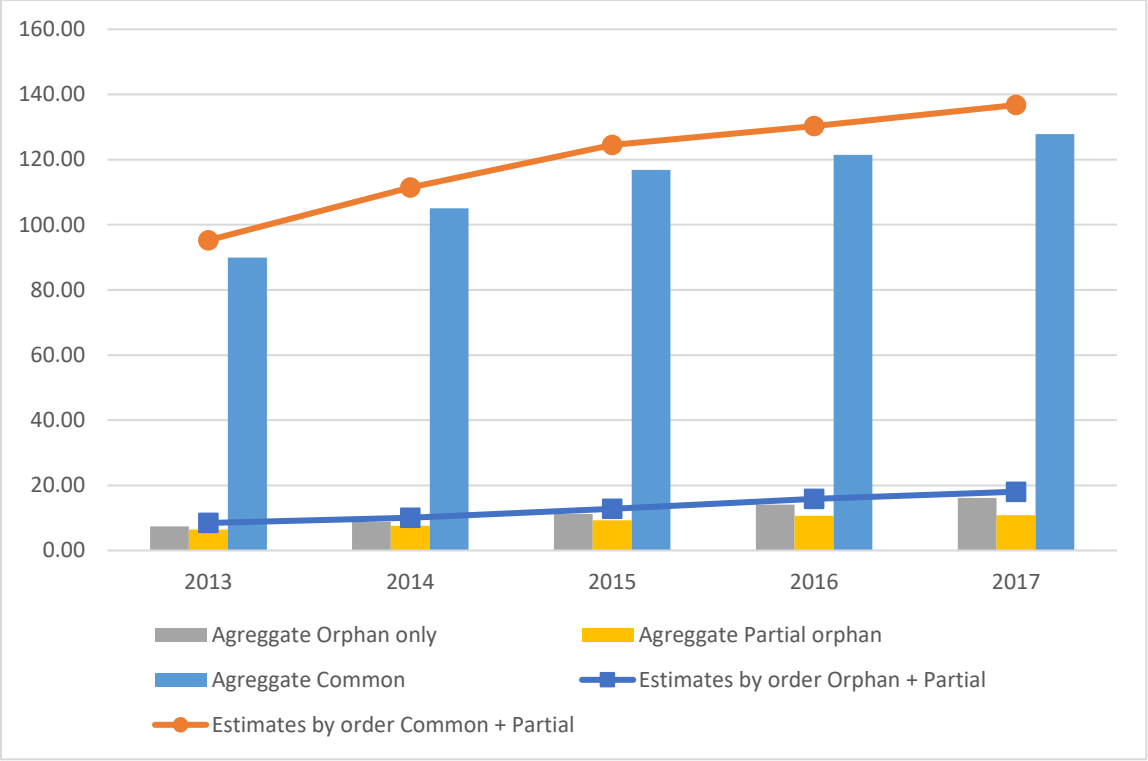
Table 11: Aggregate total and mean cost estimates for orphan associated spending using weighted models for partial orphan spending (in millions)

Results are the estimated proportional orphan associated costs for partial orphan drug spending based on three models for weighting. Weighting by mean used a consistent factor of .23941. Weighting by median used a consistent factor of 0.08365. Weighting by approval order group was applied according to approval order with 0.3808 for orphan first, 0.236 for common first, and 0.2716 for concurrent approvals.

	2013	2014	2015	2016	2017	Total
Aggregate total partial orphan estimated costs (in millions)						
By mean	1,528.841	1,817.829	2,223.444	2,554.148	2,581.263	10,705.525
By order	1,062.946	1,270.854	1,558.896	1,813.782	1,867.375	7,573.854
By median	534.146	635.113	776.826	892.368	901.841	3,740.293
Mean estimated partial orphan costs (in millions)						
By mean	21.533	25.603	30.047	33.171	32.266	28.701
By order	14.971	17.899	21.066	23.556	23.342	20.305
By median	7.523	8.945	10.498	11.589	11.273	10.028

Figure 10: Aggregate total costs in billions of dollars by drug type and weighted estimates for partial orphan costs

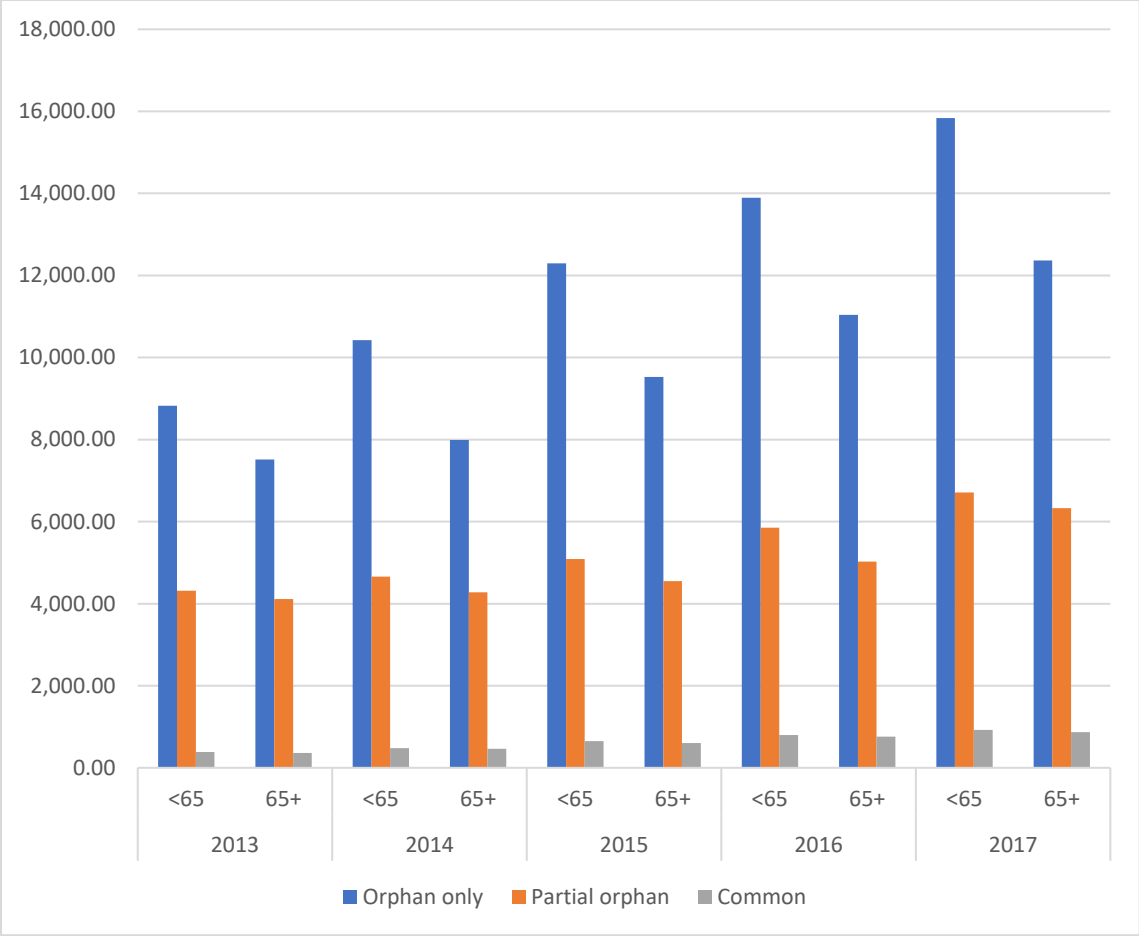
Estimates were based on the approval order weighted costs.



Age specific results

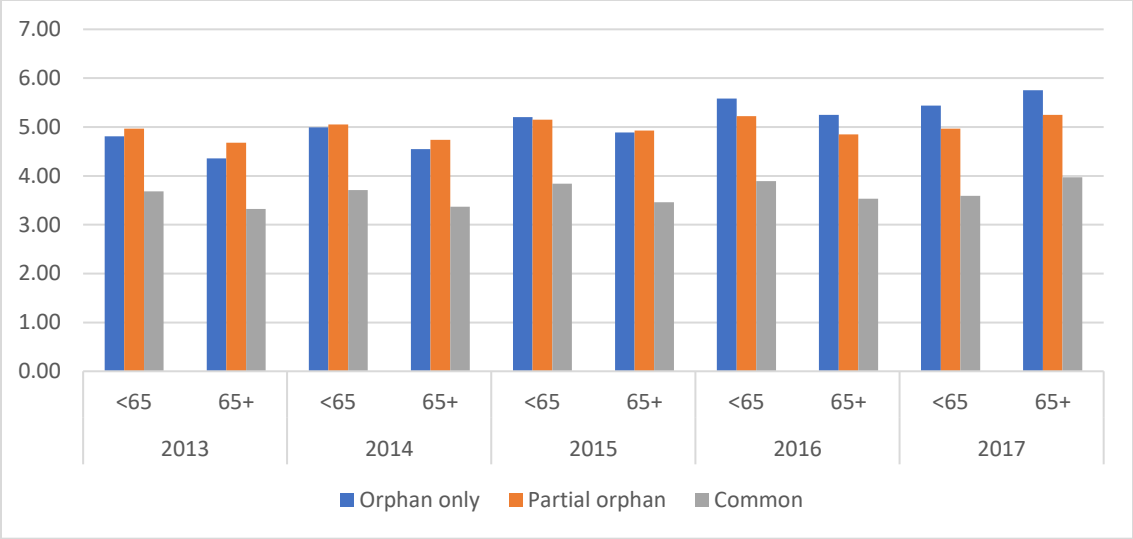
There was a statistically significant difference in the total costs, beneficiaries, claims, costs per beneficiary, and costs per claim for individuals over 65 and individuals under age 65 ($p<.0001$). We reject the null hypothesis that the two values are the same in favor of the alternate hypothesis that the value is larger for the over age 65 group in all cases except for costs per claim. For the costs per claim, we reject the null in favor of the alternate hypothesis that costs per claim are higher for individuals under 65 compared to costs per claim for individuals over. (Figure 11)

Figure 11: Average costs per claim by drug type and age



Overall, 31.11% of beneficiaries under 65. Claims per beneficiaries are highest for orphan only drugs and show more variation for orphan drugs by age. (Figure 11) Common only drugs showed less growth over time and are more similar between the age groups. Partial orphan drugs have the smallest proportional share of individuals under the age of 65 (20.32%). Individuals under 65 submitted 34.08% of all claims and 43.98% of orphan only claims. Individuals under 65 are responsible for 35% of all costs, 45.36% for orphan only costs, 38.77% for partial orphan drugs, and 34.29% for common only drugs.

Figure 12: Average claims per beneficiary by drug type and age



Costs per beneficiaries by age category steadily increased over time for orphan only drugs. Costs per beneficiaries for orphan only drug spending more than doubled in the time period ($59,548 in 2013 to $127,812 in 2017 while the costs per beneficiary for common only drugs increased from $3,109 to $4,908 in the same timeframe. (Figure 12) Orphan drug type was a statistically significant (p=.018) factor for the reason for suppression. (Table 12)

Figure 13: Average costs per beneficiary by drug type and age

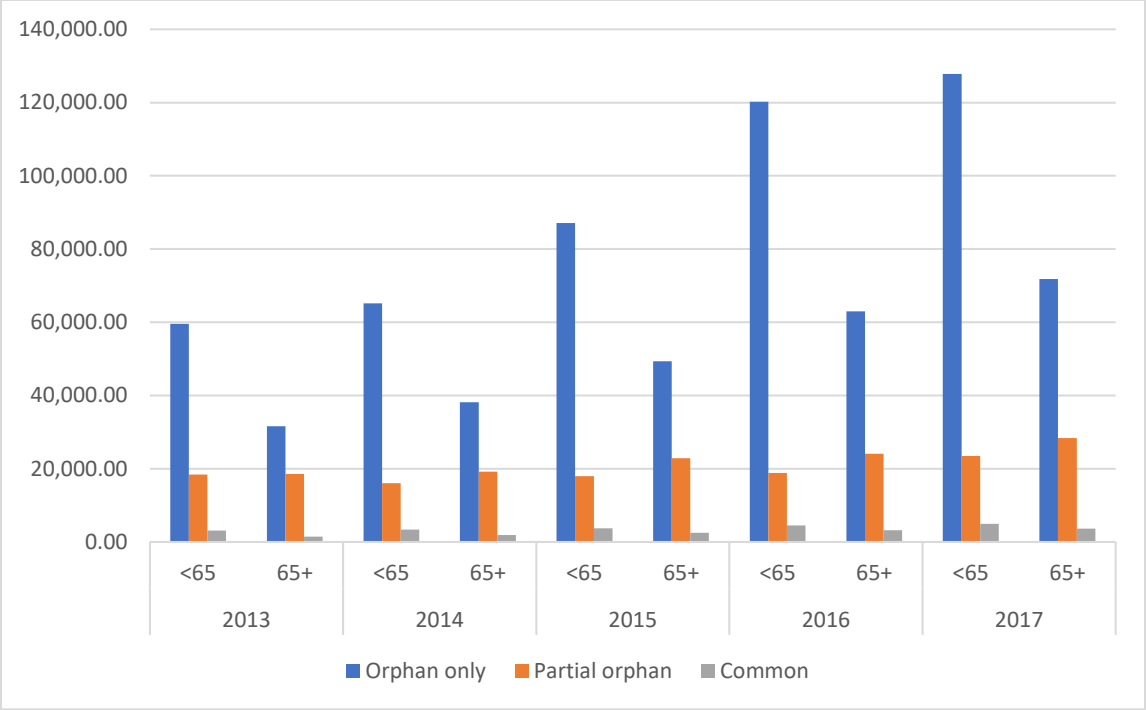


Table 12: Suppression by drug type and rare cancer status

Data was suppressed if the number of claims or beneficiaries was less than 10.

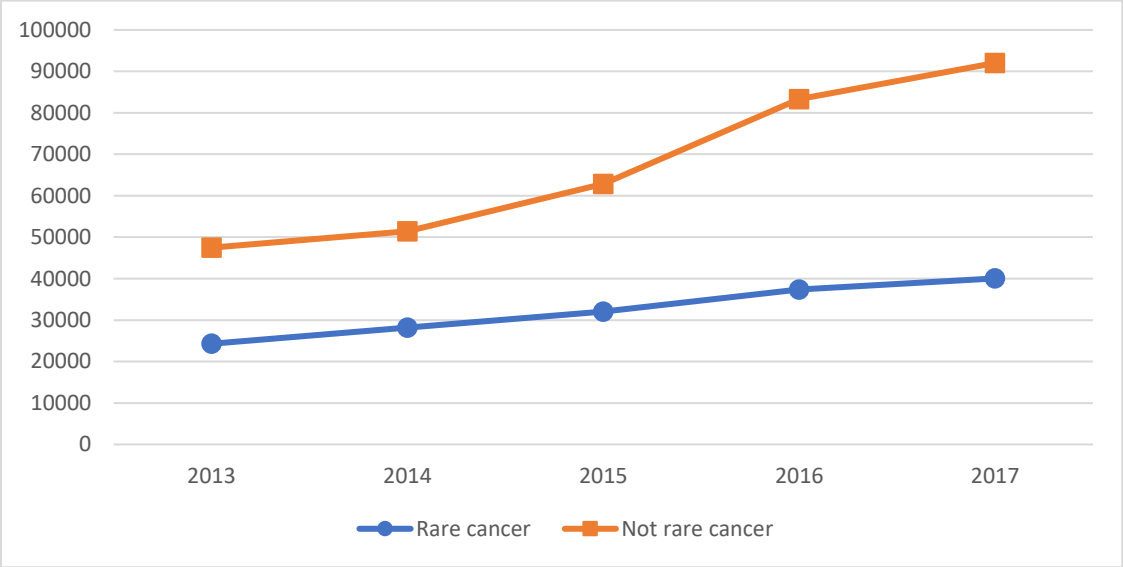
	65+ N (%)	<65 N (%)	p-value
Drug Type			0.018
Orphan only	101 (42.62)	136 (57.38)	
Partial orphan	25 (48.08)	27 (51.92)	
Common	1495 (52.05)	1377 (47.95)	
Total	1621	1540	
Orphan drug uses			<.0001
Rare cancer	61 (62.24)	37 (37.76)	
Not rare cancer	65 (34.03)	126 (65.97)	
Total	126	163	

Rare cancer

Rare cancer drugs for orphan only indications in Part D cost $24.01 billion between 2013 and 2017. This represents 3.61% of all spending in Part D and 41.68% of orphan only drug spending. There was not a statistically significant difference in the average total costs of rare cancer drugs compared to non-cancer orphan only drugs

(p=.095). (Figure 14) The average total costs of rare cancer orphan drugs were higher than their non-cancer counterparts ($97.9 million versus $70.4 million). The costs per beneficiary were seen to be statistically significant (p=.0014). With the rare cancer drugs costing $33,114.07 per beneficiary and non-cancer orphan drugs costing $68,151.63 per beneficiary. The maximum cost per beneficiary for a rare cancer drug was $146,130 per beneficiary compared to $1,306,221 for the highest cost non-cancer orphan drug per beneficiary.

Figure 14: Average costs per beneficiary for rare cancer drugs



The difference in the mean proportional costs for beneficiaries under the age of 65 was found to be statistically significant (p=.0001). The mean costs attributable to beneficiaries under the age of 65 was 21.31% for all rare cancer drug spending and 53.23% for non-cancer orphan drugs. (Table 13) A total of 98 rare-cancer drugs had suppressed records. Of those, 62% were suppressed due to data from individuals over the age of 65. For non-rare cancer drugs there were a total of 191 records with some suppression and individuals under the age of 65 represented 65.97% of the reason for suppression, which was statistically significant (p<.0001).

Table 13: Orphan drug in-group analysis for rare cancer, approval order, and multiple indications

	Average aggregate costs (in millions)			Costs per beneficiary			Costs <65
	Mean (SD)	Max	p-value	Mean (SD)	Max	p-value	%
Orphan drug uses			0.0952			0.0014	
Rare cancer	97.9 (311.3)	3,310.5		33,114.1 (26,160.76)	146,130.1		21.31
Not rare cancer	70.4 (211.2)	2,551.1		68,151.6 (133,446.4)	1,306,221.0		53.23
Approval Order			0.0001			0.0001	
Orphan first	78.3 (111.5)	347.9		60,226.9 (32,477.2)	123,787.6		28.42
Common first	119.1 (303.7)	2,551.1		25,082.3 (35,137.4)	239,713.0		27.86
Concurrent	146.0 (240.8)	1,435.4		17,201.8 (22,735.6)	80,411.2		51.41
Orphan only	62.6 (220.8)	3,310.5		70,528.0 (130,562.6)	1,306,221.0		45.36
Common only	35.7 (168.7)	7,029.3		2,686.8 (12,007.1)	533,197.3		34.29
Number of orphan indications			0.0001			0.513	
Single orphan	61.7 (198.9)	2,551.1		64,389.5 (12,743.7)	1,306,221.0		47.19
Multiple orphan	125.6 (341.9)	3,310.5		39,141.1 (60,135.3)	437,481.2		33.67

Drugs with multiple orphan indications

There was a statistically significant difference in the average total costs for orphan drugs with one indication compared to drugs with multiple orphan indications ($p<.0001$). (Table 13) Across all years, there was not a statistically significant difference ($p=.513$) in the costs per beneficiary for orphan drugs with a single indication ($64,389.50) compared to drugs with multiple indications ($39,141.09). The proportional share of spending for individuals under the age of 65 was statistically significant ($p=.0001$) for orphan drugs with one indication (47.19%) compared to orphan drugs with multiple indications (33.67%).

There is a statistically significant difference in the average costs per beneficiary based on the approval order of the drugs. Across all years, the per beneficiary costs are highest for drugs with only an orphan drug approval ($70,528) or if the orphan approval occurred first ($60,226). The per beneficiary costs were lowest for drugs with only common indications ($2,686) and concurrent designations ($17,201). The highest cost per beneficiary was $1,306,221 in 2016 for an orphan only drug. The proportional share for individuals under the age of 65 was statistically significant ($p=.0001$) and highest for concurrent designations (51.41%) and orphan only (45.36%) drugs.

Discussion

Limitations

The Medicare Part D data only includes spending through the Part D program and is not reflective of all orphan drug spending for Medicare beneficiaries. Any spending that is processed through other sources such as in a hospital setting would not be

included. The purpose of this study is to determine the impact and characteristics of orphan drug spending through Medicare Part D, therefore, this limitation is not impactful.

It is possible that suppressed records are more likely to be attributed to orphan drug spending due to the inherently small patient population for rare diseases. This could underestimate the impact of orphan drug spending in Part D. However, this impact should be very minimal as the missing data for any given year is negligible and for all years combined represents less than .18% of the total aggregate costs.

The reason for drug use was not available in the data set and it is not possible to accurately identify orphan vs. non-orphan spending for partial orphan drugs or any off-label drug use. As is consistent with other orphan drug studies,[31] results are reported by drug type with partial orphan spending as a separate category of drug use to accurately report only what is known. Even if drug use cannot be determined, partial orphan drugs with approved orphan indications still benefit from government subsidies and have different cost patterns. Understanding market trends is still important for identifying trends and formulating policies.

It is also possible that proportional spending for orphan and nonorphan use changes over time based on the rate of diffusion of awareness among patients and medical professionals for a new drug indication. Marketing dates were used to determine when official orphan drug use began, but drug data was only available based on the year. A partial orphan drug that received a marketing date after December 1st was considered a common drug until the following year to limit the over estimation of orphan associated costs. This was based on previous studies that found that there is a delay in the time it takes for orphan drugs to be included in Medicare plans.[58] It is unlikely that significant

orphan spending would occur in the final weeks of the year directly after the marketing date, however, this may impact the true impact of orphan drug spending in the weighted analysis. This was not a consideration for orphan only spending as claims did not appear in the data set prior to the approval of any of the drugs.

Estimations on the anticipated impact of partial orphan drugs was conducted through proportional weighting based on estimates from national sales data. The weighting may be different for the general marketplace compared to the Medicare population. Weighting could only be calculated on group characteristics and not by a specific drug. Additionally, weighting was only available for 2016 sales data and was applied consistently across all years. This could inaccurately represent the true weighting of orphan drug proportional spending in Medicare Part D in the timeframe of this study. Estimations on the orphan versus common spending associated with partial orphan drugs should be viewed as estimations and a starting point for future inquiry.

This paper is unable to address any claims that were denied or differences in approval patterns for orphan and non-orphan drugs. If an individual is on multiple medications or drugs, we cannot look at overall beneficiary spending patterns. We are also unable to determine differences according to tiers, formulary restrictions, or MA-PD versus PDP plans. We also do not have any context for additional reimbursement programs or financial assistance support for the cost sharing burden on patients. Any available information about cost sharing is at the aggregate drug level and we cannot calculate per beneficiary cost sharing. This analysis is critical for future studies on the overall impact of orphan drug prices for individuals and our system, but is considered out

of scope for this analysis. This study is the first to investigate the cost and claim trends for all orphan only or partial orphan spending in Medicare Part D.

Orphan drug spending

Supply-side factors of approachability, acceptability, availability and accommodation, affordability, and appropriateness are all critical in patients achieving appropriate access to needed healthcare services which result in positive health outcomes. This project focused on the affordability aspects of access, while also providing some evidence for the availability and accommodation of access to orphan drugs based on the number of prescribers per beneficiary.

In previous studies orphan drug spending accounted for between 7.9-9.5% of total pharmaceutical spending.[13,33,69] We can confidently attribute 8.6% to pure orphan only spending and an additional 6.74% to partial orphan spending. Using the estimates from the weighted models total orphan percentage is 10.3% using the mean model, 9.83% using approval order model, and 9.25% using the median model.

Despite the small proportion of total Part D spending, there was a clear difference in the average costs, costs per beneficiary, and costs per claim for orphan only drugs, partial orphan drugs, and common drugs. A previous study of orphan drug prices found that 80.4% of orphan drugs had an average cost per patient of over $6,000, this study found much higher per beneficiary costs.[13] In 2017, the average per beneficiary cost was $92,753 for orphan only drugs and $31,638 for partial orphan drugs.

A CBO report found that brand name specialty drug spending in 2015 was $33,460 per beneficiary.[29] In this study, 2015 per beneficiary partial orphan drug spending was similar at $26,229, but orphan only per beneficiary spending in the same

year was much higher at $64,618 per beneficiary. Orphan drugs are often considered a subset of specialty pharmaceuticals, but these differences provide a compelling need to further investigate our payment mechanisms for covering orphan only drugs and consider programs that specifically target the unique characteristics of rare disease patients.

The percentage of partial orphan drugs in this study was 28% which is slightly higher than in previous studies which found between 18 and 22% of orphan drugs were partial orphans.[13,31] This difference is likely due to the fact that the general market is more likely to include claims for pediatric or juvenile orphan drugs compared to the Medicare population whose target population is mainly individuals over the age of 65. Orphan only drugs in the study have a higher percentage of claims attributable to individuals under the age of 65 compared to common or combined drugs.

Aggregate average costs per drug were highest for partial orphans compared to orphan only or common drugs. For all years combined, the average cost of an orphan only drug was $62.6 million, for a common drug was $35.7 million, and for a partial orphan drug $119.8 million. These trends do not persist for per beneficiary or per claim costs, but should be acknowledged and understood when considering policy reforms for stimulating orphan drug development.

The number of beneficiaries per prescribers was statistically significant across years and was lower in each year for orphan only drugs. It is often difficult for individuals with rare diseases to find knowledgeable medical providers. This difference could point towards the overall consolidation of rare disease experts. Future research should investigate additional characteristics of providers to determine where individuals are seeking treatment and to determine if needs for this population are being met.

We only have information about the individual cost share at a total aggregate drug level and not per beneficiary. Cost sharing was significantly higher for individuals without cost-sharing subsidies. The orphan only drug that had the highest total cost-sharing amount in 2017 was Revlimid, a treatment for multiple myeloma.[30] Individuals who did not have cost sharing subsidies and received Revilimid were responsible for a total $143.9 million. The drug had a total of 37,399 beneficiaries in 2017. By comparison, individuals without cost sharing subsidies on the common drug Eliquis, an anticoagulant, were responsible for a total of $410.3 million. A total of 1,064,170 beneficiaries who used the drug. In general, 30% of people with Part D have LIS.[30] If we were to use the assumption that 70% of beneficiaries did not receive any subsidies this would mean a per beneficiary cost of $550.79 for Eliquis and $5,496.88 for Revlimid. It is unlikely that either of these drugs would be the only prescription a beneficiary would need in a single year.

Age specific results

In Medicare, 14.4% of beneficiaries are under the age of 65,[65] but in this study 34.08% of all claims and 31.11% of beneficiaries were individuals under the age of 65. Individuals in Medicare under the age of 65 are more likely to have multiple chronic conditions compared to their older counterparts, which could account for this higher percentage of overall claims.[41,46] It is possible that the total number of beneficiaries is closer to 14%, but we cannot determine if an individual beneficiary is responsible for multiple drug claims across the data set.

Higher per beneficiary and per claim costs for beneficiaries under the age of 65 compared to over the age of 65 is consistent with previous findings.[41] The difference is

more pronounced for orphan drugs and partial orphan drugs then common drugs. This could be based on the concerted effort to include rare diseases on the list of compassionate allowances.[40] It is also possible that individuals with a rare disease diagnosis have access to resources that help them to apply for Social Security benefits, which makes them eligible for Part D. The large share of orphan drug spending attributable to individuals under the age of 65 indicates the overall need for public programs to help rare disease patients access treatments. Future research should explore the additional demographic and diagnosis characteristics of Medicare enrollees on Medicare. Geographic variation based on the accessibility of rare disease providers and programs to connect individuals with additional assistance may provide additional information about equity issues or barriers to enrollment.

Rare Cancer

A total of $24.01 billion is attributed to orphan only rare cancer drugs and an additional $16.34 billion is attributed to rare cancer drugs with combined orphan and non-orphan indications. The average aggregate total cost of rare oncology drugs ($97.9 million) was higher than non-cancer orphan drugs ($70.4 million), but the costs per beneficiary were significantly higher for non-cancer drugs ($68,152) compared to rare cancer orphan drugs ($33,114). The total sum of all rare cancer spending for all years was $40.347 billion or 39.43% of all orphan drug spending from 2013 to 2017. This is consistent with the 2013 finding that oncology drugs represented 40.7% of orphan drug spending in a study of sales data.[31]

Individuals over the age of 65 account for 78.69% of the expenditures for rare oncology drugs. By contrast, individuals over the age of 65 account for 6.77% of non-

oncology products. It is possible that beneficiaries are receiving medications for both cancer and non-cancer orphan drugs, we cannot make determinations about the diagnostic characteristics of rare disease patients on Part D.

Drugs with multiple orphan indications

Per beneficiary costs for orphan drugs with multiple indications are not statistically significant compared to per beneficiary costs for orphan drugs with one indication. Previous studies have found that drugs with multiple orphan indications have higher prices,[15] however, the disease prevalence of the first indication is an additional contributing factor which was not investigated in this study.[70] The range in values for costs per beneficiaries for orphan drugs with a single orphan indication ranges from $90.42 per beneficiary to $1,306,221 per beneficiary. Orphan drugs with multiple indications range from $142.96 to $437,481.20 per beneficiary. This range provides evidence for the large range of costs in orphan drug spending. By contrast, the minimum per beneficiary cost for common drugs is $.01 per beneficiary. Drugs that entered the market as an orphan drug first or that are only indicated as orphan drugs are associated with higher costs per beneficiaries.

Policy implications and future research

Although the overall proportion of orphan drug spending is low, the per beneficiary costs and the cost share individuals may be responsible for are quite high if coinsurance is utilized. This is consistent with other findings related to orphan and specialty drugs in the U.S.[13,29,31] Policies need to be implemented to curb the burden of high costs of drugs in the United States. There have been a number of strategies proposed by researchers and advocates which focus on promoting competition, increasing

transparency, and utilizing negotiation techniques.[71] One of the most compelling policy changes would be to allow CMS to negotiate drug prices directly with pharmaceutical companies, a strategy that has been successful for our international counterparts.[71–73] Legislative efforts to implement these types of policies are consistently blocked by lobbying efforts by pharmaceutical companies.

As policies are formulated to control drug costs, it is essential to curb spending while not stifling innovation. Although pricing is an issue for orphan drugs, there is a large unmet need for patients with over 6,000 rare diseases not having any approved therapy. Understanding the patient impact and ethical implications of access to orphan therapies is crucial when formulating new policies or revisiting the incentives outlined in the ODA.[74,75] Increasing the transparency of the orphan drug development process will be critical to formulating strategies that can more successfully balance competing cost and access needs.[14,18]

This paper provides additional evidence for the use of Medicare by individuals under the age of 65 who have high drug costs. Without access to Medicare, individuals may not be able to access these drugs. Future research should investigate the ease of gaining access to orphan drugs under Medicare to understand if there are claim denials for orphan drugs. Although orphan drug spending only represented 7% of expenditures in Medicare Part D, that is unlikely to represent the need. Additional research should be conducted to determine how easy it was to gain access to Medicare for rare disease beneficiaries.

Some beneficiaries who require orphan drugs may also be dual beneficiaries with Medicaid. Additionally, many pharmaceutical companies provide patient assistance

programs to provide reduced cost drugs or waive copays. Understanding how these programs contribute to overall costs and medication adherence decisions would provide a more complete picture for the orphan drug cost ecosystem. In the future, health insurance plans designed for individuals with high drug costs may be necessary to curb unnecessary spending, while providing needed access.

Future research should be conducted to explore beneficiary level data both to capture total costs per rare disease patient and the cost-sharing mechanisms. There are clear cost differences for drugs on and off formularies,[30] it is critical for patients with high cost drugs to have an easy way to identify the correct plan. It may not be possible for rare disease patients on multiple medications to choose a plan that would provide an affordable way to access all needed drugs. Research should also be conducted to determine how patients navigate plan enrollment.

The costs per beneficiary have the potential to be very large, even after catastrophic caps are met.[30,46,60] Growing concerns related to the high out of pocket costs for U.S. patients may require that we restructure our medical assistance programs. The potential costs an individual may be responsible for may be prohibitive for most individuals contributing to overall financial toxicity or worse health outcomes. Demographic and geographic variability should be explored to determine if inequities are developing due to programmatic structures.

As conversations related to health care reform and controlling costs continue, understanding spending for the rare disease population will help ensure better health and financial outcomes. Internationally, rare disease country specific plans allow a holistic approach for addressing the needs of the rare disease population.[76,77] Addressing rare

disease needs in new national policy could provide a better roadmap for cost-effective patient centric initiatives. Some states have begun to form Rare Disease Advisory Councils and although many policy initiatives are critical to address at the state level, there should be an investment in both state and country level planning. Healthcare policy initiatives should include the patient voice and the high-costs of orphan drugs should ensure that rare disease patient advocates have a seat at the table.

Conclusion

Although orphan drug spending comprises a relatively small share of overall Medicare Part D expenditures, the per beneficiary and per claim costs can be very high. Almost half of the costs associated with orphan drugs are attributed to beneficiaries under the age of 65. Rare cancer drugs that are only indicated for rare use represent 3.6% of all spending in Medicare Part D. Drug costs will continue to be a significant portion of our medical costs. More strategies must be undertaken to address the high costs and ensure appropriate access to patients who need high cost drugs. Previous studies on Part D trends have focused on specialty drugs or a subset of orphan drug spending. The high cost and growth of orphan drugs provides a compelling reason to conduct this analysis and future studies should focus on drug use and total beneficiary costs.

References

1. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. NIH.gov. https://rarediseases.info.nih.gov/. Accessed January 13, 2017.

2. *Orphan Drug Act*. Vol USC 21 I Subchapter D Part 316.; 1983. https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21. Accessed January 13, 2017.

3. National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

4. Mooney J, Poland F, Spalding N, Scott DGI, Watts RA. "In one ear and out the other - it's a lot to take in": a qualitative study exploring the informational needs of patients with ANCA-associated vasculitis. *Musculoskeletal Care*. 2013;11(1):51-59. doi:10.1002/msc.1030

5. Babac A, Frank M, Pauer F, et al. Telephone health services in the field of rare diseases: a qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany. *BMC Health Serv Res*. 2018;18(1):99. doi:10.1186/s12913-018-2872-9

6. Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive care needs of parents with a child with a rare disease: a qualitative descriptive study. *J Pediatr Nurs*. 2016;31(3):e207-218. doi:10.1016/j.pedn.2015.10.022

7. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88. doi:10.1186/s12875-016-0488-x

8. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

9. *Report of The National Commission on Orphan Diseases.* U.S. Department of Health and Human Services Public Health Service Office of the Assistant Secretary for health; 1989. https://rarediseases.info.nih.gov/files/report_of_the_national_commission_on_orphan_diseases_february_1989.pdf. Accessed March 31, 2017.

10. Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. *Adv Exp Med Biol*. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

11. Pelentsov LJ, Laws TA, Esterman AJ. The supportive care needs of parents caring for a child with a rare disease: A scoping review. *Disabil Health J*. 2015;8(4):475-491. doi:10.1016/j.dhjo.2015.03.009

12. U. S. Government Accountability Office. *Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue*; 2018. https://www.gao.gov/products/GAO-19-83?utm_source=onepager&utm_medium=email&utm_campaign=email_HC. Accessed May 3, 2019.

13. Aitken M, Kleinrock M. *Orphan Drugs in the United States Growth Trends in Rare Disease Treatments*. Parsippany, NJ: IQVIA Institute; 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf. Accessed November 20, 2018.

14. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J Rare Dis*. 2011;6:42. doi:10.1186/1750-1172-6-42

15. Picavet E, Dooms M, Cassiman D, Simoens S. Drugs for rare diseases: influence of orphan designation status on price. *Appl Health Econ Health Policy*. 2011;9(4):275-279. doi:10.2165/11590170-000000000-00000

16. Wellman-Labadie O, Zhou Y. The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? *Health Policy*. 2010;95(2-3):216-228. doi:10.1016/j.healthpol.2009.12.001

17. Hemphill TA. Extraordinary pricing of orphan drugs: is it a socially responsible strategy for the U.S. pharmaceutical industry? *J Bus Ethics*. 2010;94(2):225-242.

18. Picavet E, Morel T, Cassiman D, Simoens S. Shining a light in the black box of orphan drug pricing. *Orphanet J Rare Dis*. 2014;9:62. doi:10.1186/1750-1172-9-62

19. Long SK, Bart L, Karpman M, Shartzer A, Zuckerman S. Sustained gains in coverage, access, and affordability under the ACA: a 2017 update. *Health Aff Proj Hope*. 2017;36(9):1656-1662. doi:10.1377/hlthaff.2017.0798

20. *The U.S. Healthcare Cost Crisis*. Gallup, Inc.; 2019. https://news.gallup.com/poll/248123/westhealth-gallup-us-healthcare-cost-crisis-report.aspx. Accessed April 25, 2019.

21. Gallo AM, Hadley EK, Angst DB, Knafl KA, Smith CAM. Parents' concerns about issues related to their children's genetic conditions. *J Spec Pediatr Nurs*. 2008;13(1):4-14. doi:10.1111/j.1744-6155.2008.00129.x

22. Zafar SY. Financial toxicity of cancer care: it's time to intervene. *J Natl Cancer Inst*. 2016;108(5). doi:10.1093/jnci/djv370

23. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin*. 2018;68(2):153-165. doi:10.3322/caac.21443

24. Barbaret C, Brosse C, Rhondali W, et al. Financial distress in patients with advanced cancer. *PloS One*. 2017;12(5):e0176470. doi:10.1371/journal.pone.0176470

25. Meeker CR, Geynisman DM, Egleston BL, et al. Relationships among financial distress, emotional distress, and overall distress in insured patients with cancer. *J Oncol Pract*. 2016;12(7):e755-764. doi:10.1200/JOP.2016.011049

26. Robinson SW, Brantley K, Liow C, Teagarden JR. An early examination of access to select orphan drugs treating rare diseases in health insurance exchange plans. *J Manag Care Spec Pharm*. 2014;20(10):997-1004. doi:10.18553/jmcp.2014.20.10.997

27. Trish E, Joyce G, Goldman DP. Specialty drug spending trends among Medicare and Medicare Advantage enrollees, 2007-11. *Health Aff Proj Hope*. 2014;33(11):2018-2024. doi:10.1377/hlthaff.2014.0538

28. Cubanski J, Damico A, Neuman T. *Medicare Part D in 2018: The Latest on Enrollment, Premiums, and Cost Sharing*. Kaiser Family Foundation; 2018. https://www.kff.org/medicare/issue-brief/medicare-part-d-in-2018-the-latest-on-enrollment-premiums-and-cost-sharing/. Accessed May 13, 2019.

29. Anderson-Cook A, Maeda J, Nelson L. *Prices for and Spending on Specialty Drugs in Medicare Part D and Medicaid: An In-Depth Analysis: Working Paper 2019-02*. Congressional Budget Office; 2019. https://www.cbo.gov/publication/55011. Accessed May 14, 2019.

30. Hoadley J, Cubanski J, Neuman T. *It Pays to Shop: Variation in Out-of-Pocket Costs for Medicare Part D Enrollees in 2016*. Kaiser Family Foundation; 2015. https://www.kff.org/medicare/issue-brief/it-pays-to-shop-variation-in-out-of-pocket-costs-for-medicare-part-d-enrollees-in-2016/. Accessed May 9, 2019.

31. Divino V, DeKoven M, Kleinrock M, Wade RL, Kaura S. Orphan drug expenditures in the United States: a historical and prospective analysis, 2007-18. *Health Aff Proj Hope*. 2016;35(9):1588-1594. doi:10.1377/hlthaff.2016.0030

32. Orofino J, Soto J, Casado MA, Oyagüez I. Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007. *Appl Health Econ Health Policy*. 2010;8(5):301-315. doi:10.2165/11531880-000000000-00000

33. Divino V, DeKoven M, Kleinrock M, Wade RL, Kim T, Kaura S. Pharmaceutical expenditure on drugs for rare diseases in Canada: a historical (2007-13) and prospective (2014-18) MIDAS sales data analysis. *Orphanet J Rare Dis*. 2016;11(1):68. doi:10.1186/s13023-016-0450-y

34. Hutchings A, Schey C, Dutton R, Achana F, Antonov K. Estimating the budget impact of orphan drugs in Sweden and France 2013-2020. *Orphanet J Rare Dis*. 2014;9:22. doi:10.1186/1750-1172-9-22

35. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. Budget impact analysis of orphan drugs in Belgium: estimates from 2008 to 2013. *J Med Econ*. 2010;13(2):295-301. doi:10.3111/13696998.2010.491427

36. Kanters TA, Steenhoek A, Hakkaart L. Orphan drugs expenditure in the Netherlands in the period 2006–2012. *Orphanet J Rare Dis*. 2014;9. doi:10.1186/s13023-014-0154-0

37. Schey C, Milanova T, Hutchings A. Estimating the budget impact of orphan medicines in Europe: 2010 - 2020. *Orphanet J Rare Dis*. 2011;6:62. doi:10.1186/1750-1172-6-62

38. Centers for Medicare and Medicaid. Prescription Drug Coverage. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/index.html. Published November 28, 2016. Accessed April 3, 2017.

39. Centers for Medicare & Medicaid Services. CMS Fast Facts Overview. CMS.gov. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Fast-Facts/index.html. Published August 29, 2017. Accessed September 22, 2017.

40. Social Security Administration. Compassionate Allowances. https://www.ssa.gov/compassionateallowances/. Accessed May 16, 2019.

41. Cubanski J, Neuman T, Damico A. *Medicare's Role for People Under Age 65 with Disabilities*. Kaiser Family Foundation; 2016. https://www.kff.org/report-section/medicares-role-for-people-under-age-65-with-disabilities-issue-brief/. Accessed May 13, 2019.

42. Chen J, Rizzo JA, Ortega AN. Racial and ethnic differences in drug expenditures and access under Medicare Part D. *J Health Care Poor Underserved*. 2011;22(3):1059-1074. doi:10.1353/hpu.2011.0070

43. Carvalho N, Petrie D, Chen L, Salomon JA, Clarke P. The impact of Medicare part D on income-related inequality in pharmaceutical expenditure. *Int J Equity Health*. 2019;18(1):57. doi:10.1186/s12939-019-0955-9

44. Park T, Jung J. The effect of Medicare Part D on prescription drug spending and health care use: 6 years of follow-up, 2007-2012. *J Manag Care Spec Pharm*. 2017;23(1):5-12. doi:10.18553/jmcp.2017.23.1.5

45. Lichtenberg FR, Sun SX. The impact of Medicare Part D on prescription drug use by the elderly. *Health Aff Proj Hope*. 2007;26(6):1735-1744. doi:10.1377/hlthaff.26.6.1735

46. Nelson RE, Nelson SL, Huttner B, Gundlapalli A. The effect of Medicare Part D on health care utilization for non-elderly Medicare recipients with disabilities. *Disabil Health J*. 2014;7(1):64-69. doi:10.1016/j.dhjo.2013.07.003

47. Alexander GC, Schiman C, Kaestner R. Association between prescription drug insurance and health care utilization among Medicare beneficiaries. *Med Care Res Rev*. 2018;75(2):153-174. doi:10.1177/1077558716681920

48. Ayyagari P, Shane DM, Wehby GL. The impact of Medicare Part D on emergency department visits. *Health Econ*. 2017;26(4):536-544. doi:10.1002/hec.3326

49. Goldman DP, Joyce GF. Medicare Part D: a successful start with room for improvement. *JAMA*. 2008;299(16):1954-1955. doi:10.1001/jama.299.16.1954

50. *The Medicare Part D Prescription Drug Benefit*. Kaiser Family Foundation; 2018. http://kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/. Accessed April 3, 2017.

51. U.S. Centers for Medicare & Medicaid Services. What drug plans cover. Medicare.gov. https://www.medicare.gov/drug-coverage-part-d/what-drug-plans-cover. Accessed May 13, 2019.

52. U.S. Centers for Medicare & Medicaid Services. Copayment/coinsurance in drug plans. Medicare.gov. https://www.medicare.gov/part-d/costs/copayment-coinsurance/drug-plan-copayments.html. Accessed April 6, 2017.

53. Costs in the coverage gap. Medicare.gov. https://www.medicare.gov/part-d/costs/coverage-gap/part-d-coverage-gap.html. Accessed April 6, 2017.

54. U.S. Centers for Medicare & Medicaid Services. Catastrophic coverage. Medicare.gov. https://www.medicare.gov/drug-coverage-part-d/costs-for-medicare-drug-coverage/catastrophic-coverage. Accessed May 14, 2019.

55. 42 U.S.C. *Patient Protection and Affordable Care Act*; 2010. https://www.hhs.gov/healthcare/about-the-law/read-the-law/index.html. Accessed January 9, 2017.

56. Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, Field MJ, Boat TF. *Profile of Rare Diseases*. National Academies Press (US); 2010. https://www.ncbi.nlm.nih.gov/books/NBK56184/. Accessed March 31, 2017.

57. U.S. Food & Drug Administration. Accelerated Approval Program. https://www.fda.gov/drugs/information-healthcare-professionals-drugs/accelerated-approval-program. Published March 10, 2016. Accessed May 17, 2019.

58. Shaw DL, Dhruva SS, Ross JS. Coverage of Novel Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval. *J Manag Care Spec Pharm*. 2018;24(12):1230-1238. doi:10.18553/jmcp.2018.24.12.1230

59. Yala SM, Duru OK, Ettner SL, Turk N, Mangione CM, Brown AF. Patterns of prescription drug expenditures and medication adherence among Medicare part D beneficiaries with and without the low-income supplement. *BMC Health Serv Res*. 2014;14:665. doi:10.1186/s12913-014-0665-3

60. Cubanski J, Koma W, Neuman T. *The Out-of-Pocket Cost Burden for Specialty Drugs in Medicare Part D in 2019*. Kaiser Family Foundation; 2019. https://www.kff.org/report-section/the-out-of-pocket-cost-burden-for-specialty-drugs-in-medicare-part-d-in-2019-findings/. Accessed June 5, 2019.

61. Dusetzina SB, Keating NL. Mind the gap: why closing the doughnut hole is insufficient for increasing Medicare beneficiary access to oral chemotherapy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34(4):375-380. doi:10.1200/JCO.2015.63.7736

62. Shen C, Zhao B, Liu L, Shih Y-CT. Financial burden for patients with chronic myeloid leukemia enrolled in Medicare Part D taking targeted oral anticancer medications. *J Oncol Pract*. January 2017:JOP2016014639. doi:10.1200/JOP.2016.014639

63. Doshi JA, Li P, Ladage VP, Pettit AR, Taylor EA. Impact of cost sharing on specialty drug utilization and outcomes: a review of the evidence and future directions. *Am J Manag Care*. 2016;22(3):188-197.

64. Levesque J-F, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *Int J Equity Health*. 2013;12:18. doi:10.1186/1475-9276-12-18

65. U.S. Centers for Medicare & Medicaid Services. Medicare Provider Utilization and Payment Data: Part D Prescriber. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html. Published January 17, 2017. Accessed April 7, 2017.

66. IQVIA Institute. https://www.iqvia.com/institute. Accessed June 6, 2019.

67. U.S. Food & Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed March 31, 2017.

68. Snedecor GW, Cochran WG. *Statistical Methods*. Eighth Edition. Iowa State University Press; 1989.

69. Aitken M, Kleinrock M. *Orphan Drugs in the United States Providing Context for Use and Cost*. IQVIA Institute; 2017. https://www.iqvia.com/institute/reports/orphan-drugs-in-the-united-states. Accessed June 11, 2019.

70. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. Issues surrounding orphan disease and orphan drug policies in Europe. *Appl Health Econ Health Policy*. 2010;8(5):343-350. doi:10.2165/11536990-000000000-00000

71. Conti RM, Rosenthal MB. Pharmaceutical policy reform--balancing affordability with incentives for innovation. *N Engl J Med*. 2016;374(8):703-706. doi:10.1056/NEJMp1515068

72. Outterson K, Kesselheim AS. How Medicare could get better prices on prescription drugs. *Health Aff Proj Hope*. 2009;28(5):w832-841. doi:10.1377/hlthaff.28.5.w832

73. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for feform. *JAMA*. 2016;316(8):858-871. doi:10.1001/jama.2016.11237

74. Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? *Orphanet J Rare Dis*. 2017;12(1):1. doi:10.1186/s13023-016-0551-7

75. Hyry HI, Roos JCP, Manuel J, Cox TM. The legal imperative for treating rare disorders. *Orphanet J Rare Dis*. 2013;8:135. doi:10.1186/1750-1172-8-135

76. Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. *Intractable Rare Dis Res*. 2018;7(4):213-222. doi:10.5582/irdr.2018.01085

77. Rodwell C, Aymé S. Rare disease policies to improve care for patients in Europe. *Biochim Biophys Acta*. 2015;1852(10 Pt B):2329-2335. doi:10.1016/j.bbadis.2015.02.008

CHAPTER 5

CONCLUSION

There are an estimated 30 million patients in the United States living with one or more rare diseases.[1] There is limited research on most rare diseases which perpetuates challenges for patients, researchers, and medical professionals.[4,6,7] High-quality data and an understanding of the patient experience are critical to establishing effective healthcare infrastructure that maximizes positive patient health outcomes and minimizes costs. This dissertation research is comprised of three papers related to key aspects of the rare disease experience in the United States.

For most rare diseases, basic information such as the natural history of the disease and epidemiological data is limited or missing.[4,10] The importance of including the patient voice has become an established theme in the rare disease community and literature.[32–35] However, it is important to note the differences in data availability for diseases with and without an orphan drug. Diseases with orphan drugs are more likely to have patient organization representation, which are often critical for driving research.[33–35] Other infrastructure such as the ability to code and track the disease in electronic health systems is also more likely if a disease has a drug, which may make it is easier to establish treatment protocols or justify medical needs to an insurance company.

Patients interfacing with insurance companies often feel that the insurance company does not understand the medical necessity of certain medical procedures or products. Caregivers describe the necessity of becoming an expert on the disease or relying on medical professionals in the care team to navigate the entire insurance experience.[36] Patients are often overwhelmed trying to identify and apply for programs

that can help them cover medical expenses. Finding the appropriate mix of insurance and social service supplemental support can be complex and there are few mechanisms to help patients plan their long-term health care needs.

Medicare Part D provides drug coverage for individuals over the age of 65 or with a qualifying disability. Roughly 85% of Medicare Part D beneficiaries are over the age of 65, but costs per claim are higher for individuals under the age of 65. The total expenditures for orphan drugs in Medicare Part D are around 10% of all expenditures, but the high costs for individuals under the age of 65 indicates the need to consider this group when preparing for future healthcare expenditures and instituting any healthcare reforms.

Our healthcare infrastructure is currently not equipped to capture detailed information about rare diseases or track diseases across information sources. Within insurance, patients have a complicated journey to navigate what will be covered and the onus falls on patients or caregivers to track the details of healthcare interactions and navigate program eligibility. Insurance and medical assistance programs allow patients to access needed services or benefits, but geographic inequities have been described. Additional research will be necessary to determine how many rare disease patients have been denied enrollment in Medicare or Medicaid benefits and the associated wait times to receive a determination of eligibility.

Policy implications

All healthcare policy initiatives should be patient-centric and consider patient privacy protections. This research did not address demographic equity issues, but based on the persistent inequities in the U.S. healthcare system, future research should identify and address disparities based on race and educational attainment. Different geographic

regions may have better access to medical knowledge through increased access to elite providers or institutions. Additionally, differences in access based on state-based eligibility differences, especially related to Medicaid expansion, can also lead to geographic disparities.

Expanding medical technologies and investing in an increased medical understanding of rare diseases, must also be met with ensuring that all patients can benefit to avoid further reinforcing health disparities in this country. One way to ensure that this is accomplished is to leverage telemedicine to access providers outside of geographic areas. Another solution is to ensure that insurance plans allow for patients to see disease specialists outside of their network without incurring additional costs, especially in cases where only a handful of medical experts may exist. It is also important that diseases without current pharmaceutical investment still have representation in policy initiatives and opportunities to establish natural history studies to generate basic research.

It is critical to continue to invest in research for rare diseases and find ways to continue to educate clinicians, insurance companies, and policymakers. Health information websites and institutions should commit to higher data quality, including providing more attribution to the previous research that has been conducted so the source and relevance of the data can be assessed. The U.S. should also continue to participate and implement efforts related to standardized nomenclature of rare diseases, such as the work being conducted by the Monarch Initiative and IRDiRC.[25,27] The U.S. should also commit to adopting the infrastructure that can help increase the visibility of rare diseases, such as establishing a plan to institute the ICD-11 codes in a reasonable timeframe.

Orphan drugs represent a large part of the focus for rare diseases, but are only available for about 300 of the identified 6,500 rare diseases.[37] Orphan drug prices are very high in the United States and represent higher per capita spending in programs for Medicare Part D compared to drugs for common conditions. However, these treatments are often life altering for patients, as is the case for individuals with spinal muscular atrophy. Payers are not always equipped to evaluate the benefit of these drugs and patients and caregivers are often tasked with building a case for their coverage when a new drug enters the market, which can delay access. Future policies should address strategies to help prepare insurance companies for newly approved drugs.

The increasing use of genetic information in the drug development process has the potential to change how we treat rare diseases.[38–41] However, our current infrastructure may not be equipped to track genetic differences for patients and inequities may dictate who can access these advanced therapies. Especially for treatments that have a high cost. Changes in pharmaceutical pricing could address some of these concerns, including allowing CMS to directly negotiate drug prices with pharmaceutical companies. As a country, we will need to find policies that can balance how we incentivize research and development, our desire for medical innovation, patient access, and overall costs.

To realize any of our policy goals it we must continue to participate internationally and include key stakeholders in policy initiatives. Rare diseases are a truly global public health challenge and should be addressed as such, while ensuring unique features of the U.S. healthcare system and our demographics are accounted for in implementation. We should recognize the unique role clinicians play as the front line of rare disease identification and treatment. Clinicians must be involved in both generating

and receiving knowledge about rare diseases and as a partner in connecting patients to appropriate resources. Clinicians are critical in helping capture data related to patient prevalence and providing details related to the medical necessity of certain treatments, therapies, and medical equipment. Payers, including private insurance companies, Medicare, and Medicaid, need to understand the importance of patient access to care that is deemed medically necessary. Finding better ways to evaluate these recommendations in a timely manner, especially for diseases with a small patient population can help patients financially prepare for needed medical expenses and cut down on more serious and costly medical complications.

Patients make up the final group of stakeholders that must hold a seat at the table for any policy reform efforts. It is important to recognize the different experience that patients may face if their disease does not have an established patient organization or if the disease has not been widely studied. It is important to facilitate programs that will help connect patients to information and to access healthcare, especially if experts fall outside of their geographic area or insurance network. It would also be beneficial to identify ways to drive collective action without splintering resources or generating too many independent data sources that cannot be integrated and shared through data sharing agreements. The rise of patient advisory councils or rare disease committees at the state level and for drug development have been a driving force in progress to date.[7,33,35] However, a rare disease national plan should be developed for the United States to keep pace with our European and international colleagues and to chart priority areas of growth and investment.

References

1. National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

2. Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. *Adv Exp Med Biol*. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

3. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

4. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17:88. doi:10.1186/s12875-016-0488-x

5. R de Vrueh, ERF Baekelandt, JMH de Haan. *Priority medicines for Europe and the world "A public health approach to innovation."* World Health Organizatoin; 2013. https://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf. Accessed July 2, 2019.

6. Basch E, Bennett AV. Patient-reported outcomes in clinical trials of rare diseases. *J Gen Intern Med*. 2014;29 Suppl 3:S801-803. doi:10.1007/s11606-014-2892-z

7. Bronstein MG, Kakkis ED. Patients as key partners in rare disease drug development. *Nat Rev Drug Discov*. 2016;15(11):731-732. doi:10.1038/nrd.2016.133

8. Koay PP, Sharp RR. The role of patient advocacy organizations in shaping genomic science. *Annu Rev Genomics Hum Genet*. 2013;14:579-595. doi:10.1146/annurev-genom-091212-153525

9. Hall JG. The role of patient advocacy/parent support groups. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd*. 2013;103(12 Suppl 1):1020-1022.

10. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. Development of the parental needs scale for rare diseases: a tool for measuring the supportive care needs of parents caring for a child with a rare disease. *J Multidiscip Healthc*. 2016;9:425-433. doi:10.2147/JMDH.S113898

11. About Monarch. https://monarchinitiative.org/page/about. Accessed July 15, 2019.

12. International Rare Diseases Research Consortium. International Consortium of Human Phenotype Terminologies (ICHPT). IRDiRC. http://www.irdirc.org/activities/task-forces/international-consortium-of-human-phenotype-terminologies/. Published December 1, 2017. Accessed March 7, 2019.

13. Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. List of FDA Orphan Drugs. https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs. Accessed July 19, 2018.

14. Dolled-Filhart MP, Lordemann A, Dahl W, Haraksingh RR, Ou-Yang C-W, Lin JC-H. Personalizing rare disease research: how genomics is revolutionizing the diagnosis and treatment of rare disease. *Pers Med*. 2012;9(8):805-819. doi:10.2217/pme.12.97

15. Schee Genannt Halfmann S, Mählmann L, Leyens L, Reumann M, Brand A. Personalized medicine: What's in it for rare diseases? *Adv Exp Med Biol*. 2017;1031:387-404. doi:10.1007/978-3-319-67144-4_22

16. Owusu Obeng A, Fei K, Levy KD, et al. Physician-reported benefits and barriers to clinical implementation of genomic medicine: a multi-site IGNITE-network survey. *J Pers Med*. 2018;8(3). doi:10.3390/jpm8030024

17. Tambuyzer E. Towards a framework for personalized healthcare: lessons learned from the field of rare diseases. *Pers Med*. 2010;7(5):569-586. doi:10.2217/pme.10.52

APPENDICES

APPENDIX A
LOGISTIC REGRESSION OUTPUT FOR DISEASE NAMING CONVENTIONS

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Table A: Broad name		
	Coefficient	SE
Orphan drugs	1.185	0.717
Rare cancers	0.767	0.73
Orphan drug* Rare cancer	-1.186	0.977
Constant	-1.386*	0.559

Table B: Specific name		
	Coefficient	SE
Orphan drugs	1.846	1.149
Rare cancers	0.000	1.451
Orphan drug* Rare cancer	0.252	1.616
Constant	-2.944**	1.026

APPENDIX B
LOGISTIC REGRESSION OUTPUT FOR DATA WEBSITES WITH PREVALENCE ESTIMATES

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Table A: Prevalence estimate listed in GARD		
	Coefficient	SE
Orphan drugs	0.747	1.268
Rare cancers	-1.210	1.202
Orphan drug* Rare cancer	-1.210	1.599
Constant	-2.944	1.026

Table B: Prevalence estimate listed in NORD		
	Coefficient	SE
Orphan drugs	2.944**	1.119
Rare cancers	1.846	1.149
Orphan drug* Rare cancer	-3.232*	1.353
Constant	-2.944**	1.026

Table C: Prevalence estimate listed in Orphanet		
	Coefficient	SE
Orphan drugs	0.811	0.645
Rare cancers	0.405	0.639
Orphan drug* Rare cancer	-1.212	0.908
Constant	-0.405	0.456

Table D: Prevalence estimate listed in Genetics home reference		
	Coefficient	SE
Orphan drugs	2.197*	0.869
Rare cancers	1.099	0.907
Orphan drug* Rare cancer	-3.296**	1.256
Constant	-2.197**	0.745

Table E: Prevalence estimate listed in Genereviews		
	Coefficient	SE
Orphan drugs	1.558	1.168
Rare cancers	1.558	1.168
Orphan drug* Rare cancer	0.000	Omitted
Constant	-2.944**	1.026

Table F: Prevalence estimate listed in Medscape		
	Coefficient	SE
Orphan drugs	2.744*	1.12
Rare cancers	1.558	1.168
Orphan drug* Rare cancer	-0.952	1.332
Constant	-2.944	1.026

Table G: Prevalence estimate listed in OMIM		
	Coefficient	SE
Orphan drugs	17.785	Omitted
Rare cancers	15.993	0.874
Orphan drug* Rare cancer	-17.322	0.974
Constant	-18.190	0.456

Convergence not achieved

APPENDIX C
LINEAR REGRESSION OUTPUT FOR PREVALENCE ESTIMATES WITH DATA QUALITY FACTORS BY DISEASE

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Table A: Number of estimates		
	Coefficient	SE
Orphan drugs	7.450	2.212
Rare cancers	2.500	2.212
Orphan drug* Rare cancer	-0.950	3.128
Constant	0.800	1.564

Table B: Number of quality estimates		
	Coefficient	SE
Orphan drugs	1.400*	0.539
Rare cancers	0.800	0.539
Orphan drug* Rare cancer	0.100	0.763
Constant	0.200	0.381

APPENDIX D
LOGISTIC REGRESSION OUTPUT FOR PREVALENCE ESTIMATES WITH DATA QUALITY FACTORS BY ESTIMATE

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Table A: Author		
	Coefficient	SE
Orphan drugs	<.0001	0.15
Rare cancers	-0.227	0.141
Orphan drug* Rare cancer	0.100	0.16
Constant	0.500***	0.135

Table B: Date		
	Coefficient	SE
Orphan drugs	-0.006	0.136
Rare cancers	-0.324*	0.127
Orphan drug* Rare cancer	0.076	0.145
Constant	0.688***	0.122

Table C: Attribution		
	Coefficient	SE
Orphan drugs	0.180	0.202
Rare cancers	0.019	0.19
Orphan drug* Rare cancer	-0.149	0.216
Constant	0.563**	0.181

Table D: All quality factors		
	Coefficient	SE
Orphan drugs	0.053	0.119
Rare cancers	-0.056	0.112
Orphan drug* Rare cancer	0.008	0.127
Constant	0.250*	0.107

APPENDIX E
LOGISTIC REGRESSION OUTPUT FOR PREVALENCE INFRASTRUCTURE VARIABLES

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Organization		
	Coefficient	SE
Orphan drugs	3.121***	0.839
Rare cancers	1.792*	0.722
Orphan drug* Rare cancer	-1.792	1.142
Constant	-1.386*	0.559

Disease specific organization		
	Coefficient	SE
Orphan drugs	2.197*	0.869
Rare cancers	1.099	0.907
Orphan drug* Rare cancer	-1.946	1.123
Constant	-2.197*	0.745

Registry		
	Coefficient	SE
Orphan drugs	3.145**	1.12
Rare cancers	1.210	1.202
Orphan drug* Rare cancer	-2.797*	1.4
Constant	-2.944**	1.026

Medical center		
	Coefficient	SE
Orphan drugs	2.140**	0.775
Rare cancers	1.253	0.668
Orphan drug* Rare cancer	-1.253	1.109
Constant	-0.405	0.456

ICD-10 specific		
	Coefficient	SE
Orphan drugs	2.539*	1.123
Rare cancers	1.210	1.202
Orphan drug* Rare cancer	-1.423	1.369
Constant	-2.944	1.026

ICD-11 specific

	Coefficient	SE
Orphan drugs	2.582***	0.794
Rare cancers	0.636	0.812
Orphan drug* Rare cancer	-0.636	1.065
Constant	-1.734**	0.626

APPENDIX F
LINEAR REGRESSION OUTPUT FOR PREVALENCE INFRASTRUCTURE VARIABLES

*Statistically significant coefficients are indicated using the following symbols: *=p<.05, **=p<.01, ***=p<.001*

Table A: Number of organizations		
	Coefficient	SE
Orphan drugs	4.200***	1.107
Rare cancers	1.850	1.107
Orphan drug* Rare cancer	-0.800	1.566
Constant	0.250	0.783

Table B: Number of medical centers		
	Coefficient	SE
Orphan drugs	15.350*	5.928
Rare cancers	7.150	5.928
Orphan drug* Rare cancer	6.950	8.384
Constant	1.500	4.192

Table C: Number of clinical trials		
	Coefficient	SE
Orphan drugs	25.55	84.229
Rare cancers	41	84.229
Orphan drug* Rare cancer	273.9*	119.117
Constant	0.9	59.559

Table D: Number of active clinical trials		
	Coefficient	SE
Orphan drugs	8.200	24.496
Rare cancers	11.150	24.496
Orphan drug* Rare cancer	83.250*	34.643
Constant	0.250	17.321

Table E: PubMed results		
	Coefficient	SE
Orphan drugs	2054.150	1702.497
Rare cancers	621.100	1702.497
Orphan drug* Rare cancer	4733.800	2407.694
Constant	425.100	1203.847

Table F: PubMed incidence or prevalence results

	Coefficient	SE
Orphan drugs	100.450	122.27
Rare cancers	85.050	122.27
Orphan drug* Rare cancer	399.450*	172.916
Constant	41.700	86.458

APPENDIX G
QUALITATIVE INTERVIEW SCRIPT

Interview Questions

Hi, thank you for taking the time to speak with me today. I am interested in speaking today about your health insurance experience.

Obtaining insurance

1. Have you ever experienced difficulty getting insurance or experienced an extended period, more than three months, of not having insurance? Could you tell me about that experience?
2. Are you satisfied with your current health insurance?
    a. Can you tell me anything about what type of insurance you have (public, private, from an employer, etc.)?

Coverage/ Orphan drugs

3. Can you tell me about a time that you might have experienced any difficulties obtaining medical care based on your insurance? (This might include things such as seeing your preferred doctor or having treatments or medications covered)
4. Did you ever experience a significant change in your insurance?
    a. What was your role in bringing that about?
    b. Was there anyone who helped you navigate or bring about that change?

Cost-sharing

Many insurance plans use a variety of methods to share the cost between insurance and the patient. I am now going to ask you about a few of these different methods. Don't worry if you are unfamiliar with any of these terms or concepts, just tell me about anything you do know or believe you have experienced.

5. A premium is the amount of money patients must pay for their insurance, usually on a monthly basis. Do you know if you have a premium and how much you pay?
6. A copay is a fee that some people have to pay before certain types of appointments or doctor's appointments. Usually, you would pay this when you arrive at the doctor. Do you know if you are required to pay a copay?
7. Sometimes insurance uses coinsurance, where insurance will cover some portion of the medical expense and the patient must cover the rest. Often you would receive this as a bill after you have attended your appointment. Do you know if your insurance company requires coinsurance
8. A deductible is sometimes set by insurance companies and is the amount a patient needs to spend before the insurance company will cover any additional costs. Do you know if you have a deductible and if you do, how much it is for?

9. Is there anything else about your experience with fees and payments you experienced?

Health literacy

10. In general, how comfortable are you navigating your insurance?
    a. Do you think your comfort level has changed over time?

Navigating the system

11. Has anyone helped you understand or navigate the system, this might include things like organizations, friends, or peer-support networks?

Additional Assistance

12. Can you tell me if there any other programs or services that you are able to use that provide any financial or medical support?
    a. How easy was it to access this source of support?
    b. How did you learn about these resources?

Final Questions

13. If you could make a wish list to make your experience better, what would that include?
14. Is there anything else you would like me to know?

APPENDIX H
QUALITATIVE CODEBOOK

	Code	Description
1.	Assistance	Financial or in-kind assistance received to cover the cost of medical treatments, equipment, services, or procedures. This also includes information related to how easy it was to access this type of support.
1.1	Early intervention	Service and supports that are available to children younger than three years old with developmental delays and disabilities. Programs exist in every state and covered services are based on needs but often include speech and physical therapy.
1.2	Grants	Financial assistance for medical equipment, treatments, services, or procedures that are received from funds that the participant applied to from the government, organizations, or foundations.
1.3	None	When the participant stated that they do not access any additional financial assistance or support programs.
1.4	Organization or companies	Financial or in-kind assistance for medical equipment, treatments, services, or procedures that is provided by a private or non-profit organization.
1.5	Peers or family	Financial or in-kind assistance for medical equipment, treatments, services, or procedures that is provided by peers, friends, or family members.
1.6	Pharma	Financial or in-kind assistance from pharmaceutical companies. Usually related to accessing low cost treatments or to cover the co-pays and associated fees for the treatment.
1.7	School	Financial or in-kind assistance for medical equipment, treatments, services, or procedures that is provided by schools or the school district.
1.8	State	Financial or in-kind assistance for medical equipment, treatments, services, or procedures that is provided by the state.
2.	Cost-sharing	The portion of costs that the individual is responsible for in order to

		access
2.1	Caps	Any experience related to limits on the benefits the insurance company will cover in a plan year.
2.2	Coinsurance	Any experience related to coinsurance.
2.3	Copay	Any experience related to copays.
2.4	Deductible	Any experience related to deductibles.
2.5	Other	Descriptions of other types of financial payments or cost sharing an individual has experienced.
2.6	Out of pocket maximum	Descriptions of the limit an individual is required to pay before insurance will cover the rest of their costs within a plan year.
2.7	Premium	Any experience related to premiums.
2.8	Savings	Any experience related to an individual's actions to attempt to save money for the insurance company. This could include deciding not to submit certain expenses or specific strategies meant to save money.
3.	Coverage	Descriptions of the health insurance coverage experience for medical procedures, equipment, providers, and services.
3.1	Consistent	The participant indicates that they always had coverage and did not experience a period of interrupted health coverage.
3.2	Equipment	Experiences related to access to equipment and medical supplies.
3.3	Hospital	Experiences related to access and coverage of hospital services.
3.4	Nursing	Experiences related to access and coverage for nursing services.
3.5	Providers	Experiences related to access and coverage to medical providers.
3.6	Therapy	Experiences related to access and coverage for therapy; including physical, occupational, and speech therapies.
3.7	Treatments	Experiences related to access and coverage for treatments; including

		medical procedures, pharmaceutical products, and vaccines.
4.	Genetics	Any description of genetic testing, genome sequencing, or the impact of genetic information on decision making.
5.	Health	Experiences related to the patient's health, disease progression, or medical recommendations.
5.1	Consequences	Real, perceived, or hypothetical health consequences of delays or denials in coverage.
5.2	Diagnosis	Experiences related to how diagnosis impacted the patient's access or coverage experience.
5.3	Doctor rec	Information related to the difference between a medical professional's recommendations for care and the health insurance company's coverage.
5.4	Transition	Experiences related to the coverage and care transitions patients experience as they age.
6.	Health literacy	An individual's ability to obtain, process, and understand health information and systems to make health decisions.
6.1	Knowledge	Descriptions related to how well an individual understands the healthcare system and the health insurance system.
6.2	Navigating	Experiences related to how an individual can navigate and work through the health insurance system to access healthcare.
7.	Improvements	Discussion on any improvements that the participant believes should be made to the system.
7.1	Automated	Discussion related to changes to automate aspects of the system.
7.2	Centralized	Discussion related to centralizing resources or information.
7.3	Communication	Discussion related to improving communication.
7.4	Cost	Discussion related to changes in the costs of the system.

7.5	Knowledge	Discussion related to changes in the insurance company's knowledge or comprehension of the experience of patients and families.
7.6	Main thing	The thing that the individuals indicated would be the most critical change to improve their insurance experience.
7.7	Personnel	Discussion related to changes in personnel at health insurance companies.
7.8	Time	Discussion related to changes in the time associated with interacting with the system.
7.9	Transparency	Discussion related to improvements around transparency.
7.10	User friendly	Discussions related to how user friendly the system is to navigate.
8.	Involvement	Experiences related to an individual's level of involvement or participation in achieving coverage or in medical decision making for their loved one.
8.1	Active	Experiences where an individual took an active role in health insurance coverage or access.
8.2	Passive	Experiences where an individual took a passive role in health insurance coverage or access.
8.3	Preplanning	Experiences where an individual took action prior to when coverage was necessary.
9.	Life	Descriptions of the interplay between life decisions and the medical or health insurance experience.
9.1	Children	Descriptions related to family planning or having additional children.
9.2	Home	Descriptions related to setting up a home or where an individual is willing to live.
9.3	Mental health	Descriptions related to mental health.
9.4	Uncertainty	Descriptions related to the fear of the unknown or uncertainty of the future.

9.5	Work	Descriptions related to employment decisions.
10.	Obstacles	Descriptions of the challenges participants have experienced while trying to access their health insurance coverage or experiences faced while working with their health insurance company.
10.1	Approval	Experiences related to what the insurance company is willing to approve for coverage.
10.2	Bounced	Experiences related to how many people or departments the participant must interact with before their issue is resolved, or their question is answered.
10.3	Changes	Experiences related to changes in the insurance policy or company.
10.4	Coding	Descriptions related to how coding impacted insurance coverage.
10.5	Cost	Experiences related to the cost or financial barriers to coverage.
10.6	Coverage	Descriptions related to the coverage experience when an individual is covered by multiple insurance plans and the interplay between the coverage.
10.7	Documentation	Experiences related to the providing the necessary documentation or paperwork.
10.8	Incomplete information	Experiences related to receiving incomplete information from the insurance company.
10.9	Knowledge	Experiences related to the overall knowledge or comprehension of the people working within the insurance system.
10.10	Network	Experiences related to accessing providers or treatment centers that are not in the network for the insurance plan.
10.11	Options	Descriptions related to available options for choosing insurance providers or the flexibility of the type of plans that are available.
10.12	Qualifying	Experiences related to gaining coverage or qualifying for a certain type of insurance plan.
10.13	Redundancy	Experiences related to the redundancy or repetition of the system.

10.14	Time	Experiences related to the time it takes to interact with insurance, to navigate the system, or to access coverage.
11.	Politics	Any discussion on how politics play into feelings of uncertainty or decision making.
11.1	Pre-existing condition	Any discussion related to preexisting conditions.
12.	Privilege	Any discussion related to how the participant's experience compares to others or the struggle that other individuals may be experiencing. This could be in relation to their successes or their commentary about overall challenges for others in a similar position.
13.	Recruitment	Offers to help recruit for the study.
14.	Satisfaction	Descriptions related to an individual's satisfaction related to health insurance.
14.1	Trust	Descriptions related to the trust an individual has for their insurance company.
15.	Support	Experiences related to receiving emotional, mental, or informational support. This includes both finding and accessing health services and utilizing connections to feel better about an individual's situation. This does not include financial support.
15.1	Coordination	Any description of multiple parties working together to solve a health insurance issue or provide emotional support.
15.2	Early intervention	Experiences related to support provided by the early intervention program.
15.3	Insurance Company	Experiences related to support provided by the health insurance company.
15.4	Organizations	Experiences related to support provided by organizations, including non-profits or other support agencies.
15.5	Peers	Experiences related to support received by peers, friends, or family.
15.6	Providers	Experiences related to support provided by medical providers

		including physicians, nurses, therapists, or other hospital workers.
15.7	School	Experiences related to support provided by the school system or individuals who work at the school.
15.8	Social media	Experiences related to support received through social media.
15.9	Social workers	Experiences related to support provided by social workers.
16.	Type	Descriptions related to the type of insurance coverage an individual has for their child.
16.1	Employer	Experiences related to employer sponsored health insurance.
16.2	Public	Experiences related to forms of public insurance coverage.

BIBLIOGRAPHY

42 U.S.C. Patient Protection and Affordable Care Act. 2010. https://www.hhs.gov/healthcare/about-the-law/read-the-law/index.html. Accessed January 9, 2017.

About Monarch. https://monarchinitiative.org/page/about. Accessed July 15, 2019.

Adang L, Rosenzweig J. Metachromatic Leukodystrophy. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/metachromatic-leukodystrophy/. Published 1986. Updated 2019. Accessed March 4, 2019.

Aday LA, Andersen R. A framework for the study of access to medical care. Health Serv Res. 1974;9(3):208-220.

Aflaki E, Westbroek W, Sidransky E. The Complicated Relationship between Gaucher Disease and Parkinsonism: Insights from a Rare Disease. Neuron. 2017;93(4):737-746. doi:10.1016/j.neuron.2017.01.018

Aitken M, Kleinrock M. Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. Parsippany, NJ: IQVIA Institute; 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf. Accessed November 20, 2018.

Aitken M, Kleinrock M. Orphan Drugs in the United States Providing Context for Use and Cost. IQVIA Institute; 2017. https://www.iqvia.com/institute/reports/orphan-drugs-in-the-united-states. Accessed June 11, 2019.

Alexander GC, Schiman C, Kaestner R. Association between prescription drug insurance and health care utilization among Medicare beneficiaries. Med Care Res Rev. 2018;75(2):153-174. doi:10.1177/1077558716681920

Alhawwashi S, Seoane-Vazquez E, Eguale T, Rodriguez-Monguio R. Prices of drugs for chronic use with orphan designation in the United States (1983–2014). Value Health. 2016;19(3):A4. doi:10.1016/j.jval.2016.03.040

American Academy of Pediatrics Council on Children with Disabilities. Care coordination in the medical home: integrating health and related systems of care for children with special health care needs. Pediatrics. 2005;116(5):1238-1244. doi:10.1542/peds.2005-2070

American Health Insurance Plans (AHIP). Orphan Drug Utilization and Pricing Patterns (2012-2014). Washington, DC; 2016. https://www.ahip.org/wp-content/uploads/2016/10/OrphanDrug_DataBrief_10.21.16.pdf. Accessed September 22, 2017.

Anderson-Cook A, Maeda J, Nelson L. Prices for and Spending on Specialty Drugs in Medicare Part D and Medicaid: An In-Depth Analysis: Working Paper 2019-02. Congressional Budget Office; 2019. https://www.cbo.gov/publication/55011. Accessed May 14, 2019.

Andrews JE, Richesson RL, Krischer J. Variation of SNOMED CT coding of clinical research concepts among coding experts. J Am Med Inform Assoc. 2007;14(4):497-506. doi:10.1197/jamia.M2372

Andrulis DP. Access to care is the centerpiece in the elimination of socioeconomic disparities in health. Ann Intern Med. 1998;129(5):412-416.

Aymé S, Bellet B, Rath A. Rare diseases in ICD11: making rare diseases visible in health information systems through appropriate coding. Orphanet J Rare Dis. 2015;10(1):35. doi:10.1186/s13023-015-0251-8

Aymé S, Kole A, Groft S. Empowerment of patients: lessons from the rare diseases community. Lancet. 2008; 371(9629):2048-51. doi: 10.1016/S0140-6736(08)60875-2.

Ayme S, Kole A, Rodwell C. Patient Registries in the Field of Rare Diseases. Rare Disease Task Force Report; 2011. http://www.eucerd.eu/EUCERD/upload/file/RDTFReportRegistriesJuly2011.pdf. Accessed April 12, 2017.

Ayyagari P, Shane DM, Wehby GL. The impact of Medicare Part D on emergency department visits. Health Econ. 2017;26(4):536-544. doi:10.1002/hec.3326

Babac A, Frank M, Pauer F, et al. Telephone health services in the field of rare diseases: a qualitative interview study examining the needs of patients, relatives, and health care professionals in Germany. BMC Health Serv Res. 2018;18(1):99. doi:10.1186/s12913-018-2872-9

Baggi F, Mantegazza R, Antozzi C, Sanders D. Patient registries: useful tools for clinical research in myasthenia gravis. Ann N Y Acad Sci. 2012;1274:107-113. doi:10.1111/j.1749-6632.2012.06771.x

Barbaret C, Brosse C, Rhondali W, et al. Financial distress in patients with advanced cancer. PloS One. 2017;12(5):e0176470. doi:10.1371/journal.pone.0176470

Basch E, Bennett AV. Patient-reported outcomes in clinical trials of rare diseases. J Gen Intern Med. 2014;29 Suppl 3:S801-803. doi:10.1007/s11606-014-2892-z

Baynam G, Bowman F, Lister K, et al. Improved Diagnosis and Care for Rare Diseases through Implementation of Precision Public Health Framework. Adv Exp Med Biol. 2017;1031:55-94. doi:10.1007/978-3-319-67144-4_4

Bellgard MI, Napier KR, Bittles AH, et al. Design of a framework for the deployment of collaborative independent rare disease-centric registries: Gaucher disease registry model. Blood Cells Mol Dis. January 2017. doi:10.1016/j.bcmd.2017.01.013

Bronstein MG, Kakkis ED. Patients as key partners in rare disease drug development. Nat Rev Drug Discov. 2016;15(11):731-732. doi:10.1038/nrd.2016.133

Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. CA Cancer J Clin. 2018;68(2):153-165. doi:10.3322/caac.21443

Carvalho N, Petrie D, Chen L, Salomon JA, Clarke P. The impact of Medicare part D on income-related inequality in pharmaceutical expenditure. Int J Equity Health. 2019;18(1):57. doi:10.1186/s12939-019-0955-9

Centers for Disease Control and Prevention. 2017 Nationally Notifiable Conditions. National Notifiable Diseases Surveillance System (NNDSS). https://wwwn.cdc.gov/nndss/conditions/search/. Accessed April 19, 2017.

Centers for Disease Control and Prevention. About Community Counts. Community Counts. https://www.cdc.gov/ncbddd/hemophilia/communitycounts/about.html. Published August 8, 2018. Accessed March 8, 2019.

Centers for Disease Control and Prevention. Birth Defects State-based Tracking. Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/birthdefects/states/index.html. Published November 30, 2017. Accessed January 10, 2018.

Centers for Disease Control and Prevention. Morbidity Frequency Measures. Principles of Epidemiology in Public Health Practice, Third Edition An Introduction to Applied Epidemiology and Biostatistics; 2012. https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section2.html. Accessed March 15, 2019.

Centers for Medicare & Medicaid Services. 2016-ICD-10-CM-and-GEMs. https://www.cms.gov/Medicare/Coding/ICD10/2016-ICD-10-CM-and-GEMs.html. Published October 8, 2015. Accessed July 18, 2018.

Centers for Medicare & Medicaid Services. CMS Fast Facts Overview. CMS.gov. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Fast-Facts/index.html. Published August 29, 2017. Accessed September 22, 2017.

Centers for Medicare and Medicaid. Prescription Drug Coverage. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/index.html. Published November 28, 2016. Accessed April 3, 2017.

Chen J, Rizzo JA, Ortega AN. Racial and ethnic differences in drug expenditures and access under Medicare Part D. J Health Care Poor Underserved. 2011;22(3):1059-1074. doi:10.1353/hpu.2011.0070

Cleveland AD. Miles to go before we sleep: education, technology, and the changing paradigms in health information. J Med Libr Assoc. 2011;99(1):61-69. doi:10.3163/1536-5050.99.1.011

ClinicalTrials.gov Background - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/about-site/background. Accessed August 6, 2019.

Cohen S. Differentials in the Concentration of Health Expenditures across Population Subgroups in the U.S., 2013. Rockville, MD: Agency for Healthcare Research and Quality; 2015. https://meps.ahrq.gov/data_files/publications/st480/stat480.shtml. Accessed September 22, 2017.

Commissioner of the Food and Drug Administration. Designating an Orphan Product: Drug and Biological Products - Frequently Asked Questions (FAQ). https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm. Accessed July 23, 2018.

Committee on Geographic Variation in Health Care Spending and Promotion of High-Value Care, Board on Health Care Services, Institute of Medicine. Variation in Health Care Spending: Target Decision Making, Not Geography. (Newhouse JP, Garber AM, Graham RP, McCoy MA, Mancher M, Kibria A, eds.). Washington (DC): National Academies Press (US); 2013. http://www.ncbi.nlm.nih.gov/books/NBK201647/.

Comprehensive Cancer Information. National Cancer Institute. https://www.cancer.gov/. Published January 1, 1980. Accessed August 5, 2019.

Conti RM, Rosenthal MB. Pharmaceutical policy reform--balancing affordability with incentives for innovation. N Engl J Med. 2016;374(8):703-706. doi:10.1056/NEJMp1515068

Costs in the coverage gap. Medicare.gov. https://www.medicare.gov/part-d/costs/coverage-gap/part-d-coverage-gap.html. Accessed April 6, 2017.

Creswell JW. Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. Thousand Oaks, California: Sage Publications, 2003.

Cubanski J, Damico A, Neuman T. Medicare Part D in 2018: The Latest on Enrollment, Premiums, and Cost Sharing. Kaiser Family Foundation; 2018. https://www.kff.org/medicare/issue-brief/medicare-part-d-in-2018-the-latest-on-enrollment-premiums-and-cost-sharing/. Accessed May 13, 2019.

Cubanski J, Koma W, Neuman T. The Out-of-Pocket Cost Burden for Specialty Drugs in Medicare Part D in 2019. Kaiser Family Foundation; 2019. https://www.kff.org/report-section/the-out-of-pocket-cost-burden-for-specialty-drugs-in-medicare-part-d-in-2019-findings/. Accessed June 5, 2019.

Cubanski J, Neuman T, Damico A. Medicare's Role for People Under Age 65 with Disabilities. Kaiser Family Foundation; 2016. https://www.kff.org/report-

section/medicares-role-for-people-under-age-65-with-disabilities-issue-brief/. Accessed May 13, 2019.

Curtis K, Foster K, Mitchell R, Van C. Models of Care Delivery for Families of Critically Ill Children: An Integrative Review of International Literature. J Pediatr Nurs. 2016;31(3):330-341. doi:10.1016/j.pedn.2015.11.009

Cutillo CM, Austin CP, Groft SC. A Global Approach to Rare Diseases Research and Orphan Products Development: The International Rare Diseases Research Consortium (IRDiRC). Adv Exp Med Biol. 2017;1031:349-369. doi:10.1007/978-3-319-67144-4_20

Dal J, Skou N, Nielsen EH, Jørgensen JOL, Pedersen L. Acromegaly according to the Danish National Registry of Patients: how valid are ICD diagnoses and how do patterns of registration affect the accuracy of registry data? Clin Epidemiol. 2014;6:295-299. doi:10.2147/CLEP.S63758

Daneshvari S, Youssof S, Kroth PJ. The NIH Office of Rare Diseases Research Patient Registry Standard: A Report from the University of New Mexico's Oculopharyngeal Muscular Dystrophy Patient Registry. AMIA Annu Symp Proc. 2013;2013:269-277.

Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. Budget impact analysis of orphan drugs in Belgium: estimates from 2008 to 2013. J Med Econ. 2010;13(2):295-301. doi:10.3111/13696998.2010.491427

Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. Issues surrounding orphan disease and orphan drug policies in Europe. Appl Health Econ Health Policy. 2010;8(5):343-350. doi:10.2165/11536990-000000000-00000

Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis. 2017;12(1):63. doi:10.1186/s13023-017-0618-0

Diseases & Conditions - Medscape Reference. https://emedicine.medscape.com/. Accessed April 19, 2019.

Divino V, DeKoven M, Kleinrock M, Wade RL, Kaura S. Orphan drug expenditures in the United States: a historical and prospective analysis, 2007-18. Health Aff Proj Hope. 2016;35(9):1588-1594. doi:10.1377/hlthaff.2016.0030

Divino V, DeKoven M, Kleinrock M, Wade RL, Kim T, Kaura S. Pharmaceutical expenditure on drugs for rare diseases in Canada: a historical (2007-13) and prospective (2014-18) MIDAS sales data analysis. Orphanet J Rare Dis. 2016;11(1):68. doi:10.1186/s13023-016-0450-y

Dolled-Filhart MP, Lordemann A, Dahl W, Haraksingh RR, Ou-Yang C-W, Lin JC-H. Personalizing rare disease research: how genomics is revolutionizing the diagnosis and treatment of rare disease. Pers Med. 2012;9(8):805-819. doi:10.2217/pme.12.97

Doshi JA, Li P, Ladage VP, Pettit AR, Taylor EA. Impact of cost sharing on specialty drug utilization and outcomes: a review of the evidence and future directions. Am J Manag Care. 2016;22(3):188-197.

Dusetzina SB, Keating NL. Mind the gap: why closing the doughnut hole is insufficient for increasing Medicare beneficiary access to oral chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(4):375-380. doi:10.1200/JCO.2015.63.7736

Elliott EJ, Nicoll A, Lynn R, Marchessault V, Hirasing R, Ridley G. Rare disease surveillance: An international perspective. Paediatr Child Health. 2001;6(5):251-260.

European Commission. Rare diseases. Public Health - European Commission. https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en. Published November 25, 2016. Accessed March 5, 2019.

European Union Committee of Experts on Rare Diseases. Smmary of the EUCERD/Eurogentest Workshop on Cross-Referencing of Terminologies. In: Paris, France; 2012. http://www.eucerd.eu/wp-content/uploads//2015/03/EGTEUCERD_Terminologies_270912_WP5.pdf. Accessed March 7, 2019.

EURORDIS, NORD, CORD. EURORDIS-NORD-CORD Joint Declaration of 10 Key Principles of Rare Disease Patient Registries. 2012. http://download.eurordis.org/documents/pdf/EURORDIS_NORD_CORD_JointDec_Registries_FINAL.pdf. Accessed April 12, 2017.

Fan J, Arruda-Olson AM, Leibson CL, et al. Billing code algorithms to identify cases of peripheral artery disease from administrative data. J Am Med Inform Assoc. 2013;20(e2):e349-354. doi:10.1136/amiajnl-2013-001827

Fine JD. Epidermolysis bullosa. Application of epidemiologic principles to the study of a group of rare diseases via a disease registry. Dermatol Clin. 1995;13(3):659-670.

Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1723-1732. doi:10.1056/NEJMoa1702752

Forsythe LP, Szydlowski V, Murad MH, Ip S, Wang Z, Elraiyah TA, Fleurence R, Hickam DH. A systematic review of approaches for engaging patients for research on rare diseases. J Gen Intern Med. 2014;29 Suppl 3:S788-800. doi: 10.1007/s11606-014-2895-9.

Fung KW, Richesson R, Bodenreider O. Coverage of rare disease names in standard terminologies and implications for patients, providers, and research. AMIA Annu Symp Proc AMIA Symp. 2014;2014:564-572.

Gallo AM, Hadley EK, Angst DB, Knafl KA, Smith CAM. Parents' concerns about issues related to their children's genetic conditions. J Spec Pediatr Nurs. 2008;13(1):4-14. doi:10.1111/j.1744-6155.2008.00129.x

Gatta G, Trama A, Capocaccia R, RARECARENet Working Group. Epidemiology of rare cancers and inequalities in oncologic outcomes. Eur J Surg Oncol. September 2017. doi:10.1016/j.ejso.2017.08.018

Geissler, Oliver, Weinman. Mapping out the Similarities and Differences between Rare Cancers and Rare Diseases. European Organisation for Rare Diseases; 2015. https://www.eurordis.org/sites/default/files/rare-cancers-2015-2016.pdf. Accessed July 8, 2019.

Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Diseases. https://rarediseases.info.nih.gov/diseases/browse-by-first-letter. Accessed July 19, 2018.

Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. NIH.gov. https://rarediseases.info.nih.gov/. Accessed January 13, 2017.

Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. List of FDA Orphan Drugs. https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs. Accessed July 19, 2018.

Genetic and Rare Diseases Information Center (GARD), National Center for Advancing Translational Sciences. Rare Cancers. https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers. Accessed July 19, 2018.

Genetics Home Reference, U.S. National Library of Medicine. Metachromatic leukodystrophy. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/metachromatic-leukodystrophy. Accessed February 7, 2019.

Genetics Home Reference, U.S. National Library of Medicine. Spinal muscular atrophy. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy. Accessed February 7, 2019.

German RR, Lee LM, Horan JM, et al. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. MMWR. 2001;50(RR-13):1-35-7.

Glaser BG, Strauss AL. The Discovery of Grounded Theory : Strategies for Qualitative Research. Hawthorne, N.Y. : Aldine de Gruyter, [1967]; 1967.

Gliklich RE, Leavy MB, Karl J, Campion DM, Levy D, Berliner E. A framework for creating standardized outcome measures for patient registries. J Comp Eff Res. 2014;3(5):473-480. doi:10.2217/cer.14.38

Goldman DP, Joyce GF. Medicare Part D: a successful start with room for improvement. JAMA. 2008;299(16):1954-1955. doi:10.1001/jama.299.16.1954

Greenlee RT, Goodman MT, Lynch CF, Platz CE, Havener LA, Howe HL. The occurrence of rare cancers in U.S. adults, 1995-2004. Public Health Rep Wash DC 1974. 2010;125(1):28-43. doi:10.1177/003335491012500106

Groft SC, de la Paz MP. Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data. Adv Exp Med Biol. 2010;686:3-14. doi:10.1007/978-90-481-9485-8_1

Groft SC, Posada de la Paz M. Preparing for the future of rare diseases. Adv Exp Med Biol. 2017;1031:641-648. doi:10.1007/978-3-319-67144-4_34

Grosse SD, James AH, Lloyd-Puryear MA, Atrash HK. A public health framework for rare blood disorders. Am J Prev Med. 2011;41(6 Suppl 4):S319-323. doi:10.1016/j.amepre.2011.09.010

Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. Field methods. doi/abs/10.1177/1525822X0527990 3. 2006.

Hall JG. The role of patient advocacy/parent support groups. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2013;103(12 Suppl 1):1020-1022.

Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010; 363(4):301-304. doi:10.1056/NEJMp1006304

Health Insurance Coverage of the Total Population. Henry J Kais Fam Found. September 2017. http://www.kff.org/other/state-indicator/total-population/. Accessed September 22, 2017.

Hemminki K, Li X, Sundquist K, Sundquist J. Familial risks for common diseases: etiologic clues and guidance to gene identification. Mutat Res. 2008;658(3):247-258. doi:10.1016/j.mrrev.2008.01.002

Hemphill TA. Extraordinary pricing of orphan drugs: Is it a socially responsible strategy for the U.S. pharmaceutical industry? J Bus Ethics. 2010;94(2):225-242.

Hennekam RCM. Care for patients with ultra-rare disorders. Eur J Med Genet. 2011;54(3):220-224. doi:10.1016/j.ejmg.2010.12.001

Hoadley J, Cubanski J, Neuman T. It Pays to Shop: Variation in Out-of-Pocket Costs for Medicare Part D Enrollees in 2016. Kaiser Family Foundation; 2015.

https://www.kff.org/medicare/issue-brief/it-pays-to-shop-variation-in-out-of-pocket-costs-for-medicare-part-d-enrollees-in-2016/. Accessed May 9, 2019.

How many people have keratoconus? NKCF.org. January 2018. https://www.nkcf.org/how-many-have-kc/. Accessed August 19, 2019.

Hutchings A, Schey C, Dutton R, Achana F, Antonov K. Estimating the budget impact of orphan drugs in Sweden and France 2013-2020. Orphanet J Rare Dis. 2014;9:22. doi:10.1186/1750-1172-9-22

Hyry HI, Roos JCP, Manuel J, Cox TM. The legal imperative for treating rare disorders. Orphanet J Rare Dis. 2013;8:135. doi:10.1186/1750-1172-8-135

ICD - ICD-10-CM - International Classification of Diseases, Tenth Revision, Clinical Modification. https://www.cdc.gov/nchs/icd/icd10cm.htm. Published July 1, 2019. Accessed July 9, 2019.

Inc G. The U.S. Healthcare Cost Crisis. Gallup.com. https://news.gallup.com/poll/248123/westhealth-gallup-us-healthcare-cost-crisis-report.aspx. Accessed April 25, 2019.

Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, Field MJ, Boat TF. Profile of Rare Diseases. National Academies Press (US); 2010. https://www.ncbi.nlm.nih.gov/books/NBK56184/. Accessed March 31, 2017.

International Rare Diseases Research Consortium. International Consortium of Human Phenotype Terminologies (ICHPT). IRDiRC. http://www.irdirc.org/activities/task-forces/international-consortium-of-human-phenotype-terminologies/. Published December 1, 2017. Accessed March 7, 2019.

IQVIA Institute. https://www.iqvia.com/institute. Accessed June 6, 2019.

Jackson JM, Crider KS, Olney RS. Population-based surveillance for rare congenital and inherited disorders: models and challenges. Adv Exp Med Biol. 2010;686:133-150. doi:10.1007/978-90-481-9485-8_9

Jadad AR, Gagliardi A. Rating health information on the internet: Navigating to knowledge or to Babel? JAMA. 1998;279(8):611-614. doi:10.1001/jama.279.8.611

Kang R, Lipner S. Assessment of internet sources on subungual melanoma. Melanoma Res. August 2018. doi:10.1097/CMR.0000000000000508

Kanters TA, Steenhoek A, Hakkaart L. Orphan drugs expenditure in the Netherlands in the period 2006–2012. Orphanet J Rare Dis. 2014;9. doi:10.1186/s13023-014-0154-0

Kaye WE, Sanchez M, Wu J. Feasibility of creating a National ALS Registry using administrative data in the United States. Amyotroph Lateral Scler Front Degener. 2014;15(5-6):433-439. doi:10.3109/21678421.2014.887119

Kennedy J, Wood EG, Frieden L. Disparities in Insurance Coverage, Health Services Use, and Access Following Implementation of the Affordable Care Act: A Comparison of Disabled and Nondisabled Working-Age Adults. Inq J Med Care Organ Provis Financ. 2017;54:46958017734031. doi:10.1177/0046958017734031

Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol. 1986;101(3):267-273.

Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for feform. JAMA. 2016;316(8):858-871. doi:10.1001/jama.2016.11237

Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. Intractable Rare Dis Res. 2018;7(4):213-222. doi:10.5582/irdr.2018.01085

Koay PP, Sharp RR. The role of patient advocacy organizations in shaping genomic science. Annu Rev Genomics Hum Genet. 2013;14:579-595. doi:10.1146/annurev-genom-091212-153525

Kodra Y, Posada de la Paz M, Coi A, et al. Data Quality in Rare Diseases Registries. Adv Exp Med Biol. 2017;1031:149-164. doi:10.1007/978-3-319-67144-4_8

Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. Adv Exp Med Biol. 2010;686:223-250. doi:10.1007/978-90-481-9485-8_14

Kotecha RS, Kees UR, Cole CH, Gottardo NG. Rare childhood cancers--an increasing entity requiring the need for global consensus and collaboration. Cancer Med. 2015;4(6):819-824. doi:10.1002/cam4.426

Kuester MK, Jackson EA, Runyan BM, Pezalla EJ, Nussbaum SR. The Effect of a Pediatric Rare Disease on Subscriber Retention Rates for Commercial Health Insurers in the United States. J Manag Care Spec Pharm. September 2018:1-9. doi:10.18553/jmcp.2018.18205

Leake J, Albani S, Kao A, et al. Acute Disseminated Encephalomyelitis in Childhood: Epidemiologic, Clinical and Laboratory Features. Pediatr Infect Dis J. 2004;23(8):756-764. doi:10.1097/01.inf.0000133048.75452.dd

Lee CD, Williams SE, Sathe NA, McPheeters ML. A systematic review of validated methods to capture several rare conditions using administrative or claims data. Vaccine. 2013;31:K21-K27. doi:10.1016/j.vaccine.2013.03.044

Lee S, Choi M. Ultra-rare Disease and Genomics-Driven Precision Medicine. Genomics Inform. 2016;14(2):42-45. doi:10.5808/GI.2016.14.2.42

Levesque J-F, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. Int J Equity Health. 2013;12:18. doi:10.1186/1475-9276-12-18

Lichtenberg FR, Sun SX. The impact of Medicare Part D on prescription drug use by the elderly. Health Aff Proj Hope. 2007;26(6):1735-1744. doi:10.1377/hlthaff.26.6.1735

Long SK, Bart L, Karpman M, Shartzer A, Zuckerman S. Sustained Gains In Coverage, Access, And Affordability Under The ACA: A 2017 Update. Health Aff Proj Hope. 2017;36(9):1656-1662. doi:10.1377/hlthaff.2017.0798

Mays GP, Claxton G, White J. Managed care rebound? Recent changes in health plans' cost containment strategies. Health Aff Proj Hope. 2004;Suppl Web Exclusives:W4-427-436. doi:10.1377/hlthaff.w4.427

Meeker CR, Geynisman DM, Egleston BL, et al. Relationships among financial distress, emotional distress, and overall distress in insured patients with cancer. J Oncol Pract. 2016;12(7):e755-764. doi:10.1200/JOP.2016.011049

Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer Lett. 2016;381(1):269-277. doi:10.1016/j.canlet.2016.07.022

Mooney J, Poland F, Spalding N, Scott DGI, Watts RA. "In one ear and out the other - it"s a lot to take in': a qualitative study exploring the informational needs of patients with ANCA-associated vasculitis. Musculoskeletal Care. 2013;11(1):51-59. doi:10.1002/msc.1030

Munshi N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. Leuk Lymphoma. 2015;56(5):1252-1260. doi:10.3109/10428194.2014.953145

National Cancer Institute, Surveillance, Epidemiology, and End Results Program. About the SEER Program. SEER. https://seer.cancer.gov/about/overview.html. Accessed March 8, 2019.

National Organization for Rare Disorders (NORD). NORD (National Organization for Rare Disorders). https://rarediseases.org/. Accessed April 19, 2017.

Nelson RE, Nelson SL, Huttner B, Gundlapalli A. The effect of Medicare Part D on health care utilization for non-elderly Medicare recipients with disabilities. Disabil Health J. 2014;7(1):64-69. doi:10.1016/j.dhjo.2013.07.003

Nsubuga P, White ME, Thacker SB, et al. Public Health Surveillance: A Tool for Targeting and Monitoring Interventions. In: Jamison DT, Breman JG, Measham AR, et al., eds. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC): World Bank; 2006. http://www.ncbi.nlm.nih.gov/books/NBK11770/.

Obama B. United States Health Care Reform: Progress to Date and Next Steps. JAMA. 2016;316(5):525-532. doi:10.1001/jama.2016.9797

Office of the Commissioner. Press Announcements - FDA approves first drug for spinal muscular

atrophy.https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm. Published December 23, 2016. Accessed February 7, 2019.

Orofino J, Soto J, Casado MA, Oyagüez I. Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007. Appl Health Econ Health Policy. 2010;8(5):301-315. doi:10.2165/11531880-000000000-00000

Orphan Drug Act. Vol USC 21 I Subchapter D Part 316.; 1983. https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=51cf70689d51f0ea4147c0a8ac649321&rgn=div5&view=text&node=21:5.0.1.1.6&idno=21. Accessed January 13, 2017.

Orphanet Report Series. Prevalence and Incidence of Rare Diseases: Bibliographic Data; 2019. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. Accessed March 11, 2019.

Orszag PR. US Health Care Reform: Cost Containment and Improvement in Quality. JAMA. 2016;316(5):493-495. doi:10.1001/jama.2016.9876

Outterson K, Kesselheim AS. How Medicare could get better prices on prescription drugs. Health Aff Proj Hope. 2009;28(5):w832-841. doi:10.1377/hlthaff.28.5.w832

Owusu Obeng A, Fei K, Levy KD, et al. Physician-Reported Benefits and Barriers to Clinical Implementation of Genomic Medicine: A Multi-Site IGNITE-Network Survey. J Pers Med. 2018;8(3). doi:10.3390/jpm8030024

Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. Adm Policy Ment Health. 2015;42(5):533-544. doi:10.1007/s10488-013-0528-y

Papoz L, Balkau B, Lellouch J. Case counting in epidemiology: limitations of methods based on multiple data sources. Int J Epidemiol. 1996;25(3):474-478.

Park T, Jung J. The effect of Medicare Part D on prescription drug spending and health care use: 6 years of follow-up, 2007-2012. J Manag Care Spec Pharm. 2017;23(1):5-12. doi:10.18553/jmcp.2017.23.1.5

Pasceri E. Analyzing rare diseases terms in biomedical terminologies. JLIS.it. 2012;3(1). doi:10.4403/jlis.it-4783

Pelentsov LJ, Fielder AL, Esterman AJ. The Supportive Care Needs of Parents With a Child With a Rare Disease: A Qualitative Descriptive Study. J Pediatr Nurs. 2016;31(3):e207-218. doi:10.1016/j.pedn.2015.10.022

Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. Development of the parental needs scale for rare diseases: a tool for measuring the supportive care needs of parents caring for a child with a rare disease. J Multidiscip Healthc. 2016;9:425-433. doi:10.2147/JMDH.S113898

Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. BMC Fam Pract. 2016;17:88. doi:10.1186/s12875-016-0488-x

Pelentsov LJ, Laws TA, Esterman AJ. The supportive care needs of parents caring for a child with a rare disease: A scoping review. Disabil Health J. 2015;8(4):475-491. doi:10.1016/j.dhjo.2015.03.009

Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic Test Availability And Spending: Where Are We Now? Where Are We Going? Health Aff Proj Hope. 2018;37(5):710-716. doi:10.1377/hlthaff.2017.1427

Picavet E, Dooms M, Cassiman D, Simoens S. Drugs for rare diseases: influence of orphan designation status on price. Appl Health Econ Health Policy. 2011;9(4):275-279. doi:10.2165/11590170-000000000-00000

Pillai RK, Jayasree K. Rare cancers: Challenges & issues. Indian J Med Res. 2017;145(1):17-27. doi:10.4103/ijmr.IJMR_915_14

Population Estimates Program, Population Division. Historical National Population Estimates: July 1, 1900 to July 1, 1999. U.S. Census Bureau; 2000. https://www.census.gov/population/estimates/nation/popclockest.txt. Accessed April 17, 2019.

Prevalence and Incidence of Rare Diseases: Bibliographic Data. European Commission; 2017. https://ec.europa.eu/health/rare_diseases/orphanet/report_en. Accessed April 19, 2017.

Priyanka P, Hadi YB, Reynolds GJ. Analysis of the Patient Information Quality and Readability on Esophagogastroduodenoscopy (EGD) on the Internet. Can J Gastroenterol Hepatol. 2018;2018:2849390. doi:10.1155/2018/2849390

Prometheus Laboratories Inc. Proleukin®(aldesleukin)Immunotherapy for mM and mRCC. https://www.proleukin.com/. Published October 2017. Accessed April 18, 2019.

R de Vrueh, ERF Baekelandt, JMH de Haan. Priority Medicines for Europe and the World “A Public Health Approach to Innovation.” World Health Organization; 2013. https://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf. Accessed July 2, 2019.

Rare Diseases Clinical Research Network. RDCRN Contact Registry. https://www.rarediseasesnetwork.org/registry. Accessed March 8, 2019.

Report of The National Commission on Orphan Diseases. U.S. Department of Health and Human Services Public Health Service Office of the Assistant Secretary for health; 1989. https://rarediseases.info.nih.gov/files/report_of_the_national_commission_on_orphan_diseases_february_1989.pdf. Accessed March 31, 2017.

https://rarediseases.info.nih.gov/files/report_of_the_national_commission_on_orphan_diseases_february_1989.pdf. Accessed March 31, 2017.

Research and Quality; 2015. https://meps.ahrq.gov/data_files/publications/st480/stat480.shtml. Accessed September 22, 2017.

Reynolds TM, Mewies C, Hamilton J, Wierzbicki AS, PATHFINDER Project Collaboration group. Identification of rare diseases by screening a population selected on the basis of routine pathology results-the PATHFINDER project: lysosomal acid lipase/cholesteryl ester storage disease substudy. J Clin Pathol. 2018;71(7):608-613. doi:10.1136/jclinpath-2017-204727

Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2015;18(6):906-914. doi:10.1016/j.jval.2015.05.008

Robinson SW, Brantley K, Liow C, Teagarden JR. An early examination of access to select orphan drugs treating rare diseases in health insurance exchange plans. J Manag Care Spec Pharm. 2014;20(10):997-1004. doi:10.18553/jmcp.2014.20.10.997

Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? Orphanet J Rare Dis. 2017;12(1):1. doi:10.1186/s13023-016-0551-7

Rodwell C, Aymé S. Rare disease policies to improve care for patients in Europe. Biochim Biophys Acta. 2015;1852(10 Pt B):2329-2335. doi:10.1016/j.bbadis.2015.02.008

Ruiz E, Ramalle-Gómara E, Quiñones C, Rabasa P, Pisón C. Validation of diagnosis of aplastic anaemia in La Rioja (Spain) by International Classification of Diseases codes for case ascertainment for the Spanish National Rare Diseases Registry. Eur J Haematol. 2015;94(5):400-403. doi:10.1111/ejh.12432

Russman B. Spinal Muscular Atrophy. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. Published 2004. Updated 2012. Accessed April 30, 2019.

San Giorgi MRM, de Groot OSD, Dikkers FG. Quality and readability assessment of websites related to recurrent respiratory papillomatosis. The Laryngoscope. 2017;127(10):2293-2297. doi:10.1002/lary.26521

Schee Genannt Halfmann S, Mählmann L, Leyens L, Reumann M, Brand A. Personalized medicine: What's in it for rare diseases? Adv Exp Med Biol. 2017;1031:387-404. doi:10.1007/978-3-319-67144-4_22

Schey C, Milanova T, Hutchings A. Estimating the budget impact of orphan medicines in Europe: 2010 - 2020. Orphanet J Rare Dis. 2011;6:62. doi:10.1186/1750-1172-6-62

Schielen PCJI, Kemper EA, Gelb MH. Newborn Screening for Lysosomal Storage Diseases: A Concise Review of the Literature on Screening Methods, Therapeutic Possibilities and Regional Programs. Int J Neonatal Screen. 2017;3(2). doi:10.3390/ijns3020006

Schieppati A, Henter J-I, Daina E, Aperia A. Why rare diseases are an important medical and social issue. Lancet Lond Engl. 2008;371(9629):2039-2041. doi:10.1016/S0140-6736(08)60872-7

Schott AF, Welch JJ, Verschraegen CF, Kurzrock R. The National Clinical Trials Network: conducting successful clinical trials of new therapies for rare cancers. Semin Oncol. 2015;42(5):731-739. doi:10.1053/j.seminoncol.2015.07.010

Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. Orphanet J Rare Dis. 2008;3:33. doi:10.1186/1750-1172-3-33

Shaw DL, Dhruva SS, Ross JS. Coverage of Novel Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval. J Manag Care Spec Pharm. 2018;24(12):1230-1238. doi:10.18553/jmcp.2018.24.12.1230

Shen C, Zhao B, Liu L, Shih Y-CT. Financial burden for patients with chronic myeloid leukemia enrolled in Medicare Part D taking targeted oral anticancer medications. J Oncol Pract. January 2017:JOP2016014639. doi:10.1200/JOP.2016.014639

Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveant lector et viewor--Let the reader and viewer beware. JAMA. 1997;277(15):1244-1245.

Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J Rare Dis. 2011;6:42. doi:10.1186/1750-1172-6-42

Smith MG, Royer J, Mann JR, McDermott S. Using Administrative Data to Ascertain True Cases of Muscular Dystrophy: Rare Disease Surveillance. JMIR Public Health Surveill. 2017;3(1):e2. doi:10.2196/publichealth.6720

Snedecor GW, Cochran WG. Statistical Methods. Eighth Edition. Iowa State University Press; 1989.

Social Security Administration. Compassionate Allowances. https://www.ssa.gov/compassionateallowances/. Accessed May 16, 2019.

Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. Am J Prev Med. 2010;38(4 Suppl):S475-481. doi:10.1016/j.amepre.2009.12.023

Stockklausner C, Lampert A, Hoffmann GF, Ries M. Novel Treatments for Rare Cancers: The U.S. Orphan Drug Act Is Delivering—A Cross-Sectional Analysis. The Oncologist. 2016;21(4):487-493. doi:10.1634/theoncologist.2015-0397

Strauss AL, Corbin JM. Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory. Thousand Oaks, California: Sage Publications, 1998.

Tambuyzer E. Towards a framework for personalized healthcare: lessons learned from the field of rare diseases. Pers Med. 2010;7(5):569-586. doi:10.2217/pme.10.52

Taruscio D, Vittozzi L, Rocchetti A, Torreri P, Ferrari L. The Occurrence of 275 Rare Diseases and 47 Rare Disease Groups in Italy. Results from the National Registry of Rare Diseases. Int J Environ Res Public Health. 2018;15(7). doi:10.3390/ijerph15071470

Terry SF, Terry PF, Rauen KA, Uitto J, Bercovitch LG. Advocacy groups as research organizations: the PXE International example. Nat Rev Genet. 2007;8(2):157-64. doi: 10.1038/nrg1991.

The Medicare Part D Prescription Drug Benefit. Kaiser Family Foundation; 2018. http://kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/. Accessed April 3, 2017.

The U.S. Healthcare Cost Crisis. Gallup, Inc.; 2019. https://news.gallup.com/poll/248123/westhealth-gallup-us-healthcare-cost-crisis-report.aspx. Accessed April 25, 2019.

Trama A, Marcos-Gragera R, Sánchez Pérez MJ, et al. Data quality in rare cancers registration: the report of the RARECARE data quality study. Tumori. 2017;103(1):22-32. doi:10.5301/tj.5000559

Trish E, Joyce G, Goldman DP. Specialty drug spending trends among Medicare and Medicare Advantage enrollees, 2007-11. Health Aff Proj Hope. 2014;33(11):2018-2024. doi:10.1377/hlthaff.2014.0538

U. S. Government Accountability Office. Orphan Drugs: FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue.; 2018. https://www.gao.gov/products/GAO-19-83?utm_source=onepager&utm_medium=email&utm_campaign=email_HC. Accessed May 3, 2019.

U.S. Centers for Medicare & Medicaid Services. Catastrophic coverage. Medicare.gov. https://www.medicare.gov/drug-coverage-part-d/costs-for-medicare-drug-coverage/catastrophic-coverage. Accessed May 14, 2019.

U.S. Centers for Medicare & Medicaid Services. Copayment/coinsurance in drug plans. Medicare.gov. https://www.medicare.gov/part-d/costs/copayment-coinsurance/drug-plan-copayments.html. Accessed April 6, 2017.

U.S. Centers for Medicare & Medicaid Services. Medicare Provider Utilization and Payment Data: Part D Prescriber. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html. Published January 17, 2017. Accessed April 7, 2017.

U.S. Centers for Medicare & Medicaid Services. What drug plans cover. Medicare.gov. https://www.medicare.gov/drug-coverage-part-d/what-drug-plans-cover. Accessed May 13, 2019.

U.S. Food & Drug Administration. Accelerated Approval Program. https://www.fda.gov/drugs/information-healthcare-professionals-drugs/accelerated-approval-program. Published March 10, 2016. Accessed May 17, 2019.

U.S. Food & Drug Administration. Rare Diseases: Common Issues in Drug Development Guidance for Industry. Food and Drug Administration; 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf. Accessed January 13, 2017.

U.S. Food & Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accessed March 31, 2017.

U.S. Health Resources & Services Administration. Recommended Uniform Screening Panel. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed March 4, 2019.

U.S. National Library of Medicine. ClinicalTrials.gov. ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed July 18, 2018.

U.S. National Library of Medicine. SNOMED CT to ICD-10-CM Map. https://www.nlm.nih.gov/research/umls/mapping_projects/snomedct_to_icd10cm.html. Accessed August 16, 2018.

Uninsurance I of M (US) C on the C of. Why Health Insurance Matters. National Academies Press (US); 2001. https://www.ncbi.nlm.nih.gov/books/NBK223643/. Accessed September 22, 2017.

United States Census Bureau. U.S. and World Population Clock. https://www.census.gov/popclock/. Accessed March 15, 2019.

Valdez R, Grosse SD, Khoury MJ. The need for a next-generation public health response to rare diseases. Genet Med. 2016;19(5):489-490. doi:10.1038/gim.2016.166

Vistnes JP, Lipton BJ. The Uninsured in America: Estimates of the Percentage of Non-Elderly Adults Uninsured throughout Each Calendar Year, by Selected Population Subgroups and State Medicaid Expansion Status: 2013 and 2014. In: Statistical Brief (Medical Expenditure Panel Survey (US)). Rockville (MD): Agency for Healthcare Research and Quality (US); 2001. http://www.ncbi.nlm.nih.gov/books/NBK447195/.

Wellman-Labadie O, Zhou Y. The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? Health Policy. 2010;95(2-3):216-228. doi:10.1016/j.healthpol.2009.12.001

What is “Early Intervention”? | CDC. https://www.cdc.gov/ncbddd/actearly/parents/states.html. Accessed December 21, 2018.

Williams SE, Carnahan R, Krishnaswami S, McPheeters ML. A systematic review of validated methods for identifying transverse myelitis using administrative or claims data. Vaccine. 2013;31 Suppl 10:K83-87. doi:10.1016/j.vaccine.2013.03.074

Wood J, Sames L, Moore A, Ekins S. Multifaceted roles of ultra-rare and rare disease patients/parents in drug discovery. Drug Discov Today. 2013;18(21-22):1043-1051. doi:10.1016/j.drudis.2013.08.006

Woodward L, Johnson S, Walle JV, et al. An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry. Orphanet J Rare Dis. 2016;11(1):154. doi:10.1186/s13023-016-0537-5

World Health Organization. ICD-11 - Mortality and morbidity statistics. https://icd.who.int/dev11/l-m/en. Accessed July 18, 2018.

Yala SM, Duru OK, Ettner SL, Turk N, Mangione CM, Brown AF. Patterns of prescription drug expenditures and medication adherence among Medicare part D beneficiaries with and without the low-income supplement. BMC Health Serv Res. 2014;14:665. doi:10.1186/s12913-014-0665-3

Yeoh ZW, Navaratnam V, Bhatt R, McCafferty I, Hubbard RB, Johnson SR. Natural history of angiomyolipoma in lymphangioleiomyomatosis: implications for screening and surveillance. Orphanet J Rare Dis. 2014;9:151. doi:10.1186/s13023-014-0151-3

Zafar SY. Financial toxicity of cancer care: It’s time to intervene. J Natl Cancer Inst. 2016;108(5). doi:10.1093/jnci/djv370