Exploring the Experiences of Patients with Rare Disease in Pennsylvania

by

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This thesis explores the experiences and barriers facing patients with rare diseases in Pennsylvania, utilizing data from the Pennsylvania Rare Disease Advisory Council's 2020 Rare Disease Needs Assessment Survey. The study examines how respondents' demographic factors, including race, gender identity, insurance type, and rare disease type, correlate with their experiences regarding diagnostic timelines, healthcare spending, and perceptions of timely diagnosis.

Analysis of demographic data unveiled that a significant majority of respondents hailed from urban counties (73.3%) and primarily reported a single primary diagnosis (74.5%). The prevalence of private commercial health insurance (41%) among respondents outweighed government-funded sources such as Medicaid or Medicare (14.6%). Although the data offered a comprehensive snapshot of respondents' demographic landscape, it also exposed potential biases in representation, notably among minority racial groups and individuals from the transgender and nonbinary community in Pennsylvania.

Chi-square tests conducted on various facets of rare disease patients' experiences yielded significant insights. The analysis uncovered a notable relationship between diagnostic time intervals and the number of incorrect diagnoses, emphasizing the critical role of accurate diagnoses in patients' diagnostic journeys. However, no statistically significant relationship emerged between age and annual spending on rare disease care, indicating a multifaceted interplay of factors influencing healthcare spending across different age groups.

Further exploration looked into the correlation between gender identity and perceptions of timely diagnosis, revealing potential disparities in patient experiences based on gender identity. Additionally, the analysis of health insurance types and perceptions of timely diagnosis illuminated differences in healthcare access and perceptions among individuals with varying insurance coverage.

Overall, this study provides valuable insights into the challenges and needs of rare disease patients in Pennsylvania, underscoring the importance of tailored support, enhanced diagnostic processes, and equitable access to healthcare services. The findings highlight the necessity for patient-centered care, comprehensive diagnostic strategies, and targeted interventions to address the diverse needs and challenges encountered by rare disease patients throughout their diagnostic odyssey. Future research and interventions grounded in these findings have the potential to enhance support and outcomes for individuals with rare diseases, not only in Pennsylvania but also globally.

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Preface

I would like to take this opportunity to thank the many people that brought this thesis project to fruition. To the faculty and staff both in and outside of the University of Pittsburgh that have advised me on this project and in my schoolwork that inspired this work I thank you for your efforts and for your guidance. To my committee members I thank you for taking the time to review my work and hope this paper lives up to having your names on it. To my friends and family who have supported me from the beginning there are no words sufficient for the support you have provided me, and my gratitude is eternal. To the members of PARDAC that did such extensive work collecting the data for this analysis I thank you for your efforts. Finally, I dedicate this work to all the people with rare diseases in Pennsylvania that took time out of their day to complete this survey and hope that the results from it will help ease your journeys ahead.

1.0 Introduction

Rare diseases encompass a range of disorders that impact a small fraction of the population, leading to notable medical, psychological, and social obstacles for those affected. In the United States the Food and Drug Administration defines any disease, disorder, illness or condition affecting fewer than 200,000 people as rare ("Rare Diseases at FDA" 2022). Although these conditions are uncommon, their cumulative impact is significant, underscoring the importance of comprehending the experiences and viewpoints of individuals coping with these disorders. While each individual rare disease or disorder (RD) impacts only a limited number of people, the collective number of distinct RDs exceeds 7,000, affecting approximately one out of every ten Americans. ((Bogart et al. 2022) Approximately 30 million individuals in the United States and over 300-400 million people globally are impacted by rare diseases, often resulting in long-term health issues, disabilities, and untimely mortality. (Marwaha, Knowles, and Ashley 2022). Many rare diseases have a heritable genetic component and can be diagnosed using modern genomic techniques. Despite this, ,more than 90% of RDs do not have current FDA-approved treatments, resulting in years long medical odysseys for patients seeking help with their conditions. (Forbes Shepherd et al. 2018). This thesis aims to analyze data collected by the Pennsylvania Rare Disease Advisory Council as part of their Rare Disease Needs Assessment Survey in 2020 to create a deeper understanding of the needs and experiences of rare disease patients within the state and to discover valuable insights for healthcare providers, policymakers, and support organizations.

1.1 Specific Aims

1.1.1 Specific Aim 1

The data from the Pennsylvania Rare Disease Advisory Council's 2020 Rare Disease Needs Assessment Survey will be used to assess the relationships between respondents' demographic makeup, including their race, gender identity, insurance type, and type of rare disease

1.1.2 Specific Aim 2

This analysis will focus on understanding how these demographic factors relate to the respondent’s time taken to receive a final diagnosis, perceived time taken to receive a diagnosis, and healthcare spending habits among respondents.

1.1.3 Specific Aim 3

Statistical analysis through chi square tests will be used to gain insights into the needs and experiences of rare disease patients in Pennsylvania for healthcare providers, policymakers, and support organizations.

2.0 Literature Review

2.1 Healthcare Equity and Disparities

Since 1980, the US Department of Health and Human Services has marked the beginning of each decade with a 10 year plan known as the Healthy People initiative to address the most vital public health priorities and challenges across the nation. ("Healthy People 2030 | Health.Gov," n.d.) Currently the plan is on its on its fifth iteration, *Healthy People 2030,* setting public health milestones that the country aims to reach by the year of 2030. ("Healthy People 2030 | Health.Gov," n.d.)

Two of the most important aspects of the *Healthy People* plan revolve around two major aspects of the field of public health; reducing health disparities and promoting equity in health. The definitions of both concepts were updated as part of *Healthy People 2020* ("Healthy People 2030 | Health.Gov," n.d.)and their definitions are still in use in the current iteration. The plan defines health equity as "the attainment of the highest level of health for all people.". ("Healthy People 2030 | Health.Gov," n.d.) This definition has multiple subcomponents which involve "valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities".("Healthy People 2030 | Health.Gov," n.d.) The plan also defines health disparities as "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage." ("Healthy People 2030 | Health.Gov," n.d.) Importantly in this definition they also acknowledge that health disparity is driven by a variety of factors that are both in and outside the realm of the broader US public healthcare system. (Ndugga and Published 2023)

In doing so they also acknowledge the fact that while healthcare disparity is often viewed through the lenses of race or ethnicity due to historical oppression of minority groups, the issues faced by people affected by these disparities are intersectional. This definition reflects the renewed emphasis on health equity as a key aspect of modern public health, which was also reflected in the 2020 revision to the *10 Essential Public Health Services* which were published by the CDC. ("CDC - 10 Essential Public Health Services - CSTLTS," n.d.)

These principles reflect the values ingrained in the US Constitution and Bill of Rights which establish every American as being born equal and deserving of the same rights regardless of demographic differences. The incorporation of these values into *Healthy People 2020* and beyond acknowledge that the United States as a country has not always lived up to these ideals and that certain groups have been historically overlooked and underserved on a systemic level. Recognizing an intersectional understanding of healthcare disparities is pivotal in comprehending the complex challenges confronting individuals with rare diseases. Rare conditions frequently intersect with various facets of identity, encompassing race, ethnicity, socioeconomic status, gender, age, and geographical location, culminating in compounded obstacles to accessing fair and timely healthcare. Furthermore, intersectionality underscores the interconnected influence of social determinants of health, such as education, employment, housing, and environmental factors, which can intensify health inequalities for individuals affected by rare diseases. By acknowledging and addressing these intersecting factors, healthcare providers, policymakers, and advocates can develop more inclusive and responsive approaches to ensure equitable care and support for all individuals grappling with rare diseases, irrespective of their intersecting identities or backgrounds.

2.2 Epidemiology of Rare Diseases

Rare diseases, also known as orphan diseases, are a global public health concern despite their low prevalence and the challenges they pose to healthcare systems. The prevalence of rare diseases varies across different countries and regions, making it difficult to estimate a global point prevalence. (Nguengang Wakap et al. 2020) The challenges are compounded by the small patient numbers and non-standardized methodologies used in studies, as well as the lack of comprehensive registries and codification of rare diseases(Thygesen et al. 2023). Furthermore, the impact of rare diseases on patients' mental health, such as affective and anxiety disorders, adds another layer of complexity to their overall burden on healthcare systems. (Uhlenbusch et al. 2021) The terminology and definitions of rare diseases also vary, with the average prevalence threshold being between 40 and 50 cases per 100,000 people. (Richter et al. 2015) In the United States, a rare disease is defined as a condition affecting fewer than 200,000 patients, (Whicher, Philbin, and Aronson 2018). The impact of rare diseases on healthcare systems is substantial, with estimates suggesting that about 30 million individuals in the United States are living with a rare disease (Whicher, Philbin, and Aronson 2018).

The burden of rare diseases on healthcare systems is challenging to gauge, and the use of machine learning and artificial intelligence has been proposed to address this issue. (Chiu et al. 2018) Artificial Intelligence, more commonly referred to as AI has the potential to assist people affected by rare disease through assisting researchers in analyzing large datasets comprised of patient healthcare records and genetic data that would be extremely time consuming for researchers to do on their own. (Wojtara et al. 2023) Machine learning enables the use of algorithms that identify patterns and classify cases based on historical data as well. An example of this is OrphaCODES, a comprehensive classification and coding system for rare diseases developed by

the international consortium Orphanet. (Chiu et al. 2018). OrphaCODES establishes connections among genes, diseases and phenotypic features that allow researchers to analyze rare diseases and cross-reference other classification systems such as the ICD-10, which currently only encompasses 500 distinct codes for rare diseases. (Chiu et al. 2018) A study in Western Australia utilized ORPHACODES and Australian version of ICD-10 to create 1084 new disease codes, forming the foundation for assessing healthcare burden linked to rare disease. This study enabled an evaluation not only of the prevalence but also of healthcare expenses related to rare diseases. Ultimately this allows researchers to streamline the diagnostic journey that many patients with rare diseases go through and can assist researchers in getting a clearer picture as to what the true burden of rare disease on their healthcare systems.

The economic burden of rare diseases is also significant, as evidenced by a study conducted by Every Life Foundation for Rare Diseases in 2019. This study assessed the direct and indirect economic burdens of rare diseases in the US in 2019. The study showed that estimated total economic burden of 379 rare disease with a prevalence of 15.5 million people in 2019 was $966 billion, including a direct medical cost of $418 billion and an additional $548 billion in indirect and non-medical costs. (Yang et al. 2022) These indirect costs such as forced retirement, increased absenteeism at work and reduction in community participation speak to the impact of RDs not only on those affected by them, but those around them as well.

2.3 Major Healthcare Disparities in Pennsylvania

One of the major healthcare disparities in Pennsylvania affecting people with rare diseases is the unequal access to healthcare services based on income and geographical location. Individuals

living in low-income neighborhoods and rural areas often have limited access to healthcare facilities and services, leading to higher rates of preventable diseases and health problems (Department of Human Services 2021). Moreover, these individuals may not have the financial resources to afford the healthcare services they need, leading to a lack of access to essential medical care. Another significant healthcare disparity in Pennsylvania is the unequal distribution of healthcare services based on race and ethnicity. For example, African American and Hispanic individuals in Allegheny County are more likely to suffer from chronic diseases such as diabetes and heart disease and have higher mortality rates compared to their white counterparts. ("Community Indicators | Health Department | Allegheny Home," n.d.) These healthcare disparities have far-reaching consequences for the population of Allegheny County, but beyond it as well. Not only do they lead to poorer health outcomes for individuals from disadvantaged backgrounds, but they also contribute to overall healthcare costs and put a strain on the healthcare system.

2.4 The Diagnostic Odyssey of Rare Disease

The path to diagnosis for someone with a rare disease is often an extended and frustrating one, aptly nicknamed the "diagnostic odyssey" (Takahashi, Hayakawa, and Abe 2021). Unlike common illnesses with well-defined symptoms and tests, rare diseases can be incredibly challenging to pinpoint. Patients typically experience a long delay, averaging three to five years, before receiving a definitive diagnosis, if one is found at all. (Takahashi, Hayakawa, and Abe 2021)

The first step in the diagnostic process typically involves consulting primary care physicians or specialists who may attempt to identify the underlying cause of the symptoms through thorough medical history taking and physical examinations. As the initial symptoms might be vague or mimic other conditions, patients can go through a cycle of misdiagnoses and unnecessary tests. The study conducted by Gong, Li and Dong showcased the differences in perception between patients and doctors regarding medical services for rare diseases, emphasizing the need for improved communication and understanding between healthcare providers and patients (Gong, Li, and Dong 2020). Something the paper notes is that patients with rare diseases faced significantly more difficulties in receiving accurate diagnoses and accessing information related to diagnosis and treatment compared to what their providers expected for them. As the diagnostic process progresses, patients may seek out rare disease experts or specialized centers with experience in diagnosing and managing rare conditions. This journey is marked by a series of doctor visits, often to multiple specialists which can take patients months to access. (Linda N, Oliver Sum, and Yong-Jian 2019)

Even with advances in genetic technology, a significant portion of rare diseases remain undiagnosed or misdiagnosed due to the complexity of genetic and molecular mechanisms involved. Even then, for some patients receiving a diagnosis can be simply the beginning of a longer therapeutic journey, which can take years if not decades if therapies have not been developed yet. The lack of awareness surrounding rare diseases further complicates matters, leaving patients feeling unheard and dismissed(APSU Rare Diseases Impacts on Families Study group et al. 2017).

2.5 Rare Disease as a Public Health Genetics Issue

Rare Diseases collectively pose a significant public health challenge, particularly in the realm of genetics. In fact it is estimated that 80% of rare diseases have an origin that is genetic in nature. (Marwaha, Knowles, and Ashley 2022b) As a result of advancing technology and reduction in cost, genome sequencing has increasingly become a staple in diagnosing rare and undiagnosed diseases, both domestically and abroad.("Rare Diseases, Genomics and Public Health: An Expanding Intersection | Blogs | CDC," n.d.) The utilization of sequencing in clinical research has experienced rapid growth in recent years, yielding promising results. This technology has been instrumental in uncovering new causal mutations for suspected genetic diseases previously devoid of diagnosis, boasting diagnostic rates ranging from 25% to 50% in recent investigations. ("Rare Diseases, Genomics and Public Health: An Expanding Intersection | Blogs | CDC," n.d.) Moreover the past four years, the National Institutes of Health (NIH) funded Centers for Mendelian Genomics have undertaken sequencing and analysis of protein-coding sections in excess of 20,000 human genomes, identifying upwards of 740 genes likely implicated in genetic diseases.("Rare Diseases, Genomics and Public Health: An Expanding Intersection | Blogs | CDC," n.d.) As a result, receiving an accurate diagnosis via genetic testing can be vital for patients with RDs, however there are a variety of barriers that may prevent them from doing so.

The disparities that exist for access to genetic testing are often intertwined with other healthcare disparities. This can make them more inherently difficult to address as communities with limited funding may often choose to prioritize access to other healthcare services that the community may need.

One of the major disparities in access to genetic testing is the unequal distribution of genetic testing services and facilities. (Dusic et al. 2022) Individuals living in low-income areas

or rural areas may have limited access to genetic testing facilities and services, leading to a lack of access to essential genetic information. (Modell et al. 2021) Moreover, the cost of genetic testing can be prohibitively expensive for some individuals, leading to a lack of access to this important healthcare service.(Hann et al. 2017)

Another significant disparity in access to genetic testing is the unequal distribution of services based on race and ethnicity. Studies have shown that certain racial and ethnic groups are less likely to have access to genetic testing and receive lower quality care.(Hann et al. 2017) For example, African American and Hispanic individuals are less likely to be offered genetic testing and may face barriers to accessing testing services, leading to a lack of knowledge about their genetic risk factors. (McCall et al. 2021) Studies have also shown individuals in minority communities are less likely to be aware of the benefits of genetic testing and the impact it can have on their health. (Hann et al. 2017) Individuals in these communities have been historically marginalized and are often exposed to more epigenetic factors that can lead to higher incidences and poorer health outcomes for genetic based conditions compared to higher SES communities. (Carethers and Doubeni 2020) These individuals are also less likely to be represented in genetic databases as well, which may preclude them from being a part of genetic research. (Carethers and Doubeni 2020)

To address these disparities and improve access to genetic testing, it is essential to implement policies and programs that address the underlying social and economic factors that contribute to healthcare inequalities. This may include initiatives to increase funding for genetic testing services, expand access to genetic testing in underserved areas, and providing education and support to individuals and communities that are underrepresented in genetic testing.

2.6 Psychosocial Impact on Patients and Families

Patients with rare diseases face a myriad of emotional and psychological challenges, impacting their quality of life and that of their caregivers. The challenges range from feelings of isolation, alienation, and uncertainty to more serious long term emotional and psychological conditions (Dwyer, Smith, and Quinton 2019) The rarity of their conditions often means limited understanding and support from the medical community, exacerbating feelings of uncertainty and fear. Patients may struggle with feelings of frustration, anger, and sadness as they navigate a healthcare system that may not have adequate resources or knowledge to address their needs effectively.(Von Der Lippe, Diesen, and Feragen 2017) Patients may also feel disconnected from others who can't relate to their experiences, leading to feelings of loneliness and depression. Likewise, family members may also experience emotional distress as they witness their loved one's struggles and feel helpless in providing support. (Von Der Lippe, Diesen, and Feragen 2017)Patients and caregivers also face a range of challenges in managing a rare condition, including the seriousness of the illness, dealing with the emotional toll, and uncertainty about the future. (Mooney, Graham, and Watts 2019) Individuals with rare diseases often struggle to perform important day-to-day tasks, experience concerns about disease progression and personal safety, and adopt different strategies to cope with stressful circumstances. (Dwyer, Smith, and Quinton 2019)

Despite these challenges, many patients and families affected by rare diseases demonstrate remarkable resilience and strength. Furthermore, patients with rare diseases are identified as 'Internet power-users', indicating their reliance on online communities for emotional support and learning from others in similar situations. (Von Der Lippe, Diesen, and Feragen 2017) They often form tight-knit communities and support networks with others facing similar struggles, providing

invaluable emotional support and understanding. (Von Der Lippe, Diesen, and Feragen 2017)Through advocacy and awareness efforts, they strive to educate others about their conditions and push for better resources and support for those living with rare diseases. These networks can look different patient to patient and can be a mixture of a patient's family, friends, provider guided support groups and communities of fellow patients with similar conditions.

The experiences and psychosocial stresses of patients with rare diseases need to be explored through qualitative studies to better understand their emotional and psychological challenges and tailor support accordingly (Chiang et al., 2018). It's essential to recognize and address the significant psychosocial impacts that rare diseases can have on patients and their families to ensure they receive the holistic care and support they need to navigate their journey effectively

2.7 Healthcare Policy and Initiatives

Currently in the United States, there are two major laws that benefit people with rare diseases. The Orphan Drug Act (ODA), enacted in the United States in 1983, stands as a pivotal piece of legislation aimed at addressing the unmet medical needs of individuals afflicted with rare diseases. (Roberts AD, 2024) Prior to its implementation, pharmaceutical companies often hesitated to invest in research and development for treatments targeting rare diseases due to the perceived lack of profitability stemming from small patient populations.(Roberts AD, 2024) Consequently, many rare conditions remained untreated, leaving patients grappling with significant health challenges. It incentivizes pharmaceutical companies to develop drugs for rare conditions by offering financial rewards like tax credits and market exclusivity. This exclusivity

allows the company to recoup development costs without competition for a set period, making research for smaller patient populations more financially attractive. (Roberts AD, 2024)

Since its enactment, numerous orphan drug designations have been granted by the U.S. Food and Drug Administration (FDA), resulting in the approval of a plethora of drugs specifically addressing rare conditions. These treatments have significantly improved the quality of life for patients, often providing much-needed relief and, in certain instances, extending their life expectancy.(Bogart et al. 2022) Furthermore, the Orphan Drug Act has catalyzed innovation in rare disease research, prompting pharmaceutical companies to recognize the potential value in developing treatments for these underserved patient populations. (Roberts AD, 2024)It has also fostered collaborations among researchers, patient advocacy groups, and industry stakeholders, facilitating a more comprehensive approach to tackling the unique challenges posed by rare diseases.

Despite the various benefits the Orphan Drug Act has provided to patients, advocates have been critical of some of its aspects as well, particularly the resulting exorbitant costs of orphan drugs, contradicting its original intent.(Herder 2017) This issue stems partly from the extended market exclusivity granted to drug developers by the FDA, preventing approval of additional applications for the same disease indication during this period. Critics argue that the incentivization process has led pharmaceutical companies to disproportionately focus on orphan drug development, exploiting market exclusivity to set high prices, limiting treatment options for rare disease patients (Herder 2017). An example was shown in a drug developed for Gaucher disease, affecting around 2,000 individuals annually in the U.S., which initially carried a staggering cost of nearly $400,000 per year per adult patient. (Roberts AD, 2024) Orphan drugs have become a significant portion of pharmaceutical sales, with substantial returns on investment,

challenging the notion that rare disease drug development lacks profitability. However, concerns persist over patient access and affordability, as patients may end up paying twice for their treatment, both through public funding during drug development and later during treatment.(Herder 2017)

The other major piece of legislation affecting people with rare diseases is The Rare Disease Act of 2002, which built upon the framework created by the Orphan Drug act. It established the Office of Rare Diseases (ORD) within the National Institutes of Health (NIH). (Khosla and Valdez 2018)The ORD acts as a central hub for research initiatives and information dissemination related to rare diseases. It also allocates dedicated funding for research on rare disease diagnosis, treatment, and interventions. Through initiatives such as the Rare Diseases Clinical Research Network (RDCRN) the act has facilitated the discovery of new insights into the underlying mechanisms of rare diseases and the development of innovative treatment approaches.(Khosla and Valdez 2018) The passing of the Rare Disease act has spurred increased awareness and advocacy efforts surrounding rare diseases, leading to greater support and resources for affected individuals and their families.

The state of Pennsylvania has been working to address the needs of patients with rare diseases through various healthcare policies and initiatives. While there are no overarching policies specifically targeted at rare diseases, the Pennsylvania Department of Health has acknowledged these difficulties. The Rare Disease Advisory Council (PARDAC), established in 2017, works to improve the lives of Pennsylvanians affected by rare diseases through collaborative efforts through various stakeholders. The Council's first preliminary report published in 2017 identified six key goals, including improved access to diagnosis, treatment, and insurance coverage. These goals

remain a work in progress. Senate Bill 36, awaiting action, aims to expand insurance coverage for metabolic disorders, demonstrating continued legislative interest.

2.8 Existing Literature and Research Gaps

The barriers faced by patients with rare diseases in accessing healthcare services, obtaining accurate diagnoses, specialized care, and affordable treatments are multifaceted and require a comprehensive understanding of the demographic characteristics of affected populations, the distribution of rare diseases across different demographic groups, and the socioeconomic factors influencing healthcare access and outcomes. By collecting data on these different factors, stakeholders can begin to understand the major factors that are putting these barriers in place and can give insight as to key areas they can focus their time and resources on to reduce them. Due to the complex nature of collecting data around these key points, the existing literature is sparse in terms of real data for researchers and advocates to utilize. Therefore, further research focusing on the demographic characteristics and distribution of rare diseases in specific populations, including Pennsylvania, would be valuable to comprehensively address the challenges faced by patients with rare diseases in accessing healthcare services. The survey that has been conducted by PARDAC addresses this need and by reviewing the information collected, it can begin to address this gap in literature that currently exists.

2.9 Public Health Significance

Understanding the experiences of people with rare diseases in Pennsylvania carries significant weight for public health, aligning directly with its core functions and essential services. (“CDC - 10 Essential Public Health Services - CSTLTS,” n.d.) Public health's first function revolves around identifying and assessing community health needs. This survey looks into the often-unheard experiences of a diverse population with both disparate and similar challenges, providing crucial data on their unique challenges and unmet needs. This information helps public health officials target resources and interventions effectively, ensuring no population falls through the cracks.

Informed policymaking is another core function of public health, and this survey offers valuable lessons for shaping policies relevant to rare diseases. Understanding the barriers individuals face in accessing healthcare, navigating insurance complexities, and encountering social stigma informs policy changes that address these specific needs. This can lead to improved access to care, financial assistance, and support systems, directly impacting the well-being of individuals with rare diseases.

Ensuring the conditions for everyone to achieve optimal health is the third core function. (“CDC - 10 Essential Public Health Services - CSTLTS,” n.d.)This study contributes to the field by shedding light on the specific factors hindering the health and well-being of individuals with rare diseases. By understanding their concerns, public health officials can develop targeted interventions to promote access to preventive care, early diagnosis, and appropriate treatment, ultimately improving health outcomes for this population.

Beyond these core functions, the survey aligns with several of the ten essential public health services. Engaging individuals with rare diseases in the research process itself fosters

collaboration and ensures their voices are heard. This builds trust and empowers the community of families and individuals with rare diseases to advocate for their needs, a crucial aspect of mobilizing partnerships. The survey's findings can also be used to raise awareness about rare diseases among the public, healthcare professionals, and policymakers, promoting understanding and reducing stigma. This improved communication empowers individual.ls with rare diseases to advocate for themselves and access necessary support. Examining the experiences of individuals with rare diseases reveals gaps and limitations in the current healthcare system. This information can be used to improve the quality of care by advocating for better access to specialists, tailored treatment plans, and culturally competent communication as well.

3.0 Data and Methods

3.1 Data Description and Collection

In 2020, the Pennsylvania Rare Disease Advisory Council (PARDAC) initiated a groundbreaking Rare Disease Needs Assessment Survey aimed at comprehensively understanding the needs and challenges faced by individuals, families, and caregivers affected by rare diseases across the Commonwealth of Pennsylvania. This pioneering effort marked the first-of-its-kind campaign within the state and was among the earliest initiatives of its kind nationally. The survey was meticulously designed to provide a platform for rare disease patients to share their personal journeys, focusing on critical aspects such as diagnosis, treatment experiences, healthcare accessibility, quality of life, and the availability of social support networks.

The study aimed to capture insights from a diverse spectrum of rare diseases, ensuring a broad representation of patient experiences to offer a holistic view of the rare disease landscape in Pennsylvania. Participants included individuals directly impacted by rare diseases, parents, or guardians of minors with rare conditions, as well as advocates advocating for improved rare disease care and support services. Following rigorous planning and beta-testing phases, the PA Rare Disease Needs Assessment Survey received approval from the Western Institutional Review Board (WIRB) and was administered through the HIPAA-compliant Survey Monkey platform. Notably, additional IRB clearance from the University of Pittsburgh was deemed unnecessary for this thesis project.

The internet-based survey was conducted in two phases, with the initial phase running from September 23, 2020, to December 31, 2022. Due to challenges posed by the COVID-19 pandemic

and funding limitations, the Council opted for a relaunch in February 2022, which concluded on December 31, 2022. While the survey itself was not offered in Spanish, in order to maximize participation and outreach, a bilingual (English/Spanish) awareness campaign titled "While You Wait ©" was spearheaded by The Cullari Group, a Pennsylvania-based communications firm. This strategic campaign engaged a wide array of rare disease stakeholders, including hospitals, caregivers, and support organizations throughout Pennsylvania, utilizing social media platforms such as Facebook, X (formerly Twitter), and Instagram to target patients during their wait times for medical appointments.

The outreach efforts yielded a robust response from across Pennsylvania, with 62 out of the state's 67 counties contributing responses from rare disease patients or their caregivers. Emphasizing inclusivity, the Council employed diverse communication channels and intentionally avoided randomization in data collection to ensure a representative sampling of rare disease experiences. Post-analysis, the survey garnered a total of 1,222 responses after excluding blank submissions. These responses encapsulated insights into over 660 distinct rare diseases and variations, with most respondents (75%) reporting a single rare disease and a notable 15% indicating multiple rare disease diagnoses.

3.2 Methods

This thesis aims to illuminate the distinctive challenges pertinent to this specific population within Pennsylvania by conducting a thorough quantitative analysis of the survey data from various questions collected by PARDAC. Ideally these quantitative findings will contribute to a comprehensive review of rare disease patients' experiences in Pennsylvania and provide

valuable insights for healthcare providers, policymakers, and patient advocacy organizations to better understand and address the needs of this population.

The data included in this study was reviewed and cleaned by members of PARDAC and the author of this paper to ensure that issues such as improper labeling of conditions would not contribute to analysis results. The quantitative analysis and corresponding graphs were created using the statistical software program Stata 17.0. Statistical analyses performed were chi-square tests of variables in the survey data to determine if there significant relationships found. The corresponding variables that were analyzed by chi-square test are included in table 1 below. To ensure that the data met the assumptions of the chosen tests, quality tests were conducted on factors such as independence of observations.

Variable 1 in Chi Square Test	Variable 2 in Chi Square Test
Number of Incorrect Diagnoses	Time to Receive a Final Diagnosis
Age of Respondents	Amount Spent on Healthcare Annually
Reported County of Residence	Diagnostic Time In Months
Type of Rare Disease (Categorized)	Diagnostic Time In Months
Type of Rare Disease (Categorized)	Perception of Timely Diagnosis
Respondents Gender Identity	Time to Receive a Final Diagnosis
Respondents Gender Identity	Perception of Timely Diagnosis
Perception of Timely Diagnosis	Insurance Type
Perception of Timely Diagnosis	Number of Providers Seen to receive a Diagnosis
Amount Spent on Healthcare Annually	Respondents Gender Identity
Amount Spent on Healthcare Annually	Respondents Racial Identity
Amount Spent on Healthcare Annually	Insurance Type

Table 1 Chi Square Tests Conducted

4.0 Results

4.1 Chi Square Tests

In this segment, the chi-square test is employed to evaluate potential associations between categorical variables relevant to individuals' experiences with rare diseases. Through chi-square tests, we aim to identify significant associations, highlighting potential disparities in healthcare access and outcomes.

Key
frequency *row percentage*

Diagnostic Time (In Months)	Incorrect Diagnoses					Total
	0	1.5	3.5	5.5	6.5	
1.5	138	67	10	1	0	216
	63.89	31.02	4.63	0.46	0.00	100.00
4.5	38	57	17	3	3	118
	32.20	48.31	14.41	2.54	2.54	100.00
9	34	61	15	1	1	112
	30.36	54.46	13.39	0.89	0.89	100.00
18	32	58	34	6	2	132
	24.24	43.94	25.76	4.55	1.52	100.00
30	14	37	33	10	6	100
	14.00	37.00	33.00	10.00	6.00	100.00
54	11	27	14	10	4	66
	16.67	40.91	21.21	15.15	6.06	100.00
60	24	69	101	34	85	313
	7.67	22.04	32.27	10.86	27.16	100.00
Total	291	376	224	65	101	1,057
	27.53	35.57	21.19	6.15	9.56	100.00

Pearson chi2(24) = 446.6641 Pr = 0.000

Table 2 Chi Square Test - Number of Incorrect Diagnoses vs Time Taken To Recieve a Final Diagnosis

Table 2 shows the first relationship analyzed using Stata, which was the association between the number of incorrect diagnoses respondents reported and the overall time they took to receive a final diagnosis. The sample size comprised 1057 responses, with diagnostic time response intervals ranging from 1.5 to 60 months. The chart key includes the number of incorrect diagnoses reported and the row percentage, which represents the proportion of incorrect diagnoses in each time interval relative to the total incorrect diagnoses. The chi-square test revealed a statistically significant relationship (p-value = 0.000) between diagnostic time intervals and incorrect diagnoses, indicating that the time taken to receive a final diagnosis was associated with the number of incorrect diagnoses reported.

Key
frequency *row percentage*

Age	Annual spending						Total
	2000	7500	15000	38000	65000	100000	
.5	3 60.00	2 40.00	0 0.00	0 0.00	0 0.00	0 0.00	5 100.00
3	34 66.67	9 17.65	5 9.80	1 1.96	0 0.00	2 3.92	51 100.00
8	44 73.33	11 18.33	2 3.33	2 3.33	1 1.67	0 0.00	60 100.00
15	65 61.32	24 22.64	12 11.32	1 0.94	2 1.89	2 1.89	106 100.00
25	40 48.19	31 37.35	10 12.05	1 1.20	1 1.20	0 0.00	83 100.00
35	68 54.84	37 29.84	16 12.90	3 2.42	0 0.00	0 0.00	124 100.00
45	60 50.42	44 36.97	11 9.24	3 2.52	1 0.84	0 0.00	119 100.00
55	74 57.81	41 32.03	11 8.59	1 0.78	1 0.78	0 0.00	128 100.00
63	44 61.97	21 29.58	3 4.23	3 4.23	0 0.00	0 0.00	71 100.00
70	64 68.09	23 24.47	5 5.32	1 1.06	1 1.06	0 0.00	94 100.00
Total	496 58.98	243 28.89	75 8.92	16 1.90	7 0.83	4 0.48	841 100.00

Pearson chi2(45) = 58.9680 Pr = 0.079

Table 3 Chi Square Test - Age of Respondents and Amount Spent Annually

As shown in Table 3, the chi-square test results looks to see if there is a potential relationship between age and annual spending for healthcare costs among individuals with rare diseases. The total sample size used for the analysis was 841 individuals who responded to the question regarding annual spending in the survey. The analysis involved tabulating frequencies of individuals across various age groups ranging from 6 months to 70 years and different annual spending categories spanning from 2000 to 100000 dollars. This relationship does not reach statistical significance at the conventional significance level of 0.05 ($p = 0.079$).

Diagnostic Time (In Months)	Rural/Urban 0	1	Total
1.5	61	153	214
4.5	29	89	118
9	35	76	111
18	36	97	133
30	25	71	96
54	12	51	63
60	89	216	305
Total	287	753	1,040

Pearson chi2(6) = 4.3093 Pr = 0.635

Table 4 Chi Square Test Diagnostic Time in Months by Reported County Of Residence

A chi-square analysis of diagnostic time in months by respondent's reported county (rural or urban) (Table 4) reveals no statistically significant difference. As shown in table 5, the chi-square test statistic (4.31) with a high p-value (0.64) indicates that the observed distribution of diagnostic times across these locations could be due to chance.

Additionally, the relationship between type of rare disease a patient may have, and the time taken to receive a diagnosis was examined. One analysis included all respondents, in recognition that many patients will go through years of a rare disease diagnostic odyssey without a confirmed or finalized diagnosis, regardless of diagnosis with a total sample size of 1,061. For additional comparison the other analysis excluded respondents without a confirmed diagnosis, with a total sample size of 1,037. For the purposes of comparison, for this dataset the respondent's reported primary diagnoses were categorized into five different groups utilizing ChatGPT, an online AI assistant tool. Rather than manually assign each disease to each group, the chatbot took each respondents primary diagnosis and assigned it into five groups (auto immune disorders,

chromosomal disorders, neurological conditions, rare genetic conditions, and a general “other” category).

Diagnostic Time (In Months)	DIseaseCategory					
	Autoimm..	Chromos..	Neurolo..	Other D..	Rare Ge..	Total
1.5	37	36	25	74	42	214
4.5	26	18	12	46	15	117
9	21	12	20	35	21	109
18	24	18	23	45	17	127
30	22	19	14	27	16	98
54	7	12	13	25	8	65
60	60	48	41	97	61	307
Total	197	163	148	349	180	1,037

Pearson chi2(24) = 22.4121 Pr = 0.555

Table 5 Chi Square Test Diagnostic Time vs Rare Disease Categories

Diagnostic Time (In Months)	DIseaseCategory						
	Autoimm..	Chromos..	Neurolo..	No Diag..	Other D..	Rare Ge..	Total
1.5	37	36	25	3	74	42	217
4.5	26	18	12	2	46	15	119
9	21	12	20	3	35	21	112
18	24	18	23	6	45	17	133
30	22	19	14	2	27	16	100
54	7	12	13	1	25	8	66
60	60	48	41	7	97	61	314
Total	197	163	148	24	349	180	1,061

Pearson chi2(30) = 26.7026 Pr = 0.639

Table 6 Chi Square Test Diagnosis Time vs Rare Disease Category (Including No Diagnosis)

In both analyses (tables 5 and 6), the chi-square test results did not show a statistically significant association between diagnostic time and disease category (p-value > 0.05).

Key

frequency
column percentage

Timely Diagnosis	DIseaseCategory						
	Autoimm..	Chromos..	Neurolo..	No Diag..	Other D..	Rare Ge..	Total
agree	96	62	55	7	141	80	441
	48.00	38.04	36.67	4.00	40.06	43.96	36.09
disagree	26	21	33	5	55	24	164
	13.00	12.88	22.00	2.86	15.62	13.19	13.42
not applicable	5	10	11	151	25	13	215
	2.50	6.13	7.33	86.29	7.10	7.14	17.59
somewhat agree	52	49	39	8	90	54	292
	26.00	30.06	26.00	4.57	25.57	29.67	23.90
somewhat disagree	21	21	12	4	41	11	110
	10.50	12.88	8.00	2.29	11.65	6.04	9.00
Total	200	163	150	175	352	182	1,222
	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Pearson chi2(20) = 686.6616 Pr = 0.000

Table 7 Chi Square Test Perception of Timely Diagnosis vs Rare Disease Category

Table 7 looks between the relationship between the categories of respondent's reported diagnoses shown in tables 6 and 7 and their perceptions of receiving timely testing and treatment after diagnosis, with a total sample size of 1222. The results revealed a statistically significant association between these variables, with a Pearson chi-square statistic of 686.6616 and a p-value of 0.000, indicating a strong link.

Gender	Diagnostic Time (In Months)							
	1.5	4.5	9	18	30	54	60	Total
female	137	84	75	84	65	48	236	729
male	76	35	35	46	35	17	72	316
non-binary	2	0	0	2	0	0	2	6
prefer not to answer	2	0	1	0	0	0	3	6
Total	217	119	111	132	100	65	313	1,057

Pearson chi2(18) = 22.0082 Pr = 0.232

Table 8 Chi Square Test Respondents Gender Identity vs Reported Diagnostic Time

The chi-square test results for gender identity and diagnostic time in months from Table 8 with a sample size of 1057 shows that there is no significant association between these two variables ($p = 0.232$). It is important to note here that individuals who identified as transgender were combined with their respective gender identities due to a lack of responses. This suggests that the distribution of diagnostic time in months does not vary significantly based on the reported gender identity of the respondents in the dataset.

Gender	Timely Diagnosis					
	agree	disagree	not app..	somewha..	somewha..	Total
female	280	120	131	202	86	819
male	156	39	66	86	24	371
non-binary	1	2	2	2	0	7
prefer not to answer	1	3	8	1	0	13
Total	438	164	207	291	110	1,210

Pearson chi2(12) = 37.9621 Pr = 0.000

Table 9 Chi Square Test Respondents Gender Identity vs Perception of Timely Diagnosis

The chi-square test results shown in table 9 examining the relationship between respondents' gender and their perception on timely diagnosis for rare diseases with a sample size

of 1210 show a statistically significant association (Pearson chi-square (12) = 37.9621, $p < 0.001$). This finding indicates that there is an association between gender identity and how respondents perceive the timeliness of their diagnosis.

The next chi square tests conducted looked at the relationship between respondents type of healthcare insurance (combined into private and public categories) and their perceptions of a timely diagnosis.

Key
frequency *column percentage*

Timely Diagnosis	private_insurance 0	1	Total
agree	140 37.74	301 45.33	441 42.61
disagree	69 18.60	95 14.31	164 15.85
not applicable	10 2.70	18 2.71	28 2.71
somewhat agree	103 27.76	189 28.46	292 28.21
somewhat disagree	49 13.21	61 9.19	110 10.63
Total	371 100.00	664 100.00	1,035 100.00

Pearson chi2(4) = 9.6508 Pr = 0.047

Table 10 Chi Square Test Timely Diagnosis and Private Insurance

Key
frequency *column percentage*

Timely Diagnosis	public_insurance 0	1	2	Total
agree	184 42.40	236 43.07	21 39.62	441 42.61
disagree	68 15.67	84 15.33	12 22.64	164 15.85
not applicable	9 2.07	17 3.10	2 3.77	28 2.71
somewhat agree	125 28.80	155 28.28	12 22.64	292 28.21
somewhat disagree	48 11.06	56 10.22	6 11.32	110 10.63
Total	434 100.00	548 100.00	53 100.00	1,035 100.00

Pearson chi2(8) = 3.7947 Pr = 0.875

Table 11 Chi Square Test Timely Diagnosis and Public Insurance

In table 10, the analysis compares the relationship between private insurance status and perceived timely diagnosis among 1,035 respondents. The Pearson chi-square test with 4 degrees of freedom suggests a statistically significant relationship (chi-square = 9.6508, p = 0.047) between having private insurance and perceptions of timely diagnosis.

In Table 11, the analysis examines the association between public insurance status and perceived timely diagnosis among 1,035 respondents. The chi-square test with 8 degrees of freedom reveals no statistically significant relationship (chi-square = 3.7947, p = 0.875) between public insurance status and perceptions of timely diagnosis.

Table 12 looks at how patients with rare diseases perceive the timeliness of their diagnosis correlates with the number of healthcare providers they consulted in the process. The number of healthcare providers ranged from 1-2 (shown as 1.5) all the way to 7+ providers. With a sample

size of 1067, there was a statistically significant relationship (p=0.0000) shown between patients' perceptions of receiving a timely diagnosis and the number of providers that they saw.

Key
frequency *column percentage*

Timely Diagnosis	HealthCare Providers 1.5	3.5	5.5	7.5	9.5	11	Total
agree	147 62.55	151 41.94	63 36.42	24 26.09	9 24.32	47 27.65	441 41.33
disagree	14 5.96	43 11.94	29 16.76	18 19.57	10 27.03	50 29.41	164 15.37
not applicable	10 4.26	30 8.33	10 5.78	4 4.35	1 2.70	9 5.29	64 6.00
somewhat agree	53 22.55	96 26.67	55 31.79	31 33.70	11 29.73	42 24.71	288 26.99
somewhat disagree	11 4.68	40 11.11	16 9.25	15 16.30	6 16.22	22 12.94	110 10.31
Total	235 100.00	360 100.00	173 100.00	92 100.00	37 100.00	170 100.00	1,067 100.00

Pearson chi2(20) = 108.8716 Pr = 0.000

Table 12 Chi Square Test Perception of Timely Diagnosis and Number of Providers Seen

Additionally, the relationship between factors like respondents' racial identity, gender identification, and type of health insurance and how they impact their reported annual healthcare expenditures incurred was examined in tables 13, 14 and 15. Respondents annual spending for these tests was represented categorically depending on the range they responded with (i.e. 2000 = 0-2000 dollars spent annually, 7500= 2000 to 7500 dollars spent annually, etc.) with the final category indicating spending $100,000 or more. As before, respondents who identified as transgender were grouped with their respective gender identities. The racial identities included were "American Indian or Alaska Native", "Asian", "Black or African American", "Hispanic or

Latino", "Middle Eastern or North African", "Native Hawaiian or other Pacific Islander" and "White".

Key
frequency *column percentage*

Spending	Gender female	male	non-bin..	prefer ..	Total
2000	330 57.89	160 62.02	4 66.67	0 0.00	494 58.95
7500	169 29.65	70 27.13	2 33.33	1 25.00	242 28.88
15000	56 9.82	16 6.20	0 0.00	3 75.00	75 8.95
38000	10 1.75	6 2.33	0 0.00	0 0.00	16 1.91
65000	5 0.88	2 0.78	0 0.00	0 0.00	7 0.84
100000	0 0.00	4 1.55	0 0.00	0 0.00	4 0.48
Total	570 100.00	258 100.00	6 100.00	4 100.00	838 100.00

Pearson chi2(15) = 35.6847 Pr = 0.002

Table 13 Chi Square Test Annual Spending and Respondents' Gender Identity

Key
frequency *row percentage*

Spending	race							
	America..	Asian	Black o..	Hispani..	Middle ..	Native ..	White	Total
2000	3	2	6	4	2	0	474	491
	0.61	0.41	1.22	0.81	0.41	0.00	96.54	100.00
7500	2	7	4	2	0	1	223	239
	0.84	2.93	1.67	0.84	0.00	0.42	93.31	100.00
15000	0	1	0	1	0	0	71	73
	0.00	1.37	0.00	1.37	0.00	0.00	97.26	100.00
38000	0	0	0	1	0	0	14	15
	0.00	0.00	0.00	6.67	0.00	0.00	93.33	100.00
65000	0	0	0	0	0	0	6	6
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	100.00
100000	0	0	0	0	0	0	4	4
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	100.00
Total	5	10	10	8	2	1	792	828
	0.60	1.21	1.21	0.97	0.24	0.12	95.65	100.00

Pearson chi2(30) = 20.6911 Pr = 0.897

Table 14 Chi Square Test Annual Spending and Respondents' Racial Identity

Key
frequency *column percentage*

Spending	insurancetype					
	Employer	Medicaid	Medicare	No Insu..	Self Pu..	Total
2000	166	190	109	4	18	487
	54.79	65.29	56.77	66.67	51.43	58.89
7500	97	71	62	0	8	238
	32.01	24.40	32.29	0.00	22.86	28.78
15000	30	26	13	1	5	75
	9.90	8.93	6.77	16.67	14.29	9.07
38000	6	3	4	0	3	16
	1.98	1.03	2.08	0.00	8.57	1.93
65000	3	0	3	0	1	7
	0.99	0.00	1.56	0.00	2.86	0.85
100000	1	1	1	1	0	4
	0.33	0.34	0.52	16.67	0.00	0.48
Total	303	291	192	6	35	827
	100.00	100.00	100.00	100.00	100.00	100.00

Pearson chi2(20) = 59.9252 Pr = 0.000

Table 15 Chi Square Test Annual Spending and Type of Insurance

With sample sizes of 827 to 838, the chi square tests indicated that there were statistically significant relationships between respondents annual spending and their gender identity and type of insurance but no significant relationship with their race.

4.2 Discussion

4.2.1 Demographics

There were 1222 respondents to this survey, which reflects the efforts of PARDAC to gather data from patients across the state to capture the full breadth of experiences of patients with rare diseases. This data shows that the respondents are overwhelmingly from Urban Counties (73.3 %). Most respondents indicated only one primary diagnosis (74.5, %); however, a notable number of respondents had 2 (15.3 %) or even 3 (10.2 %) different diagnoses. This also corresponds to the reported challenges many respondents face in receiving a formal diagnosis, let alone secondary or tertiary diagnoses after the fact. Many respondents relied on private forms of commercial health insurance (41 %) rather than government funded sources such as Medicaid or Medicare (14.6 %).

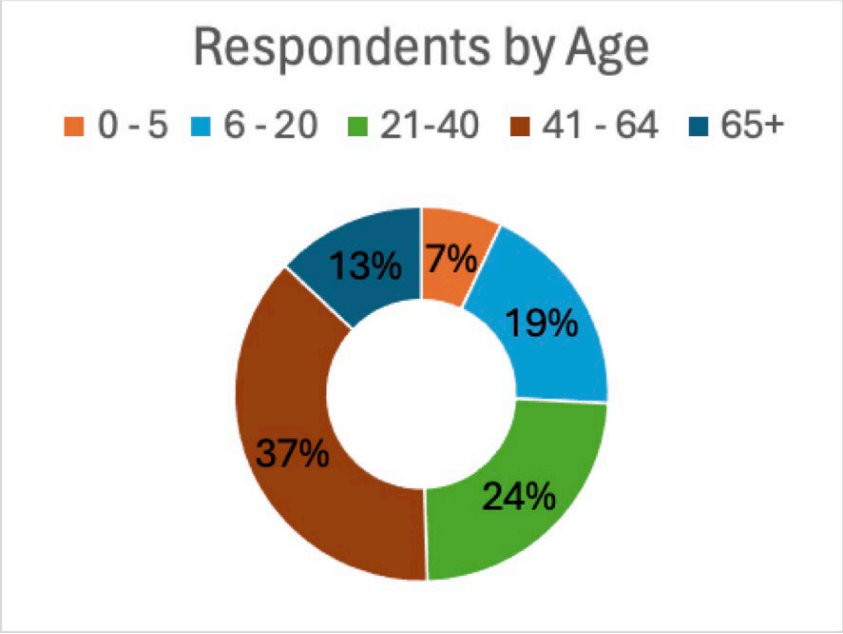

Figure 1 Age of Respondents

Figure1 shows the distribution of respondents by Age. The graph categorizes age ranges as follows: "Birth to 12 months" and "1 to 5 years" are combined into the group "0 to 5 years," "6 to 10 years" and "11 to 20 years" are merged into "6 to 20 years," "21 to 30 years" and "31 to 40 years" form "21 to 40 years," and finally, "41 to 50 years," "51 to 60 years," and "61 to 64 years" are grouped together as "41 to 64 years." There is a relatively even distribution of respondents with most falling within the adult ages of 21 to 64. This large range will be useful for looking at the impacts of age of diagnosis on patients and their subsequent diagnostic odyssey. While the noted number of respondents does not represent the whole of patients with rare diseases in Pennsylvania, their ages do fall in line with the average age distribution of the state as provided by the most recent US Census, respectively at 5% for 0-5, 17% for 5-20, 26% for 20-40, 31% for 41-64 and 21 % for 65 and older (“Census Profile: Pennsylvania,” n.d.).

The following two figures also adapted from PARDAC data represent the responses to the following questions on the survey, "What is the race/ethnicity of the person with the rare disease?" and "What is the gender identification of the person with the rare disease?"

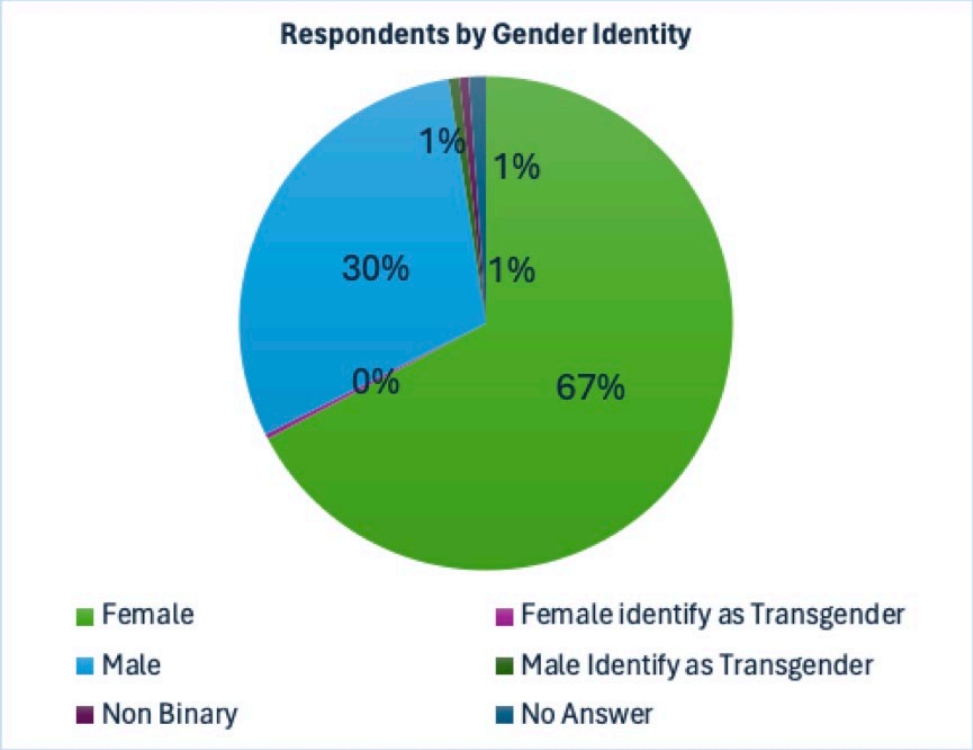

Figure 2 Gender Identification of Respondents

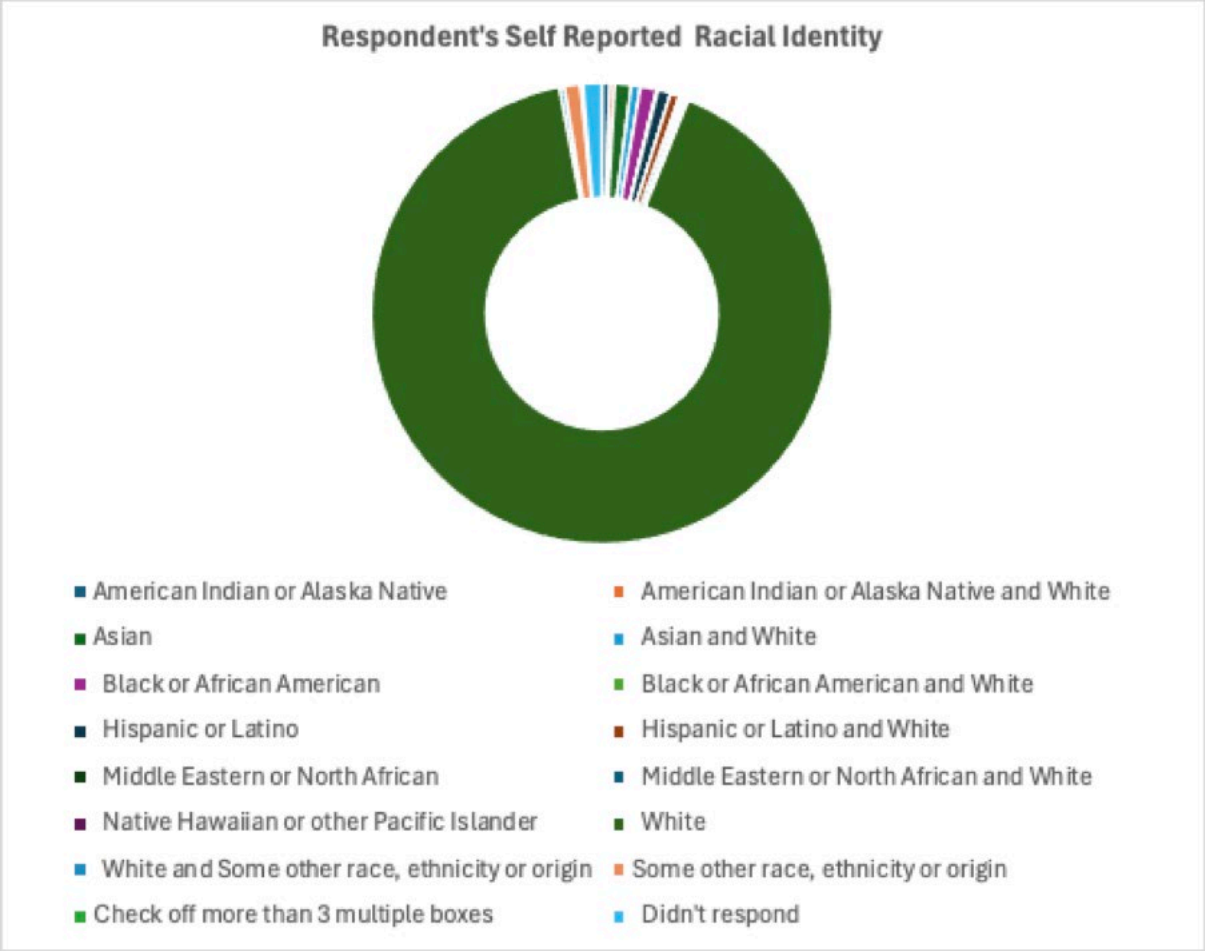

Figure 3 Respondents Self Reported Racial Identity

Figure 2 shows that the respondents slightly skewed as identifying as female, with 29.7% identifying as Male and 2.5% of respondents identifying as Transgender, non-binary, or other genders. This is closer to the reported gender make-up of the state as whole, which is showing to be a near even split gender wise according to US census data and may be more representative of the rare disease population of the state ("Census Profile: Pennsylvania," n.d.). Figure 3, showing respondents reported race or ethnicity, indicates that many respondents identified as White at 90%. This is higher than the state census reported average of 80% and indicates that minority groups such as individuals who identify as Black or African American, Asian, Middle Eastern, Hispanic

or Latino may be underrepresented in this survey data ("Census Profile: Pennsylvania," n.d.). This could be a potential area of interest for analysis, as exploring the experiences of people with rare diseases who also identify as minorities could provide insight to what specific barriers may be affecting this group of respondents in addition to the systemic barriers they face as people with rare diseases.

4.2.2 Chi Square Tests Discussion

The chi-square tests conducted provide valuable insights into various aspects of rare disease patients' experiences, shedding light on potential disparities and factors influencing their diagnostic journey and healthcare perceptions.

In Table 2, The chi-square test revealed a significant relationship (p-value = 0.000) between diagnostic time intervals and the number of incorrect diagnoses, indicating that the accuracy of diagnoses significantly impacts the duration of the diagnostic process, particularly for rare disease patients. The row percentages highlight the proportion of incorrect diagnoses within each time interval: 31.02% reported 1.5 incorrect diagnoses at 1.5 months or less, 48.31% reported 1.5 incorrect diagnoses at 4.5 months, 54.46% reported 1.5 incorrect diagnoses at 9 months, and 32.27% reported 3.5 incorrect diagnoses at 60 months or greater.

These findings have implications for patients with rare diseases, as longer diagnostic times are associated with higher rates of incorrect diagnoses. Such delays can lead to patients experiencing potential health complications and delays in receiving appropriate treatment. For rare disease patients, the diagnostic process is already fraught with complexities due to the rarity and often ambiguous nature of their conditions. The correlation highlighted in the data underscores the additional burden these patients may experience when their diagnostic journey is prolonged.

Understanding this associations is crucial for healthcare professionals involved in the care of rare disease patients. It underscores the importance of implementing efficient diagnostic protocols and leveraging advanced technologies such as genetic testing and artificial intelligence to expedite accurate diagnoses. Additionally, it emphasizes the need for heightened awareness among healthcare providers regarding the unique challenges faced by rare disease patients, urging them to adopt a proactive and collaborative approach to diagnosis and treatment planning.

The second chi-square test (Table 3) explored the relationship between individuals' ages and annual spending on rare disease care. Looking at this relationship is useful as this can help determine if there's a significant relationship between age and the amount of money spent on rare disease care annually. For example, it may reveal whether older individuals tend to incur higher costs due to increased healthcare needs associated with aging or if younger individuals face significant financial burdens early in life due to their rare diseases. It can also shed light on the long-term financial implications of managing rare diseases and how they evolve over time, considering factors like disease progression, treatment effectiveness, and changing healthcare needs.

Upon examining the table of frequencies, a noticeable trend emerges where younger age groups, particularly those between infancy to 15 years, show higher frequencies in lower annual spending categories ranging from 2000 to 15000 dollars However, as age increases within these categories, the frequencies of annual spending gradually decline. Conversely, in the higher annual spending categories of 38000 to 100000 dollars, there is greater variability across different age groups, indicating that some age groups have higher frequencies in these categories compared to others. While these observations suggest a potential association between age and annual spending among individuals with rare diseases, the obtained p-value of 0.079 from the chi-square test

indicates that this association does not achieve statistical significance based on the chosen significance level of 0.05.

Next, the analysis of diagnostic time across rural and urban areas using the chi-square test revealed no statistically significant difference (Table 4). This suggests that location may not be a major factor influencing diagnostic time for rare disease patients in Pennsylvania. However, other variables were not examined such as where specific testing centers or health care centers are located throughout the state (or potentially across state boarders) in context to where patients live. In addition to this, most patients reported being in urban counties, indicating potential bias in these survey results, as many healthcare systems tend to be in more densely populated urban areas. These aforementioned factors highlight the complexity of factors affecting diagnostic timelines in rare diseases.

The chi-square tests examining the relationship between rare disease categories and diagnostic time (Tables 5 and 6) did not show statistically significant associations, emphasizing the diverse and complex nature of rare diseases' diagnostic journeys. However, the significant association found between rare disease categories and perceptions of timely diagnosis shown originally in table 7 and below in table 17 ($p < 0.001$) is noteworthy. Table 16 shows respondents by disease category and if they agreed (including slightly agreed) or disagreed (including slightly disagreed) with a timely diagnosis.

Disease Category	Agreed	Disagreed
Autoimmune Diseases	148(74.00%)	47(26.00%)
Chromosomal Abnormalities	111(68.10%)	42(31.90%)
Neurological Disorders	94(62.67%)	45(37.33%)
No Diagnosis	15(85.71%)	2(14.29%)
Other Diseases	231(65.63%)	121(34.37%)
Rare Genetic Disorders	134(73.63%)	48(26.37%)

Table 16 Chi Square Results Disease Category and Perception of Timely Diagnosis

This table (Table 16) indicates that individuals' perceptions of timely testing and treatment post-diagnosis vary significantly across different rare disease categories. Across most disease categories, the percentage of individuals who agreed that they had a timely diagnosis (including somewhat agree) is higher than those who disagreed (including somewhat disagree), indicating a general trend of more positive timely diagnosis experience, which could lead to better health outcomes for these patients**.** The combined agreement rates of 73.63% and 68% for genetic disorders including chromosomal abnormalities suggests a relatively higher satisfaction or success rate in timely diagnoses compared to other non-genetic disease categories such as neurological disorders or other diseases**.** This may speak to the advances that have been made in recent years regarding genetic technology that have led to increased diagnoses and better health outcomes for patients with genetic conditions. It is possible that patients with rare diseases that are non-primarily genetic in nature do not share this experience.

This analysis is also based on information that ChatGPT utilized to put each patient's individual diagnosis into the categories it created, with five being chosen for statistical analysis purposes. While the results were checked for accuracy in terms of how it categorized the results, it is possible that there may be overlap in some of the categories depending on how it prioritized

certain phenotypes associated with certain conditions, i.e. a neurological disorder could also be considered an autoimmune disorder depending on the criteria it utilized. The large number of respondents in the “Other” category also speaks to the difficulty of categorizing and identifying rare diseases that systems such as OrphaCODES have tried to solve. These results also do not consider that many respondents also reported secondary and tertiary diagnoses, which may also affect their overall satisfaction with their diagnostic journeys.

Additionally, the substantial number of "not applicable" responses among individuals with No Diagnosis highlights a potential gap in healthcare communication or accessibility for this group. Improving communication and support for individuals undergoing diagnostic processes, especially when a rare disease diagnosis is uncertain or pending, could enhance patient experiences and outcomes. These findings emphasize the need for patient-centered care, comprehensive diagnostic strategies, and targeted interventions to address the varied needs and challenges faced by rare disease patients throughout their diagnostic odyssey.

Gender	Agreed	Disagreed	Total Respondents
Female	482(58.84%)	120(14.72%)	819
Male	242(64.97%)	39(10.51%)	371
Non-binary	1(14.29%)	2(28.57%)	7
Prefer not to answer	1(7.69%)	3(23.08%)	13
Total (Agreed)	726(59.92%)	–	1,210
Total (Disagreed)	–	164(13.55%)	1,210

Table 17 Chi Square Discussion Respondents Gender Identity vs Perception of Timely Diagnosis

The chi-square tests on gender identity and diagnostic time, as well as perceptions of timely diagnosis (Table 8, Table 9) shed light on important aspects of the diagnostic journey for rare disease patients. While no significant association was found between gender identity and

diagnostic time, a significant association was observed between gender identity and perceptions of timely diagnosis ($p < 0.001$).

The non-significant association between gender and diagnostic time suggests that gender identity does not play a significant role in determining how long it takes for individuals with rare diseases to receive an accurate diagnosis. This finding can be both reassuring and informative for rare disease patients, as it implies that factors other than gender are likely more influential in the diagnostic process.

Table 17 combines the responses in table 9 by Respondents by Gender Identity and if they agreed (including slightly agreed) or disagreed (including slightly disagreed) with having a timely diagnosis. Respondents who identify as male had higher rates of satisfaction proportionally compared to those who identified as female. This result highlights a potential gap in the patient experiences of people who identify as men versus people who identify as women. It should be noted that as stated previously, respondents who identified as non-binary or did not provide an answer regarding their gender identity were significantly underrepresented in the dataset and that their perspective may not be accurately represented here.

Interestingly, when looking at the relationship between the gender identity and type of diagnosis for patients and their perceived time taken to receive a diagnosis, both indicated that they were statistically significant relationships. However, when considering gender identity and type of diagnosis in relation to the actual time taken to receive a diagnosis, the statistical significance diminishes. This lack of statistical significance indicates that while gender identity and diagnosis type may influence perception, they may not directly correlate with the actual time it takes to diagnose a rare disease.

The findings from the chi square analysis regarding health insurance and perceptions of timely diagnosis and treatment (Tables 10 and 11) have significant implications for rare disease patients in Pennsylvania. Understanding how different types of health insurance influence patients' views on timely assessment can provide valuable insights into healthcare access and quality for individuals with rare diseases in the state.

The first analysis focusing on private insurance status (table 10) reveals that among 664 respondents with private insurance, a significant majority of 301 individuals strongly agreed that they received a timely diagnosis. This accounts for approximately 45.33% of the total respondents with private insurance, indicating a substantial portion of individuals perceiving their diagnosis as timely. However, it's noteworthy that 69 respondents disagreed, representing around 18.60% of those with private insurance. While the majority reporting timely diagnosis is encouraging, the presence of a considerable number who felt their diagnosis was not timely despite having private insurance underscores potential gaps in healthcare access or diagnostic processes within this subgroup.

Contrastingly, the second analysis focusing on public insurance status (table 11) paints a different picture for patients with rare diseases. Among 548 respondents with public insurance, 236 strongly agreed to timely diagnosis, constituting approximately 43.07% of the total respondents with public insurance. However, the number of individuals (68 respondents) who disagreed with timely diagnosis despite having public insurance is notably higher compared to those with private insurance. This disagreement represents around 15.67% of individuals with public insurance. The lack of a statistically significant relationship between public insurance and perceptions of timely diagnosis implies that, within this dataset, public insurance status does not seem to influence how rare disease patients perceive the timeliness of their diagnosis.

These findings suggest several crucial points for rare disease patients and healthcare providers. Firstly, the presence of private insurance appears to correlate with a higher likelihood of perceiving a timely diagnosis, highlighting potential advantages in access to specialized care or expedited diagnostic pathways for those with private insurance. However, the significant number of respondents within both insurance categories who felt their diagnosis was not timely underscores ongoing challenges in ensuring timely and accurate diagnoses for rare diseases across insurance types. This emphasizes the need for continued efforts in improving diagnostic processes, raising awareness among healthcare professionals about rare diseases, and advocating for equitable access to timely diagnostic services regardless of insurance status.

Looking at Table 12, the table presents an analysis of timely diagnosis perceptions among patients with rare diseases based on the number of healthcare providers they consulted before receiving a final diagnosis. The data reveals several notable trends that can shed light on the experiences of these patients and the challenges they face in receiving timely diagnoses.

First, looking at the "Agree" column, it's interesting to note that the percentage of patients who agreed on a timely diagnosis decreases as the number of healthcare providers increases. Patients who consulted 1-2 providers had the highest agreement rate at 62.55%, whereas those who saw 5+ providers had a lower agreement rate of 35.67%. This suggests that as patients consult more providers, their perception of a timely diagnosis tends to decline, possibly indicating a longer and more complex diagnostic journey.

Conversely, the "Disagree" column shows an opposite trend, with the percentage of patients disagreeing with timely diagnosis increasing as the number of providers increases. Patients who consulted 1-2 providers had a lower disagreement rate of 5.96%, while those who saw 5+ providers had a higher disagreement rate of 11.19%. This disparity in perceptions between agree

and disagree categories further emphasizes the variability and complexity of the diagnostic process for rare diseases.

The "Not Applicable" category, although relatively small in percentages, is worth mentioning. It represents patients who found the question of timely diagnosis not applicable, which could indicate various factors such as uncertainty about their diagnosis, ambiguity in the question, or unique circumstances in their healthcare journey. This highlights the diversity of experiences and challenges faced by patients with rare diseases.

Overall, the data underscores the challenges patients with rare diseases encounter in obtaining timely diagnoses. The decreasing agreement and increasing disagreement rates as patients consult more providers suggest a need for improved coordination and communication among healthcare providers, as well as a focus on streamlining the diagnostic process for these patients. Additionally, the presence of the "Not Applicable" category highlights the need for tailored approaches and support to address the unique needs of individuals navigating rare diseases.

For instance, in the $2000 spending category, females constitute 57.89% of respondents, while males make up 62.02%. However, as the spending increases, the percentages fluctuate. In the $38000 spending bracket, females drop to 1.75%, whereas males rise slightly to 2.33%. Similarly, non-binary respondents start at 66.67% in the lowest spending category but diminish to 0% in higher spending brackets, albeit with a small sample size.

The analysis suggests several implications for rare disease patients. Firstly, it underscores potential disparities in financial burdens based on gender identity. Females and males may experience different economic challenges related to managing rare diseases, as indicated by their varying representation across expenditure levels. Secondly, the decline in non-binary respondents'

representation at higher spending levels may hint at unique financial difficulties or barriers they face in accessing expensive medical interventions or treatments.

Overall, these findings highlight the complex interplay between gender identity and financial implications for rare disease patients. Understanding these dynamics is crucial for healthcare providers and policymakers to develop inclusive support strategies and financial assistance programs tailored to the diverse needs of individuals managing rare conditions.

Table 13 displays data on respondents' annual expenditures based on gender identity categories, showing the frequency and column percentage for each spending category. The data indicates that respondents identifying as female had the highest frequency in the 0-$2000 spending category constituting 57.89% of respondents, followed by respondents identifying as males, making up 62.02%. The higher representation of respondents identifying as females in the lower spending categories, particularly the 0 to $2000 bracket, suggests that they may bear a disproportionate burden of healthcare costs, which can be especially challenging for those with rare diseases requiring specialized and often expensive treatments. However, as the spending increases, the percentages fluctuate. In the $38000 spending bracket, respondents identifying gas females drop to 1.75%, whereas respondents identifying as males rise slightly to 2.33%, Similarly, non-binary respondents start at 66.67% in the lowest spending category but diminish to 0% in higher spending brackets, albeit with a small sample size.

However, as spending increases, the distribution among genders varies, with males having a slightly higher frequency in some higher spending categories, indicating potential differences in financial resources or healthcare utilization patterns. Non-binary and preference-not-stated respondents have lower frequencies across all spending categories, with non-binary respondents showing a decrease in representation as spending increases. Overall, the chi-square test indicates

a statistically significant relationship between spending categories and gender identity, with a p-value of 0.002, suggesting that gender identity influences annual expenditures among respondents.

These findings emphasize the need for targeted support and intervention strategies for patients with rare diseases. Healthcare providers and policymakers must recognize and address the financial constraints faced by individuals identifying as females, males, non-binary, or preference-not-stated, ensuring equitable access to healthcare services and treatments regardless of gender identity. This could involve implementing financial assistance programs, advocating for insurance coverage reforms, and promoting awareness of available resources to alleviate the financial burden associated with managing rare diseases.

Table 14 presents data on respondents' annual expenditures categorized by their racial identities, encompassing several groups such as "American Indian or Alaska Native," "Asian," "Black or African American," "Hispanic or Latino," "Middle Eastern or North African," "Native Hawaiian or other Pacific Islander," and "White." Analyzing the data reveals several insights. Firstly, White respondents overwhelmingly dominate most higher spending categories while other racial groups such as American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Middle Eastern or North African, and Native Hawaiian or other Pacific Islander, show lower representation in these spending brackets, with percentages ranging from 0.24% to 1.21%, which reflects their overall representation in the survey data.

The statistical analysis using the chi-square test with a p-value of 0.897 indicates that there is no significant relationship between racial identity and annual spending. This suggests that, based on the data, racial identity does not appear to strongly influence the amount of money individuals spend annually on healthcare-related expenses.

However, it's essential to interpret these findings cautiously. While the statistical test may not detect a significant relationship, the disparities in representation across spending categories still warrant attention. It's possible that other factors not accounted for in this analysis, such as socioeconomic status, access to healthcare, or specific healthcare needs, could play a role in determining annual expenditures among different racial groups. It is also possible that the lack of representation from minority groups in this survey data cannot accurately represent the financial barriers that they may face.

In conclusion, while the statistical analysis doesn't show a significant relationship between racial identity and annual spending, the unequal distribution of spending across racial groups highlights potential disparities that healthcare systems and policymakers should continue to monitor and address to ensure equitable access to healthcare services and resources for all individuals, regardless of their racial background.

Looking at the data from Table 15, the statistical analysis using the chi-square test with a p-value of 0.000 indicates a significant relationship between insurance types and annual spending. This suggests that the type of insurance an individual has is strongly associated with the amount of money they spend annually on healthcare-related expenses.

. Notably, individuals with employer-provided insurance make up the highest percentage of respondents across all spending categories, ranging from 54.79% to 100.00%, depending on the spending bracket. Medicaid and Medicare beneficiaries also show substantial representation, particularly in lower spending categories. In contrast, respondents with no insurance or self-purchased insurance have lower frequencies in all spending brackets, indicating potential financial constraints or differences in access to healthcare coverage.

This data provides evidence that individuals with different insurance types may face varying challenges and opportunities in accessing healthcare services, receiving necessary treatments, and managing healthcare costs. For instance, those with employer-provided insurance may have more comprehensive coverage and easier access to specialists, whereas individuals with Medicaid or Medicare may encounter restrictions or limitations in coverage for certain services or medications.

Policymakers and healthcare providers need to consider these disparities in insurance coverage and spending patterns when designing healthcare policies and interventions for patients with rare diseases. Efforts should be made to ensure equitable access to quality care and financial assistance programs for individuals across all insurance types, ultimately improving health outcomes and reducing financial burdens for rare disease patients.

Overall, the chi-square tests conducted in this study contribute valuable information to understanding the nuanced factors impacting rare disease patients' diagnostic journeys, healthcare access, and perceptions. Further research and targeted interventions based on these findings can lead to improved support and outcomes for individuals with rare diseases in Pennsylvania and beyond.

4.3 Limitations

The analysis based on the provided data and quantitative techniques has several limitations that must be considered. The survey’s representativeness is a concern; if it does not accurately reflect the broader population of rare disease patients in Pennsylvania, the findings may lack generalizability. The method of survey distribution, whether through healthcare providers or social

media, may inherently bias the respondent pool towards individuals already connected to the medical system, often comprising predominantly White and urban populations. This bias can limit the diversity of perspectives and experiences captured in the survey, potentially overlooking the unique challenges and needs of underrepresented racial groups and rural communities within the rare disease landscape, potentially perpetuating healthcare disparities. Additionally, missing variables such as disease severity, or access to healthcare facilities could have provided a more comprehensive understanding of the factors influencing annual spending among these patients. The analyses conducted were also performed due to the way the data was collected as many of the survey responses were categorical in nature, which prevented other types of quantitative analysis techniques from being performed. Furthermore, the analysis is based on correlational relationships, and causality cannot be inferred. For example, this means that while higher annual spending may correlate with certain insurance types, the analysis does not establish a causal relationship. The temporal aspect of the data is also unclear, and changes in healthcare policies, insurance coverage, or rare disease treatments over time could influence spending patterns but are not accounted for in the analysis. Moreover, potential response bias in self-reported annual spending and insurance coverage could lead to measurement errors. Lastly, the sample size and the omission of certain variables, such as socioeconomic status or comorbidities, could affect the statistical power and introduce bias or confounding effects into the analysis. Considering these limitations is crucial for accurately interpreting the results and understanding the insights provided by the data analysis.

4.4 Future Work

In addition to the quantitative analysis conducted on the survey data in this thesis, several avenues for future analysis can be explored to glean deeper insights into the experiences and challenges faced by individuals with rare diseases. One significant area is the qualitative analysis of open-response questions, which can provide rich contextual information and nuanced perspectives that quantitative measures alone may not capture. Analyzing these qualitative responses using thematic analysis or natural language processing techniques can uncover themes such as patient experiences with healthcare providers, emotional impact, coping mechanisms, and unmet needs, contributing to a more comprehensive understanding of the rare disease landscape.

Moving forward, it's crucial for to recognize and address the skewness in this survey, which heavily favors White and urban populations. For similar future studies, actively seeking out and including diverse participants from underrepresented racial backgrounds and rural areas is essential to enhancing the validity and relevance of the research findings. This inclusivity promotes equity in healthcare research, ensuring that future work can better inform policies, interventions, and support systems that serve the entire rare disease community effectively.

Furthermore, there are several variables within the survey data that were not included in the initial analysis but hold potential for further investigation. For instance, exploring the relationship between specific rare diseases and their impact on various aspects such as healthcare access, treatment outcomes, and financial burden could provide disease-specific insights crucial for targeted interventions and tailored support services. Additionally, examining the influence of geographical location and healthcare system variations on rare disease management can offer valuable insights into disparities in care delivery and accessibility challenges faced by patients in different regions.

Another aspect worth exploring is the intersectionality of demographic factors with rare disease experiences. By conducting subgroup analyses based on gender identity, age groups, racial identity, ethnicity and socioeconomic status, researchers can identify disparities, differential needs, and barriers to care experienced by marginalized or underrepresented groups within the rare disease community. This approach can inform the development of inclusive and equitable healthcare policies and interventions.

Moreover, leveraging advanced statistical techniques such as machine learning algorithms and predictive modeling can enable the identification of predictive factors associated with favorable healthcare outcomes, treatment adherence, and quality of life among individuals with rare diseases. By incorporating a wider range of variables, including genetic markers, clinical data, and environmental factors, researchers can enhance predictive accuracy and tailor personalized interventions for improved patient outcomes.

In short, future analyses of the survey data can encompass qualitative investigations of open-response questions, exploration of additional variables, subgroup analyses based on demographic factors, geographical variations, and advanced predictive modeling techniques. These approaches collectively hold promise for advancing our understanding of rare diseases, informing evidence-based practices, and advocating for improved healthcare access and support for individuals and families affected by rare diseases.

Appendix A IRB Approval

Appendix Figure 1

February 27, 2020

Dr. Evelyn Talbott
University of Pittsburgh
A532 Crabtree Hall
130 DeSoto St
Pittsburgh, PA 15261

Dear Dr. Talbott:

SUBJECT: IRB EXEMPTION—REGULATORY OPINION
Sponsor: PA Rare Disease Advisory Council
Protocol Title: Pennsylvania Rare Diseases Needs Assessment Survey

This is in response to your request for an exempt status determination for the above-referenced protocol. Western Institutional Review Board's (WIRB's) IRB Affairs Department reviewed the study under the Common Rule and applicable guidance.

We believe the study is exempt under 45 CFR § 46.104(d)(2), because the research only includes interactions involving survey procedures the information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.

This exemption determination can apply to multiple sites, but it does not apply to any institution that has an institutional policy of requiring an entity other than WIRB (such as an internal IRB) to make exemption determinations. WIRB cannot provide an exemption that overrides the jurisdiction of a local IRB or other institutional mechanism for determining exemptions. You are responsible for ensuring that each site to which this exemption applies can and will accept WIRB's exemption decision.

Please note that any future changes to the project may affect its exempt status, and you may want to contact WIRB about the effect these changes may have on the exemption status before implementing them. WIRB does not impose an expiration date on its IRB exemption determinations.

If you have any questions, or if we can be of further assistance, please contact Tara Coffin, PhD, MEd, at 360-252-2418, or e-mail RegulatoryAffairs@wirb.com.

TBC:dao
D2 Exemption – Talbott (02-27-2020)
cc: Melanie Stangl, University of Pittsburgh (via email: mvs29@pitt.edu)
Marie Conley, Conley Consulting, LLC (via email: marie@mconleyconsulting.com)
WIRB Accounting
WIRB Work Order #1-1274041-1

Western Institutional Review Board®
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Appendix B Codebook

Appendix Table 1

Variable Name	Variable Description
TimelyDiagnosis	Perceptions of Timely Diagnosis categories (agree to disagree)
HealthCareProviders	Number of Healthcare Providers Seen
Age	Respondents Ages Categorized
DiagnosticTimeinMonths	Time Taken to Receive a diagnosis in Months (categorized)
AnnualSpending	Reported Annual Spending of Healthcare (categorized)
DiagnosticTimeInMonths	Diagnostic Time in Months
RuralUrban	Urban or Rural Counties (Binary)
DIseaseCategory	Type of Rare Disease (Categorized)
Gender	Respondents Gender

Public_insurance	Public Insurance
Private_Insurance	Private Insurance
IncorrectDiagnosis	Number of Incorrect Diagnoses
Race	Respondents Racial Identity
Insurancetype	Type of Insurance

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