BARBARA DITTRICH

STATE REPRESENTATIVE • 38th ASSEMBLY DISTRICT

January 11, 2022

Assembly Committee on Health

RE: Rep. Dittrich Testimony on AB 744 – relating to: rare disease advisory council.

Greetings, Mr. Chairman and fellow members of the committee. I am so very grateful that you are hearing this important legislation on the formation of a rare disease advisory council.

As most of you are likely aware, I am a long-time advocate for individuals diagnosed with a rare disease or disorder. I have spent over twenty-four years working on this issue as two of my three children are affected by rare diagnoses. And what I most want to emphasize to you today is that the issues of diagnosing and treating those with rare diseases are bipartisan issues.

Let me start by sharing some of the eye-opening information I have uncovered over the past decades of my work in this arena. In the United States, a rare disease is one that affects fewer than 200,000 individuals. This definition comes from the Orphan Drug Act of 1983. There are estimated to be more than 7,000 rare diseases affecting 25-30 million Americans. I urge each of you to visit the Rare Disease Database on the National Organization for Rare Disorders (NORD) website at https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/. You will see diseases you recognize like cerebral palsy, various forms of muscular dystrophy, hemophilia, cystic fibrosis, and others. While these disorders may be rare, pooling all of those rare diagnoses patients into one group comprises a surprising number of citizens. More than half of this group are children. The diagnoses can range from an "invisible illness" to a life-threatening disability.

Often, in addition to dealing with their specific medical problems, people with rare diseases struggle to receive a proper diagnosis, find information, or receive a treatment. The rarity of their conditions makes medical research more difficult. Many of these diagnoses will never find a treatment. And when treatments are found, they can frequently be prohibitively expensive. The life-saving medication my son is currently on costs over $300,000 per year. You will also hear testimony after mine that details research revealing that those with rare disorders display substantially higher health-care utilization compared to discharges with common condition diagnoses, accounting for nearly half of the US national bill. (See https://www.nature.com/articles/s41436-021-01241-7)

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Rep.Dittrich@legis.wi.gov

You can see why these diagnostic groups, while they are individually very easy to ignore, together need to have a unified voice in shaping our public policy. These are individuals we, regardless of political party, intended safety-net programs and services to support.

The shaping of this legislation has taken a great deal of time because we have endeavored to have each political party and stakeholder at the table. The council is comprised of nineteen various members including patients, doctors, the majority and minority members of both the Assembly and Senate, a genetic counselor, members of the insurance and pharmaceutical communities, and others, in an effort to shape a comprehensive, non-partisan advisory panel. The council is self-funding, which sets it outside of government dollars. And yet, it helps us, as legislators, to make prudent, targeted decisions that will help thousands of Wisconsinites.

This is the overview and importance of this legislation. It will bring together many who are sensing they have no voice and at the same time, help us to positively shape sound legislation in years to come.

I thank you all for listening to my testimony. I am happy to take any questions you may have.

GREAT LAKES HEMOPHILIA FOUNDATION

WRITTEN TESTIMONY

In Support Of

AB 744: An Act to Create a Rare Disease Advisory Council

Danielle Leitner Baxter

Executive Director, Great Lakes Hemophilia Foundation

Before the Assembly Committee on Health

Chair Sanfelippo and members of the Assembly Committee on Health, thank you for the opportunity to provide testimony today on Assembly Bill 744 to create a Wisconsin Rare Disease Advisory Council.

My name is Danielle Leitner Baxter, and I am from Brookfield. I am the Executive Director of Great Lakes Hemophilia Foundation – or GLHF – a nonprofit organization based in Milwaukee. We educate, support and advocate for the bleeding disorders community of Wisconsin.

GLHF supports 673 individuals living with hemophilia and nearly 3,000 people living with von Willebrand disease or other rare bleeding disorders.

Bleeding disorders are chronic, lifelong conditions. There is no way to prevent a bleeding disorder and there is no cure.

Hemophilia is an inherited condition more common in men. About 30% of new hemophilia cases arise from spontaneous gene mutations with no family history.

People with hemophilia experience bleeding following an injury and may have frequent spontaneous bleeding episodes – bleeds that occur without obvious cause – often into their joints and muscles. These bleeds can cause permanent damage and loss of mobility. Hemophilia is often diagnosed after circumcision.

There are approximately 30,000 people in the U.S. with hemophilia.

Von Willebrand disease – or VWD – affects 1% of the population - men and women equally. The CDC estimates that it takes a woman an average of 16 years from onset of symptoms to be diagnosed with VWD.

People with bleeding disorders have complicated medical needs. In the emergency room they are often met with a medical team with little to no knowledge of bleeding disorders. They rely on expert care from hemophilia treatment centers - or HTCs. We are incredibly lucky to have four federally recognized HTCs here in Wisconsin in Milwaukee, Green Bay, Madison, and La Crosse.

HTCs provide comprehensive care via specially trained multi-disciplinary teams that include hematologists, nurses, social workers, physical therapists, geneticists, dentists, and others.

Treatment for bleeding disorders includes clotting factor replacement therapies to prevent and stop bleeding episodes. Clotting factor is a biologic drug that requires specialized storage and handling and is dispensed for home infusion. Each patient's response and tolerance to a specific factor therapy is unique.

Clotting factor is very expensive. The average annual cost of preventative medication with no complications for a person with severe hemophilia is $300,000. Treatment costs can be a financial hardship for families even with health insurance.

There are no generic treatment options for bleeding disorders.

In the bleeding disorders community, we say, "Nothing about us without us."

Individuals with rare diseases need a forum to inform policy.

Assembly Bill 744 will offer this forum and improve the lives of Wisconsin's rare disease community. With input from medical experts, patients, and caregivers, it will identify and address the challenges facing patients with rare diseases such as delays in diagnosis, lack of medical specialists and limited access to therapies and medications. It will advise on research, best practices, access to care and treatment.

More than fifteen states have created Rare Disease Advisory Councils. At least ten others are considering similar legislation right now.

Assembly Bill 744 will pave the way for better health care policy in Wisconsin.

Thank you for considering this bill and thank you for your public service. I would be happy answer any questions.

Danielle Leitner Baxter
Executive Director, Great Lakes Hemophilia Foundation

State of Wisconsin
Department of Health Services
Tony Evers, Governor
Karen E. Timberlake, Secretary-Designee

TO: Members of the Assembly Committee on Health

FROM: HJ Waukau, Legislative Director

DATE: January 11, 2022

RE: AB 744, relating to: rare disease advisory council.

The Department of Health Services (DHS) would like to submit written testimony for information only on Assembly Bill 744 (AB 744) regarding the creation of a Rare Disease Advisory Council (Council). Under AB 744 DHS would be required to establish a Council, which would then advise DHS and provide recommendations to the Governor and Legislature. Additionally, AB 744 specifies the structure of the Council; member terms; funding mechanisms; and Council roles, activities, and requirements.

AB 744 includes provisions that would allow the Council to accept funding from outside sources; however, AB 744 does not include any budgetary or staffing appropriations for DHS to staff to administer and manage the activities of the Council. As of right now there are currently no staff within DHS that are designated to focus on rare diseases. Staff resources would be necessary for completion of the required reporting and potential staffing of the Council. At this time it is not possible for DHS to support the activities of the Council as specified under AB 744 within its current budget and staffing constraints.

Additionally, DHS administers a program similar to the activities specified under AB 744 that are overseen by the Council on Birth Defect Prevention and Surveillance (CBDPS). The CBDPS is comprised of medical professionals, a parent/guardian of a child with a birth defect, a representative of a local public health department, and representatives of specified stakeholder groups. The CBDPS is statutorily required to meet four times a year and provide biannual reports to Assembly and Senate Committees on Health, and the Assembly Committee on Children and Families. Any recommendations by the CBDPS are then added to the Wisconsin Birth Defects Registry under Wis. Stat. §. 253.12. The Registry currently collects information on 87 specified birth defects and syndromes. Further, DHS is currently able to carry out its statutory requirements related to the Registry, however any additional requirements would necessitate additional financial and staffing resources.

Lastly, AB 744 could unintentionally create additional administrative complexity and confusion by creating the Rare Disease Advisory Council under Wis. Stat. ch. 255, whereas similar activities (e.g. Birth Defects Registry) already exist under chapter 253. Having similar requirements in separate statutes could cause confusion and complexity for staff and stakeholders alike.

DHS is happy to provide any additional information and serve as a resource for the Committee as needed.

Biotechnology Innovation Organization

January 11, 2022

The Honorable Joe Sanfelippo
Chair, Assembly Committee on Health
State Capitol, Room 412 East
Madison, Wisconsin 53703

Re: Testimony in Support of Assembly Bill 744: Rare Disease Advisory Council
Submitted By: The Biotechnology Innovation Organization (BIO), Washington, DC

Dear Chairman Sanfelippo and Committee Members,

The Biotechnology Innovation Organization (BIO) thanks the committee for the opportunity to comment on our support for AB 744 (Dittrich). This legislation to establish an advisory council on rare disease would give a strong voice to the rare disease community in Wisconsin.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. Our members are committed to advancing science and improving the health and well-being of our planet using biotechnology.

Of the more than 7,000 known rare diseases, approximately 80% are genetic. Fifty percent of all rare diseases affect children, while 30% die before the age of 5 years.[1] Only 5% of all rare diseases have treatments available to patients.[2] Rare disease patients typically have complex conditions that come with their own unique set of challenges that they must face from testing and disease management, as well as insurance coverage difficulties.

The creation of an advisory council on rare diseases will give patients and caregivers affected by rare diseases a unified voice. These individuals will finally be provided a forum to make recommendations about pressing health care issues of rare disease patients. This advisory committee would give the state a compelling ability to improve knowledge, awareness, and management of rare diseases in Wisconsin, and bring together various stakeholders in the healthcare ecosystem to improve public policy regarding rare diseases. The results will be a great aid to patients, their families, and caregivers.

Thank you for the opportunity to comment on this legislation and for your support of AB 744. Please do not hesitate to contact us for any further information.

Sincerely,
/s/
Lilly Melander
Director, State Government Affairs – Midwestern Region
The Biotechnology Innovation Organization (BIO)
1201 Maryland Ave., SW
Suite 900
Washington, DC 20024
202.993.0043 (mobile)

[1]National Institutes of Health, https://www.nichd.nih.gov/newsroom/resources/spotlight/020116-rare-disease-day. Accessed: December 1, 2019.
[2] https://innovation.org/about-us/commitment/research-discovery/rare-disease-numbers

BioForward WISCONSIN

January 11, 2022

Assembly Committee on Health
Chair, Representative Sanfelippo

RE: Support AB 744 – Creation of a Rare Disease Advisory Committee

Dear Chairman Sanfelippo and Members of the Committee:

On behalf of BioForward and Wisconsin's biohealth industry, I write to ask that you support Assembly Bill 744, creating a Rare Disease Advisory Council (RDAC) in the State of Wisconsin.

BioForward is the collective voice of Wisconsin's biohealth industry. Our mission is to represent Wisconsin biohealth companies and to unite the industry to develop integrated health solutions that define the future of healthcare. Our membership includes an integrated network of more than 200 health solution leaders from across Wisconsin including research institutions, biotech & biopharma, digital health, medical device & diagnostics, healthcare systems and operational support organizations.

The Rare Disease Advisory Council will be a resource for patients and families impacted by rare diseases and will also be a source of expertise and advice for healthcare providers and the Department of Health Services.

There are currently more than 7,000 rare diseases that impact more than 25 million Americans. The flexibility offered in this bill for the Council to focus on activities that are most-needed by Wisconsinites affected by rare diseases will allow the Wisconsin RDAC to maximize its ability to meet our most critical needs.

This Council also has the potential to capitalize on Wisconsin's world-renowned biohealth industry. BioForward members and researchers are at the forefront of developing treatments and cures for the most challenging diseases.

BioForward supports AB 744 and urges the Committee to recommend this bill for passage this session.

Sincerely,
Lisa Johnson
CEO

January 11, 2022

The Honorable Joe Sanfelippo
Chair
Assembly Committee on Health
State Capitol, Room 412 East
Madison, Wisconsin 53703

Re: Support for Assembly Bill 744: Rare Disease Advisory Council

Dear Chairman Joe Sanfelippo,

On behalf of the 13 undersigned organizations representing individuals with rare diseases in Wisconsin, we thank you for placing Assembly Bill 744 (AB 744) on the Assembly Committee on Health's agenda for consideration. If passed, AB 744 would establish a Rare Disease Advisory Council (RDAC) in Wisconsin and help to give a voice to the estimated 1-in-10 individuals living with a rare disease in our state.

Any condition that affects fewer than 200,000 Americans is considered rare. Overall, there are more than 7,000 known rare diseases, affecting 25-30 million Americans across a broad spectrum of medical conditions. Rare disease patients face many unique challenges every day, from obtaining an accurate diagnosis and accessing medical specialists with knowledge of their condition, to battling for fair insurance coverage of their treatment and care. However, due to small patient populations and variety of rare diseases, it can be difficult for state government officials to have an in-depth understanding of the rare disease community's needs. This lack of awareness often contributes to the obstacles faced by rare disease patients and their loved ones.

While RDACs are organized differently in each state, RDACs provide a forum for patients, families, and experts across the state to analyze the needs of the community and make recommendations on how to improve public policy related to rare diseases. RDAC members typically include a variety of rare disease stakeholders, including patients, caregivers, health care providers, health insurers, biotech industry, researchers, patient advocacy organizations, and state government officials. The council may conduct surveys to better understand common challenges rare disease patients or caregivers face, consult with experts to improve access to quality health care, or publish and compile resources related to rare diseases.

In creating this council, Wisconsin would join twenty-one other states, seven within the past year, that have enacted similar legislation in support of their rare disease community. Those states include: Alabama, Connecticut, Florida, Illinois, Kentucky, Louisiana, Massachusetts, Minnesota, Missouri, New Hampshire, New Jersey, New York, Nevada, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Utah, Virginia, and West Virginia. While many of these councils are still in their infancy, already RDACs are showing enormous promise in each of these states in addressing the barriers that prevent individuals living with rare diseases from obtaining proper treatment and care for their conditions.

Once again, we urge your swift consideration of AB 744 to give a voice to all Wisconsin residents living with rare diseases. For any questions, please contact Alyss Patel with the National Organization for Rare Disorders via email at apatel@rarediseases.org. Thank you for your consideration.

Sincerely,

National Organization for Rare Disorders
American Cancer Society Cancer Action Network
American Kidney Fund
CFC International
Cystic Fibrosis Research Institute (CFRI)
Epilepsy Foundation of Wisconsin
IGA Nephropathy Foundation
International Pemphigus and Pemphigoid Foundation
The Leukemia & Lymphoma Society
National Niemann Pick Disease Foundation
National PKU Alliance
Neuropathy Action Foundation
Sick Cells

NORD®
National Organization for Rare Disorders

RARE WI

January 11, 2021

The Honorable Joe Sanfelippo
Chair, Assembly Committee on Health
State Capitol, Room 412 East
Madison, Wisconsin 53703

Re: Support for Assembly Bill 744

Dear Chairman Sanfelippo and Members of the Assembly Committee on Health,

My name is Danyelle Sun and I am one of the volunteer co-ambassadors for NORD's Rare Action Network in Wisconsin. My fellow advocates and I work to bring those affected by rare diseases in Wisconsin together to support and engage with one another. Thank you for the opportunity to share my support for Assembly Bill 744, which would create a Rare Disease Advisory Council in Wisconsin.

While each individual rare disease is unique, there are common experiences amongst nearly everyone living with a rare disease. These challenges can include a long diagnostic odyssey, difficulty in finding expert medical professionals, and challenges accessing necessary treatments, medical equipment and daily therapies, to name a few.

As a result of these obstacles and with the desire to help others overcome them, we are asking for your support to establish a Rare Disease Advisory Council (RDAC) in Wisconsin. The Council would serve as a unified voice for all stakeholders within the rare disease space and would help inform decision-makers on issues that matter to rare disease patients and their families. Our goal is for the RDAC to raise awareness about rare disorders, to provide valuable knowledge and information to policymakers, and to be a resource to individuals and families throughout their journey with a rare disease, as well as to medical providers who are working to support a patient in their diagnosis.

Now that I've shared a little bit about the benefits of an RDAC and why we would like Wisconsin to join the 21 other states who have enacted a Rare Disease Advisory Council, I would like to tell you about what personally motivates me to support this effort.

In 2013, just before my daughter, Ruby, turned two years old, she was diagnosed with Spinal Muscular Atrophy (SMA). We had been searching for answers for nearly a year before we got the answer we hoped we'd never get - a neuromuscular disease with no treatment, no cure, and no options other than to do our best in supporting her as she would inevitably lose strength all over her body. Soon after her diagnosis, she took her last steps. Within a year or so, she couldn't crawl without her arms giving out and falling flat on her face. As you can imagine, we were devastated. We did our best to stay positive, focusing on what she *could* do and the positive impact we could have by supporting research that was ongoing for SMA.

Within six months of Ruby's diagnosis, we received the same diagnosis for our son, Landon. Although we received his diagnosis while I was still expecting him, we didn't know whether he would be less or more severely affected than his sister. It turned out that Landon was affected more severely than his sister and by the age of ten months, began to lose strength. He stopped crawling and was no longer able to stay sitting up on his own. He had trouble coughing and clearing his lungs on his own when sick. He stopped gaining weight because it was too difficult for him to eat and digest adequately and he received a g-tube at the age of two and a half years old.

Both Ruby and Landon have participated in physical therapy every week for most of their lives. We have spent a small fortune on medical equipment and therapy that insurance either wouldn't cover or would take months of denials and appeals – precious time that our kids don't have. There have been bright spots, too - three treatments have been approved by the FDA for SMA since 2016. Ruby and Landon have been able to receive two of these treatments, which have helped stabilize the progression of the disease. We also eventually connected to the amazing SMA community and have found vital support and friendship. However, we have experienced many challenges and barriers to what Ruby and Landon need to be fully functioning members of their communities and the answers and support that our family so desperately needed should not have taken so long to find.

Sadly, we are not alone. With nearly 1- in -10 people estimated to be living with a rare disease, there are hundreds of thousands of other Wisconsinites and their families having similar experiences. Enacting an RDAC in Wisconsin would help to break down these barriers. The Council would be composed of a variety of stakeholders and experts in the rare disease community and would serve as a centralized starting point for families like ours to be connected to resources. Had an RDAC existed in 2012, I may not have had to spend countless late nights, sitting next to my sleeping toddler, scouring the internet for answers as to why she was wasting away before my eyes. No family should have to go through that. As a mother of two rare children, as a committed and engaged Wisconsin citizen, and as one of NORD's Rare Action Network Volunteer Ambassadors, I urge you to support House Bill 744 in establishing a Rare Disease Advisory Council.

Sincerely,

Danyelle Sun
Volunteer State Ambassador
Wisconsin Rare Action Network

January 11, 2021

The Honorable Joe Sanfelippo
Chair, Assembly Committee on Health
State Capitol, Room 412 East
Madison, Wisconsin 53703

Re: Support for Assembly Bill 744

Dear Chairman Sanfelippo and Members of the Assembly Committee on Health,

My name is Lani Knutson, and I am the Wisconsin Rare Action Network Volunteer Community Engagement Liaison for the National Organization for Rare Disorders (NORD). Thank you for the opportunity to share my support for Assembly Bill 744, which would create a Rare Disease Advisory Council in Wisconsin.

Our family's rare disease journey began when our older son started showing signs of muscle weakness shortly after birth. After several years of physical therapy, visits with a myriad of specialists, and many expensive diagnostic tests, the doctors concluded that a muscle biopsy would be the best way to find a diagnosis. Soon after, we received a clinical diagnosis of a rare, and largely unknown, neuromuscular disease when our son was 2 and a half years old. Our second son was born six months after diagnosis. He also exhibited muscle weakness, and it was determined that he had the same disease as his brother.

Their diagnosis is so rare that I found very little information in my searches on the internet. At the time, little was known about the specific symptoms of the disease. There was no cure or treatments, and the best advice I could find was regular checkups to monitor the progression of their symptoms. I felt extremely alone and helpless as my children entered an unknown future.

Eventually, I found a research study at Boston Children's Hospital that was attempting to map the genetics of their disease. We had looked into genetic testing soon after the clinical diagnosis, but insurance would not pay for it, and we could not afford it. We enrolled in the study not knowing if we would ever find anything more about their disease. To our surprise, both boys received a genetic diagnosis of Congenital Muscular Dystrophy (SELENON subtype) in 2015. This discovery opened our world to more specific treatments for their symptoms, online support groups, and a wonderful patient organization called Cure CMD.

Symptoms of their CMD include life threatening respiratory issues and scoliosis, which requires spinal fusion surgery. Today, both of my sons receive regular care from many medical specialists, therapists, and general practitioners, and require bi-yearly Pulmonary Function Tests (PFT) and yearly sleep studies. We have multiple pieces of durable medical equipment in our home, including BiPap machines and a Cough Assist to aid their breathing, especially when they are sick.

Our family is fortunate to live two miles from Children's Wisconsin where our boys have received top notch care their entire lives. We have found wonderful care and services in Wisconsin that make it possible for our family to live a fairly normal life. I know not all rare

disease families in Wisconsin have the same advantages. Having grown up in rural northwest Wisconsin, I recognize the added layer of isolation where specialized medical care simply does not exist.

Raising two boys with an ultra-rare neuromuscular disease isn't easy. Even though every rare disease is different, many of the struggles are the same, which is why I am thankful for Senator John Jagler and Representative Barbara Dittrich introducing Senate Bill 689 and Assembly Bill 744 to establish a Rare Disease Advisory Council (RDAC). An RDAC in Wisconsin will connect families like ours in all parts of the state to life saving information and a supportive community after a rare disease diagnosis. Composed of patients, caregivers, health care providers, researchers and other members of the rare disease community, the Rare Disease Advisory Council will provide a forum for stakeholders to analyze the needs of the rare disease community and make recommendations to state government officials on how to improve public policy to support it. Increased awareness and action will improve the lives of those affected by rare disease and it will help families like ours feel less isolated and alone.

As Wisconsin's Volunteer Community Engagement Liaison and a mom to two rare disease patients, I urge you to vote in support of Assembly Bill 744 and help Wisconsin become the 22nd state to enact an RDAC.

Sincerely,

Lani Knutson
Volunteer Community Engagement Liaison
Wisconsin Rare Action Network

January 11, 2021

The Honorable Joe Sanfelippo
Chair, Assembly Committee on Health
State Capitol, Room 412 East
Madison, Wisconsin 53703

Re: Support for Assembly Bill 744

Dear Chairman Sanfelippo and Members of the Assembly Committee on Health,

My name is Kerri Engebrecht. I am the mother of a child with a rare disorder, and advocate on behalf of the entire rare disease community. I am also the Wisconsin Rare Action Network Volunteer Ambassador for the National Organization for Rare Disorders (NORD). Thank you for the opportunity to share my support for Assembly Bill 744, which would create a Rare Disease Advisory Council in Wisconsin.

My youngest son always had an above average amount of upper respiratory infections that would create more severe illness and exacerbate his asthma. As a child, his lung function was less than 50%, despite multiple inhalers. He had reactions to vaccines, though only the flu vaccine was severe (anaphylactic). Still, he was one tough kid, a tremendous athlete, a top cross-country runner at his middle school and a top defender with an elite soccer club in Wisconsin at 12. After each athletic event he would fall, in complete exhaustion, and often slept for hours. He insisted he wanted to continue, and we worked with doctors to ensure he could.

Early in 2015, we saw his athletic performance decline dramatically. We adjusted his medications for ADHD and anxiety thinking they may be making him sluggish. By the fall of 2015, he would vomit most mornings, was losing weight, complaining of "seeing black dots" and needing to rest more and more. On December 14, 2015, he begged me for answers. His pediatrician got us in for an appointment right away and sent us to Children's of Wisconsin for a brain CT. We are fortunate to be within a few miles of Children's and the doctors affiliated with them. In the emergency room, things happened in a hurry, and within a few hours we were admitted to the hospital with the knowledge that something was wrong with our son's endocrine system.

The attending physician's wife had Addison's Disease (a very rare disease) and explained that the initial labs indicated that our son had the same condition. Being a mom, I spent the night googling and found that Addison's Disease is most common in dogs and that John F. Kennedy had it, so we were between a four-legged animal and the President of the United States! In the next few days, the suspected diagnosis was confirmed and treatment began. Our son will be on steroids the rest of his life to stay alive. An emergency injection that is 13 steps long is needed within 20 minutes of severe injury or illness to save his life. This medication is not carried by EMTs in Wisconsin, but I have worked to put a protocol in place so that self-carry medications can be administered to patients.

Since joining the rare disease community, I have learned how fortunate we are. I had been a stay-at-home mom for years, allowing me the opportunity to commit my time to research and advocacy and serve as a Volunteer State Ambassador for the National Organization for Rare Disorders (NORD). My husband has a good job with great insurance that enables our son to see the specialists he needs. Since diagnosis, he has needed to see specialists in gastrointestinal, neurology, psychiatry, pain and mental health. We are fortunate that Addison's Disease is one of a small percentage of rare illnesses that has a treatment, as 90% of rare diseases do not. Not only that, but his treatment is also affordable and fairly easy to obtain, despite having times where his specific steroids are more readily available in pet pharmacies than human pharmacies. His illness does not require him to use any medical equipment; however, I have learned many rare diseases do and the cost and availability can be overwhelming to many families. His illness created challenges with assistance at school and ultimately required me to homeschool him for the last two years of high school. Now as an adult, he has faced discrimination in the workplace due to his disease. Although we have felt fortunate, our son's illness is rare, chronic, and invisible.

A Rare Disease Advisory Council (RDAC) would lessen obstacles for those with rare diseases and their caregivers, allowing their voices to be heard by legislators. Our goal is to find more treatments and cures for those with rare diseases and to ensure that they are affordable and accessible to all who need them. An RDAC can help to support earlier diagnosis of rare diseases which often results in better chances of survival and improved quality of life. Our hope is to bring everyone with a voice in the rare disease community to the table and improve access, treatments, and quality of life for rare disease patients and their families.

Please vote in support of Assembly Bill 744 and make an RDAC a reality for the 1-in-10 individuals living with a rare disease in our great state of Wisconsin.

Sincerely,

Kerri Engebrecht
Volunteer State Ambassador
Wisconsin Rare Action Network

www.nature.com/gim

Genetics inMedicine

Check for updates

ARTICLE

Can you hear us now? The impact of health-care utilization by rare disease patients in the United States

Angela A. Navarrete-Opazo[1], Maharaj Singh[1,2], Ainslie Tisdale[3], Christine M. Cutillo[3] and Sheldon R. Garrison[1]✉

PURPOSE: The vast majority of rare diseases (RDs) are complex, disabling, and life-threatening conditions with a genetic origin. RD patients face significant health challenges and limited treatments, yet the extent of their impact within health care is not well known. One direct method to gauge the disease burden of RDs is their overall cost and utilization within health-care systems.
METHODS: The 2016 Healthcare Cost and Utilization Project (HCUP) databases were used to extract health-care utilization data using International Classification of Diseases, Tenth Revision (ICD-10) codes.
RESULTS: Of 35.6 million national hospital weighted discharges in the HCUP Nationwide Inpatient Sample, 32% corresponded to RD-associated ICD-10 codes. Total charges were nearly equal between RDs ($768 billion) compared to common conditions (CCs) ($880 billion) ($p < 0.0001$). These charges were a result of higher charges per discharge and longer length of stay (LOS) for RD patients compared to those with CCs ($p < 0.0001$). Health-care cost and utilization was similarly higher for RDs with pediatric inpatient stays, readmissions, and emergency visits.
CONCLUSION: Pediatric and adult discharges with RDs show substantially higher health-care utilization compared to discharges with CCs diagnoses, accounting for nearly half of the US national bill.

Genetics in Medicine (2021) 23:2194–2201; https://doi.org/10.1038/s41436-021-01241-7

INTRODUCTION

Rare diseases (RDs) are a global health-care problem with an estimated 400 to 700 million people affected worldwide [1–3]. Currently, the number of RDs has been suggested to be more than 10,000 [4]; these diseases are often serious, quality of life-limiting, and potentially life-threatening. Most RDs have some level of genetic involvement, with 72–80% of these conditions having an identified gene or genes [5, 6]. In the United States, RDs are defined as any condition affecting fewer than 200,000 individuals, which collectively affects an estimated 33 million people [7]. In Europe, the European Medicines Agency (EMA) specifies a prevalence of less than 5 in 10,000 people (~75 million), and in Japan the Ministry of Health, Labour and Welfare defines RDs as any condition affecting less than 50,000 individuals in the country (~12.5 million) [8].

Patients living with RDs experience significant health, psychosocial, occupational, and financial burden. The financial burden of RDs includes both direct (medical and nonmedical) and indirect costs. Direct medical or health-care cost burden can reach millions of dollars annually for certain rare diseases, with cost drivers that include hospitalizations and emergency visits, medications, dental health, palliative care, outpatient visits, insurance cost and reimbursement, rehabilitation care, home health care, assistive devices, social services, and caregivers [9–15]. RD patients typically experience significant diagnostic delay averaging over 5 years [16, 17], and requires the involvement of a knowledgeable and comprehensive clinical care team to determine a definitive diagnosis.

The overall health-care utilization by pediatric and adult populations with RDs in the United States has not been well documented. Evidence is emerging that RDs may have a disproportionate and substantial impact within health care that well exceeds RD patient prevalence. A recent study analyzed health-care utilization of pediatric patients with 919 genetic diseases and found a marked increase in those patients with one or more genetic diseases [18]. Aggregate total charges for suspected genetic diseases, many of which are rare, in 2012 accounted for ~$57 billion (46%) of the "national bill" for pediatric patients [18]. However, pediatric patient inpatient stays account for only a small component of the total impact of rare disease in health care, and a current and broad inquiry of RDs is necessary.

The present study is a comprehensive investigation of health-care utilization of adult and pediatric patients with RDs compared to those without a RD in the United States. These data span all inpatient, readmission, and emergency department data within the same year (2016) using the Healthcare Cost and Utilization Project (HCUP) database. Here we report the widespread economic impact of RDs in the United States across all demographics. This amplifies the need to incorporate cost-saving measures and improved health-care access for those affected by rare disease.

MATERIALS AND METHODS

Data source

The 2016 Nationwide Inpatient Sample (NIS), Kids' Inpatient Database (KID), Nationwide Readmissions Database (NRD), and Nationwide Emergency Department Sample (NEDS) HCUP data were used to extract health-care utilization and cost data for 1,645 International Classification of Diseases, Tenth Revision (ICD-10) codes linked to RDs. The ICD-10 code list linked to 1,645 RDs, or features of them, was primarily provided by Orphanet [19], a worldwide database dedicated to providing information on rare diseases and orphan drugs [20], and does not include ICD-10 codes for all rare diseases. Common conditions (CCs) were defined as any condition not included in the RD ICD-10 list. Of the 1,645 ICD-10 codes and linked RDs, 1,091 have some level of genetic involvement (66.3%) as determined using

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Table 1. Health-care utilization and demographic characteristics, National Inpatient Stay (NIS).

	Rare disease %	Common condition %	*P* value
n	11,289,703	24,378,608	
Age (years)	58.3	44.7	<0.0001
Neonate at admission	0.7	0.9	<0.0001
Sex			<0.0001
Female	51.3	59.2	
Male	48.7	51.3	
Race and ethnicity			<0.0001
White	68.2	64.1	
Black	15.7	15.0	
Hispanic	9.8	13.4	
Asian or Pacific Islander	2.8	3.2	
Native American	0.6	0.7	
Other	3.0	3.6	
Payer			<0.0001
Private	23.8	33.0	
Medicare	53.7	33.1	
Medicaid	16.9	26.0	
Self-pay	2.8	4.4	
No charge	0.3	0.3	
Other	2.6	3.2	
Location			<0.0001
Large metro (central)	29.6	30.3	
Large metro (fringe)	24.8	23.6	
Medium metro	20.8	20.7	
Small metro	9.3	9.2	
Micropolitan	9.0	9.2	
Nonmetro, nonmicropolitan	6.6	7.0	
Income quartile by ZIP code ($)			<0.0001
1–42,999	29.9	31.1	
43,000–53,999	25.2	25.5	
54,000–70,999	24.1	23.8	
71,000+	20.8	19.6	
Discharge disposition			<0.0001
Routine	56.4	75.0	
Transfer to short-term hospital	2.7	1.6	
Transfer to other facility	20.0	11.1	
Home health care	16.0	10.0	
Left against medical advice	1.1	1.3	
Died	3.9	1.0	
Elective			<0.0001
Elective admission	17.6	23.2	
Nonelective admission	82.4	76.8	
Procedures per discharge (number)			<0.0001
0	38.2	38.8	
1–5	52.7	57.7	
6–10	7.3	3.1	
11–15	1.8	0.4	
Transfer in			<0.0001
Not transferred in/ newborn	90.2	93.5	
From acute care hospital	7.1	4.7	
From another type of health facility	2.8	1.8	
Transfer out			<0.0001
Not a transfer	77.3	87.3	
To acute care hospital	2.7	1.6	
To another type of health facility	20.0	11.1	
Hospital division			<0.0001
New England	5.1	4.4	
Middle Atlantic	14.0	13.8	
East North Central	15.9	15.0	
West North Central	6.8	7.0	
South Atlantic	21.1	20.4	
East South Central	6.6	6.9	
West South Central	10.7	12.4	
Mountain	6.1	6.3	
Pacific	13.5	13.8	
Missing values not displayed			

Demographic characteristics, NIS, weighted estimate.

OMIM and Orphanet [19, 21]. The 2016 HCUP database was selected because, at the time of analysis, it is the most recent set of data that includes the KID database, which is released every 4 years.

The NIS database is the largest publicly available all-payer inpatient health-care database designed to produce US national estimates of inpatient utilization, access, charges, and outcomes. For the year 2016, NIS contains an administrative and demographic data sample that includes an estimated 97% of discharges in the United States from hospitals in 46 states and the District of Columbia [22], from which a random 20% sample is derived. An estimated 35.6 million hospital weighted discharges were identified in the 2016 NIS HCUP database, of which 11 million correspond to the 1,645 ICD-10 codes from suspected RD diagnoses of record (32%) and 24 million correspond to CC discharges (31%) (Table 1). The types and locations of hospitals from which the NIS data were derived are described in Table S1.

The HCUP-KID database contains an all-payer, national sample of pediatric inpatient discharges for patients younger than 21 years of age [23]. The KID database includes conditions and treatments that are normally difficult to treat, including rare disease and uncommon treatments (e.g., organ transplants), allowing for health-care utilization to be thoroughly investigated [24]. In the year 2016, a total of 6 million weighted discharges were identified for children less than 21 years of age in the 2016 KID HCUP database, of which 1 million (21%) correspond to RDs versus 5 million to CCs (79%).

The HCUP NRD is drawn from 27 HCUP State Inpatient Databases (SID) and can be used to create estimates of 30-day, all-cause hospital readmissions rates and their associated costs [25]. Overall, there were 16 million readmissions in the year 2016, of which 5 million correspond to patients with RDs (32%) and 11 million (68%) to CCs patients.

The NEDS database is drawn from the SID and State Emergency Department Databases (SEDD) [26]. For the year 2016, 36 states and the District of Columbia contributed to the database, representing 78% of all US emergency department visits. In 2016, there were approximately 178 million ED visits in the United States, of which 14 million (10%) correspond to patients with RDs and 130 million (90%) to patients with CCs. All *n*'s in each database are estimates and analysis of each data element may vary due to missing values.

Data elements

Clinical and nonclinical hospitalization data elements were extracted from the HCUP NIS, KID, NRD and NEDS databases for selected ICD-10 codes linked to RDs diagnosis. Sample nonclinical data elements included (1) demographic information (sex, age, race, median household income, patient location), (2) primary payer, (3) hospital characteristics (location and region), and (4) total charges. Sample clinical related information included (1) primary diagnosis, (2) discharge status, (3) origin and disposition of the patient, (4) type of admission, (5) hospital discharges, and (6) length of stay (LOS). The following additional data elements were extracted from the KID database: (1) neonatal age and (2) uncomplicated vs. complicated in-hospital birth; from the NRD database: (1) transfer to rehabilitation, evaluation, or other aftercare; and from the NEDS database: (1) total number of ED visits. The number of discharges was provided from total discharges and the *n* was not further provided for each data element, which varied for each data element due to missing content. The description of each HCUP data element is included in table S2.

Data analysis

A retrospective analysis of 2016 HCUP NIS, KID, NEDS, and NRD was conducted. The estimated prevalence data was adjusted for the US population using the discharge weight variable (DISCWT) to minimize the margin of error and to reflect all 50 states across the United States. To establish the impact of rare disease, patients in the RD cohort were included if they had a suspected rare disease diagnosis from the list of 1,645 ICD-10 codes within the first 15 diagnoses. Descriptive statistics of the weighted national estimates were used to summarize the results. Continuous variables are presented as means and standard error of the mean (SEM). Categorical variables were shown in percentage values. Two-sided tests (chi-square and Fisher's exact for categorical measures, and Student's *t* tests for continuous measures) were used for RD and CC comparisons. Data presented in Tables 1–4 used separate chi-square tests and there were no multiple comparisons. All statistical tests used in this paper were two-tailed. Statistical significance was considered for $p < 0.05$. All analyses and appropriate weighted estimates were calculated using SAS (version 9.4; SAS Institute Inc., Cary, NC).

The study followed the required research practices based on the Agency for Healthcare Research and Quality (AHRQ)'s recommendations including (1) identifying observations as hospitalization events rather than unique patients, (2) not performing state-level or physician-level analyses, (3) not using nonspecific secondary diagnosis codes to infer in-hospital events, (4) using survey-specific analysis methods allowing for weighting of estimates to generate national estimates with an accompanying measure of variance of the estimate, and (5) not including data from any condition with ten or fewer encounters.

RESULTS

To better understand the economic impact and health-care utilization of RD, a comprehensive analysis of inpatient, readmission, and emergency visits in 2016 was conducted. A RD in a patient's record was the single biggest predictor of health-care services, and included duration, type, and cost of that utilization when comparing to CCs. These factors were analyzed in detail to provide a comprehensive assessment of the impact of RD in health care. The individual conditions included in the study, as well as average age, LOS, and total charges are included in Table S3.

Health-care utilization

Health-care utilization was captured using total aggregate inpatient charges, LOS, and charges per inpatient visit. Hospital inpatient visits reflect the single largest cost source in health care, and therefore, provide the most significant component of RD health-care utilization. Overall, total aggregate charges were $768 billion for RDs and $880 billion CCs in the 2016 NIS HCUP database, a remarkable difference of nearly $111 billion (Fig. 1a; $p < 0.0001$) despite RD patients accounting for a very small percentage of the overall US population [1–3].

The present study shows significant differences in health-care utilization between RD and CC discharges. RDs had a longer LOS (6.3 days) compared to CCs (3.8 days) (Fig. 1b; $p < 0.0001$), and nearly double the average total charges per discharge ($69,275 ± 1004) compared to CCs ($36,718 ± 389) (Fig. 1c; $p < 0.0001$).

Pediatrics are of great interest for rare disease. Despite representing only 20.9% of total inpatient stays for children less than 21 years of age, total aggregate charges were approximately $34 billion higher for RDs ($105 billion) than CCs ($70 billion) (Fig. 1a; $p < 0.0001$). The mean total charge per patient was $89,618 ± 289 for RDs and $14,226 ± 23 for CCs (Fig. 1c, $p < 0.0001$). The mean LOS was over three times longer for RDs (9.1 days) compared to CCs (2.8 days) (Fig. 1b; $p < 0.0001$).

RDs also had a disproportionate impact on readmission and emergency visits. Data from the NRD showed that patients with RDs had a lower readmission rate (32%) but higher total charges per readmission than patients with CCs ($66,675 ± 98 vs. $35,585 ± 28, $p < 0.0001$) (Fig. 1c). The impact of RDs was much lower in the emergency department (ED), accounting for 9.7% of overall ED visits. The total charges per visit were greater for RDs ($4,670 ± 108) than CCs ($3,397 ± 76, $p < 0.0001$) (Fig. 1c), resulting in $55 billion for RDs compared to $384 billion for CCs (Fig. 1a; $p < 0.0001$).

Clinical data

In addition to total charges and LOS, the overall impact of RD is more fully understood by the number of procedures per inpatient stay, patients' transfer among facilities, and mortality rate. In the NIS database, RD patients have more inpatient procedures, with 9.1% having 6–15 procedures compared to 3.5% for CCs. Furthermore, fewer RD patients were routinely discharged (e.g., home) (56.4%) compared to CC patients (75.0%). Instead, RD patients were frequently transferred to another facility (22.7%) or required home health care (16.0%). Unfortunately, four times as many RD patients died (3.9%) during their inpatient stay compared to CC (1.0%) patients ($p < 0.0001$) (Table 1).

In the pediatric population, RD patients had fewer routine discharges (88.1%) compared to CC patients (96.4%) ($p < 0.0001$), and more RD patients were transferred to another facility or home health care (5.7%) compared to CC discharges (1.9%). Mortality rates were 13 times higher in RDs (1.3%) compared with CCs (0.1%) ($p < 0.0001$; Table 2), with mortality remaining significantly higher across all age groups. One of the most striking differences between RD and CC was specific to a subset of patients at birth. When determining those patients who were born within the admitting hospital to those newborns who were transferred from another acute care hospital or health-care facility, RD patients were found to have taken a very different pathway. Approximately 58% of RD patients were transferred from another hospital or care facility compared to only 36% of CC patients. Of those born in the same hospital, 94% of RD births were complicated (e.g., cesarean section, birth trauma) compared to 55% of CC patients. Upon further evaluation of this striking difference of birth complications revealed racial disparity. Normal births were similar in breakdown by race between RD and CC patients.

For ED visits, only 56.3% of RD patients were treated and released, and 51.1% were admitted to the same hospital. In

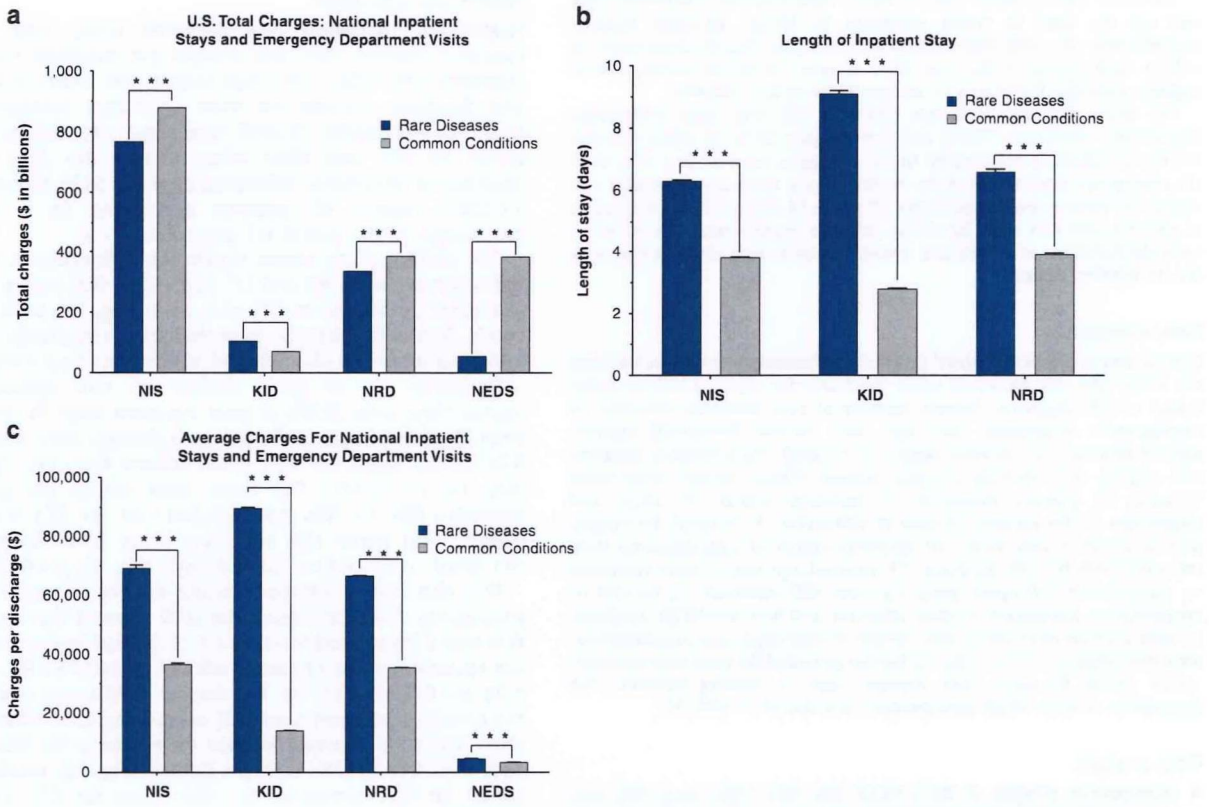

Fig. 1 Estimated total charges for US health-care utilization of rare diseases (RDs) compared to common conditions (CCs). RD patient cost burden was significantly higher than patients with common conditions (CCs) across all databases except Nationwide Emergency Department Sample (NEDS). (**a**) Estimated total charges for the Nationwide Inpatient Sample (NIS) were $768 billion (**b**) for RDs and $880 billion for CCs. Estimated total charges for RDs for Kids' Inpatient Database (KID), Nationwide Readmissions Database (NRD), and NEDS were $105 billion, $337 billion, and $55 billion, respectively. Estimated total charges for CCs for KID, NRD, and NEDS were $70 billion, $385 billion, and $384 billion, respectively. All comparisons were $p < 0.0001$ and estimated total chargers are shown. (**b**) Estimated charges per discharge for RDs was higher than for CCs. Estimated average charge per discharge for NIS was $69,275 ± 1004 compared to $36,718 ± 389 for CCs ($p < 0.0001$). Estimated average charge per discharge for KID was $89,681 ± 289 for RDs compared to $14,226 ± 23 for CCs ($p < 0.0001$). Estimated average charge per discharge for NRD was $66,675 ± 98 for RDs compared to $35,585 ± 28 for CCs ($p < 0.0001$). Estimated average charge per discharge for NEDS was $4,670 ± 108 for RDs compared to $3,397 ± 76 for CCs ($p < 0.0001$). Mean cost per discharge shown with error bars indicating standard error. (**c**) Estimated inpatient length of stay (LOS) for RDs was longer in each Healthcare Cost and Utilization Project (HCUP) database evaluated (NIS, KID, NRD, NEDS) when compared to CCs. Estimated LOS for NIS was 6.3 days compared to 3.8 days for CCs ($p < 0.0001$). Estimated average charge per discharge for KID was 9.1 days compared to 2.8 days for CCs ($p < 0.0001$). Estimated average charge per discharge for NRD was 6.6 days compared to 3.9 days for CCs ($p < 0.0001$). Mean LOS is shown with error bars indicating standard error.

contrast, most of the CC visits were treated and released (89.1%) with only 9.0% admitted to the hospital ($p < 0.0001$). Moreover, 12 times more RD patients (2.3%) died in the ED or later as an inpatient in the hospital, compared with those with CCs (0.2%) (Table 4).

Demographics

Given the large number of discharges, it was important to better understand the patient population within the sample. Overall, the frequency of RDs in males was 7.9% higher than in CCs in the NIS database. Surprisingly, the average age was higher with RD, 58.3 years, compared to 44.7 years for CCs. There was also a difference in race, with White patients more frequently diagnosed with a RD (68.2%) than CC (64.1%), and fewer Hispanic RD patients (9.8%) compared to CC (13.4%). Private insurers were the primary payer for CCs (33.0%) while public payers, Medicare and Medicaid, were the primary payer for RD visits (70.6%) (Table 1).

Children admitted with a RD were on average 4.7 years old, whereas children with a CC averaged 3.9 years old ($p < 0.0001$). Most patients were White for both RD (47.3%) and CCs (51.6%). For both RDs and CC, the primary payer was Medicaid. However, when RDs were further evaluated by race, a much higher percentage of White RD patients used private insurance (54.4%) compared to Black (22.0%) and Hispanic (22.8%) patients (Table S4). The NIS, KID, NRD, and NEDS demographic data are further described in Tables 1–4.

DISCUSSION

There is a clear and immediate public health interest relating to the socioeconomic impact and management of RDs to develop sustainable health policy measures. Systematic quantification of the economic burden of RDs at the national level will help illuminate the direct financial consequences of rare conditions in the health system. We captured various types of health-care utilization HCUP data, the largest all-payer databases of discharges in the United States, to estimate the economic burden of patients suffering from RDs by analyzing the inpatient, readmission, and ED cost burden within health care. Overall, discharges with RD-associated codes show disproportionately higher health-care cost and utilization across all age groups compared with discharges with CC diagnoses.

Table 2. Health-care utilization and demographic characteristics, Kids Inpatient Database (KID).

	Rare disease %	Common condition %	*P* value
n	1,200,587	5,065,496	
Age (years)	4.7	3.9	<0.0001
Sex			<0.0001
Female	46.8	52.6	
Male	53.2	47.4	
Race			<0.0001
White	47.3	51.6	
Black	19.9	15.4	
Hispanic	20.7	21.3	
Asian or Pacific Islander	5.1	4.9	
Native American	0.8	0.9	
Other	6.1	6.1	
Payer			0.0003
Private	41.1	43.5	
Medicare	0.5	0.4	
Medicaid	51.1	48.7	
Self-pay	3.0	4.3	
No charge	0.1	0.1	
Location			0.0001
Large metro (central)	34.6	32.7	
Large metro (fringe)	24.3	23.4	
Medium metro	20.5	20.7	
Small metro	8.1	8.7	
Micropolitan	7.5	8.6	
Nonmetro, nonmicropolitan	5.0	5.8	
Elective			<0.0001
Elective admission	15.1	7.0	
Nonelective admission	84.9	93.0	
Discharge disposition			<0.0001
Routine	88.1	96.4	
Transfer to short-term hospital	4.0	1.1	
Transfer to other facility	1.7	0.8	
Home health care	4.7	1.4	
Left against medical advice	0.2	0.2	
Died	1.3	0.1	
Mortality (within group)			<0.0001
Neonate (overall)	0.8	0.6	
<1 year	1.7	0.40	
1–4 years	0.9	<0.1	
5–9 years	0.8	<0.1	
10–13 years	0.9	<0.1	
14–16 years	1.2	<0.1	
Emergency services			<0.0001
No ED services of record	75.6	82.2	
Record of ED services	24.4	17.8	
Transfer in			<0.0001
Not transferred in/ newborn	89.6	95.4	
From acute care hospital	9.1	3.8	
From another type of health facility	1.3	0.8	
Transfer out			<0.0001
Not a transfer	94.3	98.2	
To acute care hospital	4.0	1.1	
To another type of health facility	1.6	0.8	
In-hospital birth			<0.0001
Transferred in from acute/other	58.2	35.5	
Born inside same hospital	41.8	64.5	
In-hospital birth			<0.0001
Complicated	94.4	54.6	
Uncomplicated	5.6	45.4	
Income quartile by ZIP code ($)			<0.0001
1–42,999	30.5	30.6	
43,000–53,999	24.9	24.2	
54,000–70,999	24.1	24.0	
71,000+	20.6	19.1	
Hospital region			0.9618
Northeast	17.0	16.4	
Midwest	21.6	21.6	
South	38.8	39.2	
West	22.7	22.9	
Missing values not displayed			

Demographic characteristics, KID, weighted estimate.
ED emergency department.

Rare diseases have a massive impact in US health care

People with RDs disproportionately utilized health-care systems, particularly with inpatient stays where RD patients had more discharges and readmissions, longer LOS, and greater charges per inpatient stay. Here, we report that for the year 2016, overall national total charges were similar for RDs compared to all other CCs. Moreover, pediatric charges were $34 billion greater for RDs than CCs. Limited reports of the disproportionate cost burden of RD have emerged in recent years. In Hong Kong, inpatient health care of 467 RDs was shown to account for 4.3%, or HKD 1,594,339,530 ($204,402,504), of overall inpatient costs in 2015–2016 [14]. Likewise, a systematic literature review of the

Table 3. Health-care utilization and demographic characteristics, Nationwide Readmissions Database (NRD).

	Rare disease %	Common condition %	*P* value
n	5,155,566	11,053,961	
Age (years)	57.8	44.0	<0.0001
Sex			<0.0001
Female	51.4	59.2	
Male	48.6	40.8	
Payer			<0.0001
Private	23.7	33.9	
Medicare	54.2	25.2	
Medicaid	16.5	33.1	
Self-pay	2.4	3.9	
No charge	0.4	0.5	
Location			<0.0001
Large metro (central)	26.6	26.8	
Large metro (fringe)	27.3	26.1	
Medium metro	20.1	20.2	
Small metro	9.8	10.4	
Micropolitan	9.2	9.4	
Nonmetro, nonmicropolitan	7.1	7.2	
Elective			<0.0001
Elective admission	17.0	21.7	
Nonelective admission	83.0	78.3	
Discharge disposition			<0.0001
Routine	59.0	77.2	
Transfer to short-term hospital	1.2	0.6	
Transfer to other facility	17.8	9.7	
Home health care	17.0	10.2	
Left against medical advice	1.0	1.3	
Died	4.0	1.0	
Income quartile by ZIP code ($)			<0.0001
1–42,999	29.1	30.4	
43,000–53,999	25.6	25.4	
54,000–70,999	25.6	25.2	
71,000+	19.7	18.9	
Diagnoses per discharge (number)			<0.0001
0	0.0	0.1	
1–5	9.2	38.2	
6–10	22.1	29.8	
11–15	27.3	17.4	
Procedures per discharge (number)			<0.0001
0	29.1	30.4	
1–5	25.6	25.4	
6–10	25.6	25.2	
11–15	19.7	18.9	
Same day event			<0.0001
No transfer	95.9	98.0	
Two or more different hospitals	3.8	1.9	
Hospital state residency			<0.0001
Resident	94.3	95.7	
Nonresident	5.7	4.3	
Rehabilitation transfer			<0.0001
No transfer	99.7	99.8	
To rehabilitation, evaluation or other	0.3	0.2	
Missing values not displayed			

Demographic characteristics, NRD, weighted estimate.

Table 4. Health- care utilization and demographic characteristics, National Emergency Department Sample (NEDS).

	Rare disease %	Common condition %	*P* value
n	14,072,499	130,770,243	
Age (years)	58.3	37.7	<0.0001
Sex			<0.0001
Female	53.4	55.7	
Male	46.6	44.3	
Died during ED visit			<0.0001
Did not die	97.4	99.6	
Died in ED	0.2	0.1	
Died in hospital	2.3	0.1	
Payer			<0.0001
Private	22.4	29.2	
Medicare	52.1	19.9	
Medicaid	18.1	33.8	
Self-pay	4.4	12.1	
No charge	0.3	0.4	
Location			<0.0001
Large metro (central)	28.5	30.2	
Large metro (fringe)	23.4	20.3	
Medium metro	21.6	20.8	
Small metro	9.9	10.5	
Micropolitan	9.7	10.5	
Nonmetro, nonmicropolitan	6.4	7.2	
Outcome of ED visit			<0.0001
Treated and released	46.3	89.1	
Admitted to same hospital	51.1	9.0	
Transferred to short-term hospital	2.3	1.6	
Destination unknown	0.2	0.2	
Discharge disposition			<0.0001
Routine	43.6	86.3	
Transfer to short-term hospital	2.3	1.6	
Transfer to other facility	1.5	1.2	
Home health care	0.5	0.2	
Left against medical advice	0.7	1.5	
Admitted as inpatient at ED hospital	51.1	9.0	
Income quartile by ZIP code ($)			<0.0001
1–42,999	30.8	35.2	
43,000–53,999	25.6	26.9	
54,000–70,999	22.2	20.4	
71,000+	19.6	15.8	
Diagnoses per discharge (number)			<0.0001
0	0.0	0.0	
1–5	23.3	80.3	
6–10	28.5	13.4	
11–15	21.7	3.8	
Missing values not displayed			

Demographic characteristics, NEDS, weighted estimate.
ED emergency department.

cost of illness studies assessed the indirect and direct cost of ten rare conditions in the European Union in the year 2010 [15]. Annual direct cost for patients with RDs ranged from €3,858 ($4,334) for scleroderma to €23,066 ($25,911) for hystiocytosis [15]. While these studies analyze far fewer conditions compared to the current study with limited scope, as well as report on non-US

health-care systems, the health-care utilization and financial impact is still large and suggests issues that expand well beyond the United States.

The cost of RD highlights significant concern around payer utilization. With the average cost per patient and total cost for RDs being incredibly high, payers and best practices for delivering quality health care may influence patient outcomes and long-term national spending. In the current study we report that overall, RDs accounted for an estimated $768 billion in inpatient costs alone in 2016, with each inpatient stay averaging $69,275. Following the initial inpatient stay, these costs may increase significantly, with increased rates of readmission and transfer to expensive care options (e.g., discharge to home health care or another facility). As a result, the demands placed on RD patients and their families to manage the cost burden are daunting, particularly when 70.6% require a public payer (Medicare or Medicaid). Moreover, private insurers lack meaningful and universal strategies to reduce RD cost burden, even at the level of orphan drugs that are prescribed to RD patients [27, 28]. In sum, there remains a significant opportunity to streamline RD clinical management and broaden effective treatments to reduce cost burden and improve patient outcomes.

How can the economic impact and system utilization of RDs be reduced through improved management?

Costs associated with a rare disease include frequent and multidisciplinary care expenses, costly procedures, and expensive medications [17, 29]. Diagnostic delays of RDs contribute to this financial burden [17]. The majority of RD patients must leave their health-care system (e.g., out-of-network, out-of-geographical region) and visit at least 3–10 doctors prior over the course of years before receiving a definitive diagnosis and beginning treatment [17, 30]. These diagnostic inefficiencies not only result in the potential of leading to costly and unnecessary treatments [31, 32], but they also can push the patient beyond treatment windows, a major concern for life-shortening conditions. For example, delayed diagnosis has been reported to result in poorer outcomes and substantially increased cost for the rare conditions Krabbe disease and severe combined immunodeficiency [9, 33, 34]. This may also contribute to the high average cost ($89,539) and duration (9.1 days) of pediatric RD inpatient stays reported in the current study. Therefore, to provide the most effective therapies for RD patients, multiple approaches should be taken to address the issues of diagnostic delay and initiating best-in-class treatments for RD patients, such as improved clinician education, continued development of new drugs and gene therapies, and reduced time to diagnosis due to expanded newborn screening.

Study limitations

The overall cost of RDs is likely larger than the current HCUP utilization analysis. HCUP estimate charges likely underestimate the true costs of these conditions because they do not factor direct costs such as professional (e.g., physician, dentist, and other clinicians) fees, indirect costs (e.g., lost work productivity), and secondary downstream health-care effects.

HCUP databases are useful for giving estimates on a national scale. There are, however, several limitations of HCUP sample data: (1) the frequencies represent hospital discharges, and not patients, and thus, recurrent hospitalizations by the same patient appear as distinct observations; (2) the prevalence data may be affected by hospital coding; (3) databases do not capture outpatient encounters, and the full health-care utilization of patients suffering from RDs is underrepresented; (4) data do not represent the complete universe of all discharges in the United States since not all states participate; (5) hospital charges represent the bill that is sent to the payer, not the actual cost to the hospital which may vary, depending on reimbursement, if any; (6) the number of rare conditions included in this study primarily correspond to ICD-10 codes provided by Orphanet, which is far from the nearly 7,000–10,000 rare conditions currently described; (7) patients with undiagnosed rare conditions are not included in the RD cohort; (8) conditions are heterogeneous and genetic basis may affect only a disease subpopulation; (9) the ICD-10 codes used also include CC, which are unable to be separated from RDs, and thus are included in the health-care utilization and cost data reported here; and (10) we did not distinguish conditions in Table S3 that are indicated as having a genetic basis due to genetic susceptibility, genetic role in the phenotype, or disease-causing somatic mutation(s) from those with disease-causing germline mutation(s).

CONCLUSIONS

The cost of RDs needs to be calculated to better allocate resources and to find ways to ameliorate individual and societal costs. Resources should be allocated not according to the prevalence of a certain disease, but rather according to where intervention yields the most cost-efficient value. This study demonstrates that during the year 2016, the total national cost of RDs was disproportionate and considerably greater than CCs. Pediatric and adult populations with RDs had longer hospitalizations, more charges per admission, more readmissions, and more mortality than CC patients. Improvements in patient management and health-care utilization strategy may lead to substantial improvement to clinical care and decreased cost burden. Thus, expanded newborn screening tests, health-care-focused artificial intelligence, and other approaches to detect these conditions early in the disease course must be developed and incorporated into the clinical decision-making process to streamline patient care and reduce cost.

DATA AVAILABILITY

Data sets are available upon request to the corresponding author (S.R.G.) and can be shared after consulting our local institutional review board and the Agency for Healthcare Research and Quality.

CODE AVAILABILITY

Computer code used to generate data be accessed from the corresponding author.

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AUTHOR CONTRIBUTIONS

S.R.G., A.A.N.-O., and M.S. conceptualized the study and provided the methodology; S.R.G. and M.S. participated in the HCUP data curation and analysis; S.R.G. participated in funding acquisition and project administration; S.R.G. and A.A.N.-O. drafted the first version of the manuscript; all authors participated in the writing, reviewing and editing of the manuscript and agreed on the final version for submission (based on the CRediT Contributor Roles Taxonomy categories).

ETHICS DECLARATION

This research was approved by the Advocate Aurora Health investigational review board.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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