FACTORS AFFECTING QUALITY OF LIFE OF CAREGIVERS OF CHILDREN WITH GLYCOGEN STORAGE DISEASE TYPE 1

by

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BS Biological Sciences (Genetics, Cell, and Developmental Bio), BA French

Arizona State University, 2016, 2016

Submitted to the Graduate Faculty of

the Department of Human Genetics - Genetic Counseling

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2018

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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June 12, 2018

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ABSTRACT

Glycogen storage disease (GSD) is a family of inherited metabolic disease (IMD), of which the most common type is autosomally inherited GSD type 1 (GSD1). The symptoms of GSD1, which vary among patients, are primarily hepatic in nature, though a multitude of other body systems are involved to an extent which is dependent on level of metabolic control in the patient. Treatment of the disease is rigorous and involves frequent feeds to avoid life-threatening hypoglycemic episodes, avoidance of certain sugars, and in many, consumption of uncooked cornstarch between meals to help maintain near-normal blood glucose levels. While missing scheduled feeds can have dire consequences up to and including seizures, brain damage, and death, caregivers of children with GSD1 face risks of not only undertreatment, but also overtreatment of the disease. As a rare disease, GSD1 and its management have not been well-studied in terms of effect on the quality of life (QOL) of parents caring for affected children. We administered to GSD1 caregivers the Pediatric Inventory for Parents (PIP), PROMIS Emotional Distress-Anxiety Short Form 8a measure (PROMIS), and a novel survey of disease management, mental healthcare usage, and social media usage to add to the literature a more complete understanding of caregiver QOL. Caregivers had levels of distress higher than what has previously been published and were largely interested in seeking mental healthcare for

discussion of caregiver-related challenges. Distress was driven mostly by the domain of Emotional Distress and less so by Medical Care as evidenced by the PIP and further supported by caregiver report of overall comfort with the dietary management of GSD1. Social media was reported as an overall positive support system and a resource for making medical decisions, though may be associated with increased anxiety in some caregivers. Increased support for caregiver QOL, especially in terms of emotional wellbeing, is indicated by the results of this study. The goals and results of this study demonstrate public health relevance by assessment of unique challenges facing the GSD1 caregiver population and contributing to the assurance that these caregivers are linked with necessary services and competent healthcare providers.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

Thank you to the patients and families who made this project possible and gave me something greater to focus on outside of myself. As I struggled with severe major depression from the start to finish of this work, knowing that there was a meaningful endpoint to this work at times reminded me that existence is not futile and that this pain was temporary. In this context, I feel the completion of this document speaks more to the importance of empathy and understanding for rare disease families than to any personal strength on my part in surviving this mental illness long enough to put these words on paper. I have thought at times during my genetic counseling training, “What right do I have to feel this level of depression when I am not raising a child with a life threatening genetic disorder, when I am not slowly developing signs of Huntington disease like my parent did before me, when I am not a TP53 positive ten-year old facing near-certain risk of cancer, when I am not finding out my pregnancy screens positive for a neonatal-lethal chromosome abnormality…”? And so on. Studying genetics within the Graduate School of Public Health has certainly raised my awareness of a wide range of health conditions that are out to get us, from the rarest to the most rampant, from the inherent to the environmental, from the curable to the devastating, and everything in between. But as I have sat across the table from all of those people I am not, the caregivers and patients living with genetic risks I have studied didactically but have not lived, I have seen much heartache, but more importantly, even more resiliency. It is all too easy to compare one person’s own struggles with another’s, and say, “I

know what that's like", or "At least you don't have X, Y, or Z". I hope that my experience as a patient with mental illness has bolstered my ability to remove these statements from my vocabulary as a genetic counselor and just as a human being out in the world. Whatever our "deal" is, living with genetic disease, caregiving for someone with a genetic disease, or struggling to function with clinical depression in spite of being "genetically healthy" (if there is such a thing), our feelings are valid and deserve to be heard without judgment or minimization from others (or from ourselves!). To end the digression from the document at hand, this goes for the caregivers whose voices are heard, in at least some small way, in the following pages. And because my voice is in these pages too, thanks to my thesis committee and other mentors, loved ones, and psychiatric providers who have helped immeasurably (especially at times when I did not want help) to ensure that I have voice left to give and worthwhile experiences left to live.

1.0 INTRODUCTION

Glycogen storage diseases (GSDs) constitute a family of rare inherited metabolic diseases (IMDs) affecting the assembly, disassembly, and regulation of glycogen in the human body. As many as 14 discrete GSD types have been described, of which GSD type 1 (GSD1), also known as von Gierke disease, is the most common and the first to be enzymatically described. GSD1 is associated with a wide range of clinical presentations, from, rarely, asymptomatic hepatomegaly, to long-term hepatic and renal diseases, to life-threatening hypoglycemia following a short fast (Derks and van Rijn 2015; Burda and Hochuli 2015; Chen et al 2017).

GSD1 is a pan-ethnic disease occurring at a live birth rate of 1 in 100,000 (Shieh et al 2002; Froissart et al 2011). GSD1 is further split into two subtypes, both of which are inherited in an autosomal recessive pattern. 80% of patients with GSD1 have the GSD1a subtype, caused by mutations in the *G6PC* gene, with the remaining 20% of patients being categorized as having GSD1b, caused by mutations in the *SLC37A4* gene (Kishnani et al 2014). Both GSD1a and GSD1b primarily affect the liver, where glycogen and fat are abnormally stored, with involvement of other body systems to an extent that can be dependent on level of metabolic control in the patient (Kishnani et al 2014, Talente et al 1994). In addition to hepatomegaly and risk of hepatocellular adenomas that may transform to malignancy, patients may have renal, hematologic, endocrine, dental, musculoskeletal, and neurological manifestations (Burda and Hochuli 2015; Kishnani et al 2014; Talente et al 1994; Austin et al 2013; Rake et al 2002; Lee et

al 1995; Dellinger et al 1998; Minarich et al 2012; Chen et al 2017). GSD1b includes the metabolic profile and other features of GSD1a with the added features of myeloid dysfunction often leading to neutropenia and increased risk of recurrent bacterial infection (Chou et al 2015; Burda and Hochuli 2015; Kishnani et al 2014; Chou et al 2010).

Above all else, the mainstay of treatment for GSD1 is the avoidance of fasting to prevent hypoglycemic episodes, and individuals should ideally void their diet of sucrose, fructose, and lactose (Kishnani et al 2014). Uncooked cornstarch can be consumed between meals to help promote near-euglycemia (Kishnani et al 2014). Even short fasts between meals leave patients vulnerable to metabolic decompensation; a long fast overnight as the patient and his/her caregiver sleeps presents a greater risk of prolonged hypoglycemia. Caregivers of children with GSD1 must wake often to feed their child throughout the night with food or uncooked cornstarch, trust nasogastric or gastrostomy tubes to deliver continuous nocturnal feeds, or when the child is old enough, implement a newer starch, waxy maize heat modified starch (Glycosade®) that lasts longer than uncooked cornstarch (Kishnani et al 2014; Weinstein and Wolfsdorf 2002; Chou et al 2010; Bhattacharya et al 2015; Ross et al 2015). Consequences of a skipped day or night feed can lead, in the most severe cases, to death; in other cases, the resultant prolonged hypoglycemia can cause seizures, brain damage, and delays in growth and development. Caregivers face risks of under- and over-management of their family member's disease, both of which can have consequences; the resulting stress has the potential to interfere significantly with the basic needs and wellbeing of the caregivers themselves (Storch et al 2008).

Existing literature explores quality of life (QOL) in patients with GSDs and in caregivers of patients with inborn errors of metabolism or more broadly, rare diseases, but there is a gap in knowledge about QOL specifically in caregivers of family members with GSDs (Storch et al

2008; Sechi et al 2014; Siddiq et al 2016; Michalik 2014; Dellve et al 2005; Fabre et al 2014). Research in this area has been limited in scope by small sample sizes, sampling families who receive care within a single center or region, or examining parent QOL only in relationship to the affected child's QOL without elucidating factors affecting parent QOL (Storch et al 2008; Sechi et al 2014; Siddiq et al 2016). The goal of this study was to gain a more complete understanding of QOL in caregivers of children with GSD1 and factors that influence their levels of anxiety and distress. The results of this study have the potential to shape the way healthcare providers counsel caregivers on management of their child's rare disease with more awareness of the effect certain resources, treatment regimens, and aspects of the disease itself have on the caregiver and on the family. This may guide referrals and resources provided for caregivers. By increasing knowledge of one rare disease, this study also stands to increase support for the rare disease community, which achieves, on broader levels, so much when given so little (Aymé et al 2008).

1.1 SPECIFIC AIMS

Specific Aim 1: Identify caregivers of family members with GSD1.

- These caregivers were identified through the website and newsletter of the Association for Glycogen Storage Disease (AGSD), as well as through the list-servs of professional organizations relevant to genetic metabolic disease care – National Society of Genetic Counselors (NSGC) Metabolic/Lysosomal Storage Disease Special Interest Group (SIG), metab-L, Genetic Metabolic Dietitians International (GMDI) – thereby reaching a broader and more diverse audience than a single-site study.

Specific Aim 2: Describe the QOL in these caregivers through published and/or validated survey tools.

- The survey tools included the Pediatric Inventory for Parents (PIP) and the PROMIS Short Form 8a Scale of Anxiety (PROMIS). The PIP was obtained with permission through Children's National Medical Center through contact with this tool's lead author. The PROMIS was obtained electronically at no cost from The Assessment Center.
- These survey tools quantitatively described anxiety and distress in this population.

Specific Aim 3: Develop a GSD1-specific survey tool incorporating Likert-scale items, multiple choice questions, and short-response questions to complement the aforementioned QOL scales.

- This tool was developed through an unstructured interview with a metabolic geneticist, an unstructured interview with two caregivers who together parent a child with GSD1a, review of literature and management guidelines, and guidance from a metabolic genetic counselor.
- The self-developed survey tool captured quantitative data about factors that may impact caregiver QOL specifically in GSD1 that would be otherwise missed through a generalized survey tool.
- This survey portion followed the QOL scales in one Qualtrics web survey.

Specific Aim 4: Analyze data by use of descriptive and inferential statistics.

- The statistical program used for analysis and generation of illustrative figures was R, version 3.5.0.

2.0 LITERATURE REVIEW

2.1 GLYCOGEN STORAGE DISEASE

GSDs constitute a heterogeneous group of as many as 14 discrete metabolic disorders involving deficiencies or abnormalities in the body's ability to build, break down, or regulate glycogen (Derks and van Rijn 2015; Burda and Hochuli 2015). Glycogen is needed to support the body in times of fasting and exertion in order to maintain homeostatic blood glucose. The specific deficiencies or abnormalities present in protein functionality in glycogen metabolism, as well as the tissues most affected, differentiate the many types of GSDs from one another. While individual clinical presentations may vary greatly among the types of GSDs, because glycogen is amply found in hepatic and muscle tissues, commonalities may include hypoglycemia, hepatomegaly, rhabdomyolysis, muscle weakness, exercise intolerance, and cardiomyopathy (Burda and Hochuli 2015; Chen et al 2017). Dietary supplementations or exclusions remain the most common and effective therapy for GSDs, in addition to organ transplantation when necessary (Chen et al 2017). This literature review will focus on GSD type 1, as this was the population studied in this project.

2.1.1 Glycogen Storage Disease Type 1

GSD1, also known as von Gierke disease, is an autosomal recessive metabolic disorder consisting of subtypes 1a and 1b, together occurring in live births at a rate of 1 in 100,000 (Shieh et al 2002; Froissart et al 2011). GSD1a is the most frequent type overall, accounting for 80% of GSD1 patients. While GSD1 is a pan-ethnic disease, the frequency of both 1a and 1b subtypes together in the Ashkenazi Jewish population is elevated to 1 in 20,000 prevalence (Kishnani et al 2014, Ekstein et al 2004).

2.1.1.1 Biochemical Basis of Disease

Glycogen, particularly in the liver, serves a vital role in energy storage as an interconvertible and highly branched form of glucose. The interconvertible property of glycogen allows for glucose from food to be stored through the process of glycogenesis. Then, at a later time such as during energy expenditure or fasting periods, the glycogen goes through the process of glycogenolysis to be broken into glucose to be used for energy (Adeva-Andany et al 2016; Kilimann and Oldfors 2015). In healthy individuals, glucose derived from glycogenolysis is dephosphorylated from glucose-6-phosphate (G6P) in the endoplasmic reticulum of liver cells and is then able to leave the liver cell to be of use in other tissues of the body (Adeva-Andany et al 2016; Pan et al 2011).

Both subtypes 1a and 1b of GSD are primarily known phenotypically by impaired glucose homeostasis in affected individuals, involving the production and regulation of glucose-6-phosphatase (G6Pase) (Pan et al 2011). In cells, notably in the kidney and liver, G6Pase spans the membrane of the endoplasmic reticulum (Gerin et al 1997; Annabi et al 1998). It is joined there by the glucose-6-phosphate transporter protein (G6PT), which is involved in transporting G6P into the lumen of the endoplasmic reticulum where it can be hydrolyzed by G6Pase into

glucose and phosphate (Pan et al 2011). Abnormalities in G6Pase or G6PT prevent free release of glucose from the liver cell into the bloodstream, causing G6P to follow pathways that use this glucose. As such, in GSD 1a and 1b, the inaccessible phosphorylated glucose accumulates as excess glycogen, as well as in the form of fatty acids, lactic acid, and uric acid. These may serve as markers on a metabolic workup for a patient either during the diagnostic period or to investigate a patient's metabolic control (Adeva-Andany et al 2016; Burda and Hochuli 2015).

2.1.1.2 Glycogen Storage Disease Type 1a

Clinical Features

GSD1a is primarily a hepatic disorder with additional involvement of other systems to an extent that is dependent on level of metabolic control in the patient. Children presenting with GSD1a universally have hepatomegaly due to abnormal storage of glycogen and fat (Kishnani et al 2014, Talente et al 1994). Relative liver size typically decreases with age (Kishnani et al 2014). Even in the presence of adequate treatment and metabolic control, patients with GSD1a may develop liver lesions, most commonly hepatocellular adenomas that have the potential to progress to malignancy, hepatocellular carcinoma (Kishnani et al 2014). The adenomas themselves initially present before 15 years of age on average (Kishnani et al 2014). Adenoma size has been documented to regress with achievement of better metabolic control (Burda and Hochuli 2015; Beegle et al 2014).

Glycogen is also abnormally deposited in the kidney. Renal enlargement may not be appreciated on physical exam but is usually detectable on imaging (Burda and Hochuli 2015; Kishnani et al 2014). The clinical consequences of renal involvement in GSD1a may include proximal and distal tubular dysfunction as well as glomerular injury. These complications may

significantly affect renal functioning to the point of end-stage renal disease (Kishnani et al 2014). Hypercalciuria, urinary tract calcifications, and kidney stones can be seen at high rates even in young children with GSD1a (Kishnani et al 2014). Additionally, the chronic kidney disease seen in GSD1a can be similar to diabetic nephropathy (Burda and Hochuli 2015; Kishnani et al 2014).

Hematological manifestations of GSD1a can include anemia, easy bruising, and easy and/or prolonged bleeding (Burda and Hochuli 2015; Kishnani et al 2014; Talente et al 1994). Anemia can present in both males and females and has been seen in association with the presence of renal insufficiency as well as hepatocellular adenomas (Kishnani et al 2014; Burda and Hochuli 2015). Though underlying cause is unclear, menorrhagia has also been observed in a subset of women with GSD1a (Austin et al 2013).

In regard to endocrine abnormalities in patients with GSD1a, delayed puberty, growth retardation, and short stature have been observed in both males and females (Burda and Hochuli 2015; Kishnani et al 2014; Rake et al 2002). Additionally, polycystic ovaries have been seen at an increased level when compared to that seen in the general population in both pre- and post-pubertal females without clear evidence of impaired fertility; fertility and pregnancy in affected women have overall been reported as normal (Lee et al 1995; Kishnani et al 2014; Martens et al 2008). In post-pubertal females, polycystic ovarian syndrome is often associated with hyperinsulinemia, which may play an etiological role (Lee et al 1995).

Other clinical features of GSD1a include a characteristic round and full-appearing face, often described as “doll-like”, which is due to abnormal fat distribution (Rake et al 2002, Chen et al 2017). Patients may be at increased risk for dental caries due to frequent feeds (Dellinger et al 1998). Due to abnormal fat and glycogen storage in the liver, truncal obesity is also observed (Rake et al 2002). In addition, delayed bone growth as well as low bone mineral density in both

adults and children is associated with poor metabolic control in GSD1a; in absence of optimal treatment and control, complications such as osteopenia or osteoporosis may develop (Burda and Hochuli 2015; Minarich et al 2012). Poor metabolic control leading to hypoglycemia and hyperlactacidemia can damage cerebral function and also cause seizures or coma in patients with GSD1a; hypoglycemic seizures can often be the presenting symptom in an infant (Kishnani et al 2014; Rake et al 2002; Chen et al 2017).

Molecular Basis

GSD1a is caused by mutations in the *G6PC* gene, which is located at chromosome 17q21 (http://www.uniprot.org; Froissart et al 2011). *G6PC* consists of 5 exons and encodes the protein G6Pase (Chou et al 2015). At least 89 mutations have been identified in *G6PC* in GSD1a patients, including 58 missense, 10 nonsense, 17 insertion/deletion, 3 splicing, and one no-stop mutations (Chou et al 2015). Of the missense mutations reported, 50 have been investigated for enzymatic activity; 18 of these mutations retain some level of enzymatic activity while the remaining do not exhibit any residual activity (Chou et al 2015).

2.1.1.3 Glycogen Storage Disease Type 1b

Clinical Features

GSD1b includes the metabolic profile and other features of GSD1a with the added involvement of a few distinguishing features (Chou et al 2015). A comparison of the shared features between the two types shows that some symptoms are more common and/or more severe in GSD1b than they are in GSD1a. Such symptoms include splenomegaly, diarrhea, and lower than expected

adult height (Rake et al 2002). On the other hand, hyperlipidemia is less severe and less common in GSD1b (Rake et al 2002).

One of the main differences between GSD1a and 1b is that individuals with GSD1b usually demonstrate myeloid dysfunction, developing neutropenia with variable severity, leading to increased risk of recurrent bacterial infection (Chou et al 2015; Burda and Hochuli 2015; Kishnani et al 2014; Chou et al 2010). The presence of neutropenia in a patient with GSD1b is often a precursor to development of inflammatory bowel disease (IBD), or Crohn disease-like enterocolitis (Burda and Hochuli 2015; Kishnani et al 2014; Chou et al 2010). IBD has been shown to increase the severity of anemia in these patients (Burda and Hochuli 2015; Kishnani et al 2014). Additional features which can be a result of neutrophil dysfunction are the presence of dental and other oral complications such as gingivitis or progressive periodontal disease (Dellinger et al 1998).

Compared to GSD1a, published data on pregnancy in GSD1b is rare; however, successful pregnancies have been reported (Dagley et al 2010). Presence of IBD and/or more severe neutropenia, both of which were milder or nonexistent in the pregnancies reported, are associated with poor outcomes, which can include fetal demise in non-GSD1b populations. The reported pregnancies therefore cannot rule out that these symptoms may be a factor affecting pregnancy in GSD1b as well (Dagley et al 2010).

Molecular Basis

GSD1b is caused by mutations in the *G6PT,* or *SLC37A4*, gene, which is located at chromosome 11q23 (Hirawa et al 1999; Annabi 1998). *SLC37A4* contains 9 exons and encodes the protein G6PT. At least 92 individual mutations have been identified in *SLC37A4* in GSD1b patients.

These consist of 39 missense, 11 nonsense, 22 insertion/deletion, and 19 splicing mutations (Chou et al 2015).

2.1.2 Diagnosis

GSD1 is included in the differential diagnosis for a patient who presents with clinical features of the disease, which in most GSD1 patients occurs between 3-6 months of age (Kishnani et al 2014; Chen et al 2017; Rake et al 2002). This is when the affected infant begins to sleep for longer intervals during the night and therefore have longer periods of fasting (Kishnani et al 2014). The symptoms that typically cause concern at this time are the distended abdomen due to enlarged liver as well as the symptoms of hypoglycemia, which may include seizures (Kishnani et al 2014). GSD1 is distinguished from other types of GSD by the short length of fast necessary to evoke hypoglycemia, the relatively large size of the liver, and by the biochemical profile by laboratory testing (Froissart et al 2011).

2.1.2.1 Laboratory Testing

Laboratory studies on a patient's blood can serve as initial or further evidence of a diagnosis of glycogen storage disease type 1, while enzyme assay on liver tissue from a biopsy can be diagnostic for GSD1a. Enzyme activity for G6Pase performed on liver tissue from biopsy does not detect GSD1b (Kishnani et al 2014). The laboratory findings in a patient's blood can include hypoglycemia, lactic acidosis, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and hyperlipidemia (Kishnani et al 2014; Chen et al 2017). While neutrophil counts can be normal in the first few years of life, neutropenia would be suggestive of type 1b over 1a, though it cannot strictly rule out 1a (Kishnani et al 2014).

2.1.2.2 Molecular Genetics Studies

The identification of the genes involved in GSD1a and 1b with advances in sequencing technology has allowed for a confirmed diagnosis without the invasive procedure of liver biopsy. By 2002 (Matern et al), 76 mutations were identified in *G6PC* leading to GSD1a and 65 mutations were identified in *SLC37A4* leading to GSD1b. Those numbers rose to 89 and 92 for GSD1a and GSD1b respectively by 2015 (Chou et al 2015). Over half of the mutations identified appear to be private mutations for each family of an affected person; however, patients with ethnicity that is Ashkenazi Jewish, Chinese, Hispanic, Japanese, or Turkish are more likely to have population-specific mutations in common (Matern et al 2002; Froissart et al 2011). In some such populations, the detection rates of causative mutations through targeted mutation analysis of either *G6PC* or *SLC37A4* approaches 100%. For example, in one study, 30 out of 30 Ashkenazi Jewish subjects with GSD1a were homozygous for the R83C mutation, for which the Ashkenazi Jewish carrier frequency was found to be 1.4% (Ekstein et al 2004). In patients with a more heterogeneous ethnic background, the detection rate can be lower, possibly due to deletions undetectable by current sequencing methods, or mutations in the promoter region of the gene involved, which would also fall under the limitations of current detection capabilities (Kishnani et al 2014). However, complete sequencing of either *G6PC* or *SLC37A4* detects a patient's causative mutations, no matter their ethnicity, approximately 95% of the time, with some studies achieving rates of detection between 86-100% (Bali et al 2016; Seydewitz and Matern 2000; Melis et al 2005). Overall, most disease-associated mutations are missense in nature, and may cause a completely null enzymatic phenotype or result in some residual activity (Chou et al 2015).

2.1.2.3 Prenatal Testing

Mutations causative of GSD1, if identified in a previously affected child or in prospective parents through carrier screening, can be detected prenatally by invasive prenatal diagnostic testing such as amniocentesis or chorionic villus sampling (Wong 1996). For GSD1a, before such analysis was possible, prenatal testing was only achievable through fetal liver biopsy with enzyme assay; this was because G6Pase is not expressed in blood or skin cells, which are analyzed prenatally through amniotic fluid or chorionic villus sampling (Goldberg et al 1993; Lam et al 2000). Prior to discovery of the gene responsible for GSD1b, prenatal diagnosis for this type was never achieved (Froissart et al 2011). A newer technology, noninvasive prenatal testing (NIPT), using cell-free fetal genetic material, may be available in the future to detect monogenic disorders like GSD1 (Chiu et al 2018).

2.1.2.4 Newborn Screening

Neither GSD1a nor 1b GSD1b are included on the Recommended Uniform Screening Panel (RUSP) of the United States Department of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children, or any of the newborn screening panels in the individual states or territories (http://www.babysfirsttest.org/).

2.1.3 Inheritance and Recurrence Risk

As in most other GSDs, GSD1a and GSD1b are both inherited in an autosomal recessive manner. An affected individual may be homozygous for a disease-causing mutation or compound heterozygous for two disease-causing mutations (Chen L et al 2002; Shieh J et al 2002). A couple in which the male and female partner are carriers for a disease-causing mutation will have

a 25% chance with each pregnancy of having an affected child. An affected individual in couple with a non-carrier will produce children who are carriers for a disease-causing mutation 100% of the time.

2.1.4 Genotype-Phenotype Correlation

The preponderance of private mutations in GSD1 does not lend itself to a clear genotype-phenotype correlation, and there is even phenotypic heterogeneity between siblings sharing the same mutations (Rake et al 2000, Matern et al 2002, Melis et al 2005, Chou et al 2015). However, it has been noted that for *G6PC*, mutations in the transmembrane helices of the protein reduce its enzyme activity more severely than mutations in the luminal loop of the protein (Pan et al 1998; Shieh et al 2002). Other studies have developed specific knowledge of enzymatic activity by mutation type, and by specific mutation in some cases. For example, it has been shown that mutation R415X in *SLC37A4* retains 47% of expected activity which would suggest patients with this mutation on one of their alleles would have a less severe phenotype. However, a review of patients with this mutation has shown that they may yet have neutropenia, a marker of disease severity (Melis et al 2005).

2.1.5 Management

2.1.5.1 Dietary Management

The dietary management is the same for GSD1a and GSD1b and includes primarily the avoidance of fasting to prevent hypoglycemic episodes (Kishnani et al 2014). In addition to frequent feeding, individuals with GSD1 should ideally consume a diet free of sucrose, fructose,

and lactose. Because these limitations exclude fruit and dairy, rich in certain vitamins like calcium and vitamin D, diet should be supplemented with appropriate vitamins and minerals to avoid nutritional deficiencies (Kishnani et al 2014). In the early 1980s, it was found that the addition of uncooked cornstarch between meals helped to promote near-euglycemia; since that recommendation, it has been found that uncooked cornstarch feeds may decrease the frequency of long-term complications of the disease (Kishnani et al 2014; Chou et al 2010; Weinstein and Wolfsdorf 2002). Frequent feedings are effective during the day, but are not always feasible at night, leaving patients vulnerable to hypoglycemia during this time. As such, infants can be treated with nocturnal continuous glucose feeds via nasogastric or gastrostomy tube, and are often switched to night time feeds of a newer starch, waxy maize heat modified starch (Glycosade®) at approximately three years of age (Kishnani et al 2014; Weinstein and Wolfsdorf 2002; Chou et al 2010; Bhattacharya et al 2015; Ross et al 2015).

2.1.5.2 Pharmacological Management

In individuals with GSD1b, granulocyte colony-stimulating factor (G-CSF) is used to treat neutropenia by increasing the bone marrow's production of neutrophils, which then decreases frequency and severity of infections and inflammatory bowel disease in these patients (Kishnani et al 2014). Adjunct pharmacological therapies may also be used to treat some of the complications of GSD1a and GSD1b, such as hyperlipidemia, hypertension, hyperuricemia, and microalbuminuria (Kishnani et al 2014).

2.1.5.3 Surgical Management

Liver transplantation is not indicated in all patients with GSD1 but is considered for patients in whom proper dietary treatment has not been as effective as expected and/or there is evidence of

hepatocellular carcinomas (Kishnani et al 2014; Chen et al 2017; Rake et al 2002). If transplant is performed, hypoglycemia is corrected, and growth improves after the procedure, but ultimate improvement in outcomes for renal disease have not been clearly demonstrated (Chen et al 2017). Because of this, surgery is not routinely recommended except for those cases of end-stage cirrhosis or carcinoma (Chen et al 2017; Kishnani et al 2014). Hypoglycemia is corrected in both types 1a and 1b, though for patients with GSD1b, it is important to note that neutropenia is not corrected following liver transplant (Kishnani et al 2014; Chen et al 2017). The immunosuppressive medications used following the liver transplant and the procedure itself can lead to an adverse outcome on patients' renal health even when renal disease was not present at the time of the transplant (Kishnani et al 2014). Kidney transplantation has not been shown to correct hypoglycemia, though it has been performed in the context of renal failure (Chen et al 2017). Another surgical approach to GSD1b that shows promise is bone marrow transplantation. Bone marrow transplantation has been studied in a mouse model, in which transplant addressed the loss of *SLC37A4* expression in the bone marrow and neutrophils. The results from the mouse model study suggest that bone marrow transplantation may restore near-normal myeloid function while not correcting the metabolic profile (Kim et al 2006). Bone marrow transplantation has been reported in at least one patient for whom the symptoms related to neutropenia had become life-threatening despite treatment with granulocyte colony-stimulating factor (G-CSF). In this patient, morbidity associated with frequent infections and inflammatory bowel disease (IBD) was reduced, and the patient better tolerated uncooked cornstarch (UCCS) feeds leading to improvement of metabolic control (Pierre et al 2008).

2.1.6 Prognosis

Earlier diagnosis and development of more effective treatments starting in the late 20th century have helped in decreasing the risk of prolonged hypoglycemia which can lead to significant morbidity, even mortality. Death as a result of the disease-associated metabolic dysregulation is becoming less frequent, and individuals with GSD1 are now living into adulthood, though not without complications of their disease (Rake et al 2002). Prevention of hypoglycemia allows children with GSD1 to achieve normal growth and adult height in many cases and decreases the chance of liver adenoma development and damage to cerebral function (Kishnani et al 2014; Chen et al 2017; Rake et al 2002). Certain biochemical features may persist despite treatment, for example, hyperlipidemia persists, more so in GSD1a than GSD1b, and can range from mild to severe (Rake et al 2002). The effect of treatment on kidney health and the chance of developing end-stage renal failure remains unclear (Rake et al 2002; Chen et al 2017). Complications including hepatic lesions, kidney dysfunction, and anemia are less frequent and less common in patients who began dietary treatment with UCCS at an earlier age (Weinstein and Wolfsdorf 2002). Additionally, a newer starch, extended release waxy maize starch, or Glycosade®, has been shown to maintain euglycemia for longer periods of time when compared with UCCS (Bhattacharya et al 2015). This has allowed for the use of the new starch overnight, allowing patients and caregivers to sleep through the night without sacrificing metabolic control (Bhattacharya et al 2015; Ross et al 2016). This starch has yet to be studied in children under 5 years of age or in patients during the daytime (Ross et al 2016). The starch is also new enough that studies regarding differences in long term prognosis have yet to be completed (Ross et al 2016).

2.2 CAREGIVERS

2.2.1 Defining Caregivers

The term “caregiver” is a general one which may encompass individuals who provide ongoing assistance to a person with special needs, often related to health status, whether in a formal or informal sense. This paper and respective research focuses on caregivers in the informal sense, meaning that they do not provide care as part of a paid profession, but provide care due to a close relationship with the affected individual. While this paper will focus on caregivers with a parental relationship or parental-type relationship, informal caregivers may also be siblings, friends, adult children, partners, or have a different relationship to the affected individual. Caregivers assist with activities of daily living (ADLs), which can include tasks involved with the nutrition, hygiene, grooming, transportation, and finances. They often also make medical and safety-related decisions for the affected person. Due to the close relationship that generally exists between a caregiver and the recipient of the care, there may be numerous hardships, but also benefits of being a caregiver. Caregiving may come with mental, psychological, and physical strain, but may also be associated with development of a closer relationship between the involved parties, as well as a sense of gratification due to providing for the needs of the affected individual (Fruhauf 2009).

2.2.1.1 Parent Caregivers in Rare Disease

When a child has a long-term illness or life-spanning disease, parents, relatives, or others in a parental role, are tasked with additional demands and responsibilities relating to their child’s disease. Tasks associated with managing the child’s illness are a de facto feature of providing

care to the child, which may consist of obtaining knowledge of the disease and management options, identifying and responding to both ongoing and acute symptoms, and utilizing healthcare services and support networks. Additionally, a significant result of taking on such a caregiver role is the necessity to accommodate for or adapt to the illness' effect on familial and other relationships (Smith et al 2013).

The above demands apply to parents caring for children with chronic diseases that are relatively common, such as congenital heart disease, who may experience a high level of distress associated with their child's condition and caretaking tasks (Lawoko and Soares 2002). However, in the world of rare disease, parents may meet greater challenges in many areas, such as initially securing a diagnosis, obtaining accurate medical information regarding treatment and prognosis, becoming competent with complicated and perhaps poorly-studied medical management options, and identifying sources of social support (Dellve et al 2006; Michalik 2014; Aymé et al 2008). Faced with these challenges, parents of children with rare diseases have often been drivers of advocacy, education, and research on local to global scales (Aymé et al 2008). While this grand level of involvement is not necessitated by the diagnosis of a rare disease in one's child, countless organizations now exist to support rare disease parents as a result of these efforts (Aymé et al 2008).

Parents of children with diagnosed or undiagnosed rare diseases often face a high degree of uncertainty and emotional burden which produce in many caregivers, who are mostly mothers, a clinical level of anxiety and/or depression (McConkie-Rosell et al 2018; Picci et al 2015; Yanes et al 2017; Pelentsov et al 2016). The specific needs and characteristics of parents caring for children with rare diseases are not well-delineated in the literature, but have been described as including feelings of isolation, fear of the future, dissatisfaction with level of knowledge of

healthcare providers, financial difficulties, emotional distress, yet overall confidence in personal caregiving abilities and expertise in their child's rare disease (Pelentsov et al 2016; Yanes et al 2017; Picci et al 2015; Michalik 2014; McConkie-Rosell et al 2018). Though the burden of caregiving for a child with a rare disease is high, many caregivers become experts in their child's care, adapt to uncertainty, actively engage with healthcare providers, develop active coping strategies, and in some cases, give back to the rare disease community in long-lasting and meaningful ways (Dellve et al 2006; Picci et al 2015; McConkie-Rosell et al 2018; Pelentsov et al 2016; Aymé et al 2008).

2.2.2 Support for Caregivers in Rare Disease

2.2.2.1 Roles of Support Groups

While the literature is limited for the evaluation of measurable outcomes, perceived benefits, and availability of support groups for specific disorders such as GSD1, it is known that support groups and other advocacy organizations for rare diseases have had, and continue to have, an impact on the care of rare disease patients and their families. These organizations, which are frequently founded by parents or relatives of a child who has a rare disease, participate in activities such as raising funds for research, performing research activities, educating families and healthcare providers, lobbying and advocating at a local or even national level, and allowing for social support among individuals and families experiencing the effects of the same rare disease (Aymé et al 2008).

2.2.2.2 Online Support

The internet and social media can be useful tools, especially in rare disease, because they can connect families with similar experiences who may otherwise never meet another individual living with that condition. Additionally, families who do not have easy access to specialized healthcare providers familiar with the child's disease may turn to the internet for answers (Pelentsov et al 2016). For caregivers of children with rare diseases such as IMD, the internet has been a tool identified to assist in accessing information about the child's disease, as well as communicating with other families in a similar position (Siddiq et al 2016; Khangura et al 2015). However, the literature is limited to nonexistent regarding the effect of online resources and social media, leaving the question open as to whether there is a measurable difference in the quality of life for patients or their families as a result of access to such online support. While it is impractical to evaluate the effect of every online support group or disease-related website, research in this area could better inform healthcare provider decisions to make referrals to online support groups and other online resources, as well as inform caregiver decisions to participate and to what extent.

2.3 QUALITY OF LIFE

2.3.1 Glycogen Storage Disease and Other Inherited Metabolic Diseases

Due to the rarity of individual IMDs such as GSD1, studies focusing on the QOL of either patients or caregivers in the GSD1 population have been limited in scope by small sample sizes, sampling families who are part of a single center or region, or by grouping GSD1 with other

IMD or even less specifically, by grouping IMD with other rare diseases (Storch et al 2008; Sechi et al 2014; Siddiq et al 2016; Michalik 2014).

2.3.1.1 Patients

A few studies have investigated the QOL of patients with GSD1, both children and adults, though with the limitations previously discussed (Storch et al 2008; Sechi et al 2013). Youth affected by GSD1 have reported lower functioning in areas of overall QOL, physical functioning, and social functioning than that of their healthy peers (Storch et al 2008). On the other hand, they did not report any more difficulty with psychosocial health, emotional functioning, or school functioning, suggesting that individuals with GSD1 are able to cope with the effects of the disease and its management in at least some areas of their lives (Storch et al 2008). Interestingly, there is a discrepancy between child-reported QOL and the QOL of the child as perceived by the parent, revealing that further study of parent perceptions is merited (Storch et al 2008). Studies of QOL in adults with GSD1 reflect the result of a time when treatments were less developed and available, so their relevance to newly diagnosed and current children living with GSD1 may be limited. However, at least one such study has in some ways corroborated the results from the aforementioned youth study (Sechi et al 2013). Adults with GSD1 reported a poorer perception of their general health and social functioning than expected when compared to healthy individuals. A finding that was unexpected in this study showed that adult patients reported better scores than their healthy peers on scales measuring bodily pain and mental health, suggesting that managing a lifelong disease such as GSD1 may be accompanied by helpful adaptations allowing for unimpaired health in some areas (Sechi et al 2013).

2.3.1.2 Caregivers

When comparing caregivers of children with rare diseases in general, with caregivers of children with IMD, the latter may exhibit a higher level of deterioration in social wellness and positivity towards the future (Michalik 2014). For any parent caring for a child with a long-term illness, the burden of care can disrupt relations within and outside the family. For such parents, development of social support networks is associated with the ability to cope with the child's illness. However, parents are often left to identify support groups or other means of social support on their own, rather than being provided this information through the healthcare system they interact with for their child's care (Smith et al 2013). A single-site study has investigated the quality of life in 31 parents of children with GSD1, finding that these parents experienced a significantly higher level of distress related to their child's care than parents of healthy children reported. These parents also reported that their child's QOL was lower than what the children themselves reported. This study did not examine specific aspects of the children's care or of the parents' coping mechanisms or support systems that may be associated with levels of distress in the parents (Storch et al 2008). These areas remain largely uninvestigated at present. One qualitative study from 2016 (Siddiq et al) explored the experiences of parents of children with various IMD, generating valuable themes from these parents concerning the disease-specific burden of care, such as adjusting to a 'new normal', which means for many changing or leaving an occupation to care for a child with an IMD, changing the family's diet to accommodate the child's restrictions, and managing frequent appointments with several specialists. However, the IMD covered by the study were grouped together under labels such as "Amino acid disorders"; the label containing at least one family with GSD1 was "Organic acid disorders or 'other' [IMD]", so conclusions drawn about the concerns related to any one specific disorder were limited (Siddiq et al 2016).

Examination of parent QOL as a function of disease-specific concerns and other mediating factors could lend itself to the development of interventions for those caring for children with GSD1.

3.0 MANUSCRIPT

3.1 BACKGROUND

GSDs constitute a family of rare IMDs affecting the assembly, disassembly, and regulation of glycogen in the human body. As many as 14 discrete GSD types have been described, of which GSD1, also known as von Gierke disease, is the most common and the first to be enzymatically described. GSD1 is associated with a wide range of clinical presentations, from, rarely, asymptomatic hepatomegaly, to long-term hepatic and renal diseases, to life-threatening hypoglycemia following a short fast (Derks and van Rijn 2015; Burda and Hochuli 2015; Chen et al 2017).

GSD1 is a pan-ethnic disease occurring at a live birth rate of 1 in 100,000 (Shieh et al 2002; Froissart et al 2011). GSD1 is further split into two subtypes, both of which are inherited in an autosomal recessive pattern. 80% of patients with GSD1 have the GSD1a subtype, caused by mutations in the G6PC gene, with the remaining 20% of patients being categorized as having GSD1b, caused by mutations in the SLC37A4 gene (Kishnani et al 2014). Both GSD1a and GSD1b primarily affect the liver, where glycogen and fat are abnormally stored, with involvement of other body systems to an extent that can be dependent on level of metabolic control in the patient (Kishnani et al 2014, Talente et al 1994). In addition to hepatomegaly and risk of hepatocellular adenomas that may transform to malignancy, patients may have renal,

hematologic, endocrine, dental, musculoskeletal, and neurological manifestations (Burda and Hochuli 2015; Kishnani et al 2014; Talente et al 1994; Austin et al 2013; Rake et al 2002; Lee et al 1995; Dellinger et al 1998; Minarich et al 2012; Chen et al 2017). GSD1b includes the metabolic profile and other features of GSD1a with the added features of myeloid dysfunction often leading to neutropenia and increased risk of recurrent bacterial infection (Chou et al 2015; Burda and Hochuli 2015; Kishnani et al 2014; Chou et al 2010).

Above all else, the mainstay of treatment for GSD1 is the avoidance of fasting to prevent hypoglycemic episodes, and individuals should ideally void their diet of sucrose, fructose, and lactose (Kishnani et al 2014). Uncooked cornstarch can be consumed between meals to help promote near-euglycemia (Kishnani et al 2014). Even short fasts between meals leave patients vulnerable to metabolic decompensation; a long fast overnight as the patient and his/her caregiver sleeps presents a greater risk of prolonged hypoglycemia. Caregivers of children with GSD1 must wake often to feed their child throughout the night with food or uncooked cornstarch, trust nasogastric or gastrostomy tubes to deliver continuous nocturnal feeds, or when the child is old enough, implement a newer starch, waxy maize heat modified starch (Glycosade®) that lasts longer than uncooked cornstarch (Kishnani et al 2014; Weinstein and Wolfsdorf 2002; Chou et al 2010; Bhattacharya et al 2015; Ross et al 2015). Consequences of a skipped day or night feed can lead, in the most severe cases, to death; in other cases, the resultant prolonged hypoglycemia can cause seizures, brain damage, and delays in growth and development. Caregivers face risks of under- and over-management of their family member's disease, both of which can have consequences; the resulting stress has the potential to interfere significantly with the basic needs and wellbeing of the caregivers themselves (Kishnani et al 2014; Storch et al 2008).

Existing literature explores QOL in patients with GSDs and in caregivers of patients with inborn errors of metabolism or more broadly, rare diseases, but there is a gap in knowledge about QOL specifically in caregivers of family members with GSDs (Storch et al 2008; Sechi et al 2014; Siddiq et al 2016; Michalik 2014; Dellve et al 2005; Fabre et al 2014). Parents of children with GSD1 were reported in one study to have significant ratings of distress and anxiety whereas overall family functioning was reported to be similar to that of families in a health control sample (Storch et al 2008). Research in this area has been limited in scope by small sample sizes or sampling families who receive care within a single center or region without elucidating factors that ameliorate or deteriorate parent QOL (Storch et al 2008; Sechi et al 2014; Siddiq et al 2016). Studies that have focused more broadly on parents of children with rare diseases have expounded on such themes as feelings of isolation, fear of the future, dissatisfaction with level of knowledge of healthcare providers, financial difficulties, emotional distress, yet overall confidence of these parents in their personal caregiving abilities and expertise in their child's rare disease (Pelentsov et al 2016; Yanes et al 2017; Picci et al 2015; Michalik 2014; McConkie-Rosell et al 2018). Rare disease caregivers may use the internet as a tool to assist in accessing information about the child's disease, as well as communicate with other families in a similar position (Siddiq et al 2016; Khangura et al 2015). However, the literature is limited to nonexistent regarding the effect of online resources and social media, leaving the question open as to whether there is a measurable difference in the quality of life for patients or their families as a result of access to such online support.

The goal of this study was to gain a more complete understanding of QOL in caregivers of children with GSD1 and factors that influence their levels of anxiety and distress. The results of this study have the potential to shape the way healthcare providers counsel caregivers on

management of their child's rare disease, with more awareness of the effect certain resources, treatment regimens, and aspects of the disease itself have on the caregiver and on the family. This may guide referrals and resources provided for caregivers. This study is the first to add to existing knowledge the impact made on caregiver QOL by GSD1-specific aspects of care and by involvement in social media, which can be an important tool for rare disease caregivers (Siddiq et al 2016). This study also documents for the first time the level of interest in increased mental health support in this population. By increasing knowledge of one rare disease, this study also stands to increase support for the rare disease community, which has historically achieved significant measurable outcomes on global levels in areas of advocacy, legislation, research collaboration, education, and support (Aymé et al 2008).

3.2 METHODS

3.2.1 Participants

The target population for this study included adults (18 years of age and older) who are parent (or other relation) caregivers for children who have GSD1a or GSD1b. Participants were not limited to the study site, the Children's Hospital of Pittsburgh of UPMC. The primary recruiting was completed with the help of the Association for Glycogen Storage Disease (AGSD). The AGSD president was contacted by email and after discussion of the project, a letter was sent to the AGSD Scientific Advisory Board (Appendix A.1). After reviewing the proposed project, the AGSD's Scientific Advisory Board provided written evidence of support of the project and permission to have the study survey link posted to the main page of the AGSD website, as well

as to send information about the study through the AGSD's quarterly newsletter (Appendix A.2). Any individual, regardless of AGSD membership status, had the potential to visit the website of the AGSD and have access to the study survey. Recruitment was also achieved by advertisement of the study survey through the listservs of relevant professional organizations, including the National Society of Genetic Counselors (NSGC) Metabolic/Lysosomal Storage Disease Special Interest Group (SIG), metab-L, and the Genetic Metabolic Dietitians International (GMDI). The advertisement provided through these channels included the information for the providers, as well as an information sheet and flier they would be able to pass onto their patients (Appendices B, C, D). Participants consented to participate in the study by reviewing the consent document appearing before the study survey and indicating that "yes", they would like to participate. The first question of the survey was a qualifying question confirming that the respondent was a caregiver of a child with GSD1. We tabulated the number of individuals opening the link to the study survey, consenting to and beginning the survey, and partially or fully completing the survey. Participants were informed that they would not be provided with any compensation of financial or other nature. Participants were informed that their participation was voluntary. The study was reviewed and approved by the University of Pittsburgh Institutional Review Board (IRB) committee (Appendix E).

3.2.2 Survey Development

The study survey (Appendix F) consisted of the Pediatric Inventory for Parents (PIP), the PROMIS Emotional Distress-Anxiety - Short Form 8a, a section developed by the lead researcher for the purposes of this study, which included a demographics subsection informed by Qualtrics-provided standard demographics questions. Access to the PIP and its scoring guide was

obtained with permission through that survey's lead author, Dr. Randi Streisand (Appendix F.1). The Short Form 8a is a validated measure that is free to use with registration on the Assessment Center website (https://www.assessmentcenter.net). The self-developed portion was developed through preliminary research that included literature review, an unstructured interview with a metabolic geneticist who clinically cares for patients with GSD1a and 1b at the study site, as well as unstructured interviews with two parent caregivers who form a married couple with a child with GSD1a. The interviews were not audio-recorded, but written notes were taken. These three interviews were compared for common domains (Appendix G). Questions were developed for common domains among the interviews that were not sufficiently covered by the PIP or Short Form 8a. The self-developed survey was reviewed by two genetic counselors with experience in qualitative and quantitative research as well as various metabolic disorders, a metabolic geneticist, and an expert in survey development and dispersal. The three survey tools were assembled in Qualtrics as one united survey available at a single web link. The survey was formatted with branching to account for different language for caregivers with one child with GSD1 or caregivers with more than one child with GSD1. For those with more than one child with GSD1, questions used language such as "your youngest child with GSD1" as opposed to "your child with GSD1" when applicable. Branching was implemented in other appropriate areas so that caregivers were not asked questions that did not apply to them based on previous responses.

3.2.3 Data Collection

The study survey was opened with Qualtrics survey software in October 2017 and remained open through the end of April 2018. The link to the survey was made available on the AGSD website

on 12/18/2017. The introductory script to the survey (Appendix C) was included in the AGSD Winter 2017/2018 email newsletter, “The Ray”, which was distributed on 2/23/2018. The introductory script, a letter for providers, and a flyer were sent through email list-servs to the professional organizations NSGC Metabolic/Lysosomal Storage Disease SIG, GMDI and metab-L on dates 2/26/2018, 2/27/2018 and 3/2/2018 respectively.

3.2.4 Data Analysis

The data collected from the survey were analyzed using both descriptive and inferential statistics via the open-source statistical programming language and software R, version 3.5.0. The base package of R was used along with supplementary packages “psych” and “splitstackshape”. Inferential statistics methods used depended on sample sizes and type of variables, including measures such as chi-squared goodness-of-fit test, chi-squared test of independence, *t*-test, and Fisher’s exact test. Participants were able to skip questions; due to the number of partially complete surveys, data analysis was performed for items regardless of the total number of respondents or non-respondents. Qualtrics and R were used for data analysis and R was used for development of illustrative figures. Any data collected as part of the survey that did not contribute to analysis in this document is reported in the appendices (Appendix H).

3.2.4.1 Pediatric Inventory for Parents

The results of the PIP were tabulated and then scored according to its respective scoring guide (Appendix F.2). Internal consistency was calculated for Total Frequency, Total Difficulty, as well as for each domain, using Cronbach’s alpha. The mean results for Total Frequency and Total Difficulty were compared to those found in a previous study for GSD1 caregivers using a

two-tailed one-sample *t*-test (Storch et al 2008). The Frequency and Difficulty scores for the individual domains of the PIP were also tabulated and used for analysis. The individual domains are Communication, Medical Care, Emotional Distress, and Role Function. The Communication score is based on nine items of the PIP and can range from 9-45 with a mean score of 27. The Medical Care score is based on eight items of the PIP and can range from 8-40 with a mean score of 24. The Emotional Distress score is based on fifteen items and can range from 15-75 with a mean score of 45. The Role Function score is based on ten items and can range from 10-50 with a mean score of 30. The PIP scoring guide does not offer a method for comparing scores between different individual domains. Because the individual domains do not contain the same number of items, the Frequency and Difficulty scores for each domain were compared with one another using the calculated percent deviation from each domain's expected mean score. For example, for Communication Frequency, we subtracted 27 from the mean respondent score for this domain in the Frequency section, divide this number by 27, and multiply by 100 to convert to percentage. The same would be performed for Communication Difficulty using the Difficulty score for this domain. As a second example, for Medical Care Frequency, we subtracted 24 from the mean respondent score for this domain in the Frequency section, divided the resulting number by 24, and multiplied by 100 to convert to percentage.

3.2.4.2 PROMIS Emotional Distress-Anxiety Short Form 8a

The results of the PROMIS were tabulated and then scored by calculating the raw score with the formula: (Raw sum x number of items on the short form) / (Number of items that were actually answered). Using the respective score conversion table, the mean raw score was transformed into a T-score, which has a mean of 50 and a standard deviation of 10 (Appendix F.3). The scores of participants who completed the PIP Frequency and Difficulty sections and the PROMIS were

compared. A Pearson correlation coefficient was calculated between the PIP Frequency and the PROMIS, and between the PIP Difficulty and the PROMIS and tested with a two-tailed *t*-test for significance. Pearson correlation coefficients were also calculated between the PROMIS and the scores for the individual domains of the PIP and tested with two-tailed *t*-tests for significance.

3.2.4.3 Social Media

The social media section of the self-developed survey contained two to three (depending on response and relevant branching) multiple-choice questions and six Likert scale questions, the results of which were analyzed for usage, impact, and privacy with descriptive statistics and measures of inferential statistics as indicated.

Usage

Categories of social media usage contained zero ("do not use it"), passive ("mostly read content written by other people"), and active ("equally write own content/read others' content"). Respondents who indicated on the first question that they did not typically use social media were only asked one other multiple-choice question assessing usage of social media prior to their child's diagnosis of GSD1, or prior to the most recent diagnosis of GSD1 among their affected children. Respondents who indicated that they are typically active or passive users of social media were prompted to answer the remaining questions in the social media section. Change in social media usage since diagnosis was assessed by Question 20 for zero users and by Question 18 or 19 for active and passive users. Zero users who indicated that they had used social media prior to the GSD1 diagnosis of their child were said to have decreased their use since diagnosis while those who indicated that they had not used social media prior to the GSD1 diagnosis of their child were said to have not changed their use. For participants who completed this section

as well as the PIP and PROMIS, responses were compared to these scales and tested for significant association with a Fisher's exact test.

Impact

Social media impact was assessed by the first four questions within the social media Likert scale section of the survey. Respondents who had previously indicated that they typically do not use social media were not displayed this section.

Privacy

Social media privacy was assessed by the last two questions within the social media Likert scale section of the survey. Respondents who had previously indicated that they typically do not use social media were not displayed this section. Chi-square goodness-of-fit tests were performed for each individual question to assess equal distribution of preferences and a Fisher's exact test was performed to test for association between responses to both questions.

3.2.4.4 Mental Healthcare

Respondents were asked whether they currently see a mental healthcare provider or other support specialist. Depending on this answer, they were prompted to answer whether they would be interested in starting to see such a specialist regarding challenges of being a GSD1 caregiver, or if they would like to speak more with the provider they already see, or a different provider, regarding these challenges. If the respondent indicated not being interested, they were given the option of writing in why not. If the respondent indicated interest and was not currently seeing someone, they were given the option of writing in why they have not yet sought out this service. Free responses were reported as they were written and were analyzed for commonalities. For

participants who completed this section as well as the PIP and PROMIS, responses were compared to these scales. Two-sample *t*-tests were performed to test for significant differences in these scores for those currently using and those currently not using mental healthcare services.

3.2.4.5 GSD1 Dietary Management

Management Actions

Caregivers were asked questions related to the management of their child with GSD1. Questions assessed which methods caregivers used for nighttime feeding, how often they perform glucose "finger stick" tests on their child on a typical day, and how often they have this child consume a cornstarch feed on a typical day. For nighttime feeding methods, caregivers were able to select multiple options and specify an unlisted method by writing in a text box.

Comfort with Management

Caregivers were presented with four situations regarding different aspects of the feeding schedule and management of their child with GSD1. Participants were prompted to select responses to each situation on a 5-point Likert scale ranging from "Extremely Uncomfortable" to "Extremely Comfortable". Internal consistency was calculated for this section using Cronbach's alpha.

3.3 RESULTS

3.3.1 Participants and Demographics

82 individuals opened the link to the study survey; 66 consented to participate; 53 answered some or all of the survey; and 24 completed every question of the survey. It is not known how many people were made aware of the survey due to the methods of recruitment and therefore, a response rate cannot be determined. The majority of respondents who partially or fully completed the survey were mothers of children with GSD1 (87.0%, n=40) while a smaller portion were fathers (10.9%, n=5). One additional respondent indicated that she was an aunt to her child with GSD1. Of those who partially or fully completed the survey, the majority of respondents were caregivers to children with GSD1a (75.6%, n=34), and the remaining were caregivers to children with GSD1b, (24.4%, n=11). The majority of respondents had one child with GSD1 and one child without GSD1 (respectively, n=37, 82.2%; n=18, 40.0%) (Figure 1).

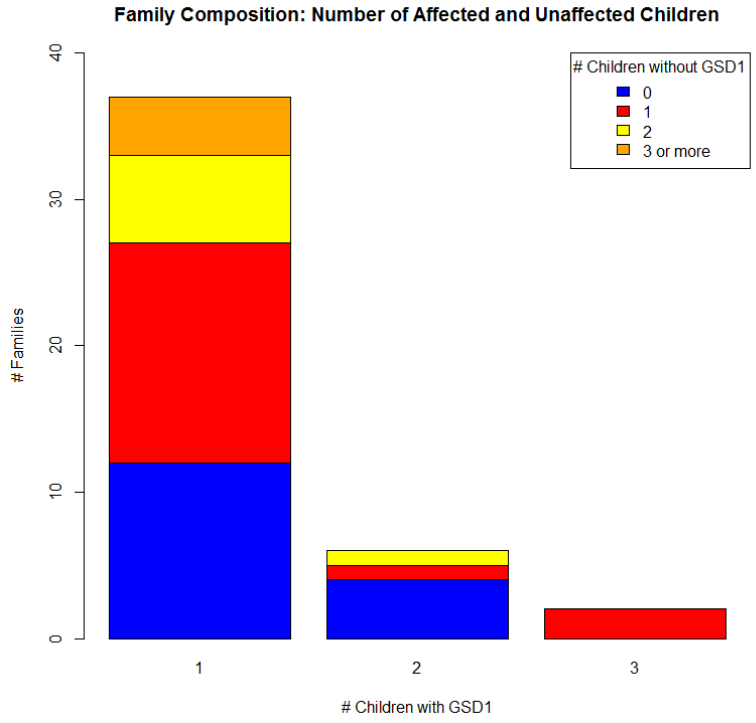


Figure 1. Number of Affected and Unaffected Children per Family

The respondents indicated a wide range of education level, household income, and employment status, though most were not working outside the home at the time of survey completion (n=15, 60%) (Table 1). The most common type of insurance used for children with GSD1 was reported to be insurance through a current or former employer or union (Table 2). Most caregivers reported using just one type of insurance for their child (n=17, 70.8%) with the remaining using two or more types of insurance (Table 2).

Table 1. Education, Income, and Employment Status of Participants

Highest Level of Education	Total (n=25)
High school graduate (high school diploma or equivalent including GED)	1 (4%)
Some college but no degree	8 (32%)
Associate degree in college (2-year)	3 (12%)
Bachelor's degree in college (4-year)	7 (28%)
Master's degree	4 (16%)
Doctoral degree	1 (4%)
Professional degree (JD, MD)	1 (4%)
Household 2017 Pre-Tax Income	**Total (n=24)**
$0-30,000	5 (20.8%)
$30,001-50,000	4 (16.7%)
$50,001-75,000	3 (12.5%)
$75,001-100,000	2 (8.3%)
$100,001-150,000	7 (29.2%)
$150,001 +	3 (12.5%)
Currently Working Outside the Home	**Total (n=25)**
Yes	10 (40%)
No	15 (60%)
Employment Status	**Total (n=26)**
Working (paid employee)	9 (34.6%)
Working (self-employed)	1 (3.8%)
Not working (looking for work)	1 (3.8%)
Not working (retired)	1 (3.8%)
Not working (disabled)	2 (7.7%)
Not working (other)	10 (38.5%)
• **"Housewife"** • **"Stay at home mom" x 2** • **"Not working too afraid to be away from gsd daughter during the day"** • **"Stay at home caregiver for my child"** • **"Caring for child, unable to work"** • **"Being a full time dad to take care of my GSD child."** • **"Homemaker"**	
Prefer not to answer	2 (7.7%)

Table 2. Insurance Type(s) Used for Child with GSD1

Type of Insurance	Total (n=24)
Insurance through a current or former employer or union	17 (70.8%)
Insurance purchased directly from an insurance company	2 (8.3%)
Medicaid, Medical Assistance, or any kind of government-assistance plan for those with a disability or low income	8 (33.3%)
Other - describe	5 (20.8%)
• **"[Country] - public-funded medical care. Insuarance (sic) is required for extras (prescriptions, dental, vision, etc.)"** • **"Husband self employed"** • **"We adopted our GSD 1A daughter so eill (sic) always have medicaid in addition to our insurance"** • **"I am in [Country], we have a state run insurance program that covers citizens. Therefore, insurance expenses for GSD kid is ok which is affordable."** • **"Health care paid by government through income taxes (doctor visits, hospital, home care supplies); Private insurance through former employer for prescriptions; tax deductions for disability"**	

(Percentages not equal to 100 due to option of selecting multiple answers)

25 respondents indicated year of GSD1 diagnosis (or year of the most recent diagnosis in families of 2 or more affected children). This ranged from 1992 to 2018 with an average of 2011 and a median of 2014 (n=25) (Figure 2). Year of diagnosis for the oldest child with GSD1 in families of 2 or more affected children ranged from 2009 to 2017 (n=2).

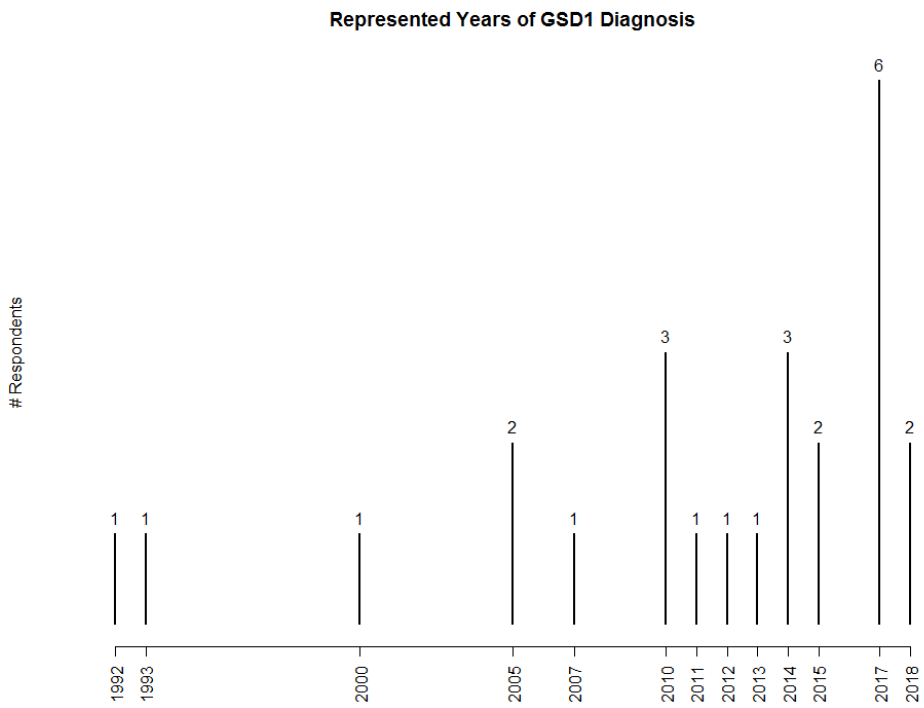


Figure 2. Year of GSD1 Diagnosis

3.3.2 Measures of Anxiety and Distress

3.3.2.1 Pediatric Inventory for Parents

37 participants completed the PIP Frequency section and 24 participants completed both the Frequency and Difficulty sections. The average total Frequency score was 145.97 and the average Difficulty score was 146.38 (Table 3). The Difficulty and Frequency scores were compared to those found in a past paper by two-tailed one-sample *t*-test (Table 4).

To compare mean scores for individual domains of the PIP, the percent deviation was calculated between the respondent mean score and the mean possible score of the domain. For Frequency, the domain with the highest percent deviation score was Medical Care and the domain with the lowest score was Role Function (Table 3). For Difficulty, the domain with the

highest percent deviation score was Emotional Distress and the domain with the lowest score was Communication (Table 3).

Internal consistency as measured by Cronbach's alpha was 0.92 for both Frequency and Difficulty total scores (Table 3). Individual domain Cronbach's alphas were all greater than 0.80 except for that of Frequency in the domain of Role Function with an alpha of 0.77 (Table 3).

Table 3. Pediatric Inventory for Parents – Results by Domain of Functioning

	PIP Frequency (n=37)			PIP Difficulty (n=24)		
Domain:	*M* ∓ *SD*	Deviation from Domain Mean	α	*M* ∓ *SD*	Deviation from Domain Mean	α
Communication (domain mean=27)	30.68 ∓ 6.75	13.6%	0.80	29.08 ∓ 7.06	7.7%	0.83
Medical Care (domain mean=24)	29.11 ∓ 7.06	21.3%	0.87	26.13 ∓ 6.87	8.9%	0.88
Role Function (domain mean=30	32.17 ∓ 7.77	7.0%	0.77	33.23 ∓ 9.48	10.6%	0.87
Emotional Distress (domain mean=45)	54.08 ∓ 10.07	20.2%	0.85	58.00 ∓ 11.70	28.9%	0.90
Total:	145.97 ∓ 28.05	N/A	0.92	146.38 ∓ 31.55	N/A	0.92

Table 4. Comparing Measure of GSD1 Caregiver Distress in Two Studies

	This paper (n=37 for PIP-F, n=24 for PIP-D)			Storch et al 2008 (n=31)		*t*-test	
PIP Section:	*M*	*SD*		*M*	*SD*	*t*	*p*-value
Frequency	145.97	28.05		108.53	26.92	8.12	1.18×10^{-9}
Difficulty	146.38	31.55		94.66	26.58	8.03	4.02×10^{-8}

3.3.2.2 PROMIS Emotional Distress-Anxiety Short Form 8a

26 participants completed the PROMIS section with all 26 answering all eight questions of the measure. The mean PROMIS score was 27.11 (Figure 3). According to the scoring manual for the PROMIS scale, this mean score of 27.11 corresponds with a T-score of 65.6 when rounded down. This T-score is over one standard deviation above the population mean of 50.

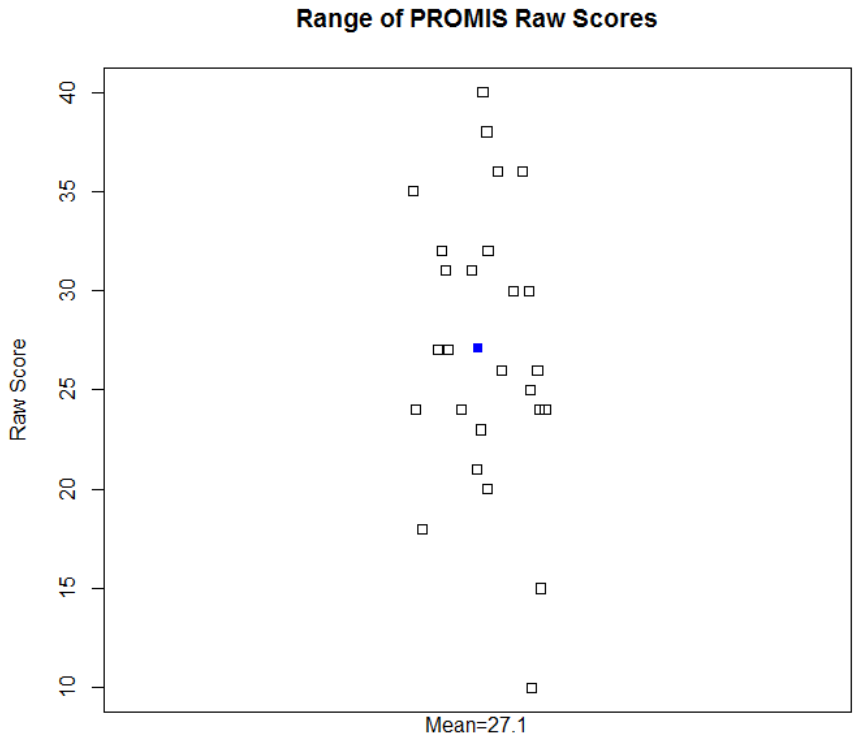


Figure 3. Caregiver Scores on the PROMIS Measure of Anxiety

3.3.2.3 Comparing the PIP and the PROMIS

24 participants completed both the Frequency and Difficulty sections of the PIP as well as the PROMIS. These participants' three scores in these sections were compared (Figure 4). The correlation between the PIP-F and the PROMIS scores was significant with a Pearson correlation coefficient of 0.58 (t=3.31, p=0.003) and the correlation between the PIP-D and the PROMIS

scores was also significant with a Pearson correlation coefficient of 0.68 (t=4.40, p=0.0002) (Table 5).

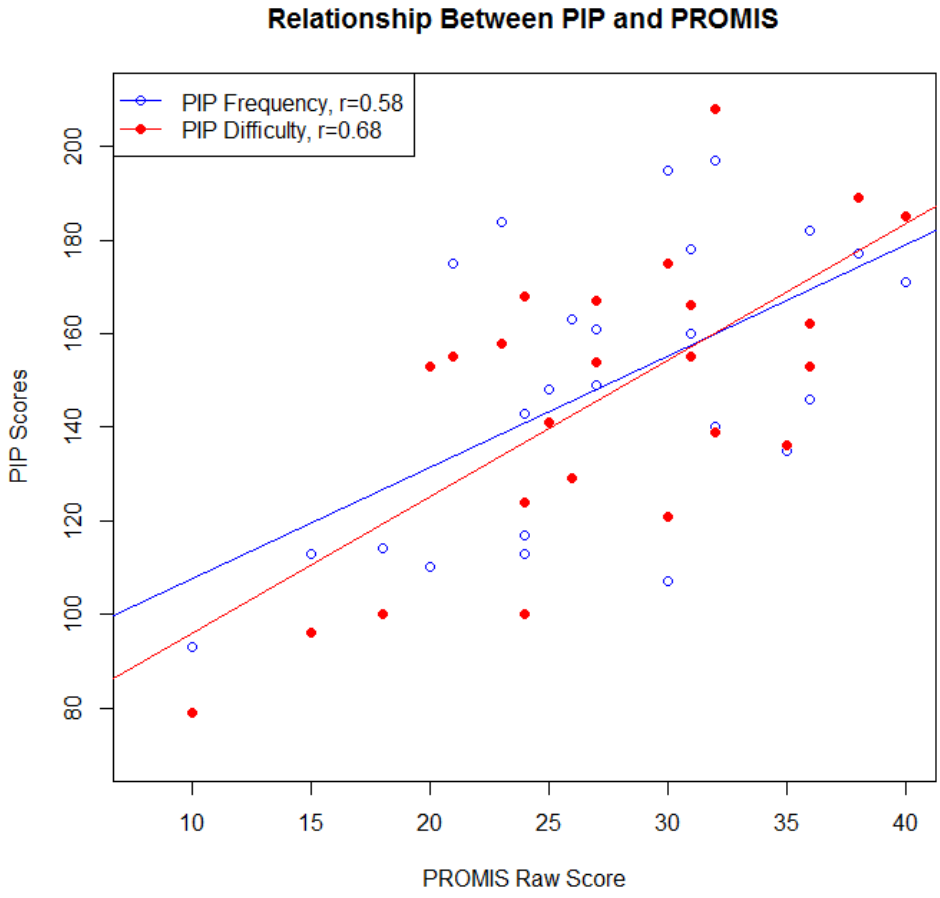


Figure 4. Linear Correlation between PIP and PROMIS Measures of Anxiety

Individual domains of the PIP, both Frequency and Difficulty scores, were also compared with the PROMIS for the same 24 participants with Pearson correlation coefficients. The highest correlation coefficient was 0.72, seen between the PIP-Emotional Distress Difficulty score and the PROMIS (Figure 5-C). The lowest correlation coefficient was 0.24, seen between the PIP-Medical Care Frequency score and the PROMIS (Figure 5-B). All correlation coefficients were

statistically significant except for the correlation between the PIP-Medical Care Frequency score and the PROMIS score (Table 5).

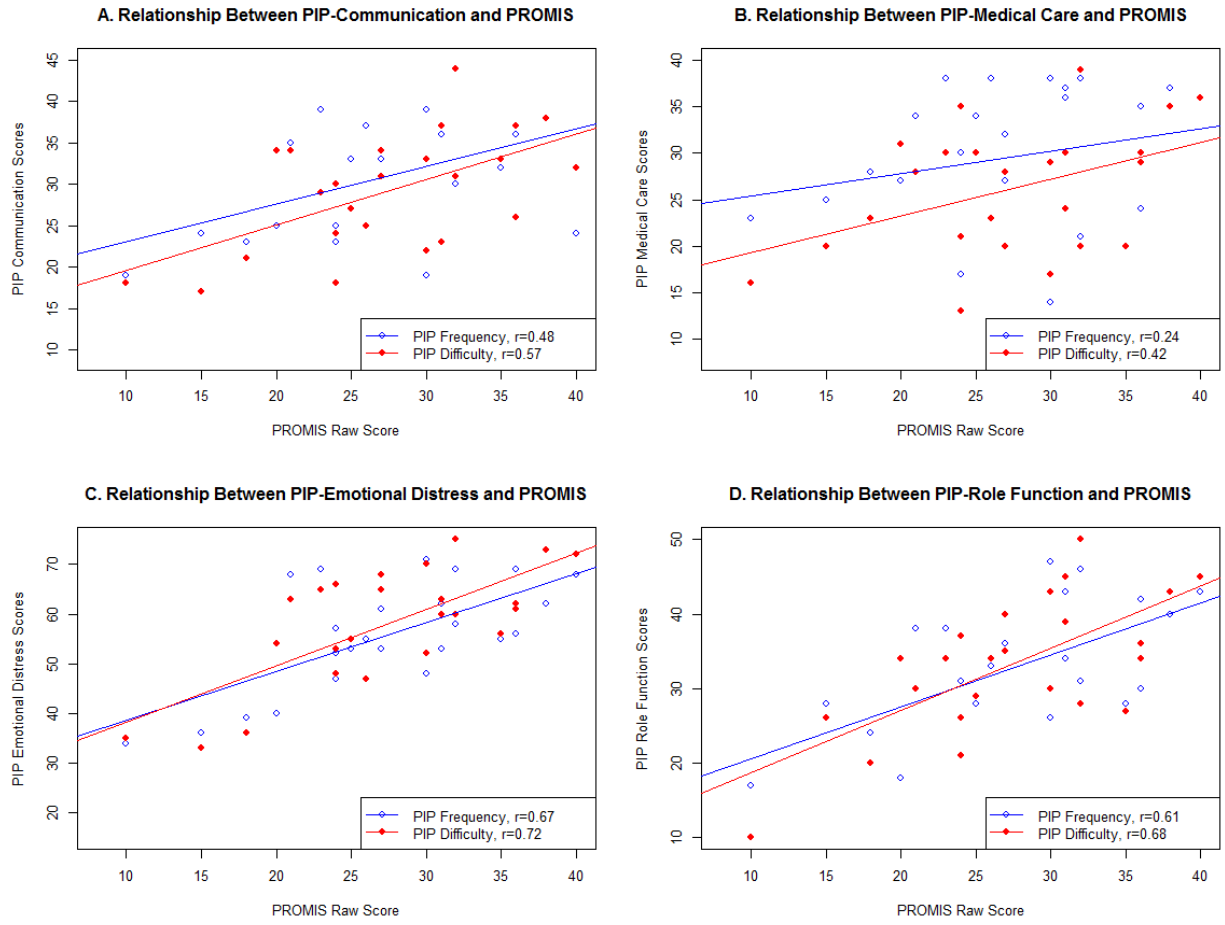


Figure 5. Correlations between PIP Individual Domain Scores and PROMIS Scores

Table 5. Relationship between PIP and PROMIS Scores

	PIP-Frequency and PROMIS		PIP-Difficulty and PROMIS	
Domain:	Correlation Coefficient	*t*-test	Correlation Coefficient	*t*-test
Communication	0.48	t=2.54 p=0.02	0.57	t=3.28 p=0.003
Medical Care	0.24	t=1.15 p=0.26	0.42	t=2.19 p=0.04
Emotional Distress	0.67	t=4.20 p=0.0004	0.72	t=4.85 p=0.00008
Role Function	0.61	t=3.64 p=0.001	0.68	t=4.32 p=0.0003
Total:	0.58	t=3.31 p=0.003	0.68	t=4.40 p=0.0002

3.3.3 Social Media

3.3.3.1 Usage

The respondents for the social media section were broken into category of usage and category of change in usage since diagnosis (Figure 6). Caregivers were not equally distributed among the three usage categories (X^2=7.2, df=2, n=30, p=0.03). The relationship between reported typical usage of social media and change in usage since diagnosis was significant (p=0.006, two-tailed Fisher's exact test).

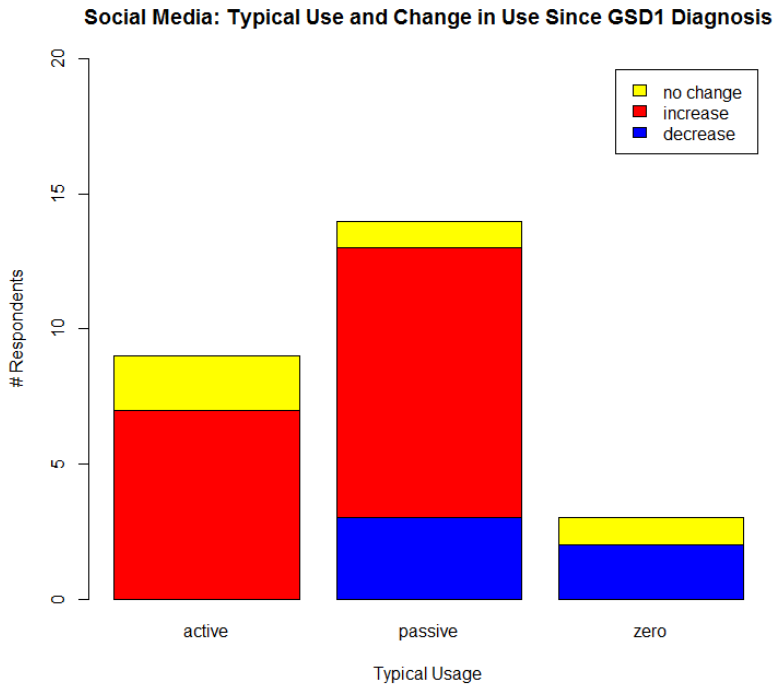


Figure 6. Caregivers' Typical Usage of Social Media and Change in Usage since Child's Diagnosis

The three categories of social media usage were also compared regarding scores for measures of anxiety (Figure 7). Active social media users had a mean PROMIS score of 27.0 (n=9), a mean PIP-F score of 151.2 (n=9), and a mean PIP-D score of 152.7 (n=9). Passive social media users had a mean PROMIS score of 28.3 (n=13), a mean PIP-F score of 144.2 (n=13), and a mean PIP-D score of 143.6 (n=12). Zero social media users had a mean PROMIS score of 28.0 (n=3), a mean PIP-F score of 170.0 (n=3), and a mean PIP-D score of 168.5 (n=2). The number of zero users was insufficient to run analysis of variance (ANOVA) for all three groups. No significant differences were found in scores for active and passive users (Appendix H.2).

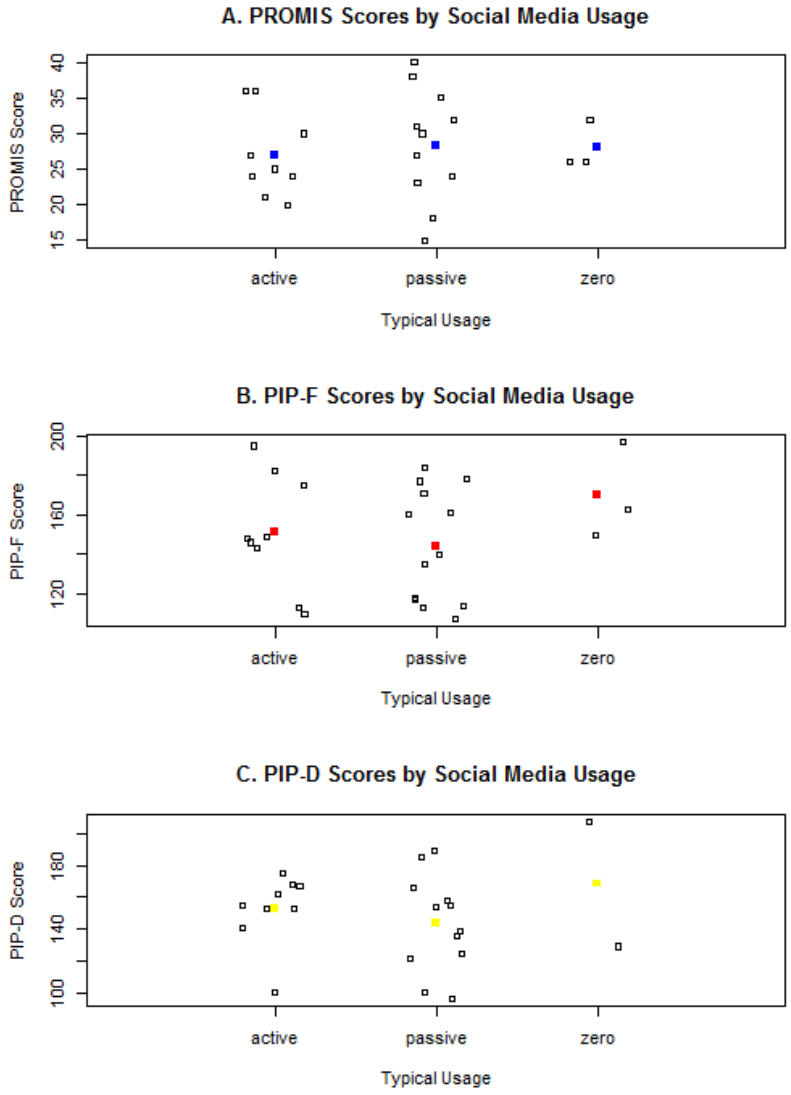


Figure 7. Measures of Anxiety Stratified by Social Media Usage

3.3.3.2 Impact

Caregiver-reported impact of social media was assessed by responses to four Likert scale statements (Figure 8). In response to the statement, “Social media is the first resource I use to help make medical decisions for my child with GSD1”, the most common response was “Somewhat Agree” (n=12, 54.5%) followed by “Neither Agree nor Disagree” (n=7, 31.8%). In response to the statement, “Social media is a positive support system for me as a GSD1

caregiver", the most common response was "Strongly Agree" (n=13, 59.1%) followed by "Somewhat Agree" (n=6, 27.3%). In response to the statement, "I have stronger personal friendships due to my use of social media with other GSD1 caregivers", the most common response was "Strongly Agree" (n=9, 40.9%), followed by "Somewhat Agree" (n=6, 27.3%). Responses to the fourth statement, "Discussing or reading about GSD1 on social media often gives me stress or anxiety about my own child" were more mixed, with the most common response being "Somewhat Agree" (n=8, 36.4%), followed by "Somewhat Disagree" (n=6, 27.3%).

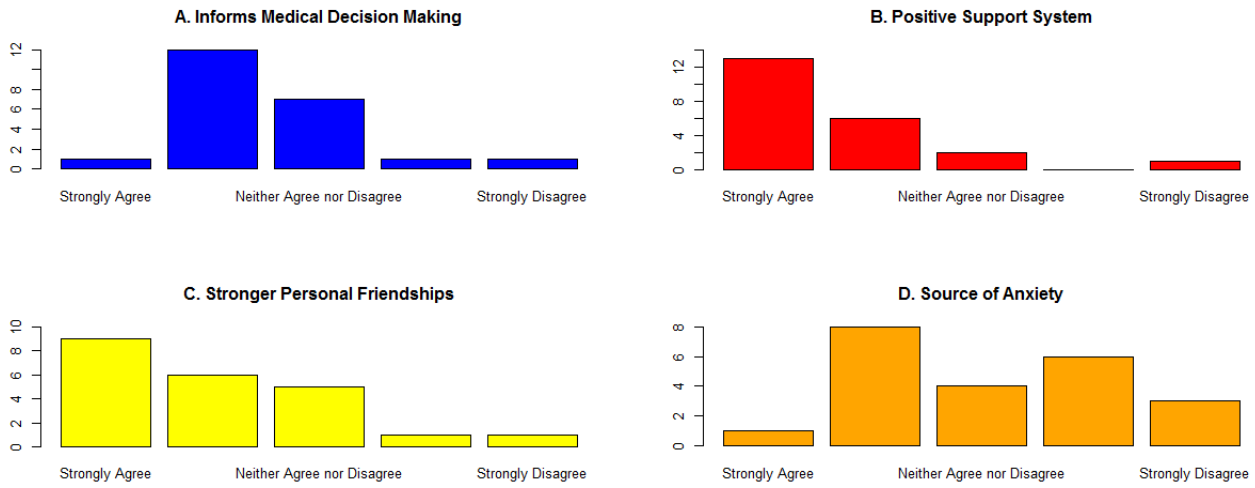


Figure 8. Caregiver-Reported Impact of Social Media as Likert Responses to Four Statements

3.3.3.3 Privacy

Social media privacy preferences regarding the diagnosis of GSD1 and related information were assessed by responses to two Likert scale statements (Table 6). Due to number of respondents, responses for both privacy-related questions were grouped into three categories for the purposes of meeting Cochran's rules for analysis by chi-square goodness-of-fit: "strongly agree or somewhat agree", "neither agree nor disagree", and "strongly or somewhat disagree". Responses

to the statement, “I make information about my child’s GSD1 diagnosis available to anyone I am connected to on social media” were not equally distributed among these three categories (X^2=9.36, df=2, n= 22, p=0.009). Responses to the statement, “I make information about my child’s GSD1 diagnosis available ONLY to other GSD1 families” were equally distributed among the same three categories, (X^2=1.9 df=2, n= 22, p=0.39). Taking into account all five response options for each statement, the association between each participant’s response to both of the statements was found to be significant (p=0.0028, two-tailed Fisher’s exact test).

Table 6. Social Media Privacy Preferences Regarding GSD1 Information

Statement 2: “…ONLY other GSD1 families.”	Statement 1: “…Anyone I am connected to on social media.”					
	Strongly Agree	**Somewhat Agree**	**Neither Agree nor Disagree**	**Somewhat Disagree**	**Strongly Disagree**	**Total:**
Strongly Agree	1	1	0	1	1	4
Somewhat Agree	1	0	0	8	1	10
Neither Agree nor Disagree	1	0	2	0	0	3
Somewhat Disagree	0	1	1	0	0	2
Strongly Disagree	2	0	1	0	0	3
Total:	5	2	4	9	2	**22**

Degree of agreement with the statements: “I make information about my child’s GSD1 diagnosis available to…”

3.3.4 Mental Healthcare Services: Current Usage and Interest

When asked about current usage of a mental healthcare provider or other support specialist, most caregivers (n=17, 65.4%) responded that they did not currently see a “counselor, therapist, psychologist, psychiatrist, clergy-person, or other provider” while the remaining reported that they were currently seeing such a provider (n=9, 34.6%). Further, participants were asked whether they would like to either start seeing such a provider regarding challenges of being a caregiver for a child with GSD1, or speak more with the existent provider or new provider about challenges of being a caregiver for a child with GSD1 (Table 7). The majority of the caregivers indicated interest in doing so (n=13, 50.0%) or possible interest in doing so (n=8, 30.8%). Participants were able to write in reasons for not being interested, or reasons for not yet seeing a provider if they were interested (Table 7).

Table 7. Mental Healthcare Usage and Interest in GSD1 Caregivers

Current Usage of Mental Healthcare Providers	Total (n=26)
Yes	9 (34.6%)
No	17 (65.4%)
Interested in Using Mental Healthcare to Discuss Caregiver Challenges	**Total (n=26)**
Yes	13 (50.0%)
Maybe	8 (30.8%)
No	5 (19.2%)
If interested or possibly interested in using mental healthcare provider to discuss caregiver challenges, why haven't you seen one?	
• **"Havent (sic) thought about it yet"** • **"No time"** • **"I have very little time for myself"** • **"I am managing on my own so far"** • **"Full time caregiver not a ton of time to do things for myself"** • **"Time, money, no childcare for daughter, but mostly time is a factor. Also I don't think my anxiety is bad enough to address at this point."** • **"I saw one briefly before finding out that insurance would not cover it."** • **"Time and money prevent that from happening."** • **"Maybe it does not [suggested word missing: help] me a lot. Since I have to deal the problem alone most of the time, it is hard for others to understand my difficulities (sic)."**	
If not interested in using mental healthcare provider to discuss caregiver challenges, why not?	
• **"I have a huge support system thru (sic) my Church"** • **"I am coping well and married to [an] MD [Specialization 1/Specialization 2] so he [is] our on staff doc lol!"** • **"I wouldn't have the time and don't have someone to watch my kids to afford me the time to talk with someone."** • **"I have been in therapy before for stress and anxiety and I have a good handle in it"**	

Current usage of mental healthcare was stratified by income bracket reported in the demographics section and there was no significant association between these two variables (p=0.63, two-tailed Fisher's exact test).

3.3.4.1 Measures of Anxiety and Mental Healthcare Usage

Levels of anxiety and distress as measured by the PROMIS and the PIP were compared between caregivers reporting current usage of mental healthcare services and those reporting they do not currently use such services (Figure 9). Caregivers currently seeing a mental healthcare provider had a mean PROMIS score of 30.6 (n=9), a mean PIP-F score of 161.2 (n=9), and a mean PIP-D score of 152.0 (n=8). Caregivers not currently seeing a mental healthcare provider had a mean PROMIS score of 26.3 (n=16), a mean PIP-F score of 143.4 (n=16), and a mean PIP-D score of 147.9 (n=15). The PROMIS scores were not significantly different between the two groups (t=1.84, df=21.1, p=0.079, two-tailed Welch two sample t-test). The PIP-F scores were not significantly different between the two groups (t=1.7368, df=22.3, p=0.096, two-tailed Welch two sample t-test). The PIP-D scores were not significantly different between the two groups (t=0.37, df=20.2, p= 0.72, two-tailed Welch two sample t-test).

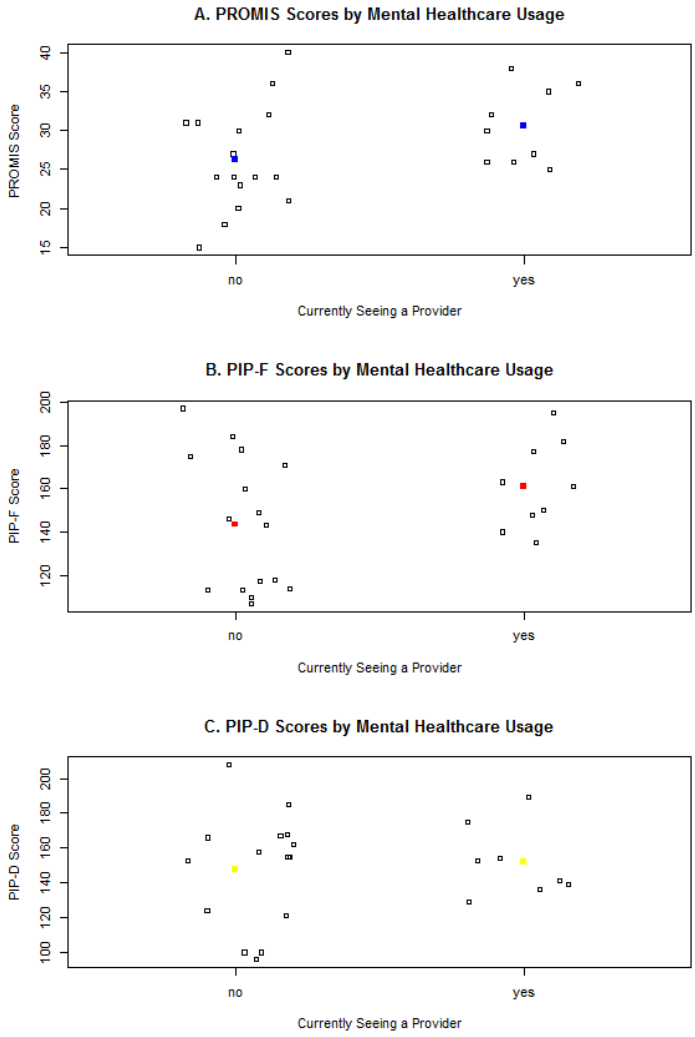


Figure 9. Measures of Anxiety Stratified by Current Usage of Mental Healthcare

3.3.5 Dietary Management of GSD1

3.3.5.1 Management Actions

25 participants completed the section of the study survey on the methods they use to feed their child with GSD1 during the night with the most common method being cornstarch, followed by gastric tube (Table 8).

Table 8. Methods Used for Management of Nighttime Feeds

Method	Prevalence
Glycosade®	6 (24.0%)
Cornstarch	20 (80.0%)
Gastric Tube (G-Tube) with feeds	15 (60.0%)
Night home nurse	3 (12.0%)
Other:	2 (8.0%):
"Feeding pump"	1 (4%)
"I feed him personally"	1 (4%)

(Percentages not equal to 100 due to option of selecting multiple answers)

Participants were also asked how often they typically, on a "non-sick day", perform glucose tests (i.e. "finger sticks") on their child with GSD1 and how often they feed this child uncooked cornstarch. Most caregivers responded that they typically perform glucose tests at a frequency that is less often than every two hours (n=11, 44%) (Figure 10-A). The next most common response was to not perform any finger sticks on a typical day (n=9, 36%) (Figure 9-A). The majority of caregivers reported feeding their child uncooked cornstarch every three to four hours (n=11, 44%) while the next common frequency was every two to three hours (n=8, 32%) (Figure 10-B). Respondents' reported frequencies for each aspect of GSD1 management were not significantly related to one another (p=0.24, two-tailed Fisher's exact test).

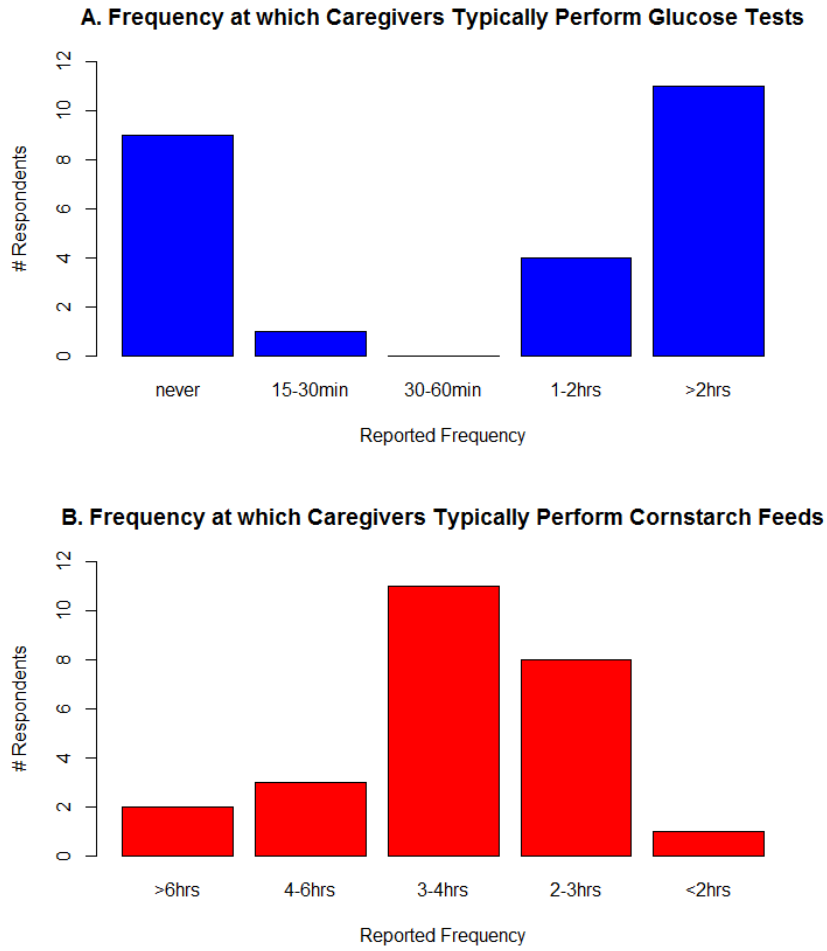


Figure 10. Caregiver-Reported Frequency of Glucose Testing and Cornstarch Feeds

3.3.5.2 Comfort with Management

25 participants completed the section of the study survey on the level of comfort they feel with four aspects of their child's dietary management of GSD1. Most caregivers felt "extremely comfortable" (n=11, 44%) or "somewhat comfortable" (n=9, 36%) with their child's daytime cornstarch/feeding schedule (Figure 11-A). Caregivers felt similarly toward their child's cornstarch/feeding schedule during the night — the majority felt "somewhat comfortable" (n=10, 40%) or "extremely comfortable" (n=9, 36%) with this aspect of management (Figure 11-B). Most caregivers reported feeling "extremely comfortable" (n=13, 52%) in terms of knowing

when their child needed to be fed (Figure 11-C). Caregivers mostly reported feeling “extremely comfortable” (n=11, 44%) or “somewhat comfortable” (n=8, 32%) with knowing that the child’s feeding plan would be carried out during the night when the caregiver slept, while 20% of the participants either felt “somewhat uncomfortable” (n=4, 16%) or “extremely uncomfortable” (n=1, 4%) with this aspect of care (Figure 11-D).

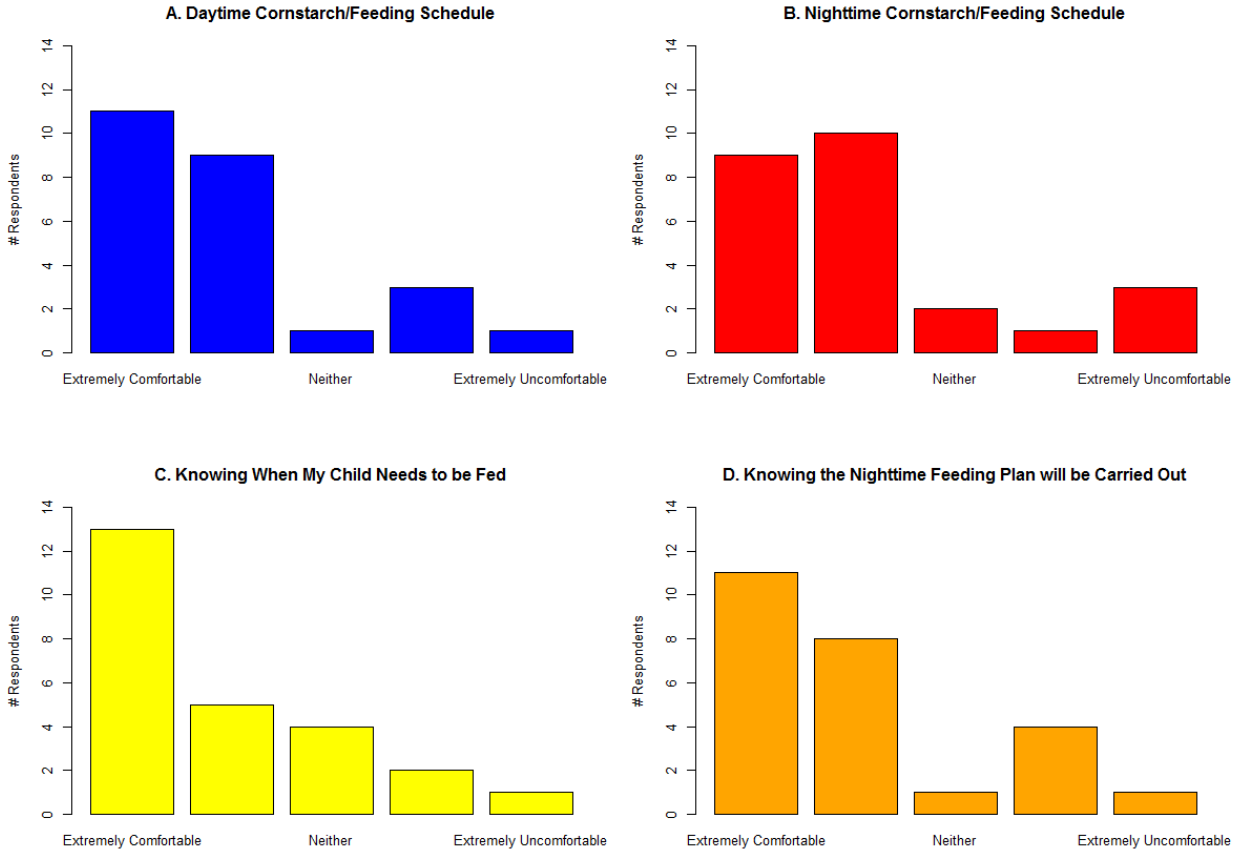


Figure 11. Caregiver Ratings of Comfort with Aspects of their Child’s Dietary GSD1 Treatment

As an overall measure of comfort with dietary management, these four Likert-scale questions had a Cronbach alpha of 0.83 (95% confidence interval: 0.72-0.94) for measure of internal consistency with the reliability scores for each of the four items ranging from 0.77 to 0.89 (Table 9).

Table 9. Internal Consistency of GSD1 Management Comfort

Question	Item Reliability (α)	Reliability if Item is Dropped (α)
1. Daytime Schedule	0.80	0.80
2. Nighttime Schedule	0.80	0.79
3. When Child Needs to be Fed	0.89	0.73
4. Nighttime Feeding Plan will be Carried Out	0.77	0.82
Total Reliability:	0.83 ∓ 0.11	

3.4 DISCUSSION

This study characterized the level of anxiety and distress of caregivers of children with GSD1 and provided insight into how this may be modulated by aspects of GSD1 management as well as caregiver participation in social media and usage of mental healthcare services.

3.4.1 Level of Anxiety in GSD1 Caregivers

Caregivers to children with GSD1 were administered the PIP in one previously published study; these data were used for comparison with the present study. Compared to the 2008 (Storch et al) study, caregivers in this study reported significantly higher scores for both the PIP-F and PIP-D. This implies that the caregivers sampled in the present study experience stressors related to caring for a child with a chronic illness more frequently and with more difficulty than was represented in the prior paper (Storch et al 2008). Several important differences exist between the present study and the prior study that may help explain the significant difference in PIP scores. The 2008 Storch et al study sampled only GSD1 families who were seen for medical

management at the Glycogen Storage Disease Program at the University of Florida whereas the present study was not limited to participants from any one center. Additionally, participants in the 2008 study were administered the PIP in-person and were offered financial compensation for their participation, whereas the participants in the present study self-administered the PIP online and were informed that there would be no financial compensation or other direct benefits from participating. It is reasonable to assume that families receiving treatment at a dedicated GSD program could have access to a greater level of support than a random sampling of families would have access to, which could be protective in terms of anxiety levels. The difference in administration of the PIP and the lack of compensation for participation in the present study may have also reduced the possibility of introducing social desirability bias or coercion as participants were able to take the survey in the privacy of their home, and the survey was not administered by individuals involved in the participants' healthcare.

In addition to the PIP, the PROMIS scores of these caregivers also confirmed that there was, on average, a level of anxiety increased by more than a standard deviation from that experienced at a population average. PROMIS scores for GSD1 caregivers have not previously been reported in the literature. The PIP and PROMIS scores were significantly correlated in this study, the Difficulty section more so than the Frequency section, further adding to the list of other psychological measures with which the PIP is correlated (Table 5) (Streisand et al 2001). The PIP Frequency had a correlation coefficient of 0.58 while the PIP Difficulty had a correlation coefficient of 0.68. For comparison, in the PIP's original publication, the highest correlation with another psychological measure was reported as 0.62 between the PIP Frequency and state anxiety as measured by the State-Trait Anxiety Inventory (STAI) (Streisand et al 2001).

Closer examination of the PIP-F and PIP-D scores by individual domains is possibly more telling in terms of what aspects of parenting a child with GSD1 have the most impact on caregiver QOL. The PIP scoring guide did not offer a method for comparing individual domain scores to one another (Appendix F.2. As such, the first step for this analysis was comparison of the average scores in each domain to the mean possible score based on the number of items contributing to that domain, followed by calculating the percent deviation from that mean possible score. Using this relative approach, the highest PIP Frequency score was in the domain of Medical Care, followed closely by Emotional Distress. The highest PIP Difficulty score was, by far, in the domain of Emotional Distress. When correlation coefficients were calculated between the individual domains of the PIP and the PROMIS, Emotional Distress Difficulty had the highest correlation at 0.72 (Table 5).

Interestingly, in the domain of Medical Care, the Frequency score was much higher than the Difficulty score. This finding would imply that dealing with GSD1 as a medical condition involves a great frequency of medical care-related activities, but may not be a major anxiety-provoking part of parenting a child with this condition. This can be interpreted in multiple ways. First, it is important to note that the Frequency section of the PIP asks caregivers about the last two weeks and the Difficulty sections asks about overall difficulty above and beyond the last two weeks. It may be reasonable to assume that caregivers had more time to complete the study survey during a particularly less hectic period of time with fewer scheduled or urgent medical appointments for their children with GSD1; in that case, the cross-section of caregiver responses captured would naturally contain a lesser reported frequency of medical care-related events. This assumption would mean that though the Medical Care score was the highest domain Frequency score, it may actually underrepresent the burden of medical care-related events such as visits to

the emergency room or to scheduled check-ups. Also in that scenario, the Difficulty score may be much lower than the Frequency score due to the availability heuristic making it more difficult to accurately rate the experienced difficulty of more distant medical care-related events. To illustrate the availability heuristic with an example, a standard clinic visit from the past month may come to a respondent's mind more quickly than a traumatic hospitalization experience that occurred a year ago, causing the respondent to report the lower level of difficulty that was associated with the more recent event. Another explanation of the high Frequency score yet low Difficulty score for Medical Care would be the "new normal" phenomenon previously described by a number of caregivers of children with IMD. In two past qualitative studies, caregivers described being used to, or even grateful for, the laborious treatment regimens and frequent clinic visits for their child's IMD, and stated that adjustment to this "new normal" makes it challenging to consider or notice the difficulty of their child's management (Siddiq et al 2016; Khangura et al 2016). Further anecdotal evidence for this explanation of the Medical Care scores lies in the unstructured GSD1 caregiver interviews performed prior to the development of the study survey; neither parent interviewed brought up their child's medical treatment as a factor they felt affected their QOL or stress levels (Appendix G).

Despite the relatively low Medical Care PIP Difficulty score, the total PIP Difficulty score was so elevated that we might speculate that caregiver anxiety levels are more robust to aspects of GSD1 medical management than to the diagnosis' effect on other areas of their lives, particularly Emotional Distress, which garnered by far the highest individual domain score for Difficulty within the PIP. Additionally, out of the Frequency and Difficulty scores for the four individual domains, the Emotional Distress Difficulty scores had the highest correlation with the PROMIS scores. This would further support that Emotional Distress related to GSD1 is the most

contributory factor to a caregiver's anxiety. The PIP items in the domain of Emotional Distress assess how frequently caregivers experience feelings of uncertainty, helplessness, fear, and worry about the child's isolation, among others, and how difficult these feelings are for the caregiver. The importance of the emotional aspects of managing a child's disease has previously been described in the literature for caregivers to children with IMD and other rare diseases (Michalik 2014; Khangura et al 2016; Dellve et al 2006; Siddiq et al 2016). One qualitative study concerning experiences of caregivers of children with IMD specifically identified "coping with uncertainty and the unknown" as a major theme in the lives of these caregivers (Khangura et al 2016) while a separate qualitative study elicited a common worry of IMD caregivers about the isolation of their child (Siddiq et al 2016). The high Emotional Distress Difficulty score in the present study further supports the presence of these emotional stressors in GSD1.

3.4.2 Social Media

In the caregiver interviews preceding the development of the survey, social media was anecdotally reported as a major source of stress and anxiety in terms of interactions within the GSD1 online community and interactions with other social circles as well. For this reason, the social media section of the survey was developed to describe patterns of usage and possible associations with anxiety and distress, as this has not been previously reported in the literature. As in most rare disease studies, inferences about the entire population of GSD1 caregivers are made with caution due to the small sample size. The results here indicated that the majority of GSD1 caregivers use social media platforms as a first resource to inform medical decision making for their child, see social media as a positive support system for GSD1 caregiving, and

have made stronger personal friendships by interacting with other GSD1 caregivers through social media.

On the other hand, results were quite mixed when caregivers were asked whether GSD1-related social media interactions instilled anxiety or stress in them regarding their own children. This result is interesting in the context of the results of the three prior social media questions, and suggests that social media can be viewed as a primary source of medical advice and positive interpersonal support but acts, in some, as a source of anxiety. It may also be concerning, but perhaps not surprising, to medical providers that caregivers turn first to social media when making medical decisions for their children. If medical decisions are often made based on information propagated through social media as this result indicates, there may be value in a genetic healthcare professional presence on social media to increase access to accurate information. A solution easier said than done, this presence would necessitate navigating issues of patient privacy and limited time of healthcare providers to engage in non-billable patient interactions, among other ethical and practical concerns (Gallagher et al 2016; Moore et al 2018). In recent years, the potential benefits, barriers, and drawbacks of patient-provider communication through social media platforms have been investigated and editorialized, but guidelines from professional organizations for how providers should or should not utilize this technology are still lacking (Muhlen and Ohno-Machado 2012; Gallagher et al 2016; Moore et al 2018). Given the results of the present study and the barriers to usage of social media by genetic professionals, it is not surprising that a recent study resulted in 75% of patient participants reporting interest in social media interactions with genetics providers while a lesser, but still significant, 58.6% of genetic counselors surveyed agreed that “social media has the potential for improving patient-provider interactions” (Moore et al 2018). This implies that interest in patient-

provider social media interaction appears to be greater on the side of the patient. In the context of the present study, the high interest in such interaction is compatible with the reported wide usage of social media by GSD1 caregivers in other aspects of care such as making medical decisions and sharing information with other caregivers.

For caregivers of children with rare diseases such as IMD, the internet has been a tool identified to assist in accessing information about the child's disease, as well as communicating with other families in a similar position (Siddiq et al 2016; Khangura et al 2015; Pelentsov et al 2016). While it is impractical to evaluate every online support group or disease-related website, further research may be warranted on social media's relationship to medical decision making and the accuracy of medical information and recommendations promulgated by these websites. This increased knowledge, combined with what we have learned in this study about the positive and negative impacts social media usage can have on caregivers, may help guide medical professionals in referring caregivers of children with GSD1 toward the most appropriate online resources.

3.4.3 Mental Healthcare

A majority of caregivers were interested in or potentially interested in the idea of pursuing mental healthcare to help manage challenges of being a GSD1 caregiver. Although there was no statistically significant difference in anxiety per PIP or PROMIS between those already seeing a mental health provider and those not, on appearance, those already seeing a provider had higher scores in all three measures of anxiety and there was decreased variance in their anxiety scores. This trend is reassuring in that the caregivers with the highest anxiety levels are the ones receiving treatment, however, we may also look at this trend as a failure of the treatment in

ameliorating levels of anxiety. A more informed conclusion could be drawn with more information about the type of mental healthcare provider being used, the duration of the therapeutic relationship thus far, and how anxiety levels have changed over time since the beginning of this therapeutic relationship.

For those caregivers not currently seeing a mental healthcare provider, there remain major barriers for those interested in pursuing treatment that could be protective against increasing anxiety levels. Though this study was not designed to be qualitative in nature, caregivers were able to write short entries explaining why they had not yet pursued a mental healthcare provider if they were interested, or why they were not interested in pursuing a mental healthcare provider. The main barrier between caregivers and mental healthcare was cited as time, followed by finances, both of which can be limited due to caring for a child with GSD1 as some of the caregivers stated. When current usage of mental healthcare was stratified by income bracket, there was no significant association between these two variables, which further suggests that time is the more limiting factor as a few of the respondents stated themselves (Table 7). Caregivers who were not currently interested in pursuing mental healthcare to help cope with challenges of being a GSD1 caregiver reported existent protective factors such as a satisfactory support system through church or family, or having been through therapy in the past. One respondent's explanation seemed to imply lack of trust in finding a provider who would understand the unique challenges of being a GSD1 caregiver, which speaks to the isolation that can commonly be felt in caregivers of children with IMD or other chronic and/or rare diseases (Pelentsov et al 2016; Michalik 2014; Siddiq et al 2016; Smith et al 2013; Waisbren et al 2004). For at least this caregiver, dissatisfaction with current social support, which may be

independently correlated with increased parenting stress, may be a perceived barrier to seeking more support through mental healthcare (Waisbren et al 2004).

While generalizations cannot be made from one participant's response, if further study finds this to be a common sentiment for caregivers to children with IMD or other rare genetic diseases, there may be a need for increased referral to professionals that offer both expertise in genetic disease and psychosocial counseling, such as a genetic counselor, to help caregivers feel understood and supported. In a 2018 qualitative study (Cunningham et al), at least one genetic counselor cited the dearth of providers who understand genetic conditions as a barrier to referring a patient to a mental healthcare provider, stating that the lack of understanding causes counterproductive frustration to the patient. While genetic counselors recognize distinctions in their scope of practice from that of a mental healthcare provider and do not typically act as longitudinal providers of psychosocial care, this type of care may be more typical of those 8% of genetic counselors who provide direct patient care in a metabolic disease setting, and perhaps even more so of those 2% of genetic counselors who have designated metabolic disease as their primary area of practice (Cunningham et al 2018; Hartley et al 2011; Doyle et al 2016; NSGC 2018). When access to a metabolic genetic counselor is not available for GSD1 caregivers, there may be other members of the GSD1 treatment team, which can include geneticists, nurses, social workers, dietitians, and other providers, who should be familiar with not only the treatment of GSD1 but the disease's unique challenges (Kishnani et al 2014; Hartley et al 2011).

3.4.4 Disease Management

As supported by the relatively low score in the PIP domain of Medical Care Difficulty, most caregivers reported in the GSD1-specific section of the survey that they were comfortable with

aspects of their child's feeding and cornstarch schedule, more so during the day than during the night. In rare diseases such as GSD1, parents often become experts in management of their child's disease and express confidence in their caregiving abilities (Pelentsov et al 2016). This confidence takes time to develop following the child's diagnosis (Dellve et al 2006). Because of this factor, participants were asked in the demographics section to provide the year of diagnosis for their child; the result was a wide range with most diagnoses occurring greater than one year prior to administration of the study survey. Though parents reported overall comfort with disease management, past studies have demonstrated a relationship between parent stress and difficulty meeting child healthcare needs in the IEM population (Waisbren et al 2004; Khangura et al 2016). However, comfort with aspects of managing the disease does not necessarily imply that this management does not have a toll on QOL of caregivers. The PIP Frequency score in the domain of Medical Care was the highest of the four individual domain Frequency scores when compared with the percent deviation measure, implying that managing care for a child with GSD1 is burdensome in terms of time, if not always perceived difficulty. One potential consequence of the time needed to care for a child with GSD1 was, for some participants, being unable to have a career, as noted in the demographics section (Table 1).

For those caregivers who did report feeling somewhat or extremely uncomfortable with aspects of their child's dietary treatment, there may be interventions available including further counseling with members of their child's treatment team, such as the metabolic dietitian, to discuss alternative strategies for management (Kishnani et al 2014). This section of the survey was designed to be a disease-specific complement to the scales of anxiety also included in this study. There is potential in using this low-burden four-item scale, which demonstrated good

internal consistency, or a similar disease-specific tool in GSD1 caregivers at regular clinic visits to assess need for interventions such as those aforementioned.

3.4.5 Study Limitations and Strengths

As previously noted, due to the time-consuming management of a GSD1 diagnosis and the high stress levels in GSD1 caregivers as previously published (Storch et al 2008) and indicated by the present study, it is plausible that those caregivers who had time to start and complete the study survey were caregivers in a less turbulent time regarding their child's medical management. In that case, though the results in this study for the PIP and PROMIS demonstrated a wide range of self-reported anxiety and stress, it is possible that the mean scores actually underrepresent the actual anxiety and stress in this population. This would be a concerning plausibility given the already elevated scores of anxiety this study defined. In this study and many studies concerning GSD1 and other rare disease populations, small sample size and bias towards mothers was also a factor that limits the extrapolation of our findings (Talente et al 1994; Storch et al 2008; Smith et al 2013; Siddiq et al 2016; Fabre et al 2013; Michalik 2014). However, mothers are often the primary caregiver and may experience a greater emotional burden than their partners experience from caring for a child with an IMD or other chronic disease (Lawoko and Soares 2003; Streisand et al 2001; McConkie-Rosell et al 2018; Pelentsov et al 2016; Picci et al 2015; Siddiq et al 2016; Smith et al 2013; Storch et al 2008; Waisbren et al 2004; Yanes et al 2017).

Unlike some previous studies of GSD1 caregivers, this study also included views of caregivers not limited to a single site or region, and may have therefore generated a more universal depiction of the GSD1 caregiving experience. This was achieved primarily through recruitment of caregivers visiting the AGSD website as well as requesting that healthcare

providers for patients with IMD consider sharing the study information with caregivers. Due to the former method, there was potential for bias toward caregivers with higher usage of internet resources like social media, which may have affected the results in the social media section of this study.

As a cross-sectional rather than longitudinal study, our results cannot determine causality between the variables we analyzed and caregiver QOL. Additionally, due to small sample size there may be moderate associations between variables that were either undetectable or not analyzed in the scope of this study. Despite its limitations, this study lays the groundwork for further evaluation of previously undescribed mediators of caregiver anxiety in the GSD1 population, including social media, access to mental healthcare services, and comfort with disease-specific dietary management.

3.4.6 Future Directions

The immediate implications of this study may include development and application of more targeted interventions for caregivers of children with GSD1; rather than focus on aspects of medical management of GSD1, interventions should target the emotional impact of having a child with this disease, as this was the largest driver of the anxiety scores reported in this study. Taking into account the overall interest of respondents in increased mental healthcare utilization that was met by many with the barrier of limited time, interventions could be most successful if they take place during existent clinic visits related to a child's GSD1 management to eliminate the need for additional coordination and time out of a caregiver's schedule.

One possible initial intervention would be to monitor caregiver mental health and QOL at specific intervals as part of a child's GSD1 treatment. This could be done by using scales of

anxiety such as those used in this study, the PIP and the PROMIS. Healthcare providers may use these or similar screening tools to make decisions regarding referral to mental healthcare providers or other providers/resources depending on responses. In addition, the four-item measure of comfort with GSD1 management developed for this study showed good internal consistency by Cronbach's alpha and could be of use as a regularly administered assessment of caregivers, perhaps especially when changes are made to their child's dietary treatment plan. Clinically, this could promote more understanding on the provider's part of which treatment options may be best for a specific family. There is also opportunity to use this tool for research to determine how caregiver ratings of comfort with management change over time in relation to changes in disease management, such as the introduction of cornstarch or Glycosade® to the regimen or placement of a G-tube, for example.

The current GSD1 guidelines already encourage the involvement of a multidisciplinary team that is aware of the unique psychosocial challenges that may be felt by patients and their families while stating that a genetic counselor should be included in GSD1 management (Kishnani et al 2014). Genetic counselors currently working primarily in a metabolic disease setting are limited in number at just 2% of respondents to the most recent NSGC Professional Status Survey (NSGC 2018). With training both in providing psychosocial support and knowledge of genetic disease, genetic counselors may be uniquely poised to offer ongoing support to caregivers of children with GSD1 as part of regular clinic visits (Doyle et al 2016). Metabolic genetic counselors in some clinics may already offer more long-term interventions to families than their non-metabolic counterparts (Hartley et al 2011). Further research is warranted to investigate genetic counseling interventions in metabolic disease clinics and compare

metabolic patient populations who do and do not have regular contact with a genetic counselor for differences in feelings of emotional distress and satisfaction with level of support.

3.5 CONCLUSIONS

The management guidelines for treating GSD1 call for healthcare providers to understand the unique impact this diagnosis may have on patients and their families in not only the physical, but also emotional aspects of health (Kishnani et al 2014). However, little is described in these guidelines or elsewhere in the literature regarding what aspects of caregiving for children with GSD1 have the most impact on caregivers and what may be done to mediate these negative effects. While we are unable to define all sources of anxiety, this study adds to the literature a more complete depiction of the level of anxiety and distress associated with caregiving for a child with GSD1, which may be higher than previously reported (Storch et al 2008). Additionally, we document for the first time the overall interest of these caregivers in seeking mental healthcare services to discuss challenges of caregiving as well as the caregiver-reported barriers to actually doing so; limited time and financial resources were reported to blockade interest in seeking support through mental healthcare services. For caregivers of children with many types of IMD, coordination of care can be key for convenience and parent satisfaction (Siddiq et al 2016). As such, a potential intervention may include offering mental healthcare support to some extent for GSD1 caregivers during their child's regular clinic visits. The disease-specific portion of the survey developed for this study, which showed that GSD1 caregivers are mostly comfortable managing diet-related aspects of their child's disease, is a step forward in establishing a tool that could be used to regularly assess caregivers for their comfort with aspects

of managing their child's disease. In this age, rare disease caregivers including those represented in this study use the internet and social media as not only a social support system, but a primary tool in making medical decisions (Siddiq et al 2016; Khangura et al 2015; Pelentsov et al 2016). There is research opportunity in further evaluating how social media engagement may mitigate or intensify feelings of anxiety, and alter decision-making processes in GSD1 caregivers. Diagnosable anxiety disorders such as Generalized Anxiety Disorder can be associated with sleep disturbances and difficulty concentrating, factors that can be dangerous in a disease setting where infants and children must be kept on a specific diet and feed frequently both day and night in order to avoid significant morbidity or even mortality (APA 2013; Kishnani et al 2014). The information gleaned from this study, therefore, not only impacts caregiver wellbeing but potentially patient wellbeing as well.

4.0 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH AND GENETIC COUNSELING

This study sought to describe and identify factors affecting the QOL of family caregivers of children with GSD1. Better understanding the specific challenges of this population may lead to more informed clinical practice and management guidelines for healthcare providers, including genetic counselors and other members of a healthcare system who provide genetic counseling, as well as the development of focused interventions for the caregivers of patients with GSD1. In this way, the goals and results of this study align with many of the essential services of public health and serve various stakeholders: 1) caregivers, often the advocates for their children, who would benefit from healthcare providers understanding the advocacy parents may need as well; 2) patients with GSD1, because identification of challenges and solutions for the caregiver are often entwined with the patient's own well-being; 3) healthcare providers, who will become more knowledgeable about the effects certain resources and treatment regimens may have on a family; and 4) the rare disease community at large, as raising awareness for one rare disease makes rare diseases and their accompanying challenges more visible.

4.1 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING

In the current setting of metabolic disorders such as GSD1, genetic counselors may make up a small or nonexistent piece of the patient's team of long-term providers, which often also includes a geneticist, nurse, and dietician specialized in metabolic diseases, in addition to the primary care physician, pharmacist, and other specialists a patient may see (Kishnani et al 2014; Hartley et al 2011). The NSGC Professional Status Survey of 2018 reported just 8% (n=117) of respondents claiming metabolic disease as an area of practice in which they provide direct patient care with 2% (n=28) reporting that metabolic disease is their primary area of practice (NSGC 2018). While genetic counselors have long been trained to identify, respond to, and help ameliorate the psychosocial concerns of patients and families in the short-term, every provider serving a family affected by GSD1 should be familiar with the particular psychosocial challenges and needs commonly faced by these families (Walker 2009; Kishnani et al 2014). Additionally, when genetic counselors are a part of a family's care in a metabolic disease setting, they may have a more longitudinal relationship with families resulting in the ability to provide psychosocial support above and beyond the short-term interventions described in the Genetic Counseling Practice-Based Competencies outlined by the Accreditation Council for Genetic Counseling (ACGC) (Hartley et al 2011; Doyle et al 2016).

Increased knowledge of GSD1-specific challenges can help any type of healthcare provider interacting with affected families deliver the most informed and helpful psychosocial support. Knowledge of QOL and its determining factors in such families is limited as existing studies have focused more on patients rather than caregivers, have had small sample sizes and/or samples from a single center or region, and/or have grouped GSD1 with other metabolic diseases (Rake et al 2002; Storch et al 2008; Sechi et al 2014; Siddiq et al 2016). The present study is the

first to add to existing knowledge the impact made on caregiver QOL by GSD1-specific aspects of care and by involvement in social media, which can be an important tool for rare disease caregivers (Siddiq et al 2016). This study also documents for the first time the level of interest in increased mental health support in this population.

As defined by the ACGC Genetic Counseling Practice-Based Competencies, part of successfully managing a genetic counseling case and helping clients, or patients, adapt to genetic information may include knowledge of and referral to appropriate services and resources, such as local to international support or mental healthcare providers (Doyle et al 2016). Needing little introduction, the internet, and specifically social media, plays such a large role in daily life that when genetic counselors present resources to clients, online resources may make the list. The past decade has seen much research interest in the potential benefits, barriers, and risks for patient-provider communication through social media platforms — von Muhlen and Ohno-Machado (2012) quantifies one side of this interest through a review of 50 publications within a span of 5 years, describing the rise of social media usage among younger cohorts of clinicians in a variety of specialties. Gallagher et al (2016) calls genetic counselors to "embrace social media" in part for the opportunity to disseminate accurate information in a way the public and non-genetic providers can understand, while also calling upon genetic counseling professional organizations to standardize the way genetic counselors interact with social media through development of professional guidelines (Gallagher et al 2016). While genetic professionals and other clinicians acknowledge potential benefits of patient-provider interactions through social media, patients may be even more interested in pursuing such interactions (Moore et al 2018). While these studies get at the professional usage of social media, what remains unstudied are those interactions between patients or caregivers with one another, and what benefits or

drawbacks this may have on their wellbeing. With the social media section of the present study, which was developed on the basis of an unstructured GSD1 caregiver interview, it is documented that caregivers frequently turn to social media when making medical decisions for their children, and yet often find it to be a stressor in and of itself. When genetic counselors and other providers recommend support groups, online or in-person, it may be important to offer anticipatory guidance that some such resources can add to rather than mitigate caregiver distress. Additionally, if calls to develop professional guidelines for provider social media interactions are answered, it may be worth ensuring that medically accurate recommendations are available where patients and caregivers check first when making medical decisions.

4.2 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH

As a rare disease, the incidence of GSD1 is, of course, low, at a level of 1 in 100,000 live births. However, taking all IMD into account, overall incidence is much higher at 1 in 1,400 live births (Applegarth et al 2000). Though nuanced psychosocial effects will differ between one IMD and another, certain motifs, such as strict dietary restrictions and a ubiquitous risk of metabolic decompensation may challenge caregivers to patients with many different kinds of IMD (Fabre et al 2013; Evans et al 2012). Research is limited for not only the GSD1 population, but for IMD at large in terms of caregiver quality of life.

For GSD1 specifically, the present study has increased knowledge of the determinants of caregiver quality of life. In doing so, we address the first core function of public health, assessment, to describe the health problems possibly facing this population and investigate the roots of these problems. The results of this study establish the level of distress and anxiety of this

population, opening the way for the policy development responsibility of public health services to work at informing caregivers and the healthcare services with which they interact. Awareness of the health impact that GSD1 and the disease's treatment has on caregivers may inform treatment guidelines and the physicians, nurses, dietitians, genetic counselors, and other healthcare professionals that utilize them. This education helps assure a competent workforce, one of the essential public health services within the function of assurance.

Also relevant to the public health function of assurance, the results of this study show the potential to link caregivers with healthcare services they may be missing, notably in the area of mental health. A majority of respondents to the study indicated that they were interested in or possibly interested in seeking mental health care specifically to discuss the challenges of being a caregiver of a child with GSD1. However, many subjects cited limited time as a reason why they had not done so already, and others stated that they simply had not considered it yet. This result, in conjunction with the anxious and distressed state of these caregivers described by the PIP and PROMIS questionnaires, opens the way for necessary referrals and open communication between providers and caregivers. Armed with a better understanding of the challenges these caregivers face, genetic counselors and other providers caring for a GSD1 family can offer more informed anticipatory guidance. Earlier discussion of possible support systems, which might include mental healthcare providers, may be an intervention to mediate the stress seen in this population and normalize the need for such care. As previously mentioned, genetic counselors in the metabolic disease setting may provide a higher level of support to their families in terms of length of care and psychosocial interventions when compared to other specializations within the genetic counseling field; research remains to be done in terms of delineating the types of interventions these counselors may use as well as their patient outcomes (Hartley et al 2011).

Since the present study identified the need for and interest in increased mental health support in the GSD1 caregiver population, it would be interesting to know whether those caregivers who do regularly interact with a genetic counselor as part of their child's healthcare have some of this need met by the genetic counselor's unique training in genetics and social wellbeing. From both a public health and genetic counseling field standpoint, this opens a relevant research opportunity to assess how this population's specific needs are, or are not, being met, and which providers have an impact on caregiver outcomes in terms of QOL.

APPENDIX A: AGSD CONTACT

A.1 LETTER TO THE AGSD

August 2, 2017

Pediatric Medical Genetics
% Jennifer Peck
4401 Penn Ave.
1st Floor - Suite 1200
Pittsburgh, PA 15224

Board of Directors
Association for Glycogen Storage Disease
P.O. Box 896
Durant, IA 52747

To the Board of Directors:

I am a graduate student at the University of Pittsburgh working towards completing my masters degree in genetic counseling. During my clinical rotation at the Children's Hospital of Pittsburgh, I had the experience of meeting patients affected by metabolic disorders, and specifically with glycogen storage disease type 1. I was impressed with the efforts and experiences of the parents that I met, and I was compelled to find out more about what it means to be a caregiver of someone with this medical condition.

Since meeting with those parents, I decided to develop my required research project to explore the experiences and quality of life of caregivers for family members with glycogen storage disease 1. I have been collaborating with metabolic experts at the Children's Hospital of Pittsburgh of UPMC and other advisors in my academic program to refine my project. It will involve use of validated and self-developed surveys to assess quality of life for caregivers of individuals who have GSD type 1, with a long term aim of formalizing this information and potentially developing materials and recommendations for healthcare providers who work with this patient population. As part of the project, I contacted Iris Ferrecchia to discuss this project and possible recruitment methods. I am requesting assistance in facilitating my recruitment of caregivers through the website and email list of the Association for Glycogen Storage Disease.

Enclosed you will find my summary of intent for this project and a description of the survey tools to be used in the study.

Please contact me if you need any additional information about my research plans. I look forward to working with you and all of the families you support to help build knowledge about glycogen storage disease.

Best,

Jennifer Peck

A.2 LETTER OF SUPPORT

Association for Glycogen Storage Disease

"Spreading our rays to shine for a brighter future"

October 10, 2017

To whom it may concern:

The Scientific Advisory Board of the Association for Glycogen Storage Disease has reviewed the project proposed by Jennifer Peck. The Board understands that the proposed project will describe the quality of life in caregivers of children who have glycogen storage disease type I, while also exploring possible contributing and ameliorating factors to the parental distress experienced in this population. We have agreed to help facilitate Ms. Peck's subject ascertainment through the Association's main web page and email newsletter and/or listserv by including the secure link to access the project's survey tool. We look forward to assisting with the completion of this important research.

Kindest Regards,

Iris Ferrecchia, President
66 Oxford St., Hartford, CT 06105
Mobile: (508) 596-6846, Office: (860) 837-7854
iferrecchia@connecticutchildrens.org

APPENDIX B: PROVIDER INFORMATION SHEET

Dear healthcare providers and other professionals,

My name is Jennifer Peck, and I am a second-year genetic counseling student at the University of Pittsburgh. Through my work and rotations at the Children's Hospital of Pittsburgh of UPMC, I have met families with children who have GSD1. I was impressed with the efforts and experiences of the caregivers in these families, and I became very interested in learning more about all of their experiences, challenges, and successes as parents (or other types of caregivers) of children who have GSD1. To accomplish this, I have developed a questionnaire that will take about 15-30 minutes to complete. The link to this questionnaire is available on the homepage of the Association for Glycogen Storage Disease (AGSD) at http://agsdus.org/.

This posting is an invitation for you to share the availability of this survey with **families you care for who are affected by GSD1a or GSD1b**. Attached to this message is a flier and an information sheet that you may pass along to caregivers who may be interested in participating.

You or your patients may reach me with questions or concerns regarding this research study at jennifer.peck@pitt.edu. Thank you very much for your time and for considering sharing this information with your families. We hope that the results of this study will help medical care providers and other professionals such as yourselves better understand caregiver concerns, health care needs, and sources of support and stress.

Best,

Jennifer Peck
Genetic Counseling Intern
Human Genetics
Graduate School of Public Health
University of Pittsburgh

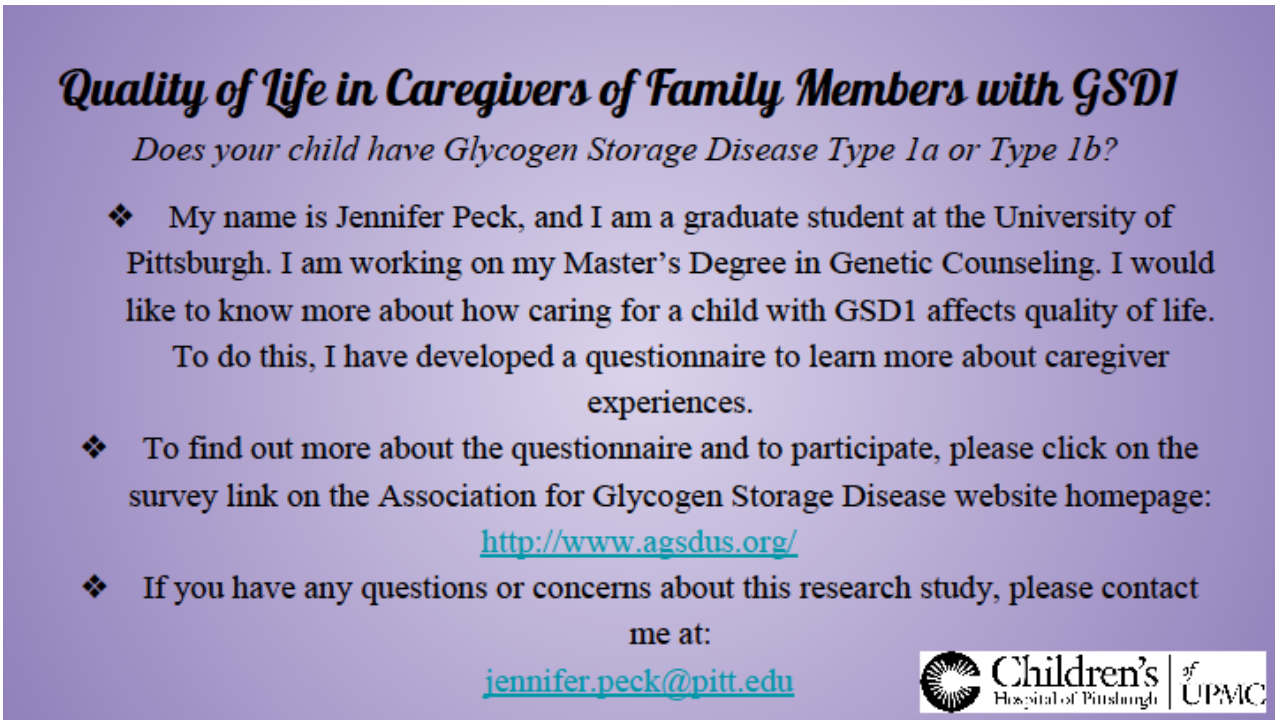
Graduate Student Researcher
Pediatric Medical Genetics
Children's Hospital of Pittsburgh of UPMC

APPENDIX C: INTRODUCTORY SCRIPT FOR PARTICIPANTS

If you are a caregiver of a child with Glycogen storage disease **type 1a** or **type 1b** (GSD1)...

I am inviting you to take part in a research study I have developed as part of my training to become a genetic counselor. My name is Jennifer Peck, and I am studying at the University of Pittsburgh. Through my work and rotations at the Children's Hospital of Pittsburgh of UPMC, I met families with children who have GSD1. I was impressed with the efforts and experiences of the caregivers in these families, and I became very interested in learning more about all of your experiences, challenges, and successes as parents (or other types of caregivers) of children who have GSD1. To do this, I have worked with the Association for Glycogen Storage Disease (AGSD) to reach you all, and I have developed a questionnaire that will take about 15-30 minutes to complete. This posting is an invitation to you to take the survey; we hope that the results of this study will help medical care providers better understand your concerns and health care needs. This questionnaire will ask about your experiences as a caregiver of a child with GSD1, your quality of life and stress levels related to caring for your child, and some background information such as your gender and age. My plan is to publish the results of this study in a medical journal that reaches physicians who provide care for patients who have GSD1. Risks associated with participating in the survey are limited, but may include negative feelings brought on by answering questions about difficult or stressful situations. There are no direct benefits to participating in the study. If you choose to participate, your answers to the questions will be collected and stored anonymously, so that your responses will not be linked to you in any way. All the answers will be confidential, and stored on secure computers within keycard-access offices of the Children's Hospital. The research data we collect may be shared with investigators conducting other research in the future; however, this information will be shared in a de-identified manner (without information that is identifiable). Your participation is voluntary, and you may withdraw from this study at any time. This study is being conducted by myself, Jennifer Peck, and you can reach me at jennifer.peck@pitt.edu if you have any questions or concerns about the research study. Thank you very much for considering participating, and I look forward to using this project to help build more knowledge about GSD1 so we can keep learning how to best support you and your child.

APPENDIX D: FLIER



APPENDIX E: UNIVERSITY OF PITTSBURGH IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Areeg El-Gharbawy
From: IRB Office
Date: 11/30/2017
IRB#: PRO17070068
Subject: Factors Affecting Quality of Life in Caregivers of Family Members with Glycogen Storage Disease Type 1

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a written informed consent for all of the research procedures described in the above-named research protocol and all of the subjects participating in the respective research procedures.

The IRB has approved the advertisement that was submitted for review as written. As a reminder, any changes to the advertisement other than to edit contact information requires IRB approval prior to distribution.

The risk level designation is Minimal Risk.

Approval Date: 11/30/2017
Expiration Date: 11/29/2018

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not

limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX F: STUDY SURVEY

Quality of Life in Caregivers of Children with Glycogen Storage Disease Type1

Survey Flow

Standard: Intro and Consent (8 Questions)
Standard: Block 2 (1 Question)
Block: Pediatric Inventory for Parents (PIP) (1 Question)
Standard: PIP - frequency - >1 child (1 Question)
Standard: PIP - severity - 1 child (1 Question)
Standard: PIP - severity > 1 child (1 Question)
Standard: PROMIS (1 Question)
Standard: Social Media Use - (6 Questions)
Standard: Social Media Use - Likert and mental health (6 Questions)
Standard: Feeding (9 Questions)
Standard: Block 11 (1 Question)
Standard: Demographics (13 Questions)

Page Break

Start of Block: Intro and Consent

Q1 If you are a family caregiver of a child with Glycogen storage disease type 1a or type 1b (GSD1)...
I am inviting you to take part in a research study I have developed as part of my training to become a genetic counselor. My name is Jennifer Peck, and I am studying at the University of Pittsburgh. Through my work at the Children's Hospital of Pittsburgh of UPMC, I met families with children who have diagnoses of GSD1. I was impressed with the efforts and experiences of the caregivers in these families, and I became very interested in learning more about your experiences, challenges, and successes as parents or other family caregivers of children who have GSD1.
I have worked with the Association for Glycogen Storage Disease (AGSD) to reach you all, and I have developed a questionnaire that will take about 20-30 minutes to complete. You may save your progress and return to the survey later if you use the same computer to complete it. This posting is an invitation to you to take the survey; we hope that the results of this study will help medical care providers better understand your concerns and health care needs. This questionnaire will address your experiences as a caregiver of a child with GSD1, your quality of life and stress levels related to caring for your child, and background information such as your gender and age. I plan to publish the results of this study in a medical journal that reaches physicians and other healthcare providers who care for patients who have GSD1. Risks associated with participating in the survey are limited, but may include negative feelings brought on by answering questions about difficult or stressful situations. There are no direct benefits to participating in the study. If you choose to participate, your answers to the questions will be collected and stored anonymously, so that your responses will not be linked to you in any way. All the answers will be confidential, and stored on secure computers within keycard-access offices of the Children's Hospital of Pittsburgh of UPMC. The research data we collect may be shared with investigators conducting other research in the future; however, this information will be shared in a de-identified manner (without information that is identifiable).Your participation is voluntary, and you may withdraw from this study at any time.
This study is being conducted by myself, Jennifer Peck, and you can reach me at jennifer.peck@pitt.edu if you have any questions or concerns about the research study. Thank you very much for considering participating, and I look forward to using this project to help build more knowledge about GSD1 so we can keep learning how to best support you and your child.

- ○ I would like to take the survey. (1)
- ○ I would not like to take the survey. (2)

Skip To: End of Survey If Q1 = 2

Q2 Do you care for at least one child who has Glycogen Storage Disease Type 1?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Block If Q2 = 2

Q3 How many children **with** GSD1 do you care for?

- ○ 1 (1)
- ○ 2 (2)
- ○ 3 or more (3)

Q4 How many children **without** GSD1 do you care for?

- ○ 0 (1)
- ○ 1 (2)
- ○ 2 (3)
- ○ 3 or more (4)

Display This Question:
If Q3 = 1

Q5 How are you related to your child with GSD1?

- ○ Mother (1)
- ○ Father (2)
- ○ Other - please describe (3) _____

Display This Question:
If Q3 = 1

Q6 Which type of GSD1 does your child have?

- ○ GSD1a (1)
- ○ GSD1b (2)

Display This Question:
If Q3 != 1

Q7 Which type of GSD1 do your children have?

- ○ GSD1a (1)
- ○ GSD1b (2)

Display This Question:
If Q3 != 1

Q8 How are you related to your children with GSD1?

- ○ Mother (1)
- ○ Father (2)
- ○ Other - please describe (3)

End of Block: Intro and Consent

Start of Block: Block 2

Display This Question:
If Q2 = 2

Q9 Thank you for your interest. This survey is only for those who care for children who have Glycogen Storage Disease Type 1. You may now close this window.

Skip To: End of Survey If Q9(1) Is Displayed

End of Block: Block 2

Start of Block: Pediatric Inventory for Parents (PIP)

Display This Question:

If Q3 = 1

Q10 Below is a list of difficult events which parents of children who have (or have had) a serious illness sometimes face. Please read each event carefully, and select HOW OFTEN the event has occurred for you in the past 7 days, using the 5 point scale below.

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Very often (5)
Difficulty sleeping (1)	○	○	○	○	○
Arguing with family member(s) (2)	○	○	○	○	○
Bringing my child to the clinic or hospital (3)	○	○	○	○	○
Learning upsetting news (4)	○	○	○	○	○
Being unable to go to work/job (5)	○	○	○	○	○
Seeing my child's mood change quickly (6)	○	○	○	○	○
Speaking with doctor (7)	○	○	○	○	○
Watching my child have trouble eating (8)	○	○	○	○	○
Waiting for my child's test results (9)	○	○	○	○	○
Having money/financial troubles (10)	○	○	○	○	○
Trying not to think about my family's difficulties (11)	○	○	○	○	○
Feeling confused about medical information (12)	○	○	○	○	○
Being with my child during medical procedures (13)	○	○	○	○	○

Knowing my child is hurting or in pain (14)	○	○	○	○	○
Trying to attend to the needs of other family members (15)	○	○	○	○	○
Seeing my child sad or scared (16)	○	○	○	○	○
Talking with the nurse (17)	○	○	○	○	○
Making decisions about medical care or medicines (18)	○	○	○	○	○
Thinking about my child being isolated from others (19)	○	○	○	○	○
Being far away from family and/or friends (20)	○	○	○	○	○
Feeling numb inside (21)	○	○	○	○	○
Disagreeing with a member of the health care team (22)	○	○	○	○	○
Helping my child with his/her hygiene needs (23)	○	○	○	○	○
Worrying about the long term impact of the illness (24)	○	○	○	○	○
Having little time to take care of my own needs (25)	○	○	○	○	○
Feeling helpless over my child's condition (26)	○	○	○	○	○

Feeling misunderstood by family/friends as to the severity of my child's illness (27)	○	○	○	○	○
Handling changes in my child's daily medical routines (28)	○	○	○	○	○
Feeling uncertain about the future (29)	○	○	○	○	○
Being in the hospital over weekends/holidays (30)	○	○	○	○	○
Thinking about other children who have been seriously ill (31)	○	○	○	○	○
Speaking with my child about his/her illness (32)	○	○	○	○	○
Helping my child with medical procedures (e.g. giving shots, swallowing medicine, changing dressing) (33)	○	○	○	○	○
Having my heart beat fast, sweating, or feeling tingly (34)	○	○	○	○	○
Feeling uncertain about disciplining my child (35)	○	○	○	○	○
Feeling scared that my child could get very sick or die (36)	○	○	○	○	○

Speaking with family members about my child's illness. (37)	○	○	○	○	○
Watching my child during medical visits/procedures (38)	○	○	○	○	○
Missing important events in the lives of other family members (39)	○	○	○	○	○
Worrying about how friends and relatives interact with my child (40)	○	○	○	○	○
Noticing a change in my relationship with my partner (41)	○	○	○	○	○
Spending a great deal of time in unfamiliar settings (42)	○	○	○	○	○

End of Block: Pediatric Inventory for Parents (PIP)

Start of Block: PIP - frequency - >1 child

Display This Question:

If Q3 != 1

Q11

Thinking of the child most recently diagnosed with GSD1 in your family, please read the directions below, and answer the following questions.

Below is a list of difficult events which parents of children who have (or have had) a serious illness sometimes face. Please read each event carefully, and select HOW OFTEN the event has occurred for you in the past 7 days, using the 5 point scale below.

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Very often (5)
Difficulty sleeping (1)	○	○	○	○	○
Arguing with family member(s) (2)	○	○	○	○	○
Bringing my child to the clinic or hospital (3)	○	○	○	○	○
Learning upsetting news (4)	○	○	○	○	○
Being unable to go to work/job (5)	○	○	○	○	○
Seeing my child's mood change quickly (6)	○	○	○	○	○
Speaking with doctor (7)	○	○	○	○	○
Watching my child have trouble eating (8)	○	○	○	○	○
Waiting for my child's test results (9)	○	○	○	○	○
Having money/financial troubles (10)	○	○	○	○	○
Trying not to think about my family's difficulties (11)	○	○	○	○	○
Feeling confused about medical information (12)	○	○	○	○	○

Being with my child during medical procedures (13)	○	○	○	○	○
Knowing my child is hurting or in pain (14)	○	○	○	○	○
Trying to attend to the needs of other family members (15)	○	○	○	○	○
Seeing my child sad or scared (16)	○	○	○	○	○
Talking with the nurse (17)	○	○	○	○	○
Making decisions about medical care or medicines (18)	○	○	○	○	○
Thinking about my child being isolated from others (19)	○	○	○	○	○
Being far away from family and/or friends (20)	○	○	○	○	○
Feeling numb inside (21)	○	○	○	○	○
Disagreeing with a member of the health care team (22)	○	○	○	○	○
Helping my child with his/her hygiene needs (23)	○	○	○	○	○
Worrying about the long term impact of the illness (24)	○	○	○	○	○
Having little time to take care of my own needs (25)	○	○	○	○	○

Feeling helpless over my child's condition (26)	○	○	○	○	○
Feeling misunderstood by family/friends as to the severity of my child's illness (27)	○	○	○	○	○
Handling changes in my child's daily medical routines (28)	○	○	○	○	○
Feeling uncertain about the future (29)	○	○	○	○	○
Being in the hospital over weekends/holidays (30)	○	○	○	○	○
Thinking about other children who have been seriously ill (31)	○	○	○	○	○
Speaking with my child about his/her illness (32)	○	○	○	○	○
Helping my child with medical procedures (e.g. giving shots, swallowing medicine, changing dressing) (33)	○	○	○	○	○
Having my heart beat fast, sweating, or feeling tingly (34)	○	○	○	○	○
Feeling uncertain about disciplining my child (35)	○	○	○	○	○
Feeling scared that my child could get very sick or die	○	○	○	○	○

(36)					
Speaking with family members about my child's illness. (37)	○	○	○	○	○
Watching my child during medical visits/procedures (38)	○	○	○	○	○
Missing important events in the lives of other family members (39)	○	○	○	○	○
Worrying about how friends and relatives interact with my child (40)	○	○	○	○	○
Noticing a change in my relationship with my partner (41)	○	○	○	○	○
Spending a great deal of time in unfamiliar settings (42)	○	○	○	○	○

End of Block: PIP - frequency - >1 child

Start of Block: PIP - severity - 1 child

Display This Question:

If Q3 = 1

Q12 Below is the same list of difficult events which parents of children who have (or have had) a serious illness sometimes face. Please read each event carefully again, and select HOW DIFFICULT the event was/or generally is for you, using the 5 point scale below.

	Not at all (1)	A little (2)	Somewhat (3)	Very much (4)	Extremely (5)
Difficulty sleeping (1)	○	○	○	○	○
Arguing with family member(s) (2)	○	○	○	○	○
Bringing my child to the clinic or hospital (3)	○	○	○	○	○
Learning upsetting news (4)	○	○	○	○	○
Being unable to go to work/job (5)	○	○	○	○	○
Seeing my child's mood change quickly (6)	○	○	○	○	○
Speaking with doctor (7)	○	○	○	○	○
Watching my child have trouble eating (8)	○	○	○	○	○
Waiting for my child's test results (9)	○	○	○	○	○
Having money/financial troubles (10)	○	○	○	○	○
Trying not to think about my family's difficulties (11)	○	○	○	○	○
Feeling confused about medical information (12)	○	○	○	○	○
Being with my child during medical procedures (13)	○	○	○	○	○

Knowing my child is hurting or in pain (14)	○	○	○	○	○
Trying to attend to the needs of other family members (15)	○	○	○	○	○
Seeing my child sad or scared (16)	○	○	○	○	○
Talking with the nurse (17)	○	○	○	○	○
Making decisions about medical care or medicines (18)	○	○	○	○	○
Thinking about my child being isolated from others (19)	○	○	○	○	○
Being far away from family and/or friends (20)	○	○	○	○	○
Feeling numb inside (21)	○	○	○	○	○
Disagreeing with a member of the health care team (22)	○	○	○	○	○
Helping my child with his/her hygiene needs (23)	○	○	○	○	○
Worrying about the long term impact of the illness (24)	○	○	○	○	○
Having little time to take care of my own needs (25)	○	○	○	○	○
Feeling helpless over my child's condition (26)	○	○	○	○	○

Feeling misunderstood by family/friends as to the severity of my child's illness (27)	○	○	○	○	○
Handling changes in my child's daily medical routines (28)	○	○	○	○	○
Feeling uncertain about the future (29)	○	○	○	○	○
Being in the hospital over weekends/holidays (30)	○	○	○	○	○
Thinking about other children who have been seriously ill (31)	○	○	○	○	○
Speaking with my child about his/her illness (32)	○	○	○	○	○
Helping my child with medical procedures (e.g. giving shots, swallowing medicine, changing dressing) (33)	○	○	○	○	○
Having my heart beat fast, sweating, or feeling tingly (34)	○	○	○	○	○
Feeling uncertain about disciplining my child (35)	○	○	○	○	○
Feeling scared that my child could get very sick or die (36)	○	○	○	○	○

Speaking with family members about my child's illness. (37)	○	○	○	○	○
Watching my child during medical visits/procedures (38)	○	○	○	○	○
Missing important events in the lives of other family members (39)	○	○	○	○	○
Worrying about how friends and relatives interact with my child (40)	○	○	○	○	○
Noticing a change in my relationship with my partner (41)	○	○	○	○	○
Spending a great deal of time in unfamiliar settings (42)	○	○	○	○	○

End of Block: PIP - severity - 1 child

Start of Block: PIP - severity > 1 child

Display This Question:

If Q3 != 1

Q13

Thinking of the child most recently diagnosed with GSD1 in your family, please read the directions below, and answer the following questions.

Below is the same list of difficult events which parents of children who have (or have had) a serious illness sometimes face. Please read each event carefully again, and select HOW DIFFICULT the event was/or generally is for you, using the 5 point scale below.

	Not at all (1)	A little (2)	Somewhat (3)	Very much (4)	Extremely (5)
Difficulty sleeping (1)	○	○	○	○	○
Arguing with family member(s) (2)	○	○	○	○	○
Bringing my child to the clinic or hospital (3)	○	○	○	○	○
Learning upsetting news (4)	○	○	○	○	○
Being unable to go to work/job (5)	○	○	○	○	○
Seeing my child's mood change quickly (6)	○	○	○	○	○
Speaking with doctor (7)	○	○	○	○	○
Watching my child have trouble eating (8)	○	○	○	○	○
Waiting for my child's test results (9)	○	○	○	○	○
Having money/financial troubles (10)	○	○	○	○	○
Trying not to think about my family's difficulties (11)	○	○	○	○	○
Feeling confused about medical information (12)	○	○	○	○	○

Being with my child during medical procedures (13)	○	○	○	○	○
Knowing my child is hurting or in pain (14)	○	○	○	○	○
Trying to attend to the needs of other family members (15)	○	○	○	○	○
Seeing my child sad or scared (16)	○	○	○	○	○
Talking with the nurse (17)	○	○	○	○	○
Making decisions about medical care or medicines (18)	○	○	○	○	○
Thinking about my child being isolated from others (19)	○	○	○	○	○
Being far away from family and/or friends (20)	○	○	○	○	○
Feeling numb inside (21)	○	○	○	○	○
Disagreeing with a member of the health care team (22)	○	○	○	○	○
Helping my child with his/her hygiene needs (23)	○	○	○	○	○
Worrying about the long term impact of the illness (24)	○	○	○	○	○
Having little time to take care of my own needs (25)	○	○	○	○	○

Feeling helpless over my child's condition (26)	○	○	○	○	○
Feeling misunderstood by family/friends as to the severity of my child's illness (27)	○	○	○	○	○
Handling changes in my child's daily medical routines (28)	○	○	○	○	○
Feeling uncertain about the future (29)	○	○	○	○	○
Being in the hospital over weekends/holidays (30)	○	○	○	○	○
Thinking about other children who have been seriously ill (31)	○	○	○	○	○
Speaking with my child about his/her illness (32)	○	○	○	○	○
Helping my child with medical procedures (e.g. giving shots, swallowing medicine, changing dressing) (33)	○	○	○	○	○
Having my heart beat fast, sweating, or feeling tingly (34)	○	○	○	○	○
Feeling uncertain about disciplining my child (35)	○	○	○	○	○
Feeling scared that my child could get very sick or die	○	○	○	○	○

(36)					
Speaking with family members about my child's illness. (37)	○	○	○	○	○
Watching my child during medical visits/procedures (38)	○	○	○	○	○
Missing important events in the lives of other family members (39)	○	○	○	○	○
Worrying about how friends and relatives interact with my child (40)	○	○	○	○	○
Noticing a change in my relationship with my partner (41)	○	○	○	○	○
Spending a great deal of time in unfamiliar settings (42)	○	○	○	○	○

End of Block: PIP - severity > 1 child

Start of Block: PROMIS

Q14 Please response to each question or statement by marking one circle per row.

In the past 7 days...

	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
I felt fearful (1)	○	○	○	○	○
I found it hard to focus on anything other than my anxiety (2)	○	○	○	○	○
My worries overwhelmed me (3)	○	○	○	○	○
I felt uneasy (4)	○	○	○	○	○
I felt nervous (5)	○	○	○	○	○
I felt like I needed help for my anxiety (6)	○	○	○	○	○
I felt anxious (7)	○	○	○	○	○
I felt tense (8)	○	○	○	○	○

End of Block: PROMIS

Start of Block: Social Media Use -

Q15 You will now be asked questions about whether and how you use social media as a caregiver for a child with GSD1. "Social media" includes websites such as Facebook, Twitter, Instagram, YouTube, and other websites or applications you may use to share, create, and comment on content. You will also be asked about other resources, such as mental healthcare provider usage. The purpose of this section is to gain information about possible resources and factors affecting stress levels in caregivers.

Q16 What is your typical use of social media?

- ○ I equally write my own content AND read content that other people have posted (2)
- ○ I mostly read content that other people have posted (1)
- ○ I do not use it (3)

Display This Question:
If Q16 != 3

Q17 Do you actively use (or have you previously used) social media to engage with other families affected by GSD1?

- ○ Yes (1)
- ○ No (2)

Display This Question:
If Q16 != 3
And Q3 = 1

Q18 How has your use of social media changed since the time of your child's diagnosis of GSD1?

- ○ Increased (1)
- ○ Decreased (2)
- ○ No change (3)

Display This Question:
If Q16 != 3
And Q3 != 1

Q19 How has your use of social media changed since the most recent diagnosis of GSD1 in your family?

- Increased (1)
- Decreased (2)
- No change (3)

Display This Question:
If Q16 = 3

Q20 Did you use social media before your child, or most recent child, was diagnosed with GSD1?

- Yes (1)
- No (2)

End of Block: Social Media Use -

Start of Block: Social Media Use - Likert and mental health

Display This Question:
If Q16 != 3

Q21

Below is a list of statements regarding your use of social media. Social media refers to Facebook, Twitter, Instagram, YouTube, and other websites you may use to communicate with others, such as blogs. Please read each statement carefully, and select how strongly you agree or disagree using the 5-point scale.

	Strongly agree (1)	Somewhat agree (2)	Neither agree nor disagree (3)	Somewhat disagree (4)	Strongly disagree (5)
Social media is the first resource I use to help make medical decisions for my child with GSD1. (1)	○	○	○	○	○
Social media is a positive support system for me as a GSD1 caregiver. (2)	○	○	○	○	○
I have stronger personal friendships due to my use of social media with other GSD1 caregivers. (3)	○	○	○	○	○
Discussing or reading about GSD1 on social media often gives me stress or anxiety about my own child. (4)	○	○	○	○	○
I make information about my child's GSD1	○	○	○	○	○

diagnosis available to anyone I am connected to on social media. (5)					
I make information about my child's GSD1 diagnosis available ONLY to other GSD1 families. (6)	○	○	○	○	○

Q22 I currently see a mental health care provider or other support specialist for myself, such as a counselor, therapist, psychologist, psychiatrist, clergy-person, or other.

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Q22 = 2

Q23 I would like to speak with a mental health care provider about challenges related to my experience as a GSD1 caregiver.

- ○ Yes (1)
- ○ Maybe (2)
- ○ No (3)

Display This Question:
If Q22 = 2
And Q23 != 3

Q24 You answered that you would like to speak with a mental health care provider about your caregiver experiences. Could you briefly explain why you have not seen one?

_____

Display This Question:
If Q23 = 3

Q25 You answered that you would not like to speak with a mental health care provider about your caregiver experiences. Could you briefly explain why not?

_____

Display This Question:
If Q22 = 1

Q26 I would like to speak **more** with my mental health care provider, or a different mental health care provider, about challenges related to my experience as a GSD1 caregiver.

- ○ Yes (1)
- ○ Maybe (2)
- ○ No (3)

End of Block: Social Media Use - Likert and mental health

Start of Block: Feeding

Q27 You will now be asked a series of questions regarding your child's feeding/cornstarch schedule.

Display This Question:
If Q3 = 1

Q28 Select from the following methods those that you use to manage your child's nighttime feeds. Choose all that apply.

- ☐ Glycosade (1)
- ☐ Cornstarch (2)
- ☐ Gastric Tube (G-tube) with feeds (3)
- ☐ Night home nurse (4)
- ☐ Other (5) _____

Display This Question:
If Q3 != 1

Q29 Thinking of your youngest child with GSD1, Select from the following methods those that you use to manage your child's nighttime feeds. Choose all that apply.

- ☐ Glycosade (1)
- ☐ Cornstarch (2)
- ☐ Gastric Tube (G-tube) with feeds (3)
- ☐ Night home nurse (4)
- ☐ Other (5) _____

Display This Question:
If Q3 = 1

Q30 On a typical, non-sick day, how often do you generally have blood glucose "finger sticks" performed on your child?

- every 15-30 minutes (1)
- every 30-60 minutes (2)
- every 1-2 hours (3)
- less often than every 2 hours (4)
- On an average day I do not have my child's glucose checked (5)

Display This Question:
If Q3 != 1

Q31 On a typical, non-sick day, how often do you generally have blood glucose "finger sticks" performed on your ***youngest child with GSD1?***

- every 15-30 minutes (1)
- every 30-60 minutes (2)
- every 1-2 hours (3)
- less often than every 2 hours (4)
- On an average day I do not have my child's glucose checked (5)

Display This Question:
If Q3 = 1

Q32 How often, on a typical, non-sick day, do you have your child consume a cornstarch feed?

- ○ more often than every 2 hours (1)
- ○ every 2-3 hours (2)
- ○ every 3-4 hours (3)
- ○ every 4-6 hours (4)
- ○ less often than every 6 hours (5)

Display This Question:
If Q3 != 1

Q33 How often, on a typical, non-sick day, do you have your ***youngest child with GSD1*** consume a cornstarch feed?

- ○ more often than every 2 hours (1)
- ○ every 2-3 hours (2)
- ○ every 3-4 hours (3)
- ○ every 4-6 hours (4)
- ○ less often than every 6 hours (5)

Display This Question:
If Q3 = 1

Q34 Please read the following situations involving your child's feeding schedule and your feelings of comfort and knowledge about it. Then, carefully read the choices and select how comfortable or uncomfortable you feel about each situation on an average day.

	Extremely uncomfortable (1)	Somewhat uncomfortable (2)	Neither comfortable nor uncomfortable (3)	Somewhat comfortable (4)	Extremely comfortable (5)
My child's current cornstarch/feeding schedule during the day (1)	○	○	○	○	○
My child's current cornstarch/feeding schedule during the night (2)	○	○	○	○	○
Knowing when my child needs to be fed (3)	○	○	○	○	○
Knowing my child's feeding plan will be carried out during the night (4)	○	○	○	○	○

Display This Question:
If Q3 != 1

Q35 When you answer this question, please think of your ***youngest child with a GSD1 diagnosis.***

Please read the following situations involving your child's feeding schedule and your feelings of comfort and knowledge about it. Then, carefully read the choices and select how comfortable or uncomfortable you feel about each situation on an average day.

	Extremely uncomfortable (1)	Somewhat uncomfortable (2)	Neither comfortable nor uncomfortable (3)	Somewhat comfortable (4)	Extremely comfortable (5)
My child's current cornstarch/feeding schedule during the day (1)	○	○	○	○	○
My child's current cornstarch/feeding schedule during the night (2)	○	○	○	○	○
Knowing when my child needs to be fed (3)	○	○	○	○	○
Knowing my child's feeding plan will be carried out I when I go to sleep at night (4)	○	○	○	○	○

End of Block: Feeding

Start of Block: Block 11

Q36 Learning more about you and your child, such as how long ago your child was diagnosed and whether you are male or female, may tell us more about factors affecting your quality of life and stress levels. Please answer the following questions, which are designed to provide information without identifying yourself or your child.

End of Block: Block 11

Start of Block: Demographics

Q37 What is the highest level of school you have completed or the highest degree you have received?

- Less than high school degree (1)
- High school graduate (high school diploma or equivalent including GED) (2)
- Some college but no degree (3)
- Associate degree in college (2-year) (4)
- Bachelor's degree in college (4-year) (5)
- Master's degree (6)
- Doctoral degree (7)
- Professional degree (JD, MD) (8)

Q38 What is your gender?

- Male (1)
- Female (2)

Q39 Information about income is very important to understand. Would you please give your best guess?Please indicate the answer that includes your entire household income in (previous year) before taxes.

- $0-30,000 (1)
- $30,001-50,000 (2)
- $50,001-75,000 (3)
- $75,001-100,000 (4)
- $100,001-150,000 (5)
- $150,001 + (6)

Q40 What is your current marital status?

- Married (1)
- Widowed (2)
- Divorced (3)
- Separated (4)
- Never Married (5)

Q41 How many adults, including yourself, live at your residence?

_____

Q42 Do you currently work outside the home?

- ○ Yes (1)
- ○ No (2)

Q43 Which statement best describes your current employment status?

- ○ Working (paid employee) (1)
- ○ Working (self-employed) (2)
- ○ Not working (temporary layoff from a job) (3)
- ○ Not working (looking for work) (4)
- ○ Not working (retired) (5)
- ○ Not working (disabled) (6)
- ○ Not working (other) (7) _____
- ○ Prefer not to answer (8)

Display This Question:
If Q43 = 1
And Q43 = 2

Q44 What is your hourly working status?

- ○ 20 or fewer hours per week (1)
- ○ Between 20 and 40 hours per week (2)
- ○ 40 or more hours per week (3)

Display This Question:
If Q3 = 1

Q45 What type of medical insurance does your family use for your child with GSD1? Select all that apply to your child.

- ☐ Insurance through a current or former employer or union (1)
- ☐ Insurance purchased directly from an insurance company (2)
- ☐ Medicaid, Medical Assistance, or any kind of government-assistance plan for those with a disability or low income (3)
- ☐ Other - describe (4) _____

Display This Question:
If Q3 != 1

Q46 What type of medical insurance does your family use for your ***youngest child*** with GSD1? Select all that apply to your child.

- ☐ Insurance through a current or former employer or union (1)
- ☐ Insurance purchased directly from an insurance company (2)
- ☐ Medicaid, Medical Assistance, or any kind of government-assistance plan for those with a disability or low income (3)
- ☐ Other - describe (4)

Display This Question:
If Q3 = 1

Q47 In what year was your child diagnosed with GSD1? Give your best estimate if you cannot remember the exact date.

_____

Display This Question:
If Q3 != 1

Q48 Thinking of your child who was most recently diagnosed with GSD1, in what year was s/he diagnosed? Give your best estimate if you cannot remember the exact date.

_____

Display This Question:
If Q3 != 1

Q49 Thinking of your child who was the first in your family to be diagnosed with GSD1, in what year was s/he diagnosed? Give your best estimate if you cannot remember the exact date.

_____

End of Block: Demographics

F.1 PEDIATRIC INVENTORY FOR PARENTS PERMISSION LETTER

Dear Colleague,

Thank you for your interest in the Pediatric Inventory for Parents. Included in this e-mail are the measure and scoring instructions. I grant you permission to use the measure in your work. Please keep me informed of any results as your work progresses, and feel free to contact me with any further questions.

In addition to the measure you will also find scoring instructions attached. Further, attached are references from investigations that have included the PIP, following the initial article from 2001*.

Best wishes on your research,

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F.2 PIP SCORING SHEET AND INSTRUCTIONS

PEDIATRIC INVENTORY FOR PARENTS
SCORING SHEET

PIP item number and brief description of event within each domain
(F = Frequency, D = Difficulty)

COMMUNICATION (CM: 9 items)	F	D
2. Arguing		
7. Speaking with doctor		
12. Feeling confused		
17. Talking with the nurse		
22. Disagreeing		
27. Feeling misunderstood		
32. Speaking with child		
37. Speaking with family		
40. Worrying		
CM TOTAL		

MEDICAL CARE (MC: 8 items)	F	D
3. Bringing my child to the clinic		
8. Watching/eating		
13. Being with my child		
18. Making decisions		
23. Helping/hygiene needs		
28. Handling changes		
33. Helping/procedures		
38. Watching/procedures		
MC TOTAL		

EMOTIONAL DIST. (ED: 15 items)	F	D
1. Difficulty sleeping		
4. Learning upsetting news		
6. Seeing mood change		
9. Waiting for test results		
11. Trying not to think/difficulties		
14. Knowing/hurting		
16. Seeing child sad		
19. Thinking about/isolated		
21. Feeling numb inside		
24. Worrying about/impact		
26. Feeling helpless		
29. Feeling uncertain		
31. Thinking about/other ill		
34. Having my heart beat fast		
36. Feeling scared		
ED TOTAL		

ROLE FUNCTION (RF: 10 items)	F	D
5. Being unable to go to work		
10. Having money		
15. Trying to attend/other		
20. Being far away from family		
25. Having little time		
30. Being in the hospital		
35. Feeling uncertain		
39. Missing important events		
41. Noticing a change		
42. Spending a great deal of time		
RF TOTAL		

CM+ED+MC+RF TOTAL:F	
CM+ED+MC+RF TOTAL:D	

Randi Streisand, Ph.D.

Pediatric Inventory for Parents
Scoring Instructions

The PIP is scored separately for each of the 4 domains (Communication, Emotional Distress, Medical Care, Role Function), across 2 scales: Frequency (F) and Difficulty (D). There is also a total score comprised of the sum for each of the 4 domains, yielding Total F and Total D scores. Items are scored as endorsed by respondents, ranging from 1-5. The range for each of the Total F and Total D scores is 42-210.

Using the item number across domains as listed on the preceding page, sum the items to yield a score for each domain. For example, for the Communication Domain, summing the Frequency scores for items **2, 7, 12, 17, 22, 27, 32, 37, 40** results in the Communication Frequency score. Summing the Difficulty scores for the same item numbers results in the Communication Difficulty score. These scores are then combined with the scores from each of the other domains to yield the PIP Total Frequency, and PIP Total Difficulty scores; the scoring sheet provided will facilitate this process.

Randi Streisand, Ph.D.

F.3 PROMIS SCORING TABLE

APPENDIX 1-SCORING TABLES

Anxiety 7a
Short Form Conversion Table

Raw Score	T-score	SE*
7	36.2	5.4
8	42.1	3.4
9	44.7	2.9
10	46.7	2.6
11	48.4	2.4
12	49.9	2.3
13	51.3	2.3
14	52.6	2.2
15	53.8	2.2
16	55.1	2.2
17	56.3	2.2
18	57.6	2.2
19	58.8	2.2
20	60.0	2.2
21	61.3	2.2
22	62.6	2.2
23	63.8	2.2
24	65.1	2.2
25	66.4	2.2
26	67.7	2.2
27	68.9	2.2
28	70.2	2.2
29	71.5	2.2
30	72.9	2.2
31	74.3	2.2
32	75.8	2.3
33	77.4	2.4
34	79.5	2.7
35	82.7	3.5

*SE = Standard Error on T-score metric

Anxiety 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	40.3	6.1
5	48.0	3.6
6	51.2	3.1
7	53.7	2.8
8	55.8	2.7
9	57.7	2.6
10	59.5	2.6
11	61.4	2.6
12	63.4	2.6
13	65.3	2.7
14	67.3	2.7
15	69.3	2.7
16	71.2	2.7
17	73.3	2.7
18	75.4	2.7
19	77.9	2.9
20	81.6	3.7

*SE = Standard Error

Anxiety 6a
Short Form Conversion Table

Raw Score	T-score	SE*
6	39.1	5.9
7	45.9	3.4
8	48.8	2.9
9	50.9	2.6
10	52.7	2.4
11	54.2	2.3
12	55.6	2.2
13	56.9	2.2
14	58.2	2.2
15	59.4	2.2
16	60.7	2.2
17	62.0	2.2
18	63.3	2.2
19	64.6	2.2
20	66.0	2.2
21	67.3	2.2
22	68.6	2.2
23	70.0	2.2
24	71.3	2.2
25	72.7	2.2
26	74.1	2.2
27	75.6	2.3
28	77.4	2.4
29	79.4	2.7
30	82.7	3.5

*SE = Standard Error

Anxiety 8a
Short Form Conversion Table

Raw Score	T-score	SE*
8	37.1	5.5
9	43.2	3.3
10	45.9	2.8
11	47.8	2.5
12	49.4	2.3
13	50.8	2.2
14	52.1	2.1
15	53.2	2.0
16	54.3	2.0
17	55.4	2.0
18	56.4	2.0
19	57.4	2.0
20	58.4	2.0
21	59.4	2.0
22	60.4	2.0
23	61.4	2.0
24	62.5	2.0
25	63.5	2.0
26	64.5	2.0
27	65.6	2.0
28	66.6	2.0
29	67.7	2.0
30	68.7	2.0
31	69.8	2.0
32	70.8	2.0
33	71.9	2.0
34	73.0	2.0
35	74.1	2.0
36	75.4	2.0
37	76.7	2.1
38	78.2	2.3
39	80.0	2.6
40	83.1	3.4

*SE = Standard Error

Adult versions

Adult versions

APPENDIX G: INTERVIEW ANALYSIS

Table 10. Interview-Generated Domains Affecting QOL in GSD1 Caregivers

Interviewee:	Daily Emotions	Social Interactions	Family Interactions	Occupation	Finances	Psychological Impact	Treatment Impact	Interactions with Metabolic Specialists	Interactions with Non-Metabolic Specialists	Education of Family	Education of Healthcare Providers	Social Media and Interactions with Other GSD1 Families
Metabolic Geneticist	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Caregiver 1 (mother)	✓	✓	✓	✓	✓				✓		✓	✓
Caregiver 2 (father)		✓	✓			✓		✓	✓	✓	✓	✓
Domain is Not Covered by PIP						*	*	*	*	✓	✓	✓

*** covered by PIP generally, but not disease-specific or specialist-specific**

APPENDIX H: ADDITIONAL RESULTS

H.1 DEMOGRAPHICS

Table 11. Household Demographics

Marital Status	Total (n=25)
Married	21 (84%)
Widowed	1 (4%)
Divorced	3 (12%)
Number of Adults Living in the Home	**Total (n=24)**
1	2 (8.3%)
2	19 (79.2%)
3 +	3 (12.5%)

Table 12. Qualities of Caregivers by PIP Completion Status

	Completed First PIP Section	
Type:	**Yes**	**No**
GSD1a	27	7
GSD1b	9	2
Relation:	**Yes**	**No**
Mother	33	7
Father	4	1
Other-Aunt	0	1
# Affected Children:	**Yes**	**No**
1	32	9
2	4	2
3	1	2
# Unaffected Children:	**Yes**	**No**
0-1	12	6
2	17	3
3-4	8	4

H.2 SOCIAL MEDIA

The PROMIS scores for active and passive users were not significantly different (t=-0.46, df=19.5, p=0.65, two-tailed Welch two sample t-test). The PIP-F scores for active and passive users were not significantly different (t=0.56, df=17.2, p=0.58, two-tailed Welch two sample t-test). The PIP-D scores for active and passive users were not significantly different (t=0.80, df=19, p=0.43, two-tailed Welch two sample t-test).

H.3 MENTAL HEALTHCARE

Table 13. Mental Healthcare Usage by Income

	Current Usage of Mental Healthcare Provider	
Reported Household Income	Yes (n=9)	No (n=15)
$0-30,000	1	4
$30,001-50,000	3	1
$50,001-75,000	1	2
$75,001-100,000	0	2
$100,001-150,000	3	4
$150,001 +	1	2

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