Treatment Choice in Urea Cycle Disorders: How Healthcare Access Contributes to the Decision to Continue Medical Management or Pursue Liver Transplant

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Abstract of Dissertation

Treatment Choice in Urea Cycle Disorders: How Healthcare Access Contributes to the Decision to Continue Medical Management or Pursue Liver Transplant

Rare diseases impact approximately 25 million individuals in the U.S. and Canada combined (Schieppati, Henter, Daina, & Aperia, 2008; Wästfelt, Fadeel, & Henter, 2006) and represent a major challenge for the health services community. Despite this, rare diseases are rarely examined within fields of public health or health service research. Inborn errors of metabolism represent one key group of rare disorders with a high prevalence of disability and death (Dionisi-Vici et al., 2002; Levy, 2009). Urea cycle disorders (UCD) are a group of eight rare inherited disorders of metabolism characterized by deficiencies in ammonia detoxification and urea synthesis – a process in the liver that converts otherwise toxic ammonia into urea for excretion in the urine. When this mechanism does not function properly, it can result in hyperammonemia, which can lead to early and recurrent brain damage or death (Mark L. Batshaw, MacArthur, & Tuchman, 2001; Krivitzky et al., 2009).

Pharmaceutical drugs in combination with highly controlled and restrictive low-protein diets and metabolic formulas are used to manage patients with UCD (M. L. Batshaw et al., 1982; Mark L. Batshaw et al., 2001). Medications and restricted diets do not completely remove the risk of hyperammonemia in patients with UCD and many patients treated conservatively through these methods have still been reported to suffer from acute episodes of hyperammonemia. Thus, an increasing number of patients with UCD have been undergoing liver transplantation as a procedure that "cures" the hyperammonemia (Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998).

However, liver transplantation is a complicated surgical procedure, which carries significant risk of both mortality and morbidity and requires a life-long regimen of medication management to avoid organ rejection. Patients, families and their providers are therefore facing a difficult dilemma. Should the patient be managed medically with diet and medications or undergo a liver transplant?

Families affected by rare conditions like UCD are also presented with unique and complex challenges related to the cost, coverage, and availability of sub-specialized care, which further complicates treatment decision-making. UCD patients require sub-specialized healthcare management not available through primary care, smaller specialty practices, or community hospitals, raising questions about how the regionalization of UCD treatment influences access among this population and as an extension, treatment choice. Variation in public and private coverage policy, narrow networks, high treatment costs, benefit denials and appeals, and fragmented financial aid programs have also been anecdotally identified as barriers to affordable treatment for UCD and other rare conditions.

This dissertation research project explores treatment decision-making in families affected by UCD, examining health care access as a key driver of the choice between medical management (MM) and liver transplant (LT). It accomplishes this through three separate but related studies.

The first study utilized grounded theory to construct a conceptual framework that describes the treatment decision making experience of parents whose children are diagnosed with UCD. The framework outlines the clinical, personal, social, and system factors that drive the decision between MM and LT and describes the circumstances that

frame families' personal perceptions of risks and benefits as well as the context within which decisions about treatment are made. Findings from this study equip providers with evidence upon which to improve their approach to treatment counseling and guidance. The study also identified access to sub-specialized medical care as a key dimension of treatment choice. It concluded, that among other factors, issues related to the availability, delivery, and coverage of UCD care all have implications for treatment decision-making thus, providing a basis for the inquiries examined through the subsequent two studies within this dissertation.

The second study utilized GIS methodology and regression analysis to examine the association between proximity to high-quality sub-specialized metabolic and/or liver transplant care and treatment. This analysis did not establish a statistically significant relationship between proximity (i.e., geographic access) to *any* high-quality care center and treatment choice (i.e., MM vs. LT) but did establish a strong, statistically significant relationship between treatment status and geographic access to certain transplant centers known in the community for their support of and excellence in transplant for UCD. The study found that patients who live nearest to one of these transplant sites were three to four times more likely to undergo a liver transplant than those who live in nearest proximity to one of the other transplant centers included in the analysis. These findings demonstrate the existence of inter-institutional variations in practice around treatment for UCD and raise questions about the impact of these variations on equitable access to care within the UCD community and as a consequence of this, treatment choice.

The third study examined cost and coverage of care for UCD through the collection and analysis of primary survey data from patients and parents affected by the

disorder. Findings highlighted high out of pocket costs and pervasive barriers to coverage across service categories related to the management of UCD including access to supplements, medical foods and formula, medications, routine consultative care, emergency medical care, and medical travel. The study also noted substantial differences in out of pocket cost and coverage experience by treatment and insurance type. Study results indicated higher out of pocket spending and more frequently reported coverage concerns under medical management than under liver transplant and among privately insured respondents when compared to Medicaid recipients. Finally, this third study highlighted the financial hardships experienced by families affected by UCD as a consequence of caring and paying for the care of a child with special health care needs. This included barriers to career development and the direct financial implications of high medical bills like credit card debt, lost savings, and even challenges paying for basic necessities like food and rent.

Together, the three studies conducted as part of this dissertation apply mixed methods research to identify and explore important health services related challenges associated with treatment choice in UCD and contribute evidence to an otherwise under-developed area of research.

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Chapter 1: Introduction

Rare diseases are defined as conditions that affects less than approximately 1 in 1250 individuals in the United States (U.S.). Despite the low prevalence of each of these distinct disorders, the number of diseases included in this category is rather large, greater than 5000 according to the World Health Organization ("WHO | International Classification of Diseases," n.d.). Thus, the actual number of patients impacted by rare diseases reaches approximately 25 million in the U.S. and Canada combined (Schieppati et al., 2008; Wästfelt et al., 2006).

Rare diseases are rarely examined or researched within fields of public health. However, rare diseases are indeed an important public-health issue and a major challenge for the health services community. Rare diseases were neglected in research for many years until the challenges impacting these populations were raised in 1989 by the report of the National Commission on Orphan Disease of the U.S. Government (National Commission on Orphan Diseases (U.S.), 1989). The commission's hearings highlighted the dearth of information available on rare diseases, challenges financing that research, issues with the provision of comprehensive insurance and coverage of medical expenses for rare disorders, and the limited availability of treatment.

Rare diseases are often severely disabling. Inborn errors of metabolism represent one key group of rare disorders with a high prevalence of disability and death (Dionisi-Vici et al., 2002; Levy, 2009). These conditions decrease life expectancy, impair physical and mental abilities, reduce quality of life, pose considerable burden on affected families and the healthcare system that serves them, and impact an individual's education and earning potential (van Weely & Leufkens, 2004; Zeltner et al., 2017).

Overview of urea cycle disorders

Urea cycle disorders (UCD) are a group of eight rare inherited disorders of metabolism caused by deficiencies of any one of eight proteins required for ammonia detoxification and urea synthesis – a process in the liver that converts otherwise toxic ammonia into urea for excretion in the urine. When this mechanism does not function properly, it can result in hyperammonemia, an excess of ammonia in the blood, which in its severe or prolonged form may have devastating effects on the development and function of the central nervous system (Msall, Batshaw, Suss, Brusilow, & Mellits, 1984). In patients with UCD, hyperammonemia can first manifest soon after birth (neonatal onset), later in childhood, or even in adulthood (Summar, Dobbelaere, Brusilow, & Lee, 2008). As a group, the combined prevalence of UCD is approximately 1:35,000 (Summar et al., 2013).

Risk of hyperammonemia and impact on the health of patients with UCD

Despite significant improvements in medical management (MM) following the wider availability of specialized low-protein diets, hemodialysis, medications, and amino-acid supplements, infants, children, and even adults with UCD are at high risk of early and recurrent brain damage from hyperammonemia (Mark L. Batshaw et al., 2001; Krivitzky et al., 2009). High blood ammonia levels can cause cytotoxic brain edema and compromise a patient's circulatory system, which frequently leads to intellectual and developmental disabilities (Butterworth, 1998; Butterworth, Giguère, Michaud, Lavoie, & Layrargues, 1987; Msall et al., 1984; Msall, Monahan, Chapanis, & Batshaw, 1988). Hyperammonemia also recurs at variable intervals in patients with UCD, causing cumulative damage to the brain and increasing the chance of irreversible coma or death

during a hyperammonemia episode. These most severe outcomes can occur even in patients whose mild-moderate condition appears to be amenable to MM through the techniques listed above. Ammonia levels can "get out of hand" during an infection or other stress and cause severe developmental disability, coma, or death (Cavicchi et al., 2014). Hyperammonemia in patients with UCD can occur at any time as a result of otherwise minor infections. Thus, an increasing number of patients with UCD have been undergoing liver transplantation (LT) as a procedure that "cures" the hyperammonemia (Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998). However, liver transplantation is a complicated surgical procedure, which carries significant risk of both mortality and morbidity and requires a life-long regimen of medication management to avoid organ rejection. Patients, families and their providers are therefore facing a difficult dilemma. Should the patient be managed medically with diet, medications and amino acid supplements or undergo a liver transplant?

Available treatment options for UCD

The most effective medical advances in the acute and chronic treatment of UCD have come with the employment of a combination of pharmaceutical drugs designed to promote alternative pathways for the disposal of waste nitrogen in the body- a process that is inhibited in patients with UCD and thus contributes to the accumulation of ammonia in the blood (M. L. Batshaw et al., 1982; Mark L. Batshaw et al., 2001). Sodium benzoate and sodium phenylacetate, or its better orally tolerated alternatives, sodium phenylbutyrate (Buphenyl) or glycerol phenylbutyrate (Ravicti), are commonly used for chronic, long-term management of UCD. Intravenous infusions of glucose, lipid,

arginine, and sodium benzoate/sodium phenylacetate (Ammonul) are used to treat acute episodes of hyperammonemia (Berry et al., 2014; Häberle et al., 2012).

All of these pharmaceutical treatments carry risks of serious side effects. Medications and restricted diets do not completely remove the risk of hyperammonemia in patients with UCD and many patients treated through these methods have still been reported to suffer from acute episodes of high ammonia. Most survivors of these episodes show significant neurodevelopmental disability, ranging in severity that seems to correlate with the severity of the disease. In a longitudinal study performed by the NIH funded Rare Diseases Clinical Research Network (RDCRN) Urea Cycle Disorders Consortium (UCDC), the proportion of patients with a poor cognitive outcome (IQ/Developmental Quotient less than 70) was high, ranging from 47-68 percent in the various UCD (Ah Mew et al., 2013).

Liver transplantation for UCD patients was initiated in the early 1990s, before effective medical therapy was widely available. Anecdotal case reports of liver transplantation among patients with UCD and a larger survey of 16 UCD patients who had received liver transplants from four major transplant centers showed promising results in terms of survival, stabilization of neurological status, and quality of life (Maestri, Clissold, & Brusilow, 1999; Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998). Most recently, a retrospective analysis of 186 patients with UCD who underwent liver transplantation showed an increased frequency of liver transplantation for UCD over the last decade and 5 year survival rates of 88%-99% depending on age (Perito, Rhee, Roberts, & Rosenthal, 2014).

Liver transplantation is now performed frequently to treat UCD and although survival rates seem to have improved over time with surgical advances (Vilca-Melendez & Heaton, 2004), there is not a great deal of data on neurocognitive function post-transplant among patients with UCD or a robust evidence-base comparing the relative value of liver transplant over conventional medical management techniques. Liver transplants come in two varieties: living donor and cadaveric. Most families with a UCD child pursue the cadaveric option. Cadaveric livers are a limited and scarce resource, and therefore all patients in need of a liver transplant are triaged according to a scoring algorithm. In the current U.S. scoring algorithm, children with metabolic disorders including UCD are greatly prioritized, typically assigned status 1B (United Network for Organ Sharing, 2017). In practice, this means that virtually any child with a metabolic disorder who is recommended for liver transplant will receive one, typically within the year.

Liver transplant in infants or children carries with it serious risk of complication including liver rejection, infection, primary non-function, blood clots, bleeding and kidney and biliary problems. In addition to immediate potential post-surgery complication, caring for a new liver requires daily medications and frequent testing for the rest of the child's life (Vilca-Melendez & Heaton, 2004). The psychological, social, and health problems resulting from successful childhood transplants are only beginning to be studied and recognized. The life expectancy among young children who have been transplanted is not well documented and little information is available on long-term complications and quality of life in this group (Kelly et al., 2013; Mohammad et al., 2012).

Stressors among families affected by UCD

UCD, although unique in their rare prevalence, share many similarities with other, serious chronic illnesses, such as cystic fibrosis, which are seen more commonly in children and whose familial impact has been described far more extensively in the literature (Atkin & Ahmad, 2000; Mitchell et al., 2007; Thomas & Taylor, 2002). Existing literature suggests that having a child with a serious chronic illness affects not only the child but the functioning of the entire family unit, including the psychological status of parents or siblings, parent employment status, the family's economic status, the parents' relationship with one another, their peers, and their community, and the internal functioning of the family (Barlow & Ellard, 2006).

Chronic illness in children can also be associated with difficult ambiguities and uncertain outcomes. This is especially relevant among families affected by UCD, as complications in children with this condition can be difficult to predict and prevent. In addition to the typical struggles that parents of a child with chronic disease face in understanding a new diagnosis, coping with questions about their child's survival and long term health, and navigating an unfamiliar and often times confusing medical system, families affected by UCD also face the additional burden of unpredictable, intermittent, but potentially devastating episodes of hyperammonemia- a phenomenon that parents of children with UCD have described anecdotally as a "ticking time bomb". Most patients with UCD are (in principle) at elevated risk of serious disability or death at various times in their lives (Mark L. Batshaw, 1994). This risk, although always present, is not easily quantified, especially among mild-moderate UCD patients with non-neonatal onset of symptoms. This level of ambiguity can make treatment decisions, like if and/or when to

pursue liver transplant, particularly challenging for the parents of children with UCD. Among other serious conditions, the decision to perform transplantation is often made because organ function has failed, and the choice is one of life or death. However, for patients with UCD, the decision can be more complex as reasonably effective medical therapy may be a viable alternative. Although UCD may share many characteristics with other chronic conditions, the level and type of uncertainty associated with this disease further complicates treatment decisions and places special burdens and pressures on families.

Access challenges

Healthy People 2020 highlights access to comprehensive, quality healthcare services as a fundamental component of health equity and a critical step towards improving quality of life. It also emphasizes high costs, poor insurance coverage, and lack of availability as key barriers to this goal ("Access to Health Services | Healthy People 2020," n.d.; Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020, 2010). Families affected by rare conditions like UCD are often presented with unique and complex challenges related to the cost, coverage, and availability of care. Patients with rare diseases require sub-specialized healthcare management not available through primary care or smaller specialty practices. For example, care for cystic fibrosis, which is considered a rare disease, is provided through a network of approximately 110 subspecialty centers with multidisciplinary services accredited by the Cystic Fibrosis Foundation (Mogayzel, Dunitz, Marrow, & Hazle, 2014). Sub-specialized care options are even further limited for patients with UCD. There are currently about a dozen hospitals in the United States with a metabolic

clinic and specialized team experienced in the diagnosis, treatment, and research of UCD. Most community hospitals are not equipped to deal with hyperammonemia and general practice pediatricians do not have the training or experience to diagnose, treat and provide ongoing care and monitoring to children with UCD without additional guidance from a metabolic geneticist. Thus, it is critically important for children with UCD to have access to a specialized team, including, at a minimum, a pediatric geneticist, metabolic dietitian, and genetic counselor who can work with a family to try and prevent medical crises and a hospital that can quickly respond to acute episodes with "rescue" treatments. Regionalization of UCD sub-specialty programs generates service areas that extend well beyond state boundaries (Perrin & MacLean Jr., 1988). Thus, metabolic specialists with UCD experience are providing care to children from all over the country, raising questions about how state variation in public and private coverage policy, narrow networks, out of pocket costs, benefit denials and appeals, and fragmented financial aid programs all influence access to care for this population.

Current treatment guidelines for UCD

Current treatment guidelines for children affected by UCD focus on clinical diagnosis of the condition, management of acute hyperammonemia, and long-term management of the disease through diet, medications, and amino acid supplementation. Current guidelines also briefly discuss liver transplantation as the only available curative treatment for UCD and suggest that transplant be considered for all patients with severe neonatal onset, for patients who are not responding to medical therapy, and for patients who report poor quality of life (Häberle et al., 2012). These guidelines were developed through professional consensus using a Delphi methodology and revised by external

specialists, medical authorities in the field of UCD and practicing pediatricians. However, the evidence presented to support these UCD guidelines rarely exceeded a level C designation (evidence for non-analytical studies like case reports and series) (Häberle et al., 2012). Medical professionals have relied on few studies and anecdotal data to guide clinical recommendations and thus, have been unable to weigh available treatment alternatives against key health outcomes like survival, neurocognitive status, and quality of life. The paucity of evidence to support clinical guidance for patients with UCD has exposed these important treatment decisions to a high level of ambiguity and personal judgment and has forced patients and their families to pursue intervention without clear, evidence-based information.

Current comparative effectiveness research

Currently, decisions about whether to pursue LT or continue MM are made in the absence of reliable and objective data about risks and benefits. The Urea Cycle Disorders Consortium (UCDC), an NIH funded Rare Disease Clinical Research Center administered from the Children's Research Institute at the Children's National Health System (CNHS), is currently leading a collaborative research study with the George Washington University (GWU) Department of Health Policy and Management at the Milken Institute School of Public Health, The National Urea Cycle Disorders Foundation (NUCDF), and the Studies of Pediatric Liver Transplantation (SPLIT) to address this issue. The study examines two UCD patient cohorts, one managed conservatively and the other treated by liver transplantation, comparing survival rate, neurocognitive function and patient and family reported quality of life. This natural history observational trial relies on existing historical and concurrently collected registry data to identify and follow

UCD patients, who, over the past 20 years, have faced this challenging treatment decision.

The current comparative effectiveness (CE) study makes use of a previously untapped data resource to systematically evaluate key clinical outcomes and provide objective evidence to support an otherwise subjective treatment decision process. The aim of this CE study is to provide affected families with evidence-based information, which they currently lack, about available management alternatives (i.e., MM vs. LT) including the disease specific risk of mortality and morbidity in the two approaches, comparative information on cognitive development, and the pros and cons of each approach in terms of its influence on patient and family quality of life.

This natural history, observational trial is augmented by a qualitative inquiry led by the team at GWU examining caretakers' experience making treatment decisions for their child with UCD. The objective of this qualitative component is to identify and describe a list of key factors that influence the choice between MM and LT as a treatment for UCD.

Purpose of the research

This dissertation expands upon the objectives described above with an additional, concurrently conducted study that highlights access to care issues for families affected by UCD by 1) developing a conceptual framework that comprehensively describes the process families undergo when choosing between MM and LT as a treatment for their child with UCD, including key drivers of this decision, themes related to treatment decision making in this population, relationships among key concepts, and an explicit focus on access to care as it relates to this decision process; 2) testing the association

between geographic availability of sub-specialized and transplant care as one measure of access and treatment choice; and 3) exploring the cost and coverage issues that facilitate or impede access to medical, pharmaceutical, and support services UCD and liver transplant for the disorder.

The first study presents the results of a grounded theory inquiry that examines the parent decision-making experience when choosing between MM and LT as a treatment for their child with UCD, highlighting, among other factors, how issues of healthcare access like cost, coverage, and availability, contribute to this decision. The study relies on a qualitative analysis of interview data from a large and diverse sample of parents and UCD providers to build a conceptual framework that describes the clinical, personal, social, and system level factors that influence this decision process and the circumstances and contexts that frame treatment choice.

Building off the conceptual framework developed through the above described grounded theory research, the second study presents the results of a Geographic Information System (GIS) mapping analysis that further examines the role healthcare access plays in driving treatment decisions for UCD. It tests empirically the association between the geographic availability of sub-specialized metabolic UCD care and/or high-quality pediatric liver transplant care and the decision to treat UCD through MM or LT. This analysis combines existing patient-level residence, treatment, diagnosis, hyperammonemia episode, and demographic data from the Urea Cycle Disorders Consortium (UCDC) Longitudinal Study of UCD, liver transplant figures from the Department of Health & Human Services' (DHHS) Organ Procurement and Transplantation Network (OPTN), and supplementary information provided by key

informants in the field, to assess how distance to care and proximity to certain treatment sites/centers, taken as one measure of healthcare access, is associated with treatment choice.

The third and final study examines access to sub-specialized medical, pharmaceutical, and support services for UCD and liver transplant through the lens of coverage and cost. The manuscript describes the development, distribution, and analysis of an exploratory parent/patient survey investigating the cost and coverage issues that most impact families affected by UCD. Findings highlight differences in out of pocket spending and coverage experience by service, treatment type, and insurance status and describe other financial implications related to caring for and paying for the care of someone affected by UCD.

The results from these studies are presented in the next three stand-alone chapters. Each chapter provides background for the specific issues addressed, detailed methodology, study results, a discussion of those results, description of study limitations, and a concluding section reflecting on the study's contribution to the field.

The final chapter (Chapter 5) of this dissertation summarizes all three studies, placing them within context of one another and within the larger health services and policy landscape. It presents overall conclusions and recommendations for future research.

Chapter 2: Choosing Between Medical Management and Liver Transplant in Urea Cycle Disorders- A Conceptual Framework for Parent Treatment Decision-Making in UCD

This manuscript describes the findings from a grounded theory, qualitative interview and focus group study that examined the decision-making experience of families affected by Urea Cycle Disorders (UCD) when making the choice between medical management and liver transplant as a treatment for their child with UCD. This study sought the perspectives of both parents and medical providers to identify the key factors that drive treatment decisions in this population and to describe how families evaluate these factors to reach a treatment choice.

Urea cycle disorders (UCD) are a group of rare inherited disorders of metabolism caused by deficiencies of any one of eight proteins required for ammonia detoxification and urea synthesis – a process in the liver that converts otherwise toxic ammonia into urea for excretion in the urine. When this mechanism does not function properly, it can result in hyperammonemia, an excess of ammonia in the blood, which in its severe or prolonged form may have devastating effects on the development and function of the central nervous system (Msall et al., 1984).

Despite significant improvements in medical management following the wider availability of specialized low-protein diets, hemodialysis, medications, and amino-acid supplements, infants, children, and even adults with UCD are at high risk of hyperammonemia (Mark L. Batshaw et al., 2001; Krivitzky et al., 2009). High blood ammonia levels can cause cytotoxic brain edema and compromise a patient's circulatory system, which frequently leads to intellectual and developmental disabilities (Butterworth, 1998; Butterworth et al., 1987; Msall et al., 1984, 1988). These most severe

outcomes can occur even in patients whose mild-moderate condition appears to be amenable to management through medications and diet. Thus, an increasing number of patients with UCD have been undergoing liver transplantation as a procedure that "cures" the hyperammonemia (Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998). However, liver transplantation is a complicated surgical procedure, which carries with it risk of mortality and morbidity and requires a life-long regimen of medication to avoid organ rejection.

Most patients with UCD are at elevated risk of serious disability or death at various times in their lives (Mark L. Batshaw, 1994). This risk, although always present, is not easily quantified, especially among mild-moderate UCD patients with non-neonatal onset of symptoms. This ambiguity can make treatment decisions, like if and/or when to pursue liver transplant, particularly challenging for the parents of children with UCD. Among other serious conditions, the decision to perform transplantation is often made because organ function has failed and the choice is one of life or death. However, for patients with UCD, the decision can be more complex as outcomes from medical therapy vary widely and because transplantation is typically initiated when patients are stable rather than critically ill. There is also limited empirical evidence to support clinical guidance on treatment alternatives for patients with UCD, which has exposed these important treatment decisions to high levels of ambiguity and personal judgment and has forced patients and their families to pursue intervention in the absence of clear, evidence-based information.

Despite the importance of, and complexity surrounding, the decision to continue medical management or consider liver transplant, no research has been conducted on how

families of UCD patients make these treatment choices and the issues that influence their decision to pursue one option over another. Research investigating parent decision making for complex pediatric disorders has been published in other disease areas, such as end-of-life care, cardiac transplantation, lung transplant in patients with cystic fibrosis, blood and marrow transplant in pediatric oncology patients, and stem cell transplant in sickle cell patients (Dellon et al., 2009; Götz, Labenbacher, Eichler, Wojnarowski, & Götz, 1997; Hankins et al., 2007; Higgins, 2001; Higgins & Kayser-Jones, 1996a; Hinds et al., 1997; Pentz et al., 2012; K. A. Pyke-Grimm, Degner, Small, & Mueller, 1999a). Although the findings from these studies can help inform an understanding of treatment decision making among families affected by UCD, the characteristics of this disease group vary in several important ways from other disease areas, effectively limiting the applicability of these previous studies and calling for better research that focuses specifically on the treatment decision-making experience of this population.

Treatment decision-making frameworks

Existing frameworks on treatment decision-making focus primarily on the relationship and exchange of treatment preferences and information between patient and physician. The shared decision-making (SDM) model has been cited and applied often as the gold standard in treatment decision-making (Austin, Mohottige, Sudore, Smith, & Hanson, 2015; Entwistle & Watt, 2006; Gordon et al., 2013a; Hargraves, LeBlanc, Shah, & Montori, 2016a; Stiggelbout et al., 2012a). It reflects a two-way exchange of information where the doctor provides all medical information needed for decision-making and the patient provides information about individual preferences. The doctor and patient both process this information, come to a place of mutual acceptance and

ultimately share responsibility when negotiating a final treatment choice (Barry & Edgman-Levitan, 2012a; Charles, Gafni, & Whelan, 1997).

Adaptations of SDM have dominated research around treatment choice and decision making with applications cited in many disease and treatment areas (Barry & Edgman-Levitan, 2012b; Charles et al., 1997; G Elwyn, Edwards, Kinnersley, & Grol, 2000; Hargraves, LeBlanc, Shah, & Montori, 2016b; Stiggelbout et al., 2012b), including organ transplant (Gordon et al., 2013b). Despite its popularity and wide proliferation in the health services literature, this model remains limited by an exclusive focus on patient-provider communication. It also assumes the existence of a substantial body of evidence-based information and clear clinical guidelines that can be shared with the patient by the provider. SDM largely overlooks the personal, social and system level issues that may contribute to treatment choice while also ignoring alternative sources of information, influence outside the doctor's office, and circumstances when evidence is limited and clinical guidance is not well-defined, as is the case in UCD. These important omissions mean that even adapted forms of the SDM model are far too limited in scope to address the unique and complex challenges surrounding treatment choice in children with UCD. Thus, this study was not guided by an existing model but rather, builds a new, holistic framework for decision making that is grounded in qualitative data collected directly from affected families and their providers.

Methods

Approach

The approach for this study is based in pragmatism, a philosophical orientation towards research where the focus is on developing actionable conclusions that can be applied in real world practice. The study aim and research questions were developed in the spirit of this philosophy, designed to broaden the field's understanding of the decision-making experience of families affected by UCD so that, in the short term, providers may better support UCD patients through difficult treatment choices and so that, in the long term, the healthcare system may evolve to better respond to the expressed needs and values of this population.

This study, which proposes the development of a new conceptual framework, utilized an adapted grounded theory approach (Strauss & Corbin, 1990) in which data collection, data analysis, and theory development are conducted in repetition until no new data can be uncovered (i.e., saturation) and a comprehensive and thoroughly refined framework emerges.

Data sources and data collection

Qualitative data was collected directly from parents of children affected by UCD and their clinical providers through semi-structured interviews and focus groups. Semi-structured interviews with parents (N=34) and providers (N=26) were conducted over the phone in sessions lasting approximately 45-90 minutes. Following these interviews, two focus groups with parents (N=19) were conducted in-person in an effort to validate interview findings and provide additional clarity on not yet fully developed concepts uncovered during interview data collection. These focus groups lasted approximately 90

minutes each. Interviews and focus groups were recorded and transcribed verbatim for use in analysis.

Draft interview and focus group guides were developed, integrating findings from a limited relevant evidence-base on health-care decision-making as well as initial discussions with key informants from the National Urea Cycle Disorders Foundation (NUCDF). Draft guides were reviewed by key informants including families with children affected by UCD and metabolic genetic physicians specializing in UCD. They were revised based on feedback from this group before being utilized in the field.

Sampling

The target population for this study included caretakers whose children were born in the US after 1996 and diagnosed with one of 4 UCDs (ALD, ASD, CPS1D, OTCD) for which liver transplantation is a consideration. In 1996, the US Food and Drug Administration (FDA) approved Buphenyl (sodium phenylbutyrate) to treat UCD. The drug allows patients to excrete waste nitrogen, which would otherwise accumulate as ammonia and cause brain damage or death. The introduction of this drug marked a major transition in the treatment and management of UCD. It is likely that UCD patients born prior to 1996 engaged in a different treatment and management experience than those born after FDA approval of this drug and were thus, excluded from this study.

Stratified purposeful sampling methods were used to recruit an initial pool of parents from NUCDF's patient community. Initial recruitment focused on identifying participants who varied in terms of 1) disease severity (i.e., neonatal vs. late onset) and 2) transplant status (i.e. medical management vs. transplant). This initial purposeful stratification accounted for the assumption that severity of disease may mediate why,

how, and when families consider liver transplant as a treatment option and the perspective of both transplanted and non-transplanted patients. It also allowed for an initial round of data collection and reflection upon which future theoretical sampling was based.

In accordance with the grounded theory approach, study participants were then selected through a theoretical sampling technique in which subjects are chosen to gain a deeper understanding of emerging key domains and to facilitate the development of new theoretical concepts. For example, initial interview discussions suggested that major childhood transitions like beginning grade school and entering adolescence have a notable influence on treatment choice. Thus, an effort was made to recruit participants who have experienced these transitions and could expound on their meaning.

Stratified purposeful sampling was also used as an initial strategy to recruit a national cross-section of UCD providers for participation in interviews. Initially, providers were recruited via NUCDF and the Urea Cycle Disorders Consortium to reflect variation in location and type of provider, including metabolic disease physicians, gastroenterologists, genetics counselors, and dieticians. This accounted for the assumption that hospital centers may vary in terms of their treatment philosophy and approach to counseling and that different individuals on the care team interact with UCD patients at different points throughout their decision-making experience. In accordance with the grounded theory approach, provider participants were then selected through theoretical sampling as discussed above. For example, later recruitment efforts focused on capturing the perspective of the liver transplant team whose role in and influence upon

the decision-making process (aside from their obvious role in the transplant procedure itself) was not yet clear.

Focus group sampling followed a similar strategy. Focus groups included 8-12 participants each and were stratified by transplant status.

Characteristics of parent and provider interview and focus group participant samples are summarized in Tables 2.2 and 2.2 below.

Table 2.1. Characteristics of UCD caretaker participants		**Interviews (N=35)**	**Focus Groups (N=19)**	**Total (N=54)**
Gender-caretaker	Male	11%	21%	15%
	Female	89%	79%	85%
Sex-child	Male	53%	63%	56%
	Female	47%	37%	44%
Age-caretaker*	21-29	9%	6%	7%
	30-39	54%	44%	51%
	40-49	23%	22%	23%
	50+	14%	28%	19%
Age-child	0-1	3%	11%	6%
	2-5	31%	31%	31%
	6-11	34%	11%	26%
	12-18	23%	36%	28%
	>18	9%	11%	9%
Disease severity-child	Neonatal onset	71%	68%	70%
	Late onset	29%	32%	30%
Treatment status-child	Conservative management	40%	42%	41%
	Liver transplant	60%	58%	59%
Age at transplant-child (if applicable)**	0-1	68%	55%	62%
	2-5	16%	18%	16%
	6-11	11%	18%	13%
	12-18	0%	0%	0%
	>18	5%	9%	6%
Race- caretaker	White	91%	95%	92%
	Black	6%	0%	4%
	Other	3%	5%	4%
Hispanic or Latino- caretaker	Yes	9%	5%	7%
	No	91%	95%	93%
Highest level of education-caretaker*	Less than high school degree	0%	0%	0%
	High school degree	3%	0%	2%
	Some college	11%	11%	11%
	Associate degree	6%	6%	6%
	Bachelors degree	40%	39%	40%
	Graduate degree	40%	44%	41%
Employment status caretaker*	Employed, part-time	34%	28%	32%
	Employed, full-time	37%	50%	41%
	Not employed	23%	17%	21%
	Retired	3%	0%	2%
	Disabled, not able to work	3%	5%	4%
Household income*	<$25,000	9%	6%	8%
	$25,000-$49,999	8%	6%	7%
	$50,000-$74,999	3%	11%	6%
	$75,000-$99,999	17%	22%	19%
	$100,000-$149,000	40%	43%	41%
	$150,000-$200,000	14%	6%	11%
	>$200,000	9%	6%	8%

*N=18 for focus group characteristic; 1 focus group participants failed to respond to some questions; ** N= 21 for interviews; N=11 for focus groups; N=32 total

Table 2.2. Characteristics of UCD provider interview participants (N=26)		
Gender	Male	34%
	Female	66%
Age	31-36	23%
	37-42	23%
	43-48	15%
	49-54	15%
	55-60	8%
	>60	16%
Clinical degree	MD	76%
	RN/NP	8%
	Genetic counseling	12%
	Nutrition	4%
Race	White	88%
	Black	0%
	Other	12%
Hispanic or Latino	Yes	8%
	No	92%
Years of UCD experience	<3	8%
	4-6	24%
	7-10	16%
	>10	47%
	Don't know/Not sure	4%

Data analysis

Data analysis was based in Strauss and Corbin's systematic procedures for grounded theory work (Strauss & Corbin, 1990). Initial data abstraction was conducted through the line-by-line open coding of a cross-section of 14 interview transcripts, which allowed key issues regarding the transplant vs. medical management decision-making process to emerge directly from the collected data and ensured that important aspects of this phenomenon were not precluded through the use of a more selective coding scheme. Open coding was utilized to generate a preliminary set of codes, which was continuously refined until a final structure of codes and sub-codes emerged. This coding structure was then applied systematically across all transcripts. Thematic content analysis was utilized to identify key patterns within the data and to categorize collected information into recurrent or common themes.

Selective and axial coding techniques were used to move beyond a typology of participant accounts to identify core concepts, explore the relationship between key themes, and ultimately build a framework that describes how patients with UCD and their families reach treatment decisions and the key clinical, social, and/or system level factors that influence this process. To facilitate this level of analysis, common qualitative analysis techniques such as charting (i.e., reorganizing data according to thematic content in side-by-side charts to visualize/compare range of perspectives across cases) and mapping and interpretation (i.e., using diagrams and tables to physically explore the relationship between themes) were employed (Green & Thorogood, 2013). Differences and similarities in reported experiences were examined to facilitate the identification of issues that are common across groups as well as the factors that create differences in the way patients and families approach/experience this decision.

All interview and focus group data were managed using QSR International NVivo 11 software ("NVivo qualitative data analysis software | QSR International," n.d.).

This study was reviewed and approved by the institutional review board (IRB) at the Children's National Health System (CNHS). An IRB authorization agreement was executed between CNHS and the George Washington University (GWU), designating CNHS as the IRB of record.

Results

Context of limited empirical evidence

Interviews and focus groups with parents and providers captured a context of limited outcomes data, insufficient empirical evidence and poorly-defined clinical guidelines as it relates to the choice between medical management and liver transplant for

children with UCD. Parents and providers alike described the challenges of treatment decision-making against a backdrop of high-uncertainty and ambiguity and detailed a decision-making experience largely defined by this context (Box 1, [1a-c]). The decision-making framework and its individual and inter-related components, described in detail below, was constructed within this landscape. It represents the shared experience of families affected by UCD who must pursue intervention in the absence of clear, evidence-based information.

Box 1: Context of limited empirical evidence

[1a] Parent participant (10016): *"The most difficult part, I guess, is the unknown….I think the most difficult piece of it was just the lack of information in one location. We had to go through so many avenues to get the information that I needed to feel better about the decision that we were making. I needed all the information, and we had to go everywhere…. That's the hardest part. It's so hard to make the decision when you don't have all this data."*

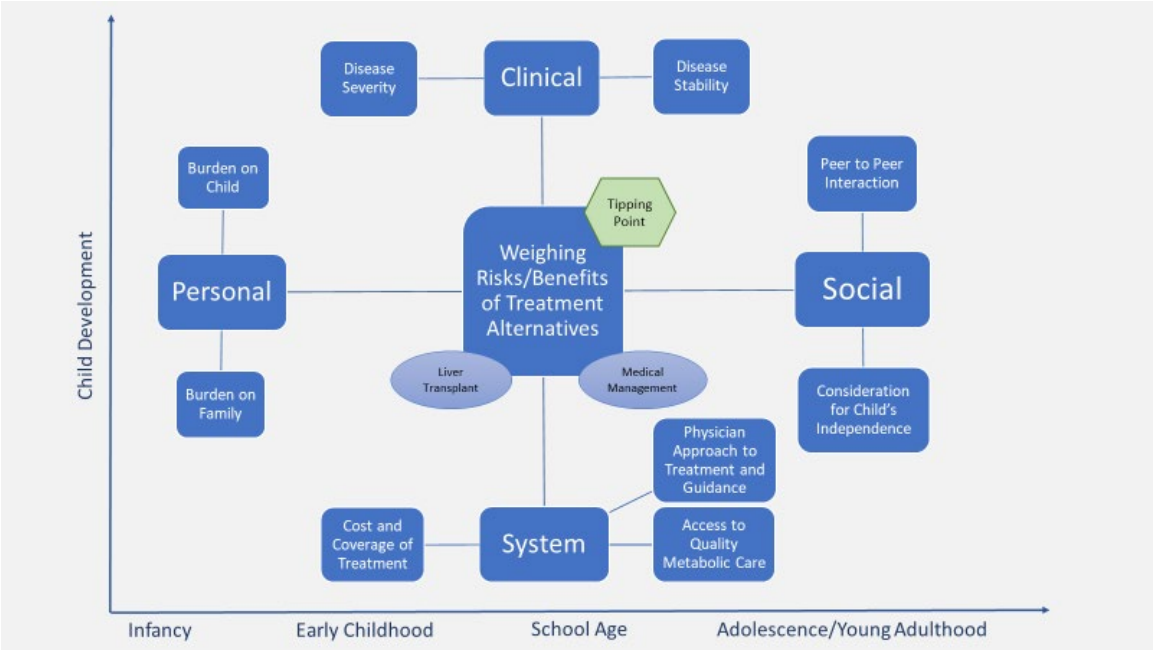
[1b] Provider participant (20001): "*I think just the uncertainty of what is going to give their child the better long-term outcome is really hard….The fact that I can't totally resolve that uncertainty."*

[1c] Provider participant (20026*): "Lack of us knowing what we're doing [is most challenging]…we need to get more data to know what we are doing. Are we really helping them or are we doing more harm? Do we need further stringent criteria to decide on this or is what we're doing okay? I think those are the questions that we need to answer…I think it's lack of data and knowing if we are doing the right thing for this child or if we are actually harming them more than we are helping."*

A framework for treatment choice in UCD

Key themes, which represent the shared decision-making experience of the study cohort, were identified through analysis of parent and provider participant interview and focus group data. These themes were positioned within a holistic framework that illustrates how elements of the decision-making experience interrelate and collectively influence the decision between medical management and liver transplant among parents whose children are diagnosed with UCD.

Figure 2.1. A conceptual framework describing the key factors that contribute to the decision between medical management and liver transplant among families whose children are diagnosed with UCD, within a context of limited empirical evidence and poorly-defined clinical guidance.



Weighing the relative risks and benefits of available treatment options

Consideration of the relative risks and benefits of medical management vs. liver transplant was a common and central component of the decision-making experience and thus, positioned at the core of the framework. Parent participants described their efforts to understand and analyze the risks and benefits of these treatment alternatives in an attempt to make rational treatment choices for their child (Box 2, [2a]). With limited empirical evidence to inform the choice between medical management and liver transplant, parents and providers also commonly discussed struggles in weighing treatment alternatives and the challenges of making a choice (Box 2, [2b-d]).

In the absence of uniform clinical guidance, families affected by UCD often relied on experience (their own, their provider's and their peer's) as inputs of imperfect information to guide the choice between medical management and liver transplant.

Participants discussed these inputs as an inter-related collection of complex clinical, personal, social, and system level factors. These factors, found on the four cardinal points of the framework, inform each family's personal perception of the risks and benefits of medical management vs. liver transplant and ultimately, their decision to pursue or not pursue liver transplant as a treatment for their child with UCD.

Box 2: Weighing the relative risks and benefits of available treatment options
[2a] Parent participant (10001): *"We wanted to be in the driver's seat…for his best interest and his life…it's the same thing as a risk benefit. You're making a pro and con list, and it's an unknown number of hyperammonemic episodes versus unknown complications from liver transplant. I think it's a hard decision, especially in those that might not be extremely sick right now."*
[2b] Provider participant (20011): *"Most challenging for the families – I think…they're probably, in many cases, wrestling that risk/benefit ratio. They're saying, 'How much chance do I want to take with my baby?' When we tell them how sick their baby can get from hyperammonemia, and then they hear from the surgeon how tricky the surgery could be… I see that as being a tough balance to accomplish."*
[2c] Provider participant (20001): "*I think the risk-benefit is much easier for families to see in kids that get transplanted for other things…where the kid is literally getting sick before your eyes in the hospital…we can tell you rather definitively that the only way your child is going to survive is to get a liver transplant as soon as possible. I think those decisions are just easier to make. The risk-benefit is much easier to assess because you can see how sick the kid is and how much medical support they're requiring… it can be much harder [in UCD] because the child looks okay and you're going along life as you've been doing and they have limitations but you get used to it. It's a really different decision, I think."*
[2d] Parent participant (10023): *"It just seems like – because there's no standard practice in these cases, it's extremely difficult. It feels like we're on the frontier of this thing, and it's not clear what the right decision is…we feel like we're making a decision, and we don't really have all of the information…Maybe that's just because that information doesn't exist."*

Phases of childhood and developmental milestones

Interviews and focus groups also highlighted the idea that changes during key developmental milestones throughout a child's life precipitate new and/or aggravate existing challenges associated with the medical management of UCD, acting as a catalyst for parents to consider for the first time or reconsider liver transplant as a viable treatment choice. As a child moves from infancy to early childhood, parents must

contend with new feeding challenges including a transition to solid foods (Box 3, [3a-b]). They may also come up against adherence issues once their child is able to refuse medications, formulas or other forms of nutrition (Box 3, [3c]). Parents may have an increasingly difficult time protecting their child from viral exposures as they transition to pre and grade school age and become increasingly more independent and interactive with others (Box 3, [3d]). As children enter grade school ages, parents described new challenges related to their child's transition to school such as concerns over management of the disorder in a school setting and worries about their child's ability to forge peer relationships and participate in "normal" childhood activities (Box 3, [3e]). Parents whose children had transitioned into adolescence and early adulthood cited new adherence issues (Box 3, [3f]), questions about their child's long-term independence, and rising concern about their child's ability to manage their own medical needs (Box 3, [3g-h]). Data suggests that the clinical, personal, social, and system level factors that were found to influence treatment choice, manifest differently throughout these key phases of childhood. Thus, major developmental transitions and milestones, found on the "x-" and "y-axes" of the framework, may change priorities for the patient, parent, and family and re-frame the parent's perception of the risks and benefits of medical management vs. liver transplant as treatment for their child's UCD.

Box 3: Phases of childhood and developmental milestones

[3a] Parent participant (10021): *"I was talking to the dietician about green beans, and she said, 'Well, once he's taking more than a few tablespoons at a time, I'm going to have to know how much he had so I can take some protein away from him out of the formula.' I really thought, 'Man, this is the easy part. Mixing formula every day and measuring, that's been easy compared to knowing specifically what's going in his mouth."*

[3b] Provider participant (20011): *"The cadence of care for these kids is they have catastrophic episodes. Then they have a little honeymoon. Then they're about roughly six months to a year old when they don't have much happen to them because you control everything that goes into them. Then you start feeding them. They get a little rockier. Then they're up and down, and up and down."*

[3c] Provider participant (20006): *"Having to deal with unpalatable medications, how to get their kids to take them, and I think dealing with compliance for a long-term, complex, medical condition is difficult, especially with – hard as toddlers, and then it gets a little bit easier, and then you have an adolescent who wants to have some control over their lives, and refuses to take their medicine, or says they do and don't, and things. I think those are a lot of things that our families struggle with."*

[3d] Parent participant (10019): *"She went to a preschool classroom two days a week, but if any of the kids were sick or if she was not feeling 100%, she was probably not there as much as half the time. She missed a lot because we just constantly had to monitor certain things."*

[3e] Parent participant (10023): *"The doctor made it pretty clear that she probably won't go to a normal school. Yeah, the diet poses serious challenges if she's going to be going to a school. We haven't figured that problem out yet."*

[3f] Parent participant (10019): "*If she would've missed one of her doses of medicine before her transplant, that was a guaranteed ticket to Hopkins. As she became older, and she didn't need mom and dad to shove medicine in her mouth anymore, and it became her job, for sure, I thought about that and worried about that, probably more as a teenager."*

[3g] Parent participant (10014): *"It's just a new chapter in our lives. In order for [my daughter] to – the possibility of her being able to maybe go to college and – I'd like for her to be able to go to college and maybe go away to college someday…just be able to think about things like that. I don't know. If we can't get it under control now, I don't' know how we're going to be able to get it under control in the next couple of years."*

[3h] Provider participant (20005): *"Especially with the older children, are you getting older, and who's going to take care of this – who's going to manage the child who doesn't have a liver transplant after you're dead and gone or if you become incapacitated? If life goes on, you never know what's going to happen around the corner. With the younger patients, I usually don't take that approach, but as the patients get into their teenage years, it's a question of, well, who is going to manage this, a sibling, and are they willing to do it? That's something that really is important to think about."*

Tipping point

Parent participants within interview and focus group cohorts who had chosen liver transplant as a treatment for their child, all reached a "tipping point" in their evaluation of the risks and benefits of transplant vs. medical management, represented as a sub-core theme in the framework. Ultimately, each of these families felt unable to continue management of their child's disorder through diet and medication, prompting (i.e., "tipping") them to pursue transplant as a treatment alternative (Box 4 [4a]). Interviews with patients and providers highlighted variation in how families approach this decision and the conditions under which they would entertain transplant as a viable treatment alternative for their child. If, when, how, and for what reason families reach this conclusion varied somewhat within the study cohort and among provider participants' patient panels. Among families affected by UCD, some described their "tipping point" shortly after diagnosis, some never reached a point where they felt transplant was a true consideration, and others faced their "tipping point" only after several years of medical management and key changes in circumstance (Box 4, [4b-d]). The family's overall tolerance of the uncertainty and ambiguity that accompanies medical management seemed to factor into this timeline (Box 4, [4e]) as did the child's clinical status, the personal burden of disease on the family, the social implications of the illness for the family and child, and the patient's experience with the health care system. Together these represent the landscape within which families affected by UCD evaluate available treatment choices and reach or do not reach a "tipping point" in favor of transplant over medical management. These framework components are detailed in the sections below.

Box 4: Tipping point

[4a] Provider participant (20010): *"Finally, push came to shove where it was the kids were coming in too frequently, or their ammonias were being too problematic, difficult to treat. Then we finally made the decision when that balance or the scale seemed to tip… Every child is different and every child comes in with a different set of issues. Whether it's the diet, whether it's the medicine, whether it's just the lack of activity or just feeling out of it all the time, whether it's hyperammonemic crises, bringing them in frequently, these are all issues that come into the play of whether or not you go ahead and you finally make a transplant decision."*

[4b] Provider participant (20011): *"Families take that information in different ways. I'll have kids that I think have a little bit milder disorder, where we've talked about transplants because I usually do in the urea cycle defects. I at least let them know what the spectrum of options are…The family, well, when can we do the transplant? I say, your kids aren't that sick. Then we have other ones where the kid's coming in once a month, and they've had many [hyperammonemic episodes]…and the families say, oh, I don't know if I want a transplant."*

[4c] Provider participant (20012): *"For some parents it's right away. They want the transplant right away. They want this condition gone. This condition scares them way more than a transplant. There are some parents who, within a year, would say, "I want a transplant."… Some families just reach it right away and others have to sit for a while with it."*

[4d] Parent participant (10026): *"It was his second crisis then at 10 months, I guess,…that tipped the scales…. After the second crisis, there was – we didn't feel like it was a – it was a decision that was definitely transplant."*

[4e] Parent participant (10002): *"Honestly, as parents we were not handling it well. We were handling it but to think of living years like that, with that kind of fear, was overwhelming…. I think for us it was the fear of her just having a completely severe decompensation to the point where she'd have a really severe brain injury and that her life could completely change in an instant... I think it's one thing that if your baby's born a certain way and that's what it is and you*
deal with that situation. When you're just constantly facing it but knowing that you're not there but that everything could change for them at any time, to me it's just a really different way to try to exist with just the fear of it."

Clinical factors

Disease severity

The severity of the child's UCD diagnosis was cited by parents and providers as a key consideration in the choice between medical management and liver transplant. For patients with neonatal onset UCD and/or zero enzyme function, liver transplant was often presented by parent and provider participants as the more evident choice. In these cases,

parents and providers commonly described liver transplant as the child's "only option" or "best chance at long-term survival" (Box 5, [5a-b]).

It is important to note that despite what most parents and providers described as a compelling clinical argument in favor of liver transplant for the most severe patients with UCD, some families affected by neonatal onset disorder still expressed hesitation in pursuing liver transplant as a treatment and continue to evaluate the potential complications of surgery against the risks of medical management (Box 5, [5c]).

In cases of late onset UCD and/or partial enzyme function where medical management is often presented as a viable treatment alternative, participants described a much more subjective and complex evaluation of the pros and cons driven by factors outside that of the child's diagnosis (Box 5, [5d]).

Box 5: Disease severity

[5a] Parent participant (10004): "*He had almost a compete deletion in his chromosome. Anything could just set it off…They were like 'It can go off anytime. It can cause another hyperammonemic episode… He could possibly die, or go into a coma, or have seizures…This is his best chance of survival.' That's what we did….it was really the only long-term option for him.*"

[5b] Parent participant (10006): *"[He] had 0% of the OTC enzyme. Honestly, we really weren't given a choice. It was sort of a no-brainer like, okay, you live in fear for the rest of your life that when he gets sick his ammonia will go up and cause further brain injury. That's what we chose really with the guidance of the metabolic team."*

[5c] Parent participant (10023): "*I don't really know. I feel like she's probably always going to be a little bit unstable. We seem to be in and out of the hospital every three months, about. I don't know. She has zero enzyme function, so it's pretty black and white in her case….I feel like things probably aren't going to change very much, but who knows?... Do we do it now and protect her neurological development, but then risk her life, or do we continue with conservative management in the hope that maybe an alternative treatment's going to develop?*"

[5d] Provider participant (20006): *"I think in the severe neonatal onsets, I think that's less of a question at this point. That's really the only way to save them….I think that in that case, there's…less question about whether it's the right thing to do…In the later onsets, where it's a little bit less clear-cut, I think – we have extensive conversations."*

Disease stability

Parent and provider participants differentiated between the child's disease severity. determined by their diagnosis, and the stability of their disease, reflected in the family's ability or inability to control the child's ammonia through diet and medications. Parents of children with both neonatal and late-onset forms of UCD often pointed to a period of instability, marked by frequent episodes of hyperammonemia and hospitalizations, as a catalyst for transplant (Box 6, [6a]). In some cases, families explained that disease control was never truly established (Box 6, [6b]), in others, families described a sudden loss of control over their child's ammonia (Box 6, [6d]).

Among the parents of children who experienced fewer episodes and hospitalizations, some viewed liver transplant as a last resort (Box 6, [6e]) while others entertained or pursued transplant as a preventive measure to avoid future complications. In these cases, parents did not interpret past or current disease stability as an indication of future disease control and cited the unpredictable and potentially devastating nature of high ammonia as a driving force in their decision to consider or pursue liver transplant for their child (Box 6, [6f-g]).

Box 6: Disease stability

[6a] Parent participant (10007): "*He was in the hospital every week or so because his ammonia would shoot up, and we really had no control over it. No matter what diet, how we adjusted his diet or his medications, his ammonia would always just go up. It was necessary for him to get a transplant because we couldn't really control his ammonia."*

[6b] Parent participant (10002): *"In her case, we just couldn't keep her stable. She was pretty stable for two months before she was hospitalized again, but she had a handful of decompensations within the first few months. We were already feeling pretty desperate in talking about transplant within the first three months of her life".*

[6d] Parent participant (10005): *"Initially, we were not for transplant. I, of course, did all the Google stuff, which I know you probably shouldn't do, but I just saw all the complications and the constant taking of medication. It just didn't seem like something that we wanted to do. We thought, oh, we can keep him managed, but basically, it started getting to the point where [he] was beginning to have to be hospitalized every couple of months for illness."*

[6e] Parent participant (30002): *"From everything that I've heard, it should be for us more of a last resort scenario. My daughter's condition, for the most part, has been pretty well-controlled. She's had some, a few, maybe three or four high ammonia episodes in the last ten years that required hospitalization, and those were mostly well-controlled. In my mind, if that is still feasible for us, why would we take on the risks that are associated with the liver transplant?"*

[6f] Parent participant (10008): "*Tons of reasons as to why we felt transplant was a better option, even though he was quite a stable kid so far, but everybody told me that might not be the case forever. That can change literally overnight, so that's why we decided to go for the transplant."*

[6g] Parent participant (10031): "*She is stable. She's met all her developmental milestones. She is thriving. You look at her, and she is very typical…So when she went into the [transplant] doctor's office, they're looking at us like, okay, she's fine right now…but what about when she has her next one and…what is that going to look like? That terrifies us."*

Personal factors

Burden on family

Parent interview and focus group participants extensively discussed the day-to-day challenges of managing their child's illness and the ways in which the disorder has altered their family life. Parents called attention to the challenges of 24/7 medical caregiving, the impact of fear, worry, and anxiety on the family's emotional health, and the ways in which the family has had to alter their relationship to and expectation of "normal life" comforts like food and travel. For many parents, these daily burdens provided a compelling reason to consider liver transplant for their child (Box 7, [7a-c]). For other parents, these day-to-day challenges, although present in some form, did not prompt them to pursue transplant as a treatment option. In these cases, parents often described having reached a point of both mastery and comfort in their child's routine and

cited concerns about the new and unfamiliar risks and burdens of post-transplant life, including liver rejection, immunosuppression, and mortality (Box 7, [7e-f]).

Box 7: Burden on familial unit

[7a] Parent participant (10010): *"I'm like, oh my God, she never would've been able to do this…It would've impacted our lives, as well…just your daily life and meal planning. Those little things that I sit and think about, when I get overwhelmed with anything going on in her life now, I'm like, what would it have been without [transplant]?' and then I'm like, okay, I'll take it."*

[7b] Parent participant (10011): *"Before it was every night I never left things undone because it was always, oh, is tonight a night we're going to have to race off to the hospital?...Like I said, [transplant] changed our lives in a lot of ways."*

[7c] Parent participant (10017): *"It really impedes your life, your family, and I wouldn't want that for any new family. If we could protect them and they don't ever have to go through it, and if transplant is safe, with it being as safe as it is, then that's always an option. That's the best option…the lack of sleep and constant worry, completely sleep deprived because you check to make sure they're fine all night long. The stress of what if something happens, that takes many years off your life."*

[7e] Parent participant (10013): *"That has definitely been a challenge, just to have a healthy amount of and realistic amount of worry, not to let yourself fall into that pattern of panicking…this condition is not for the faint of heart. Managing it, I'm not going to say it's easy by any means, but it is doable…Despite all of our ups and downs and things we have to go through when we think she's sick, I'd still rather deal with that than have to deal with X% dying and all the issues that come with having a major organ transplant… I just don't see a reason. The path unknown is really frightening to me, and there's no reason for us to go down that path unless we need to."*

[7f] Parent participant (10027)*: "Right now, he is living a 100% functional, wonderful life. Getting a liver transplant would just be replacing his urea cycle disorder with another condition. He would be on…immunosuppressant drugs for his whole life. I feel the way I manage his urea cycle disorder, I would have time if something were to happen. If he were to get the flu, or some horrendous illness that would spiral his urea cycle disorder into a horrible ammonia attack, we'd have time to deal with that….If he gets the flu, I can usually manage it from home…I feel like if it was a liver rejection, and say there wasn't another liver available, I wouldn't have all these options. I wouldn't have the options to save him the way I could now with a urea cycle disorder. That's why I've chosen not to transplant him."*

Burden on child

Parent participants also spoke specifically about the burden of illness on their child's quality of life, a seemingly small, but important distinction from the familial challenges of UCD that also influence treatment choice. Many parent participants described deep concern over how UCD has impacted and may continue to impact their child's intellectual and social development. Parent's often labeled their children's demeanor in immeasurable terms such as "foggy", "unfocused", "disorganized", or "cloudy", and worried their child was suffering due to heightened levels of ammonia. Those who considered or pursued liver transplant often believed that surgery could offer their child an opportunity at a "normal" and better-quality life (Box 8, [8a-c]).

Among those who did not pursue liver transplant, some described a much more optimistic picture of their child's current intellectual and social growth, including participation in school and sports. In these cases, parents seemed less motivated to pursue transplant as an alternative treatment option (Box 8, [8e-f]).

Box 8: Burden on child

[8a] Parent participant (10012): *"I remember she would wake up every morning, and she'd be just moaning…I don't know if it was pain or if it was…just foggy ammonia brain….She was just never normal…. It was just very – I don't know. It was very sad…It was day-to-day. It was hell. She would be stuck to a pump for an hour, and then we were still at that time trying to feed her orally. We'd sit her down at the table, and she'd sit for hours just trying to get a little bit of food in, and then by that time, it was time for another feeding. I mean, she had no life. She couldn't play. I mean, she was miserable…her thoughts were disorganized and cloudy. She wasn't a normal kid. It was heartbreaking."*

[8b] Parent participant (10018): *"That was one of the things in school. He learned how to count money, and that was a huge thing because he worked and worked at it. Then he had a high ammonia level…He remembered that he knew how to count money, but he couldn't count it anymore. We thought, oh, that quality of life's horrible. That was another one of the things that*

– especially he had to work so hard to learn it more than just a normal kid, and then to lose that functionality was devastating for him. That played into [the decision to transplant] too."

[8c} Parent participant (10019): *"We didn't let her do a whole lot outside of our house, in terms of being normal, regular kids that can go play, and go swim, and go to school. We were too worried constantly about what she was going to get into, or was she going to burn too many calories, or was she going to wear herself out. We just kept her in a bubble. It was very stressful."*

[8d] Parent participant (10024): *"He's very active. He's very involved in sports…he plays football. He plays basketball. He plays lots of sports. [The doctor] adjusted his metabolic formula. She adjusted some things…He, obviously, is gaining weight. He's growing. His height, he's getting taller. He's doing so much better."*

[8e] Parent participant (10013): *"Of course, there's worry, but she doesn't live in a bubble and she never will. I want her to be out and about and to be part of normal life. It's just she's going to have to take more precautions than other people."*

Social factors

Peer-to-peer interaction

Parent participants reflected on conversations (in person, on the phone, and online) with other families affected by UCD and the role of their peers' experiences in shaping their own treatment choices. Most parents interacted, to varying degrees, with other families affected by UCD. Many pursued connections to other parents for the specific purpose of informing treatment choice and others connected organically through the UCD community. Regardless of how connections were made, many parents described being influenced, at least in part, by others' experiences with medical management and transplant. Parents described being motivated to transplant based both on the positive surgical and post-surgical experiences of some families (Box 9, [9a-c]) and the negative outcomes shared by others who had delayed or foregone transplant (Box 9, [9d]). Other parents described being deterred from transplant by stories of surgical complication (Box

9, [9e-f]) and/or encouraged to continue medical management by others who had done so with success (Box 9, [9g]).

Box 9: Peer-to-peer interaction

[9a] Parent participant (10008): "*I probably wrote back and forth with probably about six, or seven, or eight different moms for a couple months. Just hearing their experiences, asking if they feel that dealing with transplant life is easier than a UCD life, and all of them told me that they absolutely thought the transplant parent life was better than UCD life. A lot of their opinions really helped make my decision."*

[9b] Parent participant (10017): *"Recently, a girl that is 14 that's had a really hard time for the past 5 years, she was transplanted. That's someone that is close to [my daughter's] age, someone that [my daughter] has known... Seeing that and hearing how well she's doing, I think that's going to make her process a little easier."*

[9c] Parent participant (10014): "*There is a girl…We met her at a urea cycle disorder conference...Wonderful young girl and she got a liver transplant, and she is doing wonderful...It's neat because [my daughter} is like you're just like me. You're just like me."*

[9d] Parent participant (10015)*: "I had talked to one parent who had lost her child with ASA when she was 18 years old, and other parents whose kids' livers were doing really poorly in their teens, and I thought, I should just preempt this now. I'm not going to do this struggle of trying to get him to have nutrition, watch his brain deteriorate when it's not preventing the hyperammonemias, and just to get him to a teenager where he's going to die anyway. That made me request the transplant."*

[9e] Parent participant (10011): *"A good friend of mine lived nearby in. Their daughter was transplanted. She died. It was a bad – things just went poorly the whole way through... I don't think she ever even came home from the hospital after being transplanted. That left a bad taste in my mouth, and between that and the fact that our doctor was very adamantly opposed to doing a transplant, for a long time we didn't even really give it much thought."*

[9f] Parent participant (10013): "*We've lost touch with them because now they're on a different track; they're being followed…post-liver transplant. From what I understand, it hasn't been an easy road for them at all. She's been stable…but it hasn't been easy at all. It, in my opinion, reaffirms why we never went down that path. What I've heard from other people going to various conferences is that it's trading one set of issues for another set of issues. If we don't have to find out what those other set of issues are, why would we? That's our thought process.*"

[9g] Parent participant (10027): *"We felt like we were all alone, and then all of a sudden, these people just pop up, and here they are. They have this son who is…I think he was five at that point. It was just incredible…This mom was like, 'Look, this could be [your son]. This could be [your son] in five years.' It was a completely different outlook on what we were thinking….They're handing our infant to us, and we're thinking that he's going to die. Then all of a sudden, we have this other family that says, 'No. Look. Look. We have this son. It hasn't been easy but look at him. He is beautiful and healthy.'"*

Consideration for child's independence

Parent participants often discussed their child's short-term and long-term independence as a point of continuous concern and worry. Parents considered shorter-term steps towards independence like participating in preschool or grade-school programs as well as longer-term goals like living outside the home and attending college. Most parents did not trust others to appropriately manage their child's strict nutritional needs. Others worried about how rising ammonia levels would impede their child's ability to recognize a crisis and make appropriate medical choices as an adult. For many of these parents, transplant represented the only viable way to remove the threat of hyperammonemia and thus, afford their child independence, including spending the night with other family or friends, attending school and school functions, and living autonomously (Box 10, [10a-b]).

Other parent participants, who had not considered or pursued liver transplant as a treatment for their child, offered a different perspective on living independently with UCD. These parents described incremental efforts aimed at teaching their child to manage their own medical needs. They shared a belief that their children could live safe and independent lives with UCD outside the home and thus, were not driven to pursue liver transplant by these specific concerns (Box 10, [10c-d]).

Box 10: Considerations for child's independence

[10a] Parent participant (10018): "*At one of the meetings at the Urea Cycle Foundation…they talked about…He was living on his own, and he died because his parents couldn't get hold of him. When they found him, he had had a high ammonia episode and nobody was there…That made it an easy decision. We'd never let him live alone…When he'd get sick spending the night at his cousins, we were like heck, we don't want to let him spend the night anywhere. We don't want to take the chance…What kind of a life can he have if someone has to be watching him 24-hours a day?...Some of those episodes came on so fast that even if he was a normal adult, he might not have been even able to call 911 in time to manage it for himself."*

[10b] Parent participant (10017): "*Because [she] has done so well in school and has done so well socially, going to college…that is a very good possibility, where we never really thought that was a possibility. For her independence, a transplant is necessary…It is something that with OTC and when her ammonia level starts to rise, she can't make decisions on how to help herself. There always has to be someone there to help her identify and help her make changes to her diet and to her medication before it gets too bad. Living on her own and going away to college was not going to be an option."*

[10c] Parent participant (10013): "*It's a constant struggle as I'm trying to prepare her to be a young adult, understanding that in order for her to live her life, she has to be her own caretaker. That's another huge hurdle of what we're going through right now, saying, 'Okay, this was your responsibility. We're not going to be here all the time to monitor what you eat, whether you're taking your medicines,' and right now that's the biggest challenge we're having as a family…Like I tell her, if she wants to go off to college and wants to have a job, I'm not going to be there to ask her what she's eaten or whether she's done her medicine; it's all going to be on her. It's definitely a process. She's not fully aware yet, but there are signs that she's finally getting it."*

[10d] Parent participant (10025): *"Even right now, she's 9 and in the third grade. We're trying to transition into getting her to read food labels. Getting her to understand what everything – right now I mix up her medications, and I measure everything. We already talked about, okay, how old does she need to be before she starts getting old enough to do that? Yeah, that's our goal. We understand some day she's going to leave the nest. She's going to need to know how to do all of this. At one point do we start teaching her?"*

System factors

Access to quality metabolic care

Parent participants also considered their level of access to and overall quality of metabolic care when weighing treatment options for their child. Parents who lacked confidence in their local metabolic care team often held concerns over the long-term and emergency medical management their child was receiving and pursued transplant to address what they saw as inadequacies in their child's care (Box 11, [11a-b]). This issue was further framed by the family's geographic residence and their relative proximity to specialized UCD care (often found only in large, urban, academic settings). Families who lived farther from a large hospital center with experience in UCD worried about accessing timely and appropriate rescue care during an episode of hyperammonemia. In some cases, this fear was a key driver in the parents' decision to pursue liver transplant (Box 11, [11c-d]).

On the other hand, parents who conveyed satisfaction with the local long-term and emergent metabolic care options available to them expressed greater confidence in their physician's ability to help control their child's ammonia and in the hospital's capacity to address any potential medical crises. These parents were often less motivated to explore alternatives to medical management (Box 11, [11e]).

Box 11: Access to quality metabolic care

[11a] Parent participant (10008): *"Yeah, the quality of care. Part of my decision [to transplant] too was UCD being so rare. What I was told is I can't be on vacation and be sure to find somebody that's even going to know what I'm talking about. Even our local hospital didn't even – they had no idea what a UCD was. They had no idea how to care for him. I just felt it was really dangerous for him to live with that disorder in the future, for his life…. I didn't feel like I was getting much help with the nutrition aspect, and I was worried about that for the future because it's such a huge part of keeping him healthy… Then a couple of times…he had an emergency. He had been vomiting all day, and we took him to the ER. Of course, the ER was terrible. They don't know anything about urea cycles."*

[11b] Parent participant (10026): *"All these little things were adding up for us. Okay, he didn't have a crisis for eight months, but they're not able to quickly handle it. This is a hospital that actually knows about it. I had talked to plenty of parents whose child had brain damage because they were in a place…where the hospital didn't know about it. Ours knew, and they still took days to get this going and get him stabilized….we just looked at each other and said, if we weren't here watching like hawks all the time, would he survive?…When we went in there, my faith was that these people were going to save his life, and suddenly, I couldn't count on them to do it right. You know?... The head of transplant came in, and said again, 'I think you need to talk to us again.' We said, yes, we wanted to get him – we changed our minds. We want a transplant."*

[11c] Parent participant (10012): *"We're here…with very limited access to a decent metabolic geneticist. I've been told there just aren't that many, I guess. There certainly aren't any in this state, and so it's just access to good care, basically…It seems that there are only a handful of specialists throughout the country, and if you're not in that location, you're really subject to pretty subpar care…. Not being able to rely on your healthcare provider. I mean, I think the question had to do with local – not having local access to good physicians. We never felt like they had our backs here. We could never rely on them. We would put a call in and not – we wouldn't get a call back for a week. When you're trying to manage day-to-day, it's like, oh, we got these labs back. What do we do now? You can't wait a week. I mean, it was horrible, so that was a huge stress for me knowing that we were basically on our own."*

[11d] Provider participant (20021): "*If you have a medically unstable child who lives a long way from a facility with any special expertise with urea cycle disorders, he could get into trouble quite easily and not have medication at hand that they need. That obviously does change the balance of how you would recommend liver transplant… I have a [adolescent] patient who – she was really well her whole life, but then…had one or two hyperammonemic episodes, not even that severe, quite moderate. Because of her geographic location, I recommended transplant because her ammonia control baseline wasn't that good. I was worried about compliance, and I was worried about her geographic location, so we listed her, and she was transplanted last year."*

[11e] Parent participant (10028): "*I'm confident that if she does get sick that we're in the right place. I trust the team here very much… Here, anytime there's been a question of high ammonia, they're like come in. Let's do labs. We wait in the hospital until we know what the number is…The reason [liver transplant is] not forefront in my mind is because we are with [this] department, and we're with [this] doctor. I'm very confident in our team on our day-to-day management and how we do everything…If it's decided that we can't stay here… I pretty much know transplant would happen in one of two facilities, and then we'd go from there."*

Metabolic physician approach to treatment and guidance

Physician opinion and overall approach to treatment and guidance seemed to hold a great deal of influence on parent treatment choice. Many parents described the relationship with their metabolic doctor as one of great significance to their family and defined the physician as a critical part of their child's care and welfare (often since birth and/or diagnosis). Thus, clinical guidance from the metabolic doctor in favor of or against liver transplant was highly valued with many parent participants (Box 12, [12a-b]). In the absence of clear, evidence-based information specifying the conditions for one treatment path over another, physician opinion and approach to treatment did seem to vary substantially from person to person and institution to institution. Qualitative data suggests that these differences are driven, in part, by the physician's previous experience with transplant and its outcomes, the location of their training and that institution's position on transplant for UCD, as well as their experience with medical management and the survival and neurocognitive outcomes they have observed among their patient pool (Box 12, [12c]).

Some families described their physician as inherently opposed to liver transplant as a treatment for UCD and credited their physician's opposition as a major deterrent to transplant, even in circumstances that they now feel may have warranted it (Box 12, [12d-e]). Other parents described their doctor as pro-transplant and were encouraged to

explore transplant as an alternative treatment choice, leading some to pursue it (Box 12, [12f]). Still, other providers described a position neither for or against transplant and an approach that deferred all treatment choices to the family. Some families valued this impartial approach and felt empowered to explore both treatment options with the support of their metabolic doctor (Box 12, [12g]). However, others described feeling paralyzed by their provider's ambivalence and wished that their metabolic doctor had done more to assist them in weighing the risks and benefits of treatment alternatives (Box 12, [12h-j]).

Box 12: Metabolic physician approach to treatment and guidance

[12a] Parent participant (10027): *"I had such an incredible team that I really didn't have to navigate it alone. They were really there for me…The doctors have been incredible…I never really had to navigate those things alone medically."*

[12b] Provider participant (20001): "*I think [the family's] view of transplant is impacted significantly by the impression they're getting from both the metabolic genetic team, who usually know them really well and is really involved with them, and the transplant team that they see. From what I've heard from other doctors and from families, they may get a very different impression of what transplant involves and what the long-term outcomes are depending on who they talk to."*

[12c] Provider participant (20001): *"It seems like the discussions I've had with geneticists is that people have very different approaches at different institutions….Some people have very clear ideas about who they refer for transplant, and some people don't. I don't think we know which one is the right approach…I was definitely surprised about that when I started talking more to metabolic geneticists at other centers or that had recently come from another center to ours…. I think it has a lot to do with, especially if you only have a few cases and then you have even fewer cases who decide to go through transplant, what happens to them afterwards. If you see a bad outcome or two that can totally change your impression for the next 20 years versus if you see some who do really, really great, then that may also change your referral pattern."*

[12d] Parent participant (10011): "*He was very, very anti transplant, very anti transplant, just really had nothing positive to say about it, and he remained that way. I will say that's part of the reason [my son] was so much older; why we didn't give it more consideration…There were a few periods where he was really sick for a really long time and almost died a couple times, and still, this doctor held fast. He did not think transplant was the way to go…When I'd bring it up to the doctor, he still was not in favor of it, so we just didn't really push…. I still was not positive it was the right – at that point, I still was a little unsure. I mean, having a doctor for 20 years that is the top of the field saying don't do it. Don't do it. It's like, oh, man, are we asking for trouble doing this?"*

[12e] Parent participant (10019): "*I would say, for our family, one of the biggest challenges was that we didn't have support from our genetic team… They weren't encouraging a transplant. [The hospital] believes that you're much better to manage the disorder. Because we trusted these people because they saved her life and because they kept her alive, we had our full trust in them with how to handle her. Then when we decided to look into transplant, and it wasn't even something that we could bounce ideas off of them; it was something we just didn't talk about. I would say that was, for us, one of the bigger challenges."*

[12f] Parent participant (10012): *"We mostly spoke with the geneticist…and if you're familiar with him at all, he is of the mindset that if you're born with OTC, basically, you need a transplant. With that mindset, it just – it was like this is happening. This is the best solution. Oh, yeah. By the way, there are risks, and here is what they are. It wasn't even like a risk benefit analysis so much. It was just be prepared. These are the things that could happen, full well knowing that this is going to be a far better choice for your daughter at this stage. That was already the foregone conclusion, I think, when we arrived."*

[12g] Parent participant (10031): "*We did pursue transplant. [Our doctor] has just been open to what we as parents feel comfortable doing. He thought it was important for us to explore and see what would be beneficial for [our son]."*

[12h] Parent participant (10023); "*It just seems like – because there's no standard practice in these cases, it's extremely difficult. It feels like we're on the frontier of this thing, and it's not clear what the right decision is, and nobody really wants to say one way or the other."*

[12i] Parent participant (10008): "*I mean, if I could change it, I really wanted to have more guidance from [my son's] metabolic doctor, but he never really gave much of an opinion."*

[12j] Provider participant (20006): *"What we often tell the family is that there's not a right answer here. It's not wrong to choose one or the other. It's what's right for them as a family together. That, I think, is difficult for families because in something so major, I think what they really want to hear often is, 'This is what you should do. This is what you need to do for your child.' Making that decision and putting it on a family is really difficult. I always feel that when we have these discussions that I wish I could just tell them what to do. I think that would take a lot of the burden off the family."*

Cost and coverage of treatment

Parent participants cited costs of care and the burden of navigating insurance coverage for their child's UCD treatment as a major challenge of the condition. Interviews and focus groups highlighted clear differences in the cost and coverage landscape of medical management vs. liver transplant. Parents with transplant experience described transplant as a fully covered procedure after obtaining prior authorization from

their insurance company. These parents described little out of pocket cost associated with the surgery, hospital stay, short-term and long-term post-transplant medications, and follow ups (Box 13, [13a-b]). In contrast, parents described many on-going struggles with the cost and coverage of their child's pharmaceutical and nutritional needs under medical management of UCD. Parents cited time-consuming disputes with insurance companies over coverage of medically necessary medications, lack of coverage for metabolic formulas and medical foods, and indirect financial costs related to travel for medical care and reduced time at work (Box 13, [13c-d]). Despite significant differences in the cost and coverage of medical management vs. liver transplant, parent participants did not point directly to their finances as a driving force behind their treatment choices. However, for many participants, the financial implications of UCD treatment did contribute to the overall burden of disease and the context within which treatment decisions were made.

Box 13: Cost and coverage of UCD

[13a] Parent participant (10005): "*In the very beginning I had to do a lot of navigating with [my child's] medication, the sodium phenylbutyrate…They did not want to cover it…I spent many hours on the phone for about a month after [he] was born, having to get him what he needed…The actual cost and coverage with [his] transplant, we have not had to worry about that at all. That was covered. We never got any issues and trouble for it."*

[13b] Parent participant (10030): *"The transplant coverage has been beautiful…After surgery, we accidentally left [medication] in our refrigerator, and we went [on vacation]…Even though we were out of state, the insurance company was more than willing to pay for a small amount of medicine to be made right there…at 10 o'clock at night. Otherwise, we were looking at turning around and coming right home. That's what we would've had to do, and we were prepared to do that…The insurance was like, no, no, we'll pay for five days' worth."*

[13c] Parent participant (10017): *"It's too hard…insurance, and the cost, and the struggle between insurance, and where you work, and getting covered, and it's not just one medication, it's multiple, it's a full-time job just to get medication. The amount of hours that I have spent just to get medication sent to our front door, we've driven all over the place and had things flown in overnight all the time. It's too much…First is what is covered under your insurance. Part of the treatment is medication, but the other part of the treatment is the nutrition. The nutrition many times is not considered medically necessary, but is medically necessary...Then you're constantly battling with your insurance company. It's hard enough emotionally to deal with the condition, but then to have to be bullied by insurance companies. So many, my family included, but so many families have given up so much of their time and money. The amount of money that we spent the first five years that [she] was diagnosed, we were living in poverty, but our income was well above poverty…we couldn't comprehend how it could cost this much money out of our pocket to be able to keep her alive….Then your insurance company – every time you get a call, you think this is when they're going to cancel us; this is when they're going to say they're not going to pay for this anymore."*

[13d] Provider participant (20023): *"I've had with families that surprises me they think about this early is cost of care. I've had families who really want to know how many outpatient visits are they going to have per year. How many expected inpatient visits are they going to have per year? What are the costs of the medications? Really very financial detail… we cover such a large geographic area, so it's not uncommon for our patients to be 12 or 14 hours away each way. They're really thinking about time away from work, spending the night, and coming to see us. I've been surprised how many patients have made medical treatment decisions based on those kinds of cost."*

Discussion

This paper presents a newly developed conceptual framework that reflects how parents make the decision to pursue liver transplant or continue with medical management as a treatment for their child with UCD. The framework describes the clinical, personal, social and system factors that drive treatment choice and the repeated nature of weighing these factors depending on the child's development milestones, all within a context of limited evidence to support clinical guidance and significant uncertainty related to both medical management and transplant.

To date, there have been no commensurate studies published that examine treatment decision making among families affected by UCD within which study findings can be placed. However, with the advent of new treatments and technologies over the last decade and thus, the increasing complexity of decisions in pediatric medicine, several studies have been undertaken more broadly to understand the process of decision-making for children with illness and disease. The most relevant of these available studies, which examine decision making for a large gamut of pediatric illnesses ranging from relatively minor incidents of upper respiratory infection to complex disorders like cancer and cystic fibrosis (Glyn Elwyn, Gwyn, Edwards, & Grol, 1999; Gagnon & Recklitis, 2003; Götz et al., 1997; Hankins et al., 2007; Higgins & Kayser-Jones, 1996b; Jedeloo, van Staa, Latour, & van Exel, 2010; Lan, Mu, & Hsieh, 2007; McKenna, Collier, Hewitt, & Blake, 2010; Merenstein, Diener-West, Krist, Pinneger, & Cooper, 2005; K. A. Pyke-Grimm, Degner, Small, & Mueller, 1999b; Kimberly A. Pyke-Grimm, Stewart, Kelly, & Degner, 2006; Stewart, Pyke-Grimm, & Kelly, 2005; Zwaanswijk et al., 2007), are those where transplant is offered as a treatment. Among limited studies examining decision making

for high-risk pediatric interventions like transplant, several cited themes that align with components of this study's framework for decision-making in UCD.

Dellon et al. and Higgins & Kayser-Jones both described engaging with other affected families and prior transplant recipients as an element of decision making among patients with cystic fibrosis and complex heart conditions, respectively (Dellon et al., 2009; Higgins & Kayser-Jones, 1996b). These types of peer-to-peer interactions are also reflected in this study's framework as a key driver of treatment choice in UCD. Dellon et al, Hankins et al, and Pentz et al described trust in the recommendations of medical providers as another common factor for transplant related decision-making in cystic fibrosis, sick cell anemia, and pediatric cancer patients (Dellon et al., 2009; Hankins et al., 2007; Pentz et al., 2012). This concept is discussed in the framework in terms of the metabolic physician's relationship with the family and the impact of their opinion and approach on the parent's perception of transplant vs. medical management. Together with the previously published literature, study findings further support the notion that engagement with peers and guidance from providers both greatly influence treatment choice in complex, chronic pediatric conditions like UCD where transplant is a consideration.

Study findings also suggest that developmental transitions throughout childhood act as a catalyst for treatment decision making among families affected by UCD. Previously published qualitative studies addressing patient and family experiences with inherited metabolic disorders identified life-transitions as a major challenge for children and families. One such study cited problems with adherence to diet for phenylketonuria patients during adolescence (Ievers-Landis et al., 2005). Others highlighted social

transitions across the lifespan as a challenge for patients diagnosed with various inherited metabolic disorders (Henderson, Packman, & Packman, 2009; Khangura et al., 2016; Vegni, Fiori, Riva, Giovannini, & Moja, 2010). The existing literature does not explicitly discuss the role of life-transitions in influencing treatment decisions but rather, highlights these transitions as a challenge for patients and families. Findings from this study expand on the existing literature by describing not only the inherent challenges of childhood transitions while managing rare-disease but the ways in which developmental milestones frame treatment choice among families affected by inherited metabolic disorders like UCD.

In addition to the concepts noted above, this study contributes new qualitative evidence supporting the role of other factors, not previously described within this context, in driving treatment decisions for children diagnosed with UCD. This study distinguishes between the function of disease severity and disease stability in mediating treatment choice, expounds on the implications of disease for the family and the child and its role in treatment decision-making, and explores issues of health care quality, cost, and access as they relate to the choice between medical management and liver transplant. This study also describes and applies the concept of a "tipping point" to decision-making in UCD. Finally, this study organizes all factors into a conceptual framework that illustrates these various considerations as inputs to a highly complex and dynamic personal evaluation of the risks and benefits of treatment alternatives.

Strengths and limitations

This study applied qualitative methodology to a population and field for which qualitative methods have been scarcely used. Patients with rare diseases are generally

heterogeneous, limited in numbers, and spread through a large geographic region. Thus, identifying subjects and obtaining sufficient interview and focus group data for a rigorous qualitative study can pose a significant challenge, resulting in a dearth of published, qualitative literature in this field. This study leveraged partnerships with key patient groups and specialist provider networks and employed strategies for remote interviewing and focus group facilitation to demonstrate a viable approach for identifying qualitative research subjects and conducting qualitative data collection in rare-disease populations. This approach may be applied to future qualitative inquiries that aim to investigate otherwise understudied health services issues facing patients and families affected by rare-disease.

Although this study focused explicitly on the UCD experience, the framework may be translatable to other rare genetic metabolic disorders of childhood for which analogous decisions must be made between conventional therapy and transplantation. Examples include hereditary tyrosinemia type I (Grompe, 2001), glycogen storage disease type I (Muraca et al., 2002), propionic and methylmalonic acidemia (Kasahara et al., 2006) and hyperoxaluria type I (Shapiro et al., 2001). The developed decision-making framework may be adapted and applied through additional research to these other disease areas.

The participant sample for this qualitative study may be biased by recruitment source and strategy. Most caretaker recruitment was conducted via NUCDF, a non-profit advocacy organization for UCD patients and a resource of information and education for families affected by UCD. Therefore, the study sample may not capture the perspective of individuals who have not engaged on some level with this organization. It is possible

that the experience of these individuals differs systematically from the experience of those who were interviewed. The provider participant sample is less vulnerable to selection bias, as recruitment source varied more substantially.

Given the sensitive nature of their experience, caretakers with a child who had passed away from complications related to UCD or liver transplant were not interviewed. Efforts were made to reach out and offer study participation to several families in this position but contacted families declined. Thus, the study sample may not capture the perspective of individuals who lost a child in response to either treatment choice and may omit key elements of their experience.

Finally, the framework developed through this analysis has yet to be validated systematically with experts, providers, and patients. Some initial validation of emerging concepts was conducted through parent focus groups, but additional measures should be taken in future studies to further validate the final framework and the concepts within it. Future research should operationalize and test empirically the factors for decision-making described in this study in order to evaluate the strengths of these findings.

Conclusion

The framework developed through this study provides clinicians and others involved in counseling families affected by UCD with new information on the shifting clinical, personal, social, and system drivers of treatment choice as well as the developmental milestones that mediate how these factors are perceived by parents in their effort to weigh the risks and benefits of medical management vs. liver transplant for their child. With a more holistic understanding of the circumstances that motivate families to

evaluate or re-evaluate treatment options and consider, pursue, or exclude transplant as a viable choice for their child, providers may be better positioned to respond to the needs and priorities of families. Evidence suggests that effective communication between providers and patients can improve overall understanding of treatment risks and options (Bogardus, Holmboe, & Jekel, 1999). With more consideration given to the patient and family experience as it is described in this article, UCD providers may better communicate information on the risks and benefits of medical management vs. liver transplant as practice continues to evolve and more data become available on their relative merits.

Chapter 3: The Relationship Between Geographic Availability of Sub-specialized Metabolic or Pediatric Liver Transplant Care and Treatment Choice in Patients with Urea Cycle Disorders- A GIS Analysis

This paper describes a Geographic Information System (GIS) study that examined the association between the geographic availability of sub-specialized metabolic care for Urea Cycle Disorders (UCD) and/or high-quality pediatric liver transplant care for UCD and the decision to continue medical management or pursue liver transplant as a treatment in patients diagnosed with UCD.

Urea cycle disorders are a group of rare inherited disorders of metabolism caused by deficiencies of any one of eight proteins required for ammonia detoxification and urea synthesis – a process in the liver that converts otherwise toxic ammonia into urea for excretion in the urine. When this mechanism does not function properly, it can result in hyperammonemia, an excess of ammonia in the blood, which in its severe or prolonged form may have devastating effects on the development and function of the central nervous system (Msall et al., 1984).

Despite significant improvements in medical management following the wider availability of specialized low-protein diets, hemodialysis, medications, and amino-acid supplements, infants, children, and even adults with UCD are at high risk of hyperammonemia (Mark L. Batshaw et al., 2001; Krivitzky et al., 2009). High blood ammonia levels can cause cytotoxic brain edema and compromise a patient's circulatory system, which frequently leads to intellectual and developmental disabilities (Butterworth, 1998; Butterworth et al., 1987; Msall et al., 1984, 1988). These most severe outcomes can occur even in patients whose mild-moderate condition appears to be amenable to management through medications and diet. Thus, an increasing number of

patients with UCD have been undergoing liver transplantation as a procedure that "cures" the hyperammonemia (Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998). However, liver transplantation is a complicated surgical procedure, which carries with it risk of mortality and morbidity and requires a life-long regimen of medication to avoid organ rejection.

A recent qualitative study examining the decision-making experience of families affected by UCD when making the choice between medical management and liver transplant as a treatment for their child found that parents considered their level of access to and overall quality of metabolic care when weighing treatment options for their child. Interviews and focus groups with the parents of children diagnosed with UCD suggested that families who live farther from a large hospital center with experience in UCD worried about their access to timely and appropriate rescue care and that this fear was, at times, a key driver in the parents' decision to pursue liver transplant. Qualitative findings from this study also suggested that parents who were satisfied with their local long-term and emergent metabolic care options were more confident in their providers' capacity to address their child's needs through medical management and thus, less motivated to explore alternatives like transplant (Gerstein, In progress)

Geographic Information System-based measures have been used in research to explore the relationship between geographic access to healthcare and a variety of health-related measures like utilization, quality and clinical outcomes. The integration of geographically referenced data from a variety of sources has enabled researchers to visualize trends and relationships over space and time and monitor the impact of geographic dimensions of healthcare access ("GIS and Public Health," n.d.). Many

studies have used spatially disaggregate data to calculate accessibility measures based on patient zip code, examining straight-line or travel-time distances to the nearest health facility (Bamford et al., 1999; John Fortney, Rost, & Warren, 2000; Kohli et al., 1995; Parker & Campbell, 1998; Perry & Gesler, 2000; Rosero-Bixby, 2004). For example, GIS was used by Fortney et al. to measure the impact of travel-time to mental health providers on outcomes in the rural areas of Arkansas (J. Fortney, Rost, Zhang, & Warren, 1999) and by Fishman et al. to examine the relationship between individual and neighborhood level spatial access to care and utilization of emergency departments for preventable conditions in the city of Chicago (Fishman, McLafferty, & Galanter, 2016). Another study conducted in the UK used GIS to examine the influence of distance to a renal unit on the utilization rates of renal replacement therapy like dialysis and noted a decrease in the prevalence of this therapy with increasing distance from renal replacement centers (Maheswaran et al., 2003).

Despite the increasing use of GIS in the health services literature, spatial technologies have not been applied as widely to rare metabolic diseases like UCD. Little research has been produced on the relationship between geographic access to sub-specialized metabolic care and outcomes. This study applied GIS methods to examine the association between proximity to sub-specialized metabolic and/or pediatric liver transplant care and treatment choice (i.e., medical management vs. liver transplant) in patients with UCD.

Methods

Research questions

This study sought to answer the following research questions:

- Is there a significant association between the geographic availability of sub-specialized metabolic care, defined in terms of distance from personal residence to a site with expertise in diagnosis, treatment and research of UCD, and the decision to treat the disorder through diet and medications or pursue liver transplant?
    - Does the association between geographic availability to sub-specialized UCD metabolic care and treatment choice change in response to disease severity or control?
- Is there a significant association between the geographic availability of a high-quality pediatric liver transplant center, defined in terms of distance from personal residence to a liver transplant site with expertise in transplant for children with UCD, and the decision to pursue liver transplant or continue medical management as treatment for the disorder?
    - Does the association between geographic availability of a high-quality pediatric liver transplant center and treatment choice change in response to disease severity or control?
- Is there a significant association between the geographic availability of a "gold standard" pediatric liver transplant center, defined by the nearest transplant center to a personal residence being one of two centers identified by key informants as providing the "gold standard" in transplant care for

pediatric UCD patients, and the decision to pursue liver transplant or continue medical management as treatment for the disorder?

- Does the association between geographic availability of a "gold standard" pediatric liver transplant center and treatment choice change in response to disease severity or control?

Hypotheses

The alternative and null hypotheses stated below (hypotheses 1.1) are based in the assumption that frequent and convenient access to a specialized team of geneticists, dietitians and counselors with expertise in UCD care improves a family's overall ability to manage UCD through diet and medication as well as their confidence in the expert emergency medical care they would receive in the event of a hyperammonemia episode. Thus, the alternative hypothesis posits a positive association between the geographic availability of sub-specialized UCD metabolic care, defined as the distance between patient residence and a hospital with significant experience diagnosing, treating, and researching UCD, and the decision to medically manage a child with UCD using diet and medication.

Hypotheses 1. 1
H_0: There is *no* association between geographic availability of sub-specialized UCD metabolic care and the decision to conservatively manage a child with UCD through diet and medication
H_A: There is a *positive*[1] association between geographic availability of sub-specialized UCD metabolic care and the decision to conservatively manage a child with UCD through diet and medication

[1] As the geographic availability of sub-specialized UCD metabolic care increases (a function of the distance between residence and sub-specialized care) the likelihood of choosing medical management over liver transplant as treatment for UCD also increases.

Similarly, the second set of null and alternative hypotheses tested in this study (hypothesis 1.2) posit a positive association between the geographic availability of a high quality pediatric liver transplant center and the decision to pursue liver transplant as a treatment for UCD. This hypothesis is based in the assumption that convenient access to pediatric liver transplant experts with strong reputations and positive patient outcomes may lead families to see liver transplant as an increasingly viable treatment option and improve their confidence in the safety of the procedure.

Hypotheses 1. 2
H_0: There is *no* association between the geographic availability of a high quality pediatric liver transplant center and the decision to pursue liver transplant as a treatment for UCD.
H_A: There is a *positive*[2] association between the geographic availability of a high quality pediatric liver transplant center and the decision to pursue liver transplant as a treatment for UCD.

The third set of null and alternative hypotheses tested in this study (hypotheses 1.3) posit a positive association between the geographic availability of a "gold standard" pediatric liver transplant site for patients with UCD, defined as the nearest high-quality pediatric liver transplant center being one of two centers identified by key informants as offering the "gold standard" in UCD related transplant care, and the decision to pursue liver transplant as a treatment for the disorder. This hypothesis is based on qualitative data that suggests that transplant as a treatment for UCD is both common and strongly supported within certain highly-regarded liver transplant programs in the UCD community and that close, geographic access to these institutions may render parents

[2] As the geographic availability of a high quality pediatric liver transplant center increases (a function of the distance between residence and transplant center) the likelihood of choosing liver transplant over medical management as treatment for UCD also increases.

more likely to explore liver transplant as a viable treatment alternative for their child's disorder.

Hypotheses 1. 3
H_0: There is *no* association between the geographic availability of a "gold standard" pediatric liver transplant center for UCD and the decision to pursue liver transplant as a treatment for the disorder.
H_A: There is a *positive*[3] association between the geographic availability of a "gold standard" pediatric liver transplant center for UCD and the decision to pursue liver transplant as a treatment for the disorder.

The final set of null and alternative hypotheses tested in this study (hypotheses 1.4) posit that the association between geographic availability and treatment choice is stronger among patients with a less severe manifestation of the disorder and fewer instances of hyperammonemia. Qualitative data has suggested that the caretakers of children with more severe and poorly controlled forms of UCD may pursue liver transplant as a "life-saving" or "quality of life preserving" treatment measure and thus, may be less vulnerable to the influence of other decision-making factors like the patients level of access to sub-specialized metabolic or transplant care.

Hypotheses 1. 4
H_0: The association between the geographic availability of sub-specialized UCD metabolic or pediatric liver transplant care and treatment choice does *not* change in response to disease severity or control.
H_A: The association between the geographic availability of sub-specialized UCD metabolic or pediatric liver transplant care and treatment choice is stronger among patients with mild-moderate late onset UCD and less frequent hyperammonemia episodes.

[3] As the geographic availability of a "gold standard" pediatric liver transplant center for UCD increases (a function of the nearest pediatric liver transplant center to patient residence) the likelihood of choosing liver transplant over medical management for UCD also increases.

Data source and data collection

To model the geographic availability of sub-specialized UCD metabolic care, locations in the United States (U.S.) with significant experience in the diagnosis, treatment and research of UCD were identified through the Urea Cycle Disorders Consortium (UCDC) participating sites list and cross-checked against information provided by key informants from the field including UCD clinicians and patient advocates. According to clinical and patient advocate informers, the UCDC represents the pre-eminent network of hospitals with expertise in metabolic care for patients with UCD in the US. High-quality UCD care may also be offered by other practitioners outside of the consortium but based on the guidance provided by key informants in the field, this analysis was limited to the 13 sub-specialized care locations included as part of the UCDC network. These 13 sites were geocoded to point locations based on their hospital address using ArcGIS software.

To model the geographic availability of large, expert pediatric liver transplant centers, historical liver transplant figures were pulled from the Department of Health and Human Services (DHHS) Organ Procurement and Transplant Network (OPTN) database, capturing all metabolic disease related liver transplants performed on children 0-18 years old in the U.S. between the years 1988-2017. Large, expert pediatric liver transplant centers were identified based on absolute annual volume. This definition is grounded in a large compendium of literature demonstrating the association between transplant volume and patient outcomes. Studies have shown that low volume centers produce significantly higher mortality rates and other poor post-transplant outcomes while high volume centers produce improved survival among transplant patients. This association has been shown

consistently across varying organ types and patient age groups (Reese, Yeh, Thomasson, Shults, & Markmann, 2009; Shuhaiber, Moore, & Dyke, 2010; Tracy et al., 2010). Pediatric liver transplant centers were categorized as low, medium or high volume by dividing the number of metabolic disease related pediatric liver transplants performed over the last 10 years and over the full 30 year data set, into three tertiles of approximately equal size (Reese et al., 2009). Those performing in the highest volume tertile on either list were then cross-checked against information provided by key informants in the field including UCD clinicians and patient advocates and the list refined to those that would be considered by UCD medical specialists for transplant referral. Ultimately, seven relevant transplant sites were identified through this evaluation utilizing a combination of hospital statistics and the subjective assessment of key informants in the field. These sites were geocoded to point locations based on their hospital address using ArcGIS software.

UCD patient data was extracted from the Children's Hospital Research Information System (CHRIS) database at Children's National Hospital System (CNHS) and the Data Management and Coordinating Center (DMCC) of the Rare Disease Clinical Research Network (RDCRN), which both house data collected from patients enrolled in the Longitudinal Study of Urea Cycle Disorders, a natural history observational study of UCD patients. Patient address data was used to geocode patient residence point locations relative to sub-specialized metabolic care and high-volume liver transplant center locations using ArcGIS software. Treatment history data was used to categorize patients into one of two treatment decision categories: (1) liver transplant or (2) medical management. Together, these data were used to assess the association between the

availability of (i.e., distance to) sub-specialized metabolic care and/or a high volume liver transplant center and treatment choice. Diagnosis and hyperammonemia episode data was extracted from the database as relative metrics for disease severity and control, both of which were included as interaction terms in this analysis. Diagnosis information was used to classify patients as either (1) neonatal onset or (2) late onset and hyperammonemia episode data was used to calculate the number of hyperammonemia episodes experienced by each patient. Available patient characteristics including patient age, sex, race, and ethnicity were included as control variables in this analysis. Since household income was not available for most participants in the longitudinal study data set, 2015 American Community Survey median household income figures were matched to participants by zip code to provide a proxy for household income.

Patient age was included as a co-variate to account for potential differences in treatment frequency by age. For example, existing descriptive data suggests that most UCD related liver transplants are conducted at less than 2 years of age (Perito et al., 2014). Researchers have also seen a comparative increase in the uptake of liver transplant as a treatment for UCD over the last decade, suggesting that older patients within the data set may be less likely to have undergone liver transplant during early childhood than those born within the last several years. Patient sex has been shown in the literature to contribute to gender differentials in health and health care delivery (Krieger, 2003) and thus, also included as a co-variate in this study's analysis. Although researchers may not fully understand how sex contributes to differences in treatment or treatment outcomes in patients with UCD, the impact of sex and gender on health care delivery and outcomes in other disease areas suggests it is a suitable control variable for this study. Racial, ethnic,

and income disparities in health care delivery and outcomes have been shown consistently across a spectrum of childhood conditions including areas of chronic disease, special health care needs, and organ transplantation (Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Flores & Research, 2010; Newacheck, Hung, & Wright, 2002). Co-variates for race, ethnicity, and income were included in this study's analysis to account for a large collection of evidence demonstrating the extensive, pervasive, and persistent impact of race, ethnicity, and income on disparities in children's health and health care. Table 3.1 details the main exposures, interaction terms, outcome variables and co-variates included within the analyses conducted for this study.

Table 3.1. List of main-exposures, interaction terms, outcome variables, and co-variates included in study analyses	
Variable	**Variable Description**
Main Exposures	
Straight-line distance to sub-specialized metabolic care (miles)	= 1-900*
Straight-line distance to high-quality pediatric liver transplant center for UCD related transplant (miles)	= 1-900*
Nearest pediatric liver transplant site	= non-"gold standard" site = "gold standard" site
Interaction Terms	
Disease severity	= late onset = neonatal onset
# of hyperammonemia episodes	= 0-42*
Main Outcome	
Treatment	= conservative management = liver transplant
Co-variates	
Patient age	= 1-23
Patient sex	= female = male
Patient race	= white = asian = black = multiple races
Patient ethnicity	= non-Hispanic/Latino = Hispanic/Latino
Median household income by zip code	=<$34,999 = $35,000-$49,999 = $50,000-$74,999 =$75,000-$99,999 =>$100,000

*Also included as dummy coded dichotomous categorical variables.

Sampling

The target population for this GIS analysis includes symptomatic (at least one hyperammonemic episode) UCD patients born in the US after 1996 who have been diagnosed with one of 4 UCDs (ALD, ASD, CPS1D, OTCD) for which liver transplantation is a consideration (it is typically not considered in the remaining 4 disorders). In 1996, the US Food and Drug Administration approved Buphenyl (sodium

phenylbutyrate) to treat UCD. The drug allows patients to excrete waste nitrogen, which would otherwise accumulate as ammonia and cause brain damage or death. The introduction of this drug marked a major transition in the treatment and management of UCD. UCD patients born prior to 1996 likely had a very different treatment and management experience than those born after FDA approval of this drug and are thus, excluded from this analysis. All individuals enrolled in the longitudinal study with complete and up-to-date residence, treatment, diagnosis, medical complication, and demographic data who met these criteria were included in the final analysis.

As of this analysis, the longitudinal study had collected data on 710 UCD patients, with 612 still "on study" (i.e., not lost to follow up, withdrawn, or deceased). Researchers at CNHS estimate this figure to represent 20%-25% of the entire U.S. UCD population. Of these 612 participants, 252 met eligibility criteria and had up to date residence information that could be used for geocoding. Approximately 40% of the original longitudinal study sample was excluded based on the patients date of birth/age. An additional 25 patients were excluded from analysis on the basis of their UCD diagnosis (i.e., were diagnosed with a condition other than ALD, ASD, CPS1D, of OTCD) and an additional 101 patients were further excluded from analysis because they did not have complete and/or up to date residence information available (Table 3.2).

Table 3.2. Sample size for GIS analysis	
Total number of longitudinal study participants	612
Excluded based on date of birth/age	-234
Excluded based on diagnosis	-25
Excluded based on incomplete residence data	-101
Total number of eligible longitudinal study participants included in GIS analysis	**252***

*Total number of participants varies by model and may be lower than this figure in some analyses due to incomplete/missing data

Data analysis

Shortest straight-line distances[4] were measured between (1) each patient's residence and the nearest hospital with sub-specialized UCD metabolic care (i.e., UCDC site) and (2) each patient's residence and the nearest high-volume pediatric liver transplant center with experience transplanting UCD patients. Distances were calculated using ArcGIS software. Calculated distances were extracted as variables and linked with patient-level longitudinal study data on treatment status (medical management vs. liver transplant), diagnosis (neonatal vs. late onset), complications (# of hyperammonemia episodes), and demographics (patient age, sex, race, ethnicity, median household income by zip code).

Regression analyses were utilized to test the association between (1) straight-line distance to sub-specialized UCD metabolic care and treatment choice and (2) straight-line distance to a high-volume pediatric liver transplant center with UCD experience and treatment choice. Distance was also dummy coded into several separate dichotomous categorical variables to assess whether the geographic availability of sub-specialized metabolic care or a high-volume liver transplant center affects treatment choice above a

[4] Also referred to as Euclidean distances: the "ordinary" straight-line distance between two points.

particular distance threshold. Categorical variables were constructed based on the spatial distribution of patient residence relative to treatment center observed through GIS mapping.

Regression analysis was also conducted to test the association between a patient's nearest transplant site being one of two transplant centers identified by key informants as the "gold standard" in transplant care for pediatric UCD patients and treatment choice. Qualitative discussions with families affected by UCD, UCD patient advocates, and UCD clinicians both inside and outside these institutions identified these two centers as delivering the "gold standard" in transplant care for pediatric UCD patients, based, at least in part on their own personal experience, patient anecdotes, and the reputation of the organization within the UCD community. The centers were also described by key informants as a "pro-transplant" environment for patients with UCD. Based on OPTN figures, the two transplant centers included in this analysis also reported the highest volume of metabolic-disease-related pediatric liver transplant in the U.S. over the last decade.

Interaction terms for neonatal vs late-onset diagnosis and the # of hyperammonemia episodes were utilized in regression models to examine if the relationship between geographic availability and treatment choice changes in response to disease severity or control. Total hyperammonemia episodes was dummy coded into a dichotomous variable (equal to or greater than 4 HA episodes; less than 4 HA episodes), based on the frequency distribution of hyperammonemia events in the data, to assess the influence of disease control on the relationship between geographic availability and

treatment decision once reaching a particular threshold. All statistical analyses were performed in STATA 12.0.

Results

Patient sample characteristics

Table 3.3 presents select demographic and clinical characteristics of the patient sample (N=252). UCD study participants were primarily white with a mean age of 12.2 years and a mean household income by zip-code of $68,102. Over 50% of participants in the sample were female. Approximately 44% of study participants were diagnosed with UCD in the neonatal period, with the remaining 66% diagnosed with late-onset UCD. The mean total number of hyperammonemia episodes among study participants was 4.2 and just under 30% of the sample had undergone liver transplant at the time of analysis (Table 3.3)

Table 3.3. Characteristics of patient sample included in analysis	
Patient demographic characteristics	**N=252**
Age, mean ± SD (y)	12.2 ± 5.5
Female, %	53.2
White, %	77.4
Hispanic/Latino, %	18.3
Household income at zip code, mean ± SD ($)	68,102 ± 27,840
Patient dx, treatment, hyperammonemia episodes	**N=252**
Neonatal onset, %	44.4
Liver transplant, %	29.4
Total # of HA events, mean ± SD	4.2 ± 5.7

GIS Analysis

Figures 3.1 and 3.2 provide a geographical representation of the UCD patient sample and their location relative to the 13 UCDC sites and 7 pediatric liver transplant

centers included in this analysis, respectively. It is important to note that relevant pediatric liver transplant centers geocoded for this analysis are concentrated on the coasts and large metropolitan regions (Figure 3.2) as are the majority of UCD expert care sites, which are largely found on the east and west coasts with fewer located in middle or northern states (Figure 3.1). The patient sample for this analysis, extracted from enrollees of the UCDC longitudinal study, is similarly dispersed. Relatively few patients within the sample reported residence in middle or northern regions of the U.S.

Figure 3.1. Straight line distance from UCD patient residence to nearest hospital center (UCDC site) with significant experience in diagnosis, treatment and research of UCD (N=252)

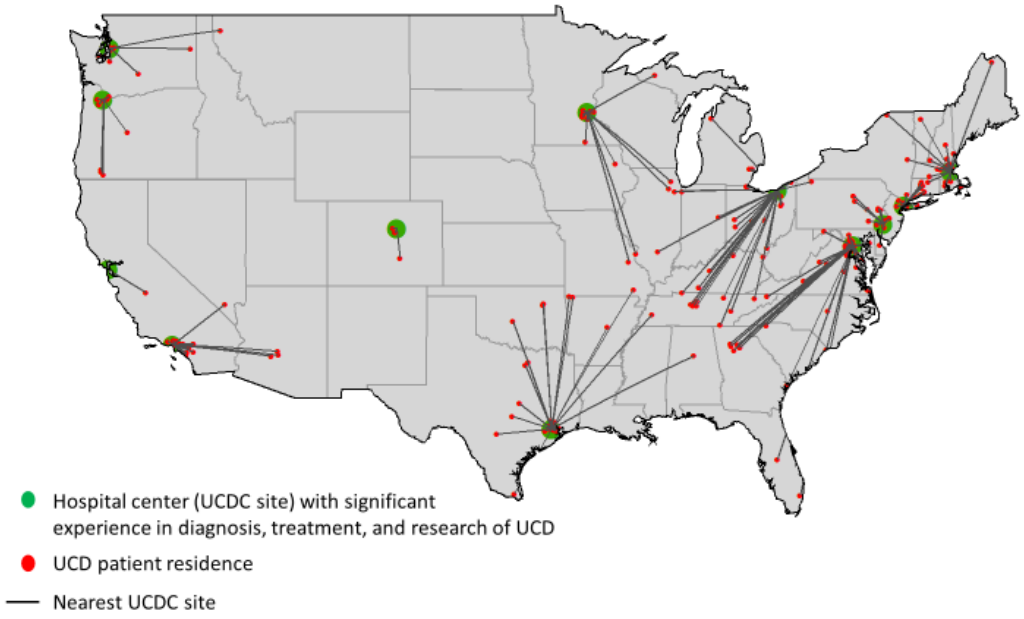
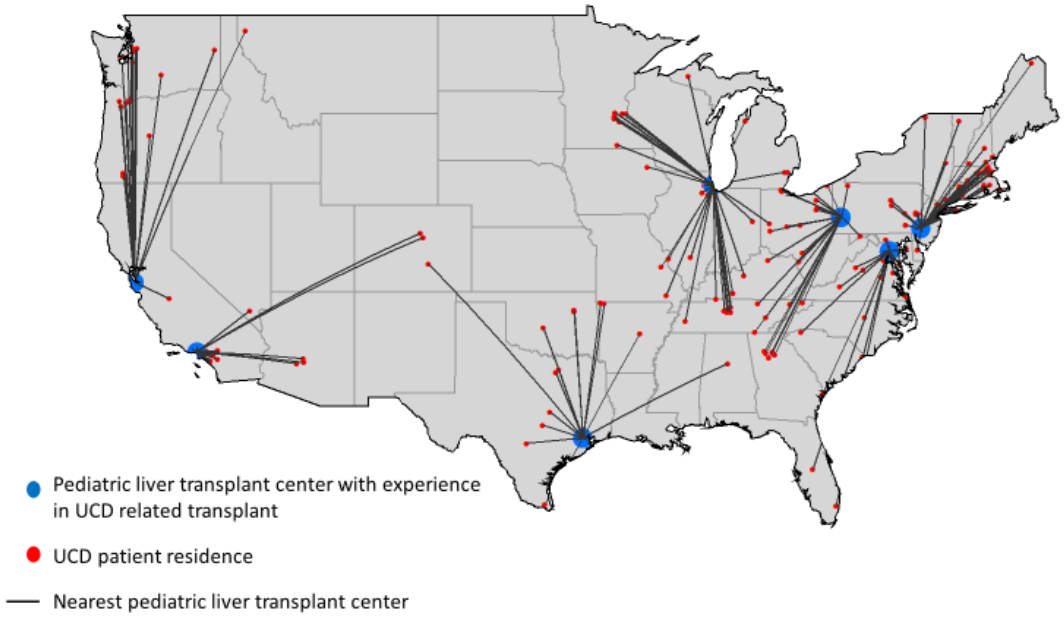


Figure 3.2. Straight line distance from UCD patient residence to nearest pediatric liver transplant center with experience in UCD related transplant (N=252)



Descriptive statistics from geocoding and relative mapping of patient residences, UCDC expert care sites and expert pediatric liver transplant centers are presented in Table 3.4. Mean straight-line distance from patient residence to nearest site with expertise in UCD diagnosis, treatment and research was 138.9 miles among the patient sample. Mean straight-line distance from patient residence to nearest expert pediatric liver transplant center was approximately 65% farther than this figure at 229.6 miles. Despite differences in measured mean distance, both UCDC sites and pediatric liver transplant centers ranged between 1-900 miles in distance from patient residences in the sample (Table 3.4).

Table 3.4. Descriptive statistics for the geographic distribution of patient residence relative to UCD metabolic care and transplant site	
Patient distance to expert care centers (mi)	**N-252**
Straight line distance to nearest UCDC site	
Mean ± SD	138.9 ± 173.7
Range	1.0 — 900.1
Straight line distance to nearest pediatric liver transplant center	
Mean ± SD	229.6 ± 211.9
Range	1.3 — 900.1

Figures 3.3 and 3.4 represent the distribution of distances from UCD patient residences to the 1) nearest center with sub-specialized experience in diagnosis, treatment, and research of UCD and 2) nearest transplant center with experience in pediatric liver transplants for patients with UCD. Both distributions are skewed right with the bulk of observations between 0-200 miles. The main variation seen in these two distributions is in the number of observations between 200-600 miles. More observations are seen within this range in the distribution of distances to nearest transplant center depicted in figure 3.4 (N=102) when compared to the distribution of distances to UCDC sites represented through figure 3.3 (N=63)

Figure 3.3. Distribution of distances from UCD patient residence to nearest sub-specialized UCD care center (N=252)

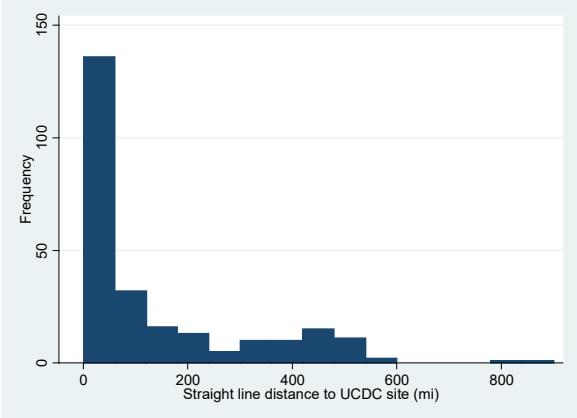
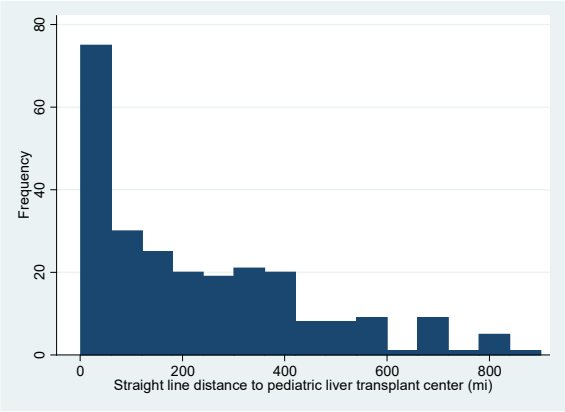


Figure 3.4. Distribution of distances from UCD patient residence to nearest pediatric liver transplant center (N=252)



Association between geographic availability and treatment choice

Regression analyses revealed no significant association between distance to a sub-specialized UCD care site or pediatric liver transplant center and treatment choice (i.e., liver transplant status). No association was detected when examining distance both as a continuous variable and as a number of separate dichotomous categorical variables based on the observed spatial distribution of patient residence and treatment center.

However, regression analyses did yield significant results when testing the association between treatment choice (i.e., transplant status) and nearest transplant center. Table 3.5 provides odds-ratio (OR), confidence interval (CI), and p-value results from a model that examines the odds of a patient undergoing liver transplant as a treatment for UCD if their nearest transplant site is one of two centers considered to deliver the "gold standard" in transplant care for UCD, adjusted for patient age, sex, race, ethnicity, and median income at zip-code. Results can be interpreted as follows: the odds of undergoing a liver transplant as a treatment for UCD is 3.22 times higher among patients whose nearest expert pediatric liver transplant center is one of two considered by the community to deliver the "gold standard" in transplant care for UCD patients when compared to those whose nearest expert transplant center is one of five others included in this analysis. These findings suggest that treatment choice may be driven not by the total distance to ANY sub-specialized center, but rather, by the patient's distance to certain highly-regarded programs within the UCD community where liver transplant as a treatment for UCD is both common and strongly supported

Table 3.5. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients, adjusted for patient age, sex, race, ethnicity, and income proxy (N=236)

Variable (comparison category)	Variable Categories	Odds Ratio (95%CI)	P-Value
DV: LT as treatment for UCD			
Nearest LT center (non-"gold standard" LT site)	"Gold standard" LT site	3.22 (1.59-6.51)	0.001
Patient age	1-23*	0.95 (0.90-1.01)	0.09
Patient sex (female)	Male	2.87 (1.55-5.31)	0.001
Patient race (white)	Asian	2.18 (0.78-6.11)	0.14
	Black	0.96 (0.23-3.98)	0.95
	Multiple races	1.50 (0.48-4.65)	0.48
Patient ethnicity (non-Hispanic)	Hispanic	1.49 (0.67-3.36)	0.34
Median income at patient zip-code ($50,000-$74,999)	<$35,000	1.89 (0.54-6.62)	0.32
	$35,000-$49,999	0.83 (0.37-1.87)	0.65
	$75,000-$99,999	0.65 (0.26-1.58)	0.34
	=>$100,000	0.67 (0.27-1.65)	0.38

*Continuous variable

Interaction terms for neonatal vs. late-onset diagnosis and the number of hyperammonemia episodes were independently added to subsequent models to examine if the relationship between nearest transplant center and treatment choice changes in response to disease severity or control. Table 3.6 presents the OR, CI, and p-values from these models. The OR represents the odds of undergoing a liver transplant if the patient's nearest liver transplant center is one of two considered to deliver the "gold standard" in transplant care for UCD under various other independent conditions that reflect the patients level of disease severity and control: 1) that the patient was diagnosed after the neonatal-period (i.e., late-onset), 2) that the patient was diagnosed within the neonatal period (i.e., neonatal-onset), 3) that the patient reported less than 4 episodes of hyperammonemia in their lifetime, and 4) that the patient reported at least 4 episodes of hyperammonemia in their lifetime. Expanded tables detailing the results of each individual model reflected in Table 3.6 can be found in Appendix A (Tables A1-A4).

Table 3.6. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients when accounting for relative disease severity and control

Variables	OR[a] (95%CI)	P-Value	N
DV: Liver transplant as treatment for UCD			
All patients: Nearest center provides "gold standard" in transplant care	3.22 (1.59-6.51)	0.001	236
Late-onset patients: Nearest center provides "gold standard" in transplant care	4.45 (1.08-18.42)	0.04	232
Neonatal-onset patients: Nearest center provides "gold standard" in transplant care	3.10 (1.08-8.85)	0.04	232
<4 HA episodes: Nearest center provides "gold standard" in transplant care	1.56 (0.52-4.62)	0.43	185
≥ 4 HA episodes: Nearest center provides "gold standard" in transplant care	2.69 (0.83-8.70)	0.10	185

[a.] Odds ratios are from models adjusted for patient age, sex, race, ethnicity, and median income at patient zip-code (see Appendix A; Tables A1-A4)

For patients diagnosed with late-onset UCD, the odds of undergoing a liver transplant is 4.45 times higher if their nearest transplant site is one of two "gold standard" transplant centers included in the analysis, whereas for patients diagnosed with neonatal-onset UCD, the odds of undergoing liver transplant under this same condition is 3.10 times higher. The difference between these two OR suggests that treatment decisions among patients with a less severe condition may be even more responsive to other drivers of treatment choice, like the characteristics of their nearest expert institution. For patients diagnosed with neonatal-onset UCD, the severity of their condition may drive them to consider transplant regardless of the geographic availability of "gold standard" transplant care, reflected in the lower OR yielded through this model.

Models integrating interaction terms for disease control (i.e., # of HA episodes) did not yield statistically significant findings, which may be a result of the reduced sample size of the models.

Discussion

Published literature suggests a significant interest in the use of spatial technologies to 1) measure geographic access to healthcare, 2) follow patterns of geographic accessibility, and 3) investigate the influence of geographic healthcare access on health outcomes. However, GIS methodology has seldom been used to address such objectives for patients diagnosed with rare and ultra-rare conditions, who must access their care through fewer, regionalized centers with sub-specialized expertise. This paper begins to address the gap in GIS applications among populations diagnosed with rare-disease, presenting the results of a geo-mapping study examining the relationships between the geographic availability of sub-specialized pediatric metabolic and liver transplant care and treatment choice in patients with UCD.

Geocoding and analysis of UCD patient residence relative to sub-specialized metabolic care sites and relevant pediatric liver transplant centers demonstrated clustering of health care sites with sufficient expertise in diagnosis, treatment (i.e., medical management and liver transplant), and research of UCD around the coastal regions of the U.S. Mapping exercises revealed large areas in the middle and northern regions of the country without nearby access to expert UCD care. Although most patients within the study sample reported a residence within 200 miles of the nearest metabolic or pediatric liver transplant center, geocoding of patient addresses also suggests key geographic gaps in existing UCD datasets, which do not seem to capture a representative sample of patients diagnosed with UCD from middle or northern states.

A 2005 published clinical UCD case study anecdotally discussed issues related to geographic access of sub-specialized metabolic care as a consideration in treatment

choice. The case study outlined the experience of one child for whom medical management seemed to be a viable treatment option as long as the child stayed close to an expert metabolic center. However, the family was moving 8 hours away from any sub-specialized care and after weighing the risks of being so far away from a healthcare team with the expertise and training to address medical management of UCD, the family elected to liver transplant (Lee et al., 2005). This case study highlights the unique ways in which geographic access can influence treatment for UCD and provided anecdotal experience upon which to base a more systematic evaluation of the relationship between geographic healthcare availability and treatment choice in this population.

Even though case reports (Lee et al., 2005) and qualitative interview data (Gerstein, In progress) suggest that the geographic availability of UCD care may play a role in driving treatment decisions, this study was not able to detect a significant association between the overall straight-line distance from patient residence to a sub-specialized UCD metabolic care site or expert pediatric liver transplant center and treatment choice (i.e., liver transplant status) in UCD. This null finding may be a product of several factors: 1) Low representation of UCD patients in the sample from middle, northern and rural regions of the country. These patients likely experience greater challenges in accessing sub-specialized care and thus, their decision to transplant or continue with medical management may be driven more strongly by the geographic availability of expert metabolic care or a high-quality transplant team. It is likely that these experiences were under-represented in this analysis. 2) Expert and high-quality UCD care may be offered by other practitioners outside of the UCDC network. These providers may not have been captured by the study's inclusion criteria. 3) The association

between distance to sub-specialized care and treatment choice in UCD may be more complex than what was captured through this analysis. Distance to other health care resources like competent emergency departments, supportive primary care providers, and responsive specialty pharmacies may also impact a family's ability to manage UCD through diet and medications and thus, their decision to continue medical management or pursue liver transplant. This study was not designed to measure the impact of these resources.

This study was able to detect a statistically significant association between the UCD patient's nearest transplant center and treatment choice. The analysis found that patients whose nearest transplant center was one of two considered by the UCD community to offer the "gold standard" in transplant care were three times more likely to undergo liver transplant than those whose nearest center was one of five others included in the analysis. These two institutions, which have performed the most metabolic related pediatric liver transplants in the U.S, were also described by UCD patients and providers as highly supportive of transplant as treatment for UCD. With limited empirical evidence to guide the decision between medical management and liver transplant, there is significant institutional variation in how providers approach treatment and counsel patients and families on available treatment alternatives. Findings from this study suggest that this variation does indeed impact treatment decisions and that a family's treatment choice may be guided, at least in part, by the culture of the institution where they access their care. The association between nearest transplant center and transplant status was strongest among patients with late-onset UCD, who were over four times more likely to undergo transplant if living nearest to a "gold standard" transplant center. This suggests

that treatment decisions for patients with a less severe condition may be more responsive to non-clinical drivers of treatment choice, like the characteristics of their nearest expert institution. This also aligns with findings from a recent qualitative study on the decision-making experience of families affected by UCD, which noted more variation in physician opinion and guidance around liver transplant as a treatment for the disorder when providing counseling to late-onset patients whose condition may be considered amenable to management through diet and medications(Gerstein, In progress).

It is important to note that the "gold standard" site designation utilized in this study to distinguish certain liver transplant centers from others who perform pediatric liver transplants on patients diagnosed with UCD, although based in part on publicly available transplant statistics including the relative volume of metabolic-related transplants performed at each site, also reflects a more subjective assessment of the centers' management of UCD cases by key informants. Clinicians and patient advocates in the field may base these assessments, at least in part, on personal experience, patient anecdotes, and hospital reputation. Given the results of this study, which suggest an association between proximity to "gold-standard" transplant centers and treatment choice in UCD, researchers and practitioners must consider the implications of these designations on patient decision making and whether it appropriate for treatment choice to be influenced in such a manner by patient proximity and widely-accepted subjective judgements of center quality within the field.

Additional limitations

In some cases, longitudinal hyperammonemia episode data for this analysis was incomplete, reflecting gaps in hospital records. This resulted in a smaller sample size for

models integrating metrics for disease control and may have limited the study's ability to detect significance in these models.

Geocoding of expert pediatric liver transplant centers and sub-specialized metabolic care sites was driven by a combination of objective (e.g. volume) and subjective (e.g. key informant opinion) measures. Despite efforts to capture and categorize all relevant treatment sites correctly, some care centers may have been inadvertently excluded or included in this GIS analysis.

Finally, this GIS analysis provided information about patterns of treatment in relation to the geographic availability of sub-specialized and transplant care but findings from this study should not be interpreted as causal.

Conclusion

This study, which applied GIS methods to an examination of sub-specialized care for rare metabolic illness was a logical extension of existing geographic access research. Treatment for rare conditions generally requires specialized competence that cannot be found at primary care or smaller specialty practices. Thus, children with rare diseases are usually served regionally through large children's hospital programs with sufficient patient volume to support clinical expertise and special supplementary services (Cooley, Kemper, & Medical Home Workgroup of the National Coordinating Center for the Regional Genetic and Newborn Screening Service Collaboratives, 2013; Perrin & MacLean Jr., 1988). The diffuse nature of sub-specialized metabolic care has major implications for healthcare delivery that have not been sufficiently examined in the

literature as most GIS applications have focused on decentralized care for common conditions through primary care or smaller specialty settings.

This study provided new and important information on the relative spread of a sub-sample of UCD patients in the U.S. and the critical healthcare services they require, highlighting the existing challenges of concentrated and regionalized care for UCD and identifying gaps in existing geographic data for this population. It also provided new findings on the relationship between geographic access to certain institutions with a reputation of "high quality" liver transplant care for UCD and treatment choice, suggesting a need for additional research to understand how institutional variations in practice and guidance as well as widely-accepted judgements on center quality may contribute to differences in treatment decisions and outcomes for patients with UCD. Finally, this analysis highlights clinical longitudinal study data as an important source for inquiries outside the traditional confines of clinical research and demonstrates uses for nationally collected rare disease consortium data in the field of social science. Currently, NIH-RDCRN funds 21 consortia of rare disease, representing opportunities for additional health services research that targets rare disorders and investigates understudied issues of healthcare access, quality, and costs (Lohr & Steinwachs, 2002) within these communities.

Chapter 4: An Exploratory Survey Analysis Examining the Cost, Coverage, and Financial Challenges Related to Accessing Care for Urea Cycle Disorders

This paper describes the results of a patient/parent survey-based exploratory analysis examining the current state of cost and coverage for sub-specialized medical, pharmaceutical, and support services for Urea Cycle Disorders (UCD). This study explored sources of coverage for UCD, out of pocket costs of care across multiple service categories and treatment options (medical management and liver transplant), cost and coverage barriers to UCD-related care, and other key financial implications reported by families affected by UCD.

Rare diseases are often severely disabling. Inherited disorders of metabolism represent one key group of rare disorders with a high prevalence of disability and death (Dionisi-Vici et al., 2002; Levy, 2009). These conditions decrease life expectancy, impair physical and mental abilities, reduce quality of life, pose considerable burden on affected families and the healthcare systems that serves them, and impact an individual's education and earning potential (van Weely & Leufkens, 2004; Zeltner et al., 2017). Despite the considerable burden rare diseases pose on millions of affected families and the high medical, pharmaceutical, and ancillary service needs of this population, cost, coverage and payment issues related to care and treatment for rare diseases have seldom been studied and thus, there is little available literature in this area.

Urea cycle disorders and their treatment

Urea cycle disorders are a group of rare inherited disorders of metabolism caused by deficiencies of any one of eight proteins required for ammonia detoxification and urea synthesis – a process in the liver that converts otherwise toxic ammonia into urea for excretion in the urine. When this mechanism does not function properly, it can result in

hyperammonemia, an excess of ammonia in the blood, which in its severe or prolonged form may have devastating effects on the development and function of the central nervous system (Msall et al., 1984). Urea cycle disorders are medically managed through a combination of pharmaceutical drugs designed to promote alternative pathways for the disposal of waste nitrogen in the body (sodium phenylbutyrate-Buphenyl or glycerol phenylbutyrate- Ravicti), highly restricted low-protein diets, metabolic formula for nutrition supplementation, and amino acid supplements (M. L. Batshaw et al., 1982; Mark L. Batshaw et al., 2001; Häberle et al., 2012). Intravenous infusions of glucose, lipid, arginine, and sodium benzoate/sodium phenylacetate (Ammonul) are used to treat acute episodes of hyperammonemia (Berry et al., 2014; Häberle et al., 2012).

Despite significant improvements in medical management following the wider availability of specialized low-protein diets, medications, and amino-acid supplements, infants, children, and even adults with UCD are at high risk of hyperammonemia (Mark L. Batshaw et al., 2001; Krivitzky et al., 2009). High blood ammonia levels can cause cytotoxic brain edema and compromise a patient's circulatory system, which frequently leads to intellectual and developmental disabilities (Butterworth, 1998; Butterworth et al., 1987; Msall et al., 1984, 1988). These most severe outcomes can occur even in patients whose mild-moderate condition appears to be amenable to management through medications and diet. Thus, an increasing number of patients with UCD have been undergoing liver transplantation as an alternative treatment for UCD and a procedure that "cures" the hyperammonemia (Saudubray et al., 1999; Todo et al., 1992; Whitington et al., 1998). However, liver transplantation is a complicated surgical procedure, which

carries with it risk of mortality and morbidity and requires a life-long regimen of medication to avoid organ rejection.

Rare diseases and the cost, coverage and availability of care

Healthy People 2020 highlights access to comprehensive, quality healthcare services as a fundamental component of health equity and a critical step towards improving quality of life. It also emphasizes high costs, poor insurance coverage, and lack of availability as key barriers to this goal ("Access to Health Services | Healthy People 2020," n.d.; Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020, 2010). Families affected by rare conditions like UCD are often presented with unique and complex challenges related to the cost, coverage, and availability of treatment and care. Patient with rare diseases, like those affected by UCD, require 1) sub-specialized long-term and emergent healthcare management not available through primary care, smaller specialty practices or community hospitals, 2) access to orphan-drugs developed (often at a high-cost) for the treatment of rare conditions, 3) medical formulas, foods, and supplements, which are less-tightly regulated and thus vulnerable to inequities in coverage, and 4) ancillary services to address any physical, behavioral, occupational, speech, or learning challenges commonly experienced by those diagnosed with UCD and other rare inherited disorders of metabolism. Barriers to coverage of any of these services may cause significant financial strain on families affected by UCD. For example, the out of pocket cost of low-protein foods, nutritional products, and prescription drugs for UCD can be prohibitively high. One 2011 published estimate stated that a case of standard powdered infant formula cost the Mississippi Women, Infants and Children (WIC) program $17.66. This is

compared to $202.32 for a case of specialized medical food formula, which is a more than 11-fold cost differential. A case of medical food formula designed for an older child cost this same WIC program $405.60 in 2011 (Berry et al., 2013a). Ravicti, a nitrogen binding agent used to treat UCD, is sold by its pharmaceutical company at an annual cost of nearly $794,000 (America's Health Insurance Plans, 2016). Since, anecdotally, coverage of these expensive pharmaceuticals is inconsistent across insurance plans and vulnerable to insurance plan denials, many UCD patients report participating in pharmaceutical company sponsored patient assistance programs (PAPs) to help support the otherwise overwhelming out of pocket cost of these drugs.

There are also only approximately a dozen hospitals in the United States with a metabolic clinic and specialized team experienced in the diagnosis, treatment, and research of UCD. Most community hospitals are not equipped to deal with episodes of hyperammonemia and general practice pediatricians do not have the training or experience to diagnose, treat and provide ongoing care and monitoring to children with UCD. Regionalization of UCD sub-specialty programs generates service areas that extend well beyond state boundaries (Perrin & MacLean Jr., 1988). Thus, metabolic specialists with UCD experience are providing care to children from all over the country, raising questions about how variation in public and private coverage policy, narrow networks, out of pocket costs, benefit denials and appeals, and other coverage challenges influence access to care for this population.

Coverage landscape for children with special health care needs

An estimated 19 percent of all children in the U.S. have special health care needs (Musumeci & Foutz, 2018b), defined by the U.S Department of Health and Social

Services as children who "have or are at increased risk for chronic physical, developmental, behavioral, or emotional conditions and also require health and related services of a type or amount beyond that required by children generally"(McPherson et al., 1998) . Children diagnosed with inherited metabolic conditions like UCD fall well within this definition. Children with special health care needs (CSHCN) are a highly insured population, with approximately 97 percent estimated to have some form of insurance coverage (Musumeci & Foutz, 2018a). In 2016, Medicaid and the Children's Health Insurance Program (CHIP) covered about half of CSHCN. Of these Medicaid and CHIP recipients, about 7 percent were covered by both private and public insurance sources (Musumeci & Foutz, 2018a). For these individuals, Medicaid or CHIP act as a wrap-around source of coverage to fill existing gaps in private insurance benefits (Musumeci & Foutz, 2018b). Medicaid benefit determinations are held to a federal medical necessity standard, which mandates that Medicaid cover any treatment that is considered "medically necessary" for the child. Although federal law does not define medical necessity for the state, it does mandate that the treating health professional's recommendation for medically necessary care play a prominent role in determinations of coverage. Thus, Medicaid tends to provide a wide range of medical and long-term care services that may not be covered or covered only in limited amounts through private insurance plans, which are not held to this same medical necessity standard (Markus & West, 2014).

Previous research

A recent qualitative study examining the decision-making experience of families affected by UCD when making the choice between medical management and liver

transplant as a treatment for their child highlighted costs of care and the burden of navigating insurance coverage for their child's UCD treatment as a major challenge of the condition. Parent participants reported differences in the cost and coverage landscape of medical management vs. liver transplant in terms of out of pocket costs, disputes with insurance companies, and indirect financial implications related to travel for medical care and reduced time at work. The study also suggested that the financial implications of UCD treatment did contribute to the overall burden of disease and the context within which treatment decisions for the condition were made (Gerstein, In progress).

Other studies holding relevancy to a discussion of costs, coverage and payment for UCD are limited and outdated. To date, only two studies (detailed in greater detail in the *Discussion* section of this paper) were identified that contributed relevant evidence on cost and coverage of treatment for metabolic disease and the financial implications of living with UCD. Thus, collectively, the existing evidence base is quite weak, lacking both depth and breadth of analysis and discussion. This study contributes to the field through the use of a patient/parent survey to better characterize the cost and coverage landscape for UCD-related care and provide a more comprehensive portrait of the cost, coverage and financial challenges faced by families affected by UCD.

Methods

Research questions

This study sought to answer the following research questions:

- What key barriers and challenges do families with UCD encounter when navigating coverage related to their child's UCD care?
- How does the cost and coverage experience of families affected by UCD vary by insurance type?
- What kind of differences in cost and coverage are seen across service categories and treatment options for UCD?

Approach

This study is characterized as an exploratory analysis of cost and coverage issues related to accessing care for UCD. Exploratory analyses are appropriate when the phenomenon under question is not well understood, as is the case in this research.

Data source and data collection

To inform the development of the parent/patient cost and coverage survey utilized in this study, semi-structured phone interviews were conducted with three different parents whose children were diagnosed with UCD. Parent participants were referred to the study by the National Urea Cycle Disorders Foundation (NUCDF) and a key metabolic physician informant. In these interviews, parents were asked about their child's current insurance coverage situation, their monthly and annual out of pocket expenses for their child's UCD care, any non-insurance sources of coverage for their child's UCD, challenges they have experienced with the cost and coverage of their child's care, and the ways in which the financial implications of their child's UCD diagnosis have impacted

various aspects of their life. Interviews lasted forty-five minutes to one hour and were recorded and transcribed verbatim for use in analysis. Interview data was used, alongside information obtained through key clinical and patient advocate informers, to identify key concepts, questions, and answer categories for inclusion in the survey, which was distributed to a larger sample of UCD parents and patients.

Where appropriate, survey questions and answer categories were adapted from the National Survey of Children with Special Health Care Needs (NSCSHCN) ("SLAITS - National Survey of Children with Special Health Care Needs," n.d.) and the Commonwealth Fund Health Insurance Survey (HIS) ("Biennial Health Insurance Surveys | Commonwealth Fund," n.d.). Adapted questions from NSCSHCN and HIS covered issues related to current health insurance coverage status and continuity of coverage, out of pocket costs of care, access to appropriate physicians and services, satisfaction and experience with insurance coverage, and the implications of health care costs on family life, including job choices and career development. The final survey was composed of 64 multiple choice questions (with skip patterns), including demographic and insurance information on patient and parent, basic diagnosis and treatment information, questions related to total and stratified out of pocket costs, multiple survey sections dealing with the various challenges related to cost and coverage of UCD, and a set of questions targeting the various financial implications of caring for and paying for the care of a family member diagnosed with UCD.

Sampling and sample size

Survey data was collected both from parents of children diagnosed with UCD and from adult patients currently managing their own UCD care. Two separate versions of the

self-administered online questionnaire were distributed to these two groups through NUCDF's membership list-serv. NUCDF members were excluded from this distribution if they lived outside the United States, did not have current e-mail contact information available, or did not consider themselves to be the child's primary caregiver. The survey received a total of 64 responses with 58 individuals completing the survey (Table 4.1).

Table 4.1. Sample summary for UCD cost and coverage survey

Total number of respondents	64
Parent respondents	53
Adult UCD patient respondents	11
Survey completion rate	92%
Total number of completed responses	58

Data analysis

Descriptive statistics (i.e., frequencies) were applied to survey data to identify patterns and present quantitative summaries of survey question responses. Survey data was examined both as a total sample and as stratified samples by insurance type to identify differences in out of pocket costs and coverage experience across different forms of health insurance. Frequencies related to total and service-category stratified out of pocket expenses were also compared between liver transplant and medical management treatment arms within the sample to identify differences in the cost and coverage of these two treatment alternatives. Key findings from the analysis of survey data are presented through the tables and graphs detailed below.

Results

Patient characteristics

Table 4.2 provides summary demographic and basic clinical statistics for the survey respondent/patient sample included in this study. Patient ages ranged from 0 to over 40 with the greatest frequency reported between ages 2-5. The majority (59 percent) of the patient survey sample was female. Fifty-five percent of parent respondents/patients reported a diagnosis of late onset UCD and thirty-three percent of the sample reported a neonatal onset diagnosis (the remaining twelve percent did not know/were unable to provide a response). Most of the patient sample included in this analysis were diagnosed before the age of one (52 percent) and nearly half of the sample (48 percent) reported a diagnosis of OTC deficiency. Among the study survey sample, 18 percent of patients had undergone liver transplant as a treatment for UCD at a relatively even spread of ages between infancy and adulthood. The survey sample is comprised of a relatively high-income population with over 50 percent reporting a household income above $75,000 a year (Table 4.2). The sample included in this analysis also represents a wide geographic spread with respondents reporting residence throughout 23 states.

Table 4.2. Summary of patient demographics and basic clinical information (N=58)

Patient Age	**% (#)**
0-1	9% (5)
2-5	29% (17)
6-11	16% (9)
12-17	10% (6)
18-30	17% (10)
31-40	7% (5)
>40	12% (7)
Patient Sex	
Male	41% (24)
Female	59% (34)
Disease Severity	
Neonatal Onset	33% (19)
Late Onset	55% (32)
Unknown	12% (7)
Age at Diagnosis	
<1	52% (30)
1-2	15% (9)
2-5	13% (8)
5-11	9% (5)
12-17	2% (1)
>18	9% (5)
UCD Diagnosis	
CPS1D- Carbamyl Phosphate Synthetase 1 Deficiency	5% (3)
OTCD- Ornithine Transcarbamylase Deficiency	48% (28)
ASD- Argininosuccinic Acid Synthetase Deficiency (Citrullinemia)	14% (8)
ALD- Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)	31% (18)
AGD- Arginase Deficiency	2% (1)
Liver Transplant Status	
Yes	18% (11)
No	81% (47)
Age at Transplant*	
<1	18% (2)
1-2	27% (3)
3-5	27% (3)
12-17	9% (1)
>18	18% (2)
Household Income**	
$0-$24,999	4% (2)
$25,000-$49,000	7% (4)
$50,000-$74,999	20% (11)
$75,000-$99,999	20% (11)
$100,000-$149,999	13% (7)
$150,000-199,999	6% (3)
>$199,999	19% (10)
Prefer not to answer	11% (6)

*(N=11); **(N=54)

Table 4.3. provides summary statistics on the coverage status of the survey sample. Nearly all (98 percent) patients within the sample reported currently having some form of health insurance. Most of the sample reported utilizing a private health insurance plan offered through an employer or union as their primary source of coverage and 18 percent of the sample reported utilizing multiple forms of health insurance to support coverage of their/their child's UCD care. Of the 10 individuals who reported multiple forms of coverage, 6 identified Medicaid or CHIP as their source of secondary or supplementary insurance. Most of the sample (54 percent) also reported a high continuity of coverage (more than 3 years on current health insurance plan). Among the survey sample, 70 percent reported utilizing non-insurance sources to help pay for their/their child's UCD care, including therapy services provided through schools, programs offered through local health departments, programs offered through the state, programs offered through a hospital, grants/programs offered through local or national foundations, and grants/programs offered through pharmaceutical companies.

Table 4.3. Summary of patient coverage (N=57)

Has Health Insurance Coverage	
Yes	98% (57)
No	0% (0)
Don't know	2% (1)
Primary Health Insurance*	
Private health insurance offered through an employer or union	69% (39)
Private health insurance plan that you bought yourself	4% (2)
Medicaid	12% (7)
Children's Health Insurance Program (CHIP)	4% (2)
Military of Veteran's Coverage	2% (1)
Medicare	9% (5)
Multiple Forms of Health Insurance Coverage	
Yes	18% (10)
No	82% (47)
Length of Time on Current Health Insurance Plan	
<1 year	16% (9)
1-2 years	12% (7)
2-3 years	16% (9)
>3 years	54% (31)
Don't know	2% (1)
Utilized Non-Insurance Sources to Help Pay for UCD Related Care**	
Yes	70% (38)
No	30% (16)

*N=56; **N=54; Includes therapy services provided through school, programs offered through local health departments, programs offered through the state, programs offered through the hospital, grants/programs offered through local or national foundations, grants/programs offered through pharmaceutical companies.

Out of pocket costs

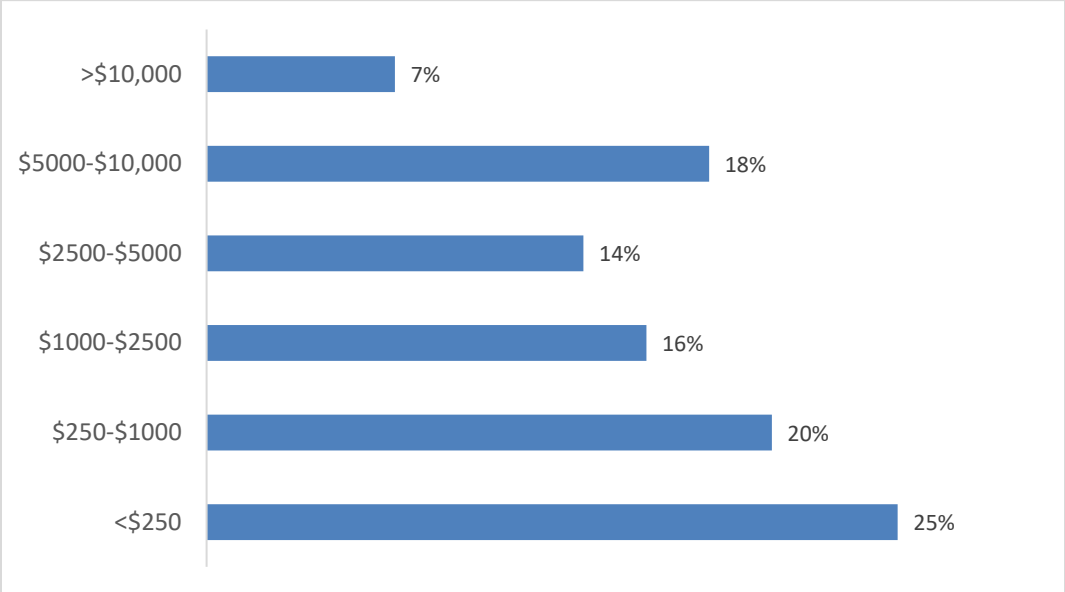
A previously published analysis on the impact of health care costs for CSHCN on family financial burden suggested that health care expenditures for a SHCN child of $250 or more annually are associated with family perception of financial burden (Lindley & Mark, 2010). This precedent was applied throughout this analysis. The next several sections present a comparison of out of pocket costs across service categories, treatments, and forms of insurance coverage. Based on the previous literature, out of pocket costs that fell below $250 for the year were utilized as a relative marker for low out of pocket spending. Thus, the graphs produced for this analysis were designed to represent this

assumption. More detailed breakdowns of out of pocket spending by cost category are available in table format where appropriate.

Out of pocket costs related to medical management of UCD

Survey participants were asked to estimate their total out of pocket expenditures for services related to their or their child's UCD care over the past 12 months. A quarter of the survey cohort (excluding liver transplant recipients) reported total out of pocket expenditures under $250 for the year. The rest of the sample reported total out of pocket costs exceeding this amount, with a quarter of the sample reporting spending over $5000 in UCD related care over the past 12 months (Figure 4.1).

Figure 4.1. Total Out of Pocket Costs Related to UCD Care; Past 12 months (N=44*)



*Liver transplant patients excluded

Figure 4.2 and Table 4.4 provide comparisons of reported out of pocket costs for a cross-section of services and products related to the medical management of UCD among the survey sample (N=43). Frequencies were calculated by excluding "not applicable/did

not receive service" responses to account for out of pocket costs only when services and products were indeed utilized. Liver transplant respondents were also excluded from this particular analysis to ensure that reported out of pocket costs related directly to the medical management of UCD and did not integrate costs associated with liver transplant for the disorder.

Amino acid supplements seemed to pose a moderate cost burden on a large segment of survey respondents. Nearly half of all respondents reported spending less than $250 for supplements over the last 12 months but only 17 percent reported no out of pocket expenses for amino acid supplements in the last year. Forty percent reported spending between $250 to $1000 out of pocket on these products and seven percent reported spending over $1000 annually.

Fifty-seven percent of survey respondents reported less than $250 in out of pocket costs related to routine consultative and follow-up medical care for UCD and fourteen percent reported over $1000 in out of pocket spending for these services. This suggests that a subset of individuals within the survey sample experienced insufficient coverage for routine medical care related to management of the disorder, leading to higher out of pocket expenses.

Out of pocket spending on travel/accommodations for UCD related care was spread within the survey sample. Sixty-two percent reported less than $250 in out of pocket costs related to this service category but the remaining thirty-eight percent of respondents reported a pattern of spending distributed relatively evenly between $250 to $2,500 for the year, with few reporting out of pocket costs in excess of this amount.

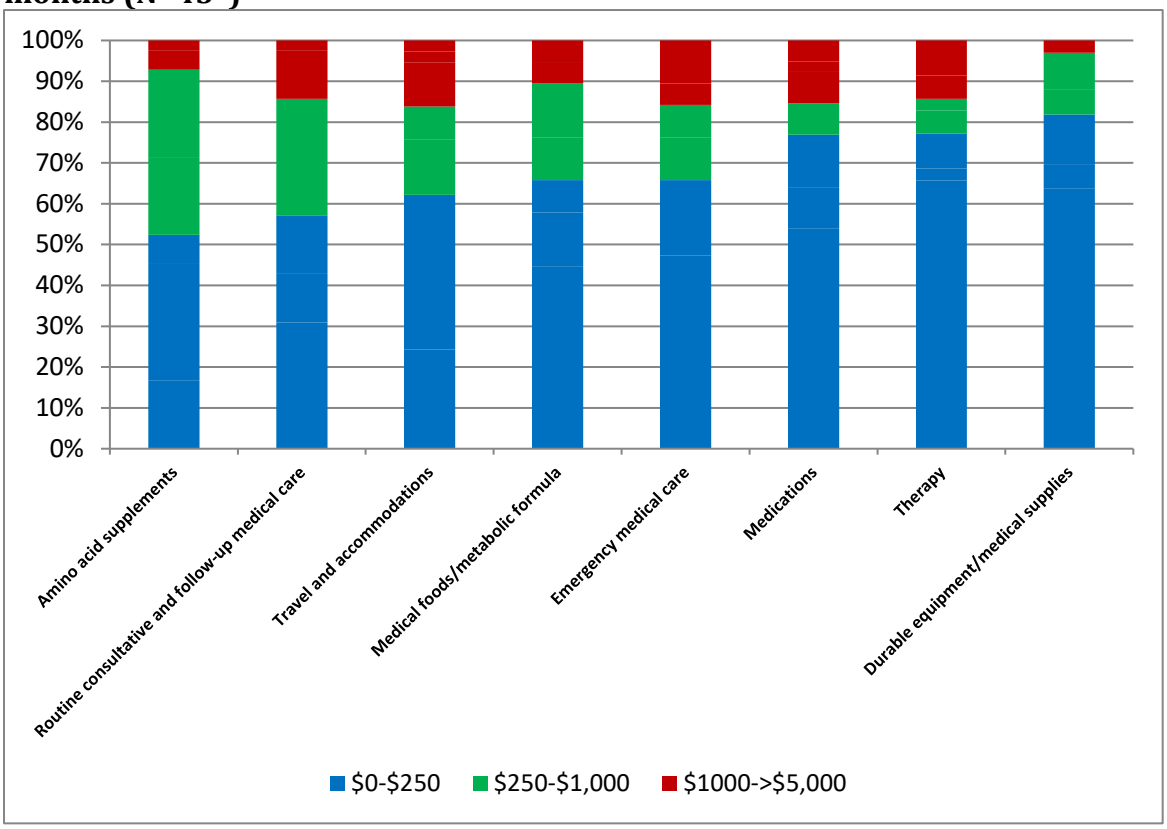
Medical foods represent another notable out of pocket cost among survey respondents. Sixty-six percent of the sample reported spending less than $250 on medical foods over the previous 12 months, 24 percent reported spending $250 to $1000 annually and over 10 percent of the sample reported costs in excess of $1000 for the year.

In terms of emergency medical care, over 60 percent reported spending less than $250 out of pocket over the last year, suggesting that for the majority of the sample, emergency medical care represents a low out of pocket expense. However, 16 percent of the sample reported out of pocket costs in excess of $1000 for the year suggesting that for a subset of patients with less generous/insufficient insurance coverage, emergency care may pose a much higher cost burden.

Although 77 percent of survey respondents reported less than $250 in out of pocket costs for UCD related medications over the last 12 months, 15 percent reported costs in excess of $1000 and 8 percent reported catastrophic costs surpassing $2500 or even $5000 for the year. These figures suggest that when coverage for UCD related pharmaceuticals is poor, out of pocket costs may rise to notably high levels.

Therapy (i.e., speech, behavioral, physical, occupational) and medical equipment related to UCD were well covered services within the respondent pool. Approximately 80 percent of respondents in both categories reported less than $250 in out of pocket costs over the last 12 months. Fourteen percent of survey participants did report spending more than $1000 on therapies in the prior year, suggesting that for some within the sample, coverage for therapies was insufficient.

Figure 4.2. Out of pocket costs for medical management of UCD; Past 12 months (N=43*)



*Not applicable/Did not use service excluded; Liver transplant patients excluded

Table 4.4. Out of pocket costs for medical management related UCD Care; Past 12 months (N=43*)

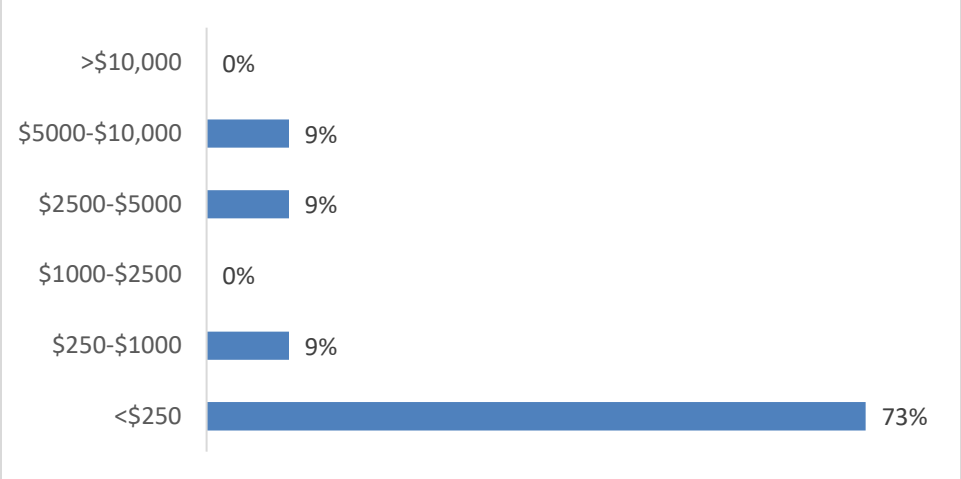
	$0	<$100	$100-$250	$250-$500	$500-$1000	$1000-$2500	$2500-$5000	>$5000
Routine consultative and follow-up medical care	31.0%	11.9%	14.3%	11.9%	16.7%	11.9%	0.0%	2.4%
Emergency medical care	47.4%	15.8%	2.6%	10.5%	7.9%	5.3%	10.5%	0.0%
Medications	53.8%	10.3%	12.8%	0.0%	7.7%	7.7%	2.6%	5.1%
Medical foods, including metabolic formula	44.7%	13.2%	7.9%	10.5%	13.2%	5.3%	5.3%	0.0%
Amino acid supplements	16.7%	28.6%	7.1%	19.0%	21.4%	4.8%	2.4%	0.0%
Therapy (e.g. speech, occupational, physical)	65.7%	2.9%	8.6%	5.7%	2.9%	5.7%	8.6%	0.0%
Durable equipment/medical supplies	63.6%	6.1%	12.1%	6.1%	9.1%	3.0%	0.0%	0.0%
Travel and accommodations	24.3%	27.0%	10.8%	13.5%	8.1%	10.8%	2.7%	2.7%

*Respondents who have undergone liver transplant excluded; Not applicable/did not utilize responses excluded

Out of pocket costs for services related to liver transplant for UCD

Survey participants who had themselves or whose child had undergone transplant for treatment of UCD were asked to estimate the total out of pocket cost of their or their child's liver transplant and initial hospital stay. Nearly three-fourths of the liver transplant survey cohort reported spending less than $250 on these initial transplant services. Nine percent of the sample reported spending $250 to $1000 on the transplant surgery and initial hospital stay, nine percent reported out of pocket costs between $2500 and $5000, and nine percent reported costs between $5000 and $10,000 (Figure 4.3).

Figure 4.3. Out of pocket costs for liver transplant and initial hospital stay (N=11*)

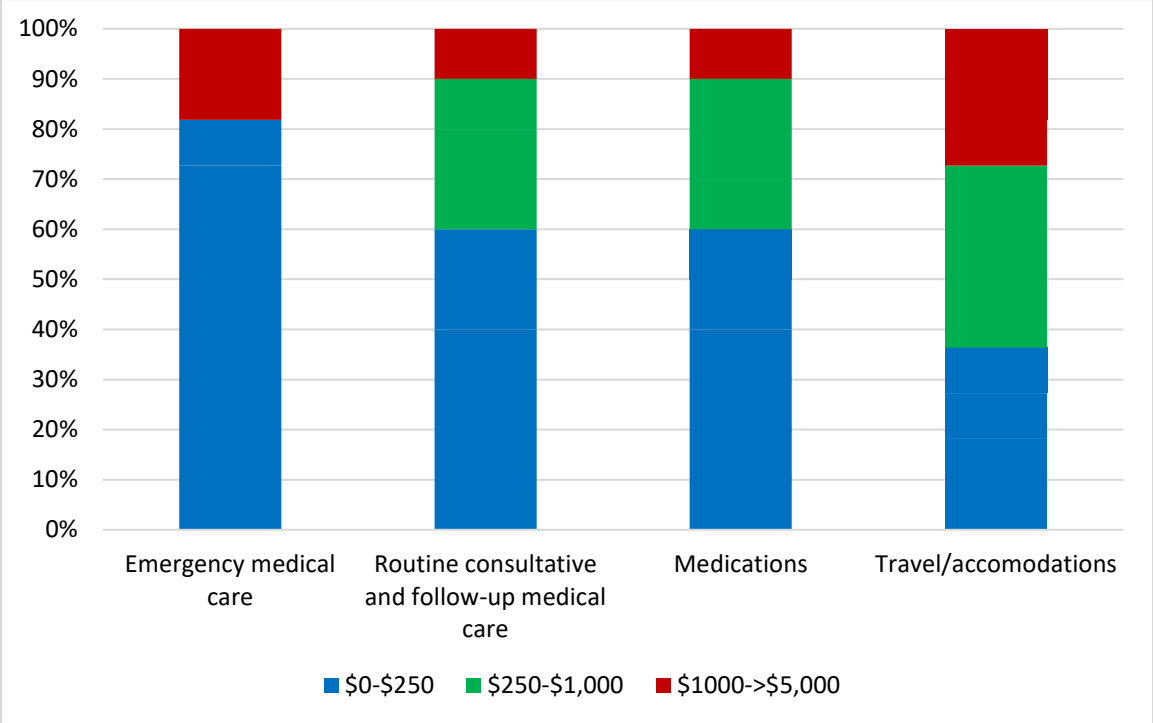


*Medical management patients excluded

Among respondents who had undergone liver transplant, 82 percent reported spending less than $100 on emergency medical care related to transplant in the past 12 months and 60 percent reported spending less than $100 on routine consultative or follow-up medical care related to liver transplant (Table 4.5). Out of pocket costs for transplant related pharmaceuticals also remained low for the majority of survey

respondents with 60 percent reporting spending less than $250 on medications for the year. Travel and accommodations related to liver transplant posed the greatest cost burden on survey respondents with 27 percent reporting out of pocket spending in excess of $1000 over the past 12 months. These heightened out of pocket costs may be due to families needing to travel longer distances to the few regional centers with expertise in liver transplant for individuals affected by UCD, longer hospital stays for transplant surgery and follow-up care, and lack of coverage for medical travel related expenses. Figure 4.4 and Table 4.5 provide a comparison of out of pocket costs for emergency medical care, routine and follow-up medical care, transplant related medications, and travel/accommodations among the survey sample.

Figure 4.4. Out of pocket costs related to liver transplant, Past 12 months (N=11*)



*Not applicable/Did not use service responses excluded; Medical management patients excluded

Table 4.5. Out of pocket costs for liver transplant related care, Past 12 months (N=11*)								
	$0	**<$100**	**$100-$250**	**$250-$500**	**$500-$1000**	**$1000-$2500**	**$2500-$5000**	**>$5000**
Routine consultative and follow-up medical care	40.0%	20.0%	0.0%	20.0%	10.0%	10.0%	0.0%	0.0%
Emergency medical care	72.7%	9.1%	0.0%	0.0%	0.0%	18.2%	0.0%	0.0%
Medications	40.0%	10.0%	10.0%	10.0%	20.0%	10.0%	0.0%	0.0%
Travel and accommodations	18.2%	9.1%	9.1%	36.4%	0.0%	9.1%	9.1%	9.1%

*Includes all respondents who have undergone liver transplant; Not applicable/did not utilize or don't know responses excluded

Comparison of cost and coverage between medical management and liver transplant

Among the 11 survey respondents who/whose child had undergone liver transplant as a treatment for UCD, none reported difficulties or delays because the transplant related services they/their child needed were not available in their area or because of issues related to the cost of their/their child's transplant care. This compares to 44 percent of `all survey respondents reporting some type of difficulty or delay throughout their or their child's lifetime because the UCD (i.e., medical management) services they/their child needed were not available in the area and 47 percent reporting difficulties or delays because of issues related to the cost of their/their child's UCD care.

A direct comparison of the out of pocket costs reported by survey respondents for liver transplant vs. medical management of UCD within comparable categories of service suggests a higher cost burden under medical management when compared to liver transplant for emergency medical care (i.e., 66 percent <$250 vs 82 percent <$250 respectively).

In terms of routine consultative and follow-up medical services, medical management seems to hold a less pronounced, but still present, increased cost burden when compared to liver transplant (i.e., 57 percent <$250 vs 60 percent <$250

respectively). When comparing routine consultative and follow-up out of pocket spending under $100 for the year, the differential between medical management and liver transplant is more apparent (i.e., 43 percent <$100 vs. 60 percent <$100 respectively).

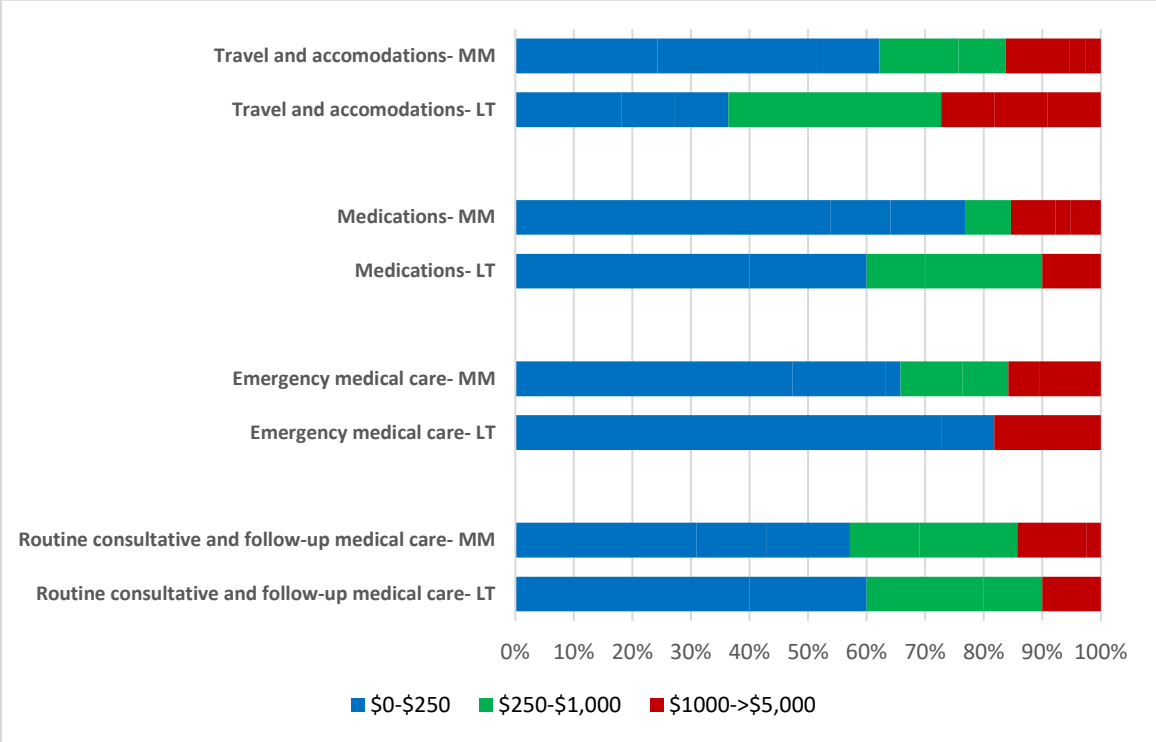
The comparison between medication related out of pocket expenses for medical management vs. liver transplant is a bit more nuanced. Although a larger percentage of respondents reported low costs related to UCD medical management medications compared to liver transplant medications (i.e., 76 percent <$250 vs 60 percent <$250), catastrophic out of pocket costs were also more commonly reported for medications related to medical management. Eight percent of survey respondents reporting spending more than $2500 on medications related to the management of UCD over the last 12 months. No respondents cited out of pocket costs over $2500 for medications related to liver transplant. This suggests that when prescription coverage for UCD related drugs is comprehensive, out of pocket costs for these medications may be less compared to transplant related drugs. However, gaps in prescription coverage may be more common for UCD related drugs than for post-transplant medications, explaining the catastrophic cost burden associated with medical management prescriptions for some individuals within the sample.

Finally, liver transplant respondents reported higher spending on travel and accommodations related to their transplant care compared to the out of pocket travel spending reported by medically managed respondents. Sixty-two percent of medically managed respondents reported spending less than $250 on travel and accommodations related to their UCD care, while only thirty-six percent of liver transplant respondents reported less than $250 in transplant related travel. Liver transplant respondents were also

more likely to report markedly high travel related costs. Eighteen percent of transplant respondents reported spending more than $2500 out of pocket on travel and accommodations related to their transplant care while only five percent of medically managed respondents reported travel related spending in this amount.

Figure 4.5 and Table 4.6 provide compare liver transplant and medical management out of pocket costs as detailed above.

Figure 4.5. Comparison of medical management and liver transplant out of pocket costs for UCD; Past 12 months (N=43*, N=11)**



*Not applicable/Did not use service excluded; Liver transplant patients excluded; **Not applicable/Did not use service excluded; Medical management patients excluded

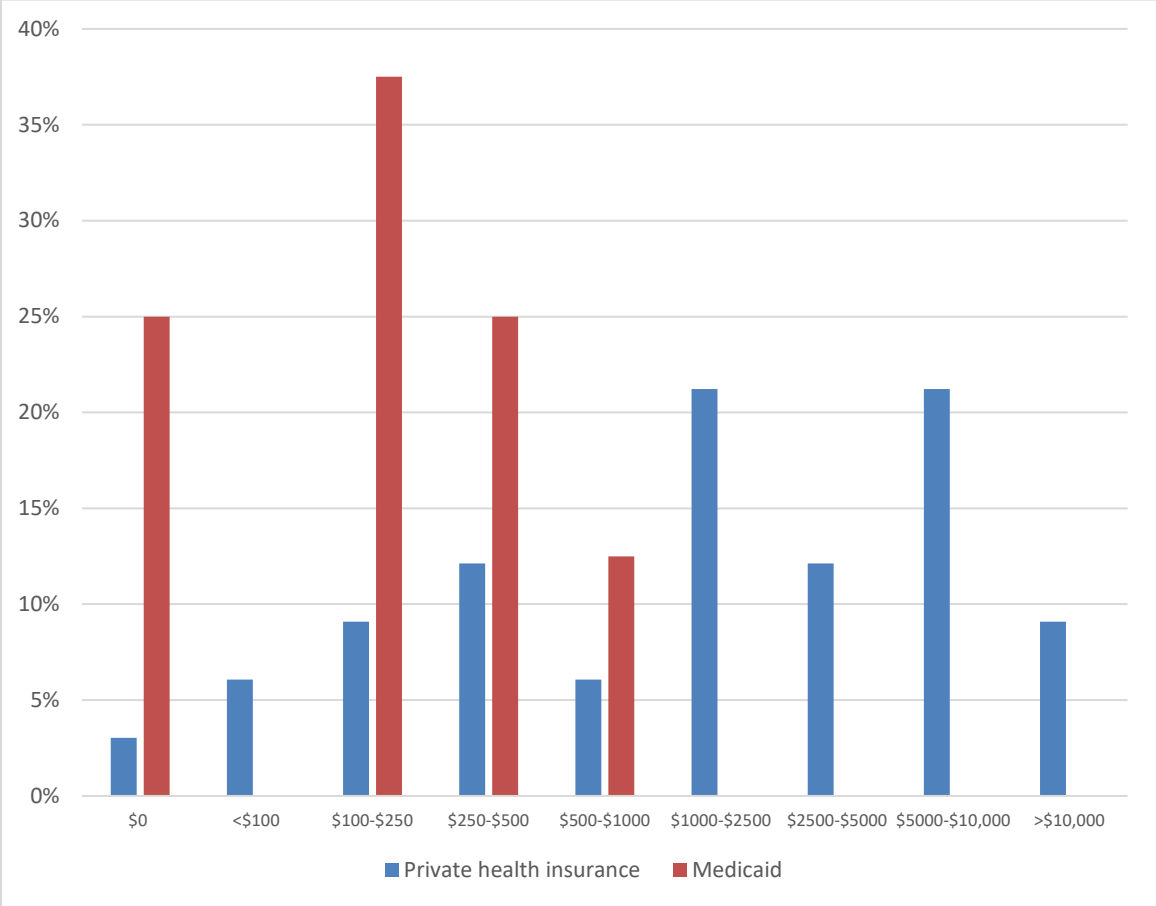
Table 4.6. Comparison of out of pocket costs for liver transplant vs medical management of UCD; Past 12 months (N=43*; N=11**)								
	$0	**<$100**	**$100-$250**	**$250-$500**	**$500-$1000**	**$1000-$2500**	**$2500-$5000**	**>$5000**
Routine consultative and follow-up medical care- LT	40.0%	20.0%	0.0%	20.0%	10.0%	10.0%	0.0%	0.0%
Routine consultative and follow-up medical care- MM	31.0%	11.9%	14.3%	11.9%	16.7%	11.9%	0.0%	2.4%
Emergency medical care- LT	72.7%	9.1%	0.0%	0.0%	0.0%	18.2%	0.0%	0.0%
Emergency medical care- MM	47.4%	15.8%	2.6%	10.5%	7.9%	5.3%	10.5%	0.0%
Medications- LT	40.0%	10.0%	10.0%	10.0%	20.0%	10.0%	0.0%	0.0%
Medications- MM	53.8%	10.3%	12.8%	0.0%	7.7%	7.7%	2.6%	5.1%
Travel- LT	18.2%	9.1%	9.1%	36.4%	0.0%	9.1%	9.1%	9.1%
Travel- MM	24.3%	27.0%	10.8%	13.5%	8.1%	10.8%	2.7%	2.7%

* Liver transplant patients excluded; Not applicable/did not utilize responses excluded; **Medical management patients excluded; Not applicable/did not utilize or don't know responses excluded

Out of pocket costs by insurance type

A comparison of total out of pocket costs related to UCD care over the past 12 months by insurance type suggests a greater overall cost burden among respondents with private health insurance when compared to those with Medicaid coverage. All Medicaid respondents reported less than $1000 in total out of pocket spending for the year, with the largest percentage (38 percent) reporting out of pocket costs between $100 to $250 over the previous 12 months. In contrast, survey respondents covered by private health insurance reported a wide spread of total out of pocket costs for the year ranging from $0 (3 percent) to spending in excess of $10,000 (9 percent). The majority (54 percent) of private health insurance respondents reported spending between $1000 to $10,000 on UCD related care over the last 12 months (Figure 4.6).

Figure 4.6. Total out of pocket costs related to UCD; Past 12 months; By insurance type (N=41*)

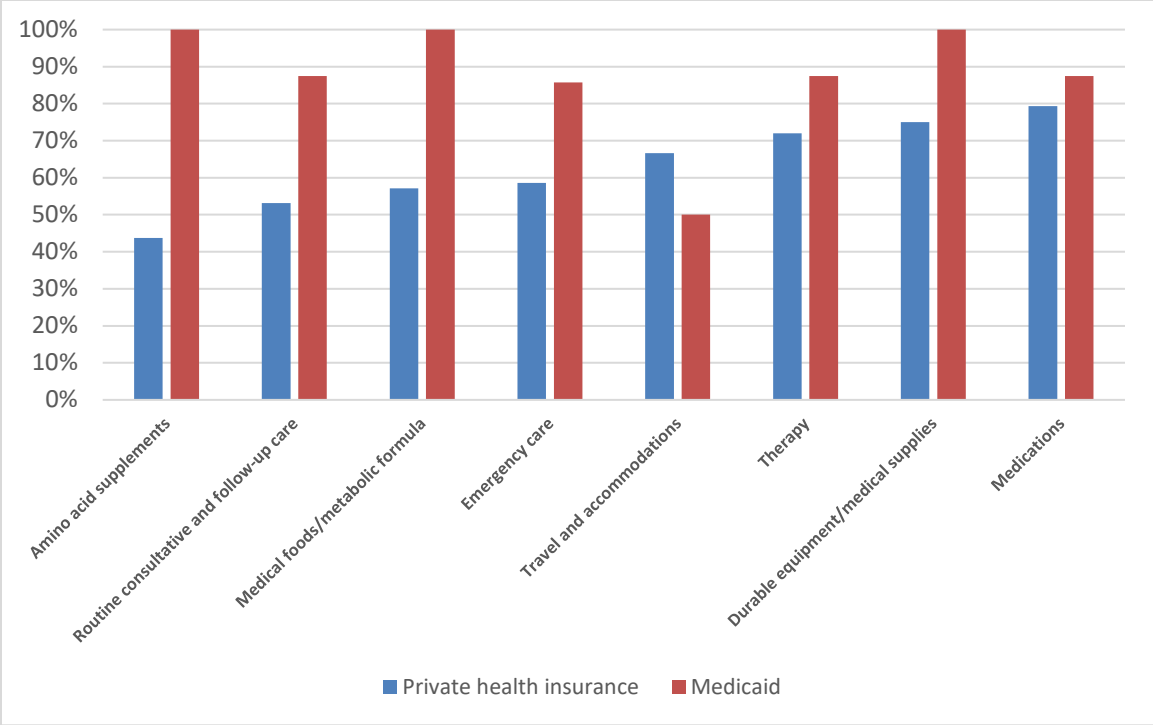


*Liver transplant patients excluded

An examination of stratified out of pocket costs for UCD related care by insurance type across various service categories aligns with findings for total out of pocket spending. When compared to survey respondents covered by private insurance, Medicaid respondents more often reported low out of pocket spending (less than $250) across all service categories except medical related travel. Excluding travel related costs, low (less than $250) out of pocket spending was reported by anywhere from 86 to 100 percent of survey respondents with Medicaid coverage depending on the service category. In contrast, low (less than $250) out of pocket spending was reported by 44 to 79 percent of private insurance holders. Out of pocket spending on travel and

accommodations related to UCD care was the only service category in which the inverse relationship was observed. Sixty-seven percent of respondents with private health insurance reported spending less than $250 on medical related travel over the last year, compared to fifty percent of Medicaid covered respondents (Figure 4.7).

Figure 4.7. Respondents reporting less than $250 in out of pocket costs for UCD related care; Past 12 months; By insurance type (N= 41*)



*Not applicable/Did not use service excluded; Liver transplant patients excluded

Cost and coverage barriers

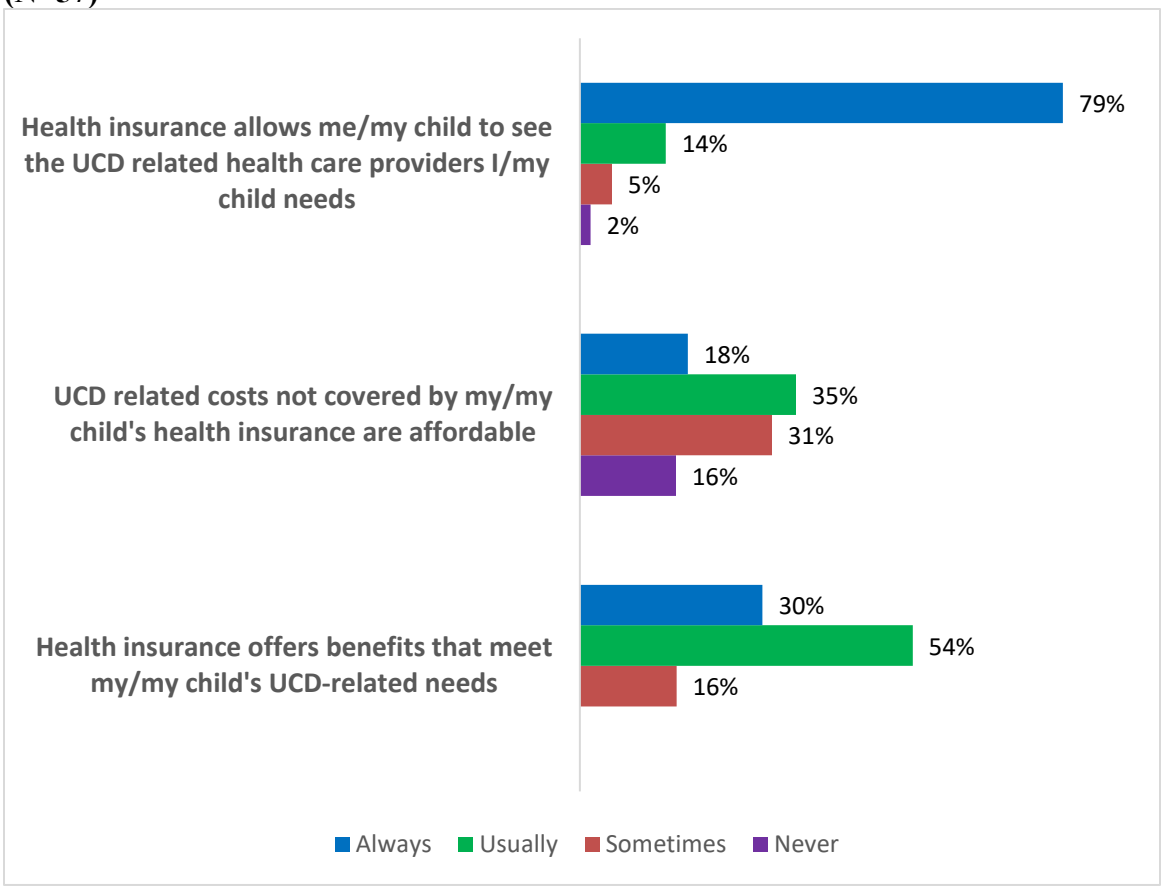
An analysis of survey respondent perceptions of UCD related coverage, costs, and insurance benefits, suggests that insurance coverage is not a common barrier to accessing UCD related health care providers. Nearly 80 percent of those surveyed reported that their coverage always allowed them to see the UCD related health care providers they

needed while only 7 percent reported that their coverage only sometimes or never allowed them to access UCD physician services (Figure 4.8).

Affordability of services not covered by insurance was reported with some consistency as an issue for UCD patients and parents. Only 18 percent of survey respondents said that their un-covered care was always affordable, while nearly 50 percent reported that their un-covered UCD care was either sometimes or never affordable (Figure 4.8).

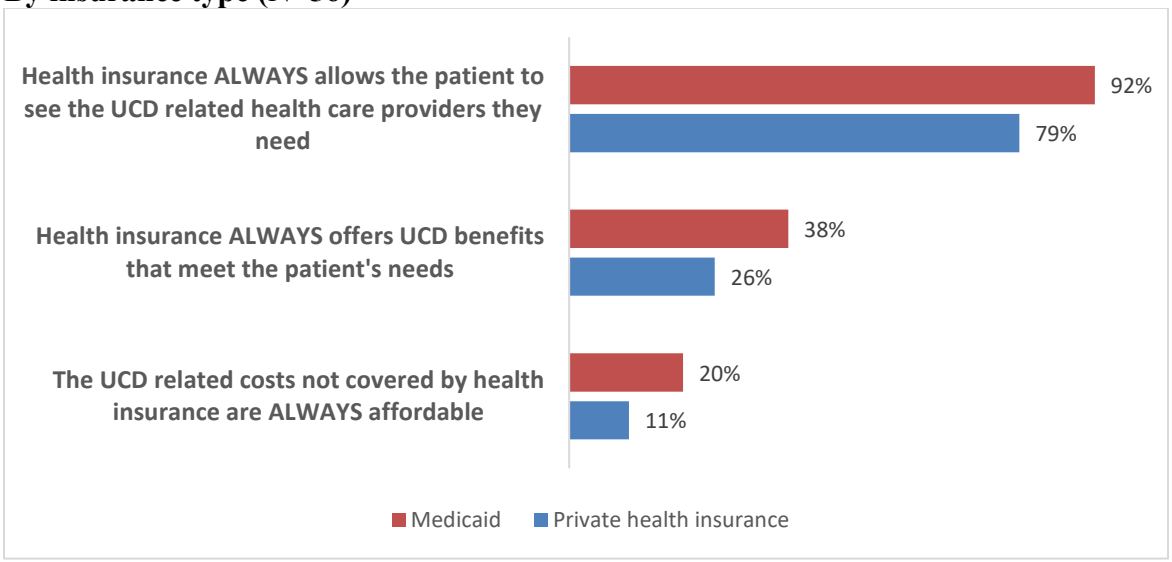
Perceptions of UCD related insurance benefits were generally positive, with 84 percent of respondents indicating that their/their child's health insurance offers benefits that either always or usually meet their/their child's UCD needs (Figure 4.8).

Figure 4.8. Respondent perceptions of UCD coverage, costs, and insurance benefits (N=57)



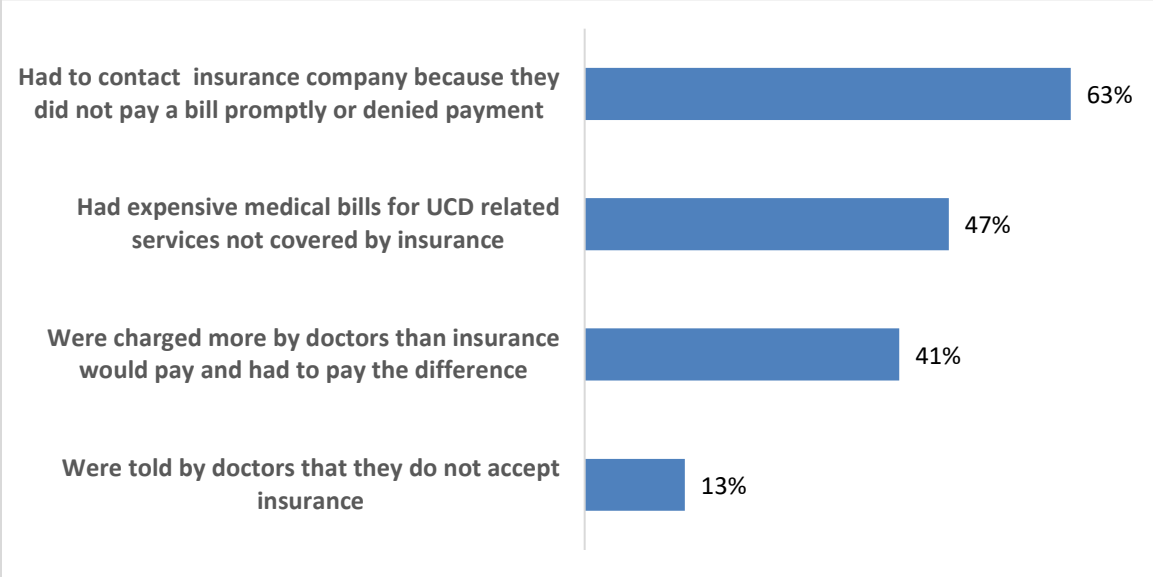
An examination of these same survey questions stratified by insurance type revealed moderate difference between private insurance and Medicaid covered respondents. Medicaid covered survey participants more often reported strongly positive perceptions of their insurance coverage including their access to UCD related health care providers, the affordability of their care, and the suitability of their UCD-related benefits. Ninety-two percent of Medicaid covered respondents, compared to seventy-nine percent of private insurance respondents, indicated that their health insurance always allowed them/their child to see the UCD related health care providers they/their child needed. Thirty-eight percent of Medicaid covered respondents, compared to twenty-six percent of private insurance respondents, indicated that their/their child's health insurance always offers UCD benefits that meet their/their child's needs. Finally, 20 percent of Medicaid covered respondents, compared to 11 percent of private insurance respondents, indicated that the UCD related costs not covered by their/their child's health insurance were always affordable (Figure 4.9).

Figure 4.9. Respondent perceptions of UCD coverage, costs, and insurance benefits; By insurance type (N=56)



When asked about commonly reported challenges with insurance coverage, most survey respondents (63 percent) reported having to contact their insurance company because they did not pay a bill promptly or denied payment for a UCD related service. Forty-seven percent reported having expensive medical bills for UCD related services that were not covered by insurance and just over forty percent reported that they were charged more by their doctors than an insurance company would pay and had to pay the difference (Figure 4.10). Only 13 percent of respondents reported being told by their doctors that they do not accept their insurance (Figure 4.10), which aligns with previously discussed survey responses that suggest that the large majority (79 percent) of participants believed their insurance coverage was not in any way a barrier to seeing UCD related health care providers (Figure 4.8).

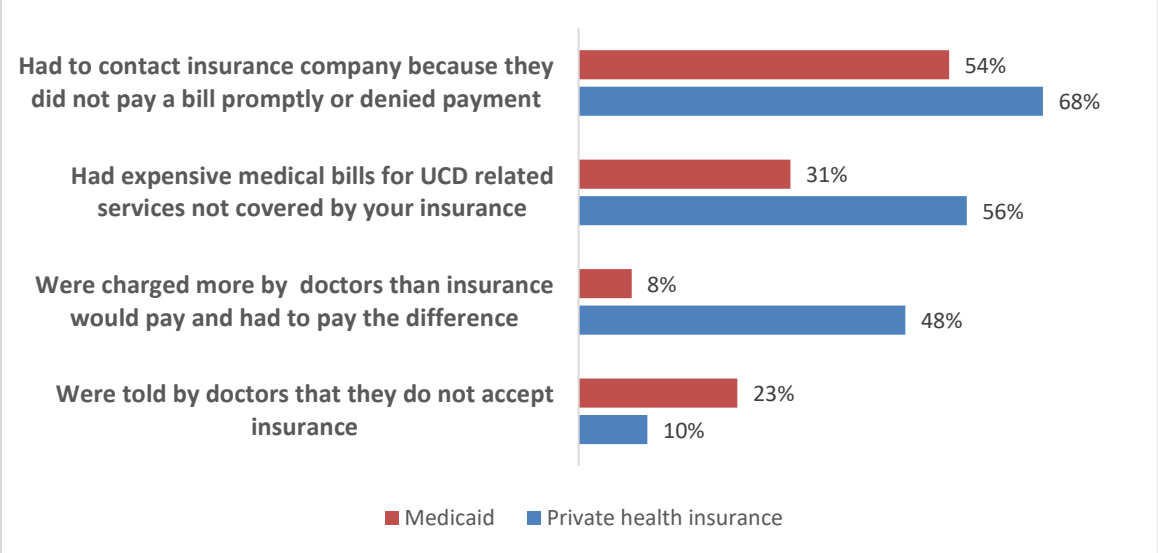
Figure 4.10. Challenges with insurance coverage (N=54)



In addition to the insurance related challenges noted above, the majority of survey participants (54 percent) also reported spending a lot of time on paperwork and disputes related to medical bills and health insurance coverage and nearly 40 percent encountered a time they were unable to pay for their or their child's UCD related medical bills.

An examination of these same survey questions stratified by insurance type revealed some key differences between private insurance and Medicaid covered respondents. Overall, Medicaid covered survey participants were less likely to report experiencing challenges with their insurance coverage compared to respondents with private health insurance. Most notably, very few (8 percent) Medicaid respondents reported that they were charged more by doctors than their insurance would pay and had to pay the difference. This is compared to the nearly 50 percent of privately insured respondents who reported experiencing this issue. Also, Medicaid participants were more likely to report (23 percent) being told by UCD doctors that they do not accept their insurance when compared to privately insured survey respondents (10 percent). This is the only insurance coverage related challenge for which Medicaid covered participants reported higher rates than their privately insured counterparts (Figure 4.11).

Figure 4.11. Challenges with insurance coverage; By insurance type (N=52)

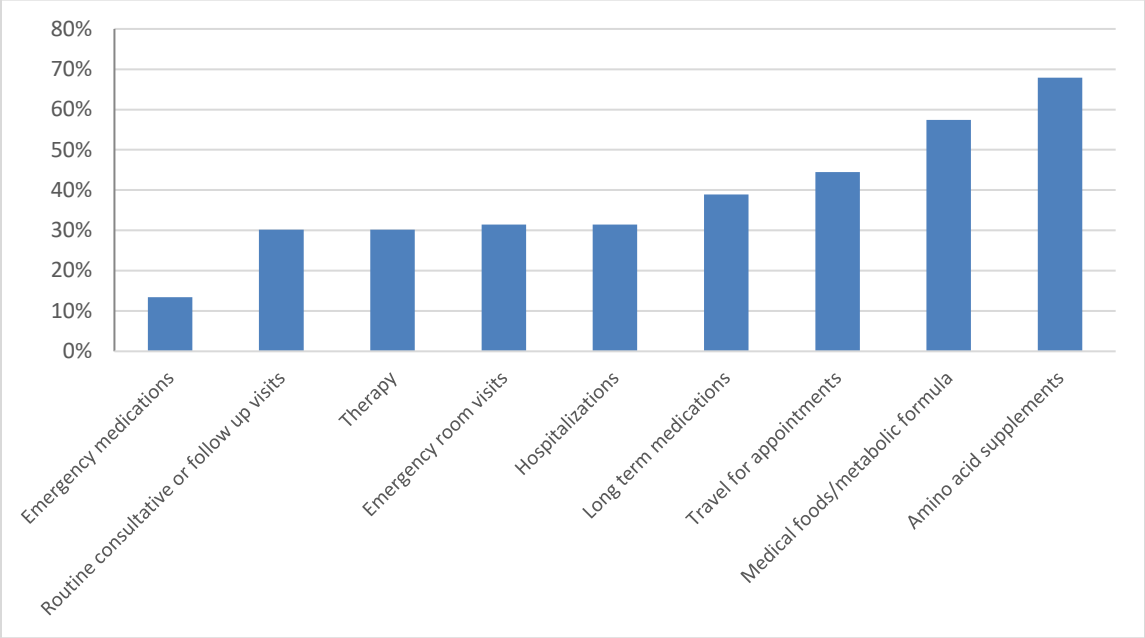


Survey participants were asked about whether or not they encountered any issues related to the cost or coverage of various UCD medical, pharmaceutical, and ancillary

services throughout their/their child's life including routine physician care, emergency medical care, hospitalizations, long-term management medications, emergency medications, medical foods including metabolic formula, amino acid supplements, therapies, and medically related travel. Issues with cost and coverage were most commonly reported for amino acid supplements with 68 percent of survey respondents reporting some type of issue with the cost and/or coverage of these products since their/their child's birth (Figure 4.12). This seems to align with previously described survey findings on out of pocket costs, where comparatively few survey participants reported no or low out of pocket spending towards supplements over the last 12 months (Figure 4.2; Table 4.4).

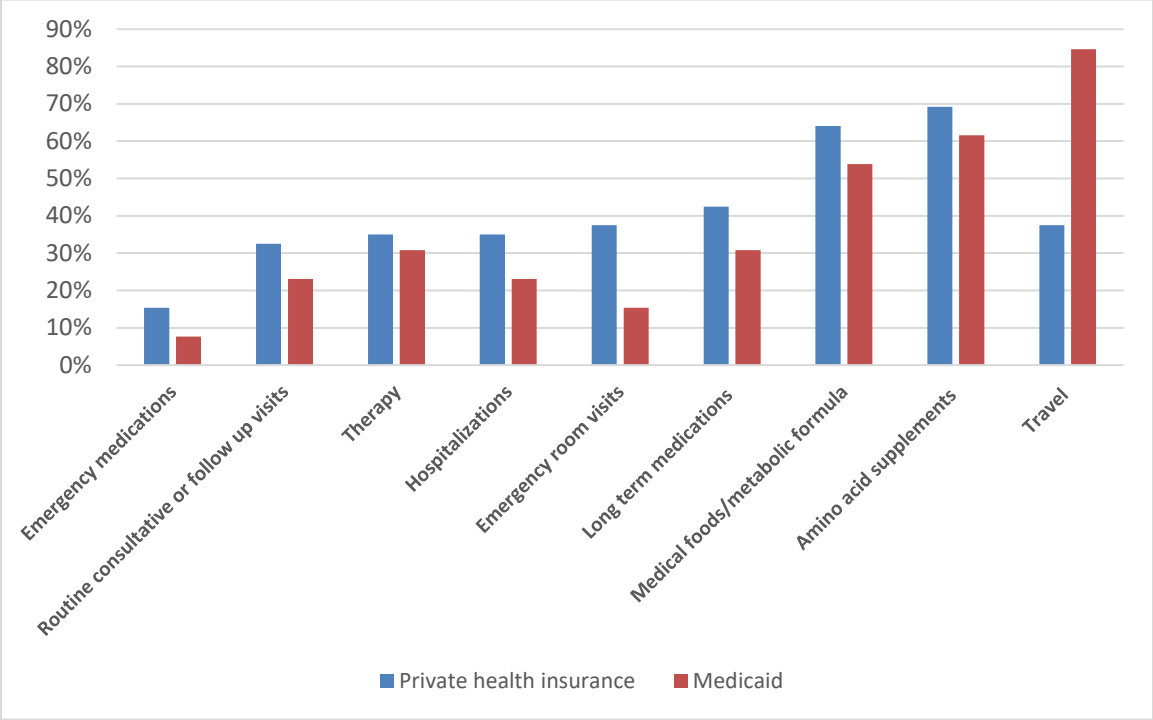
Issues with the cost and/or coverage of medical foods/metabolic formula were also commonly reported with 57 percent of survey participants indicating that they experienced challenges related to accessing these items. Reported issues with the cost and/or coverage of both travel and long-term medications hovered just above and below 40 percent. Issues with cost and/or coverage of routine physician visits, emergency room visits, hospitalizations, and therapies were each reported by approximately 30 percent of survey respondents. Survey participants least commonly reported cost and/or coverage issues in accessing emergency medications (i.e., those administered during episodes of hyperammonemia) with only 13 percent noting any issues over their/their child's life (Figure 4.12).

Figure 4.12. Encountered issues related to cost or coverage during lifetime (N=54)



Results from an examination of these same survey responses stratified by insurance type were consistent with previously described findings from the survey comparing UCD related out of pocket costs for Medicaid and privately insured survey respondents. Medicaid covered survey participants less often reported issues related to the cost and/or coverage of UCD care across all medical, pharmaceutical, and ancillary service categories except medically-related travel (Figure 4.13). This same pattern was noted in examining reported out of pocket costs by insurance type, which found that Medicaid respondents were more likely to report low out of pocket spending compared to their privately insured counterparts (Figure 4.6; Figure 4.7).

Figure 4.13. Encountered issues related to cost or coverage during lifetime; By insurance type (N=52)

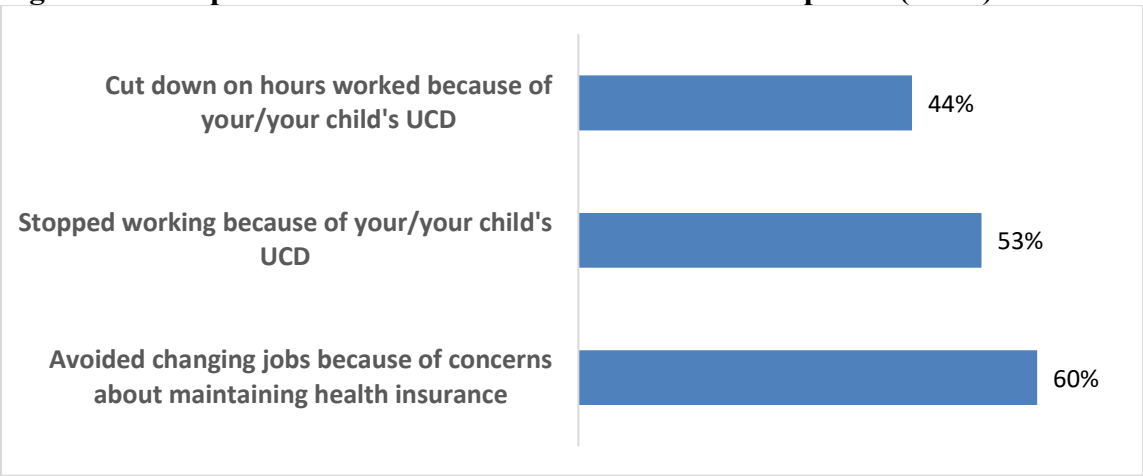


Other financial implications of UCD

Most survey respondents (65 percent) reported that UCD had caused some sort of financial problem for them or their family over their/their child's life. These financial complications manifest in various forms including barriers to career development, high costs of care and spending, and other life choices (e.g., decisions about where to live). Sixty percent of survey respondents reported that they had avoided changing jobs because of concerns about maintaining their health insurance. Fifty-three percent of survey participants had stopped or had a family member stop working to care for their or their child's UCD and forty-four percent cut down or had a family member cut down on hours at work to care for their or their child's health care needs (Figure 4.14). In addition to these figures, 38 percent of survey respondents also reported having moved to a new

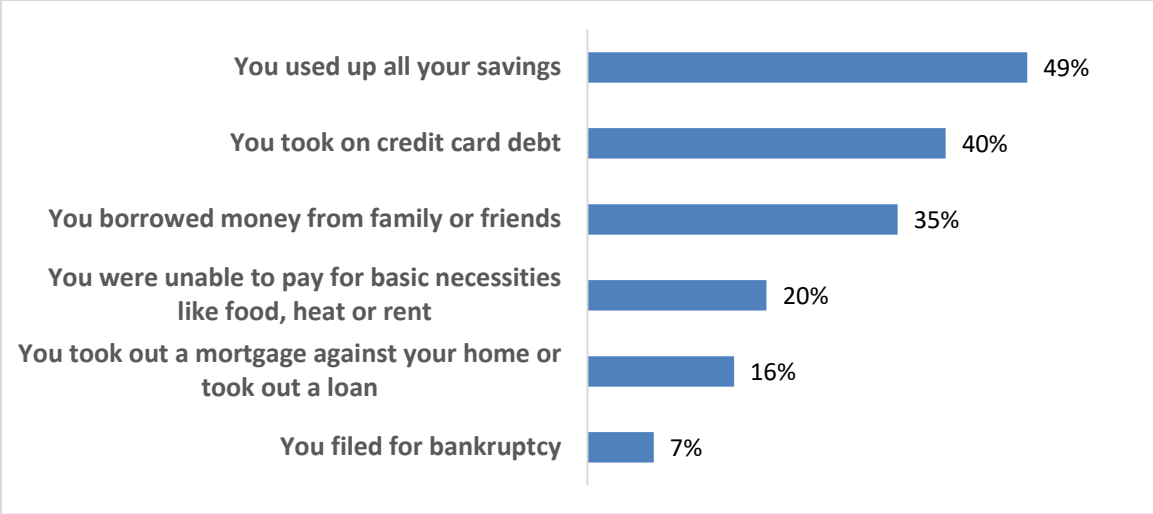
place or avoided moving somewhere new because of concerns over the cost and coverage of their or their child's UCD care.

Figure 4.14. Impact of UCD on career decisions and development (N=55)



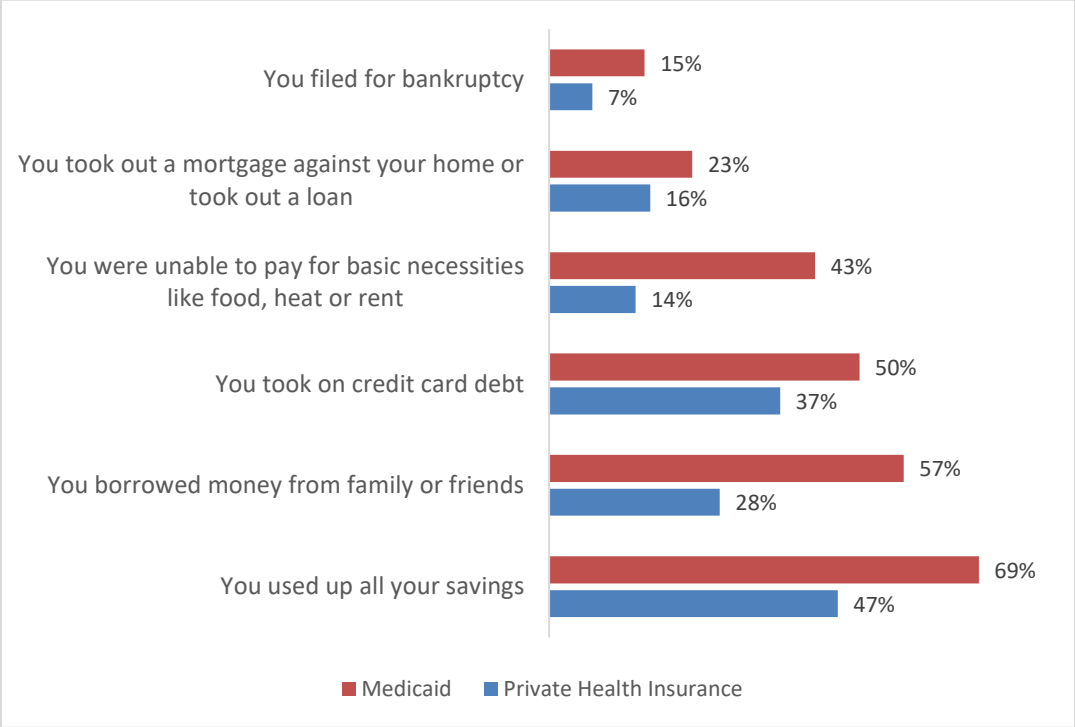
When asked about the impact of medical bills on their/their family's life, 35 percent of survey respondents said they had to change their way of life significantly in order to pay medical bills related to UCD. When asked specifically about the various financial consequences of high-cost care, nearly 50 percent of respondents reporting using their savings to pay for medical bills related to their or their child's UCD. 40 percent reported taking on credit card debt for this same reason and 35 percent reported borrowing money from family or friends to help pay for their or their child's UCD related medical care costs. Twenty percent and sixteen percent respectively reported being unable to pay for basic necessities like food, heat or rent or taking out a loan as a result of their or their child's medical bills. Finally, seven percent reported filing for bankruptcy as a result of the high cost of their or their child's UCD care (Figure 4.15).

Figure 4.15. Financial consequences of medical bills related to UCD (N=55)



These financial consequences were even more pronounced among respondents who reported Medicaid insurance coverage when compared to those reporting coverage under a private insurance plan. A staggering 43 percent of Medicaid covered respondents reported being unable to pay for basic necessities like food, heat or rent because of medical bills related to their or their child's UCD, compared to 14 percent among privately insured participants. Sixty-nine percent of Medicaid covered respondents reported having used up all their savings, fifty-seven percent reported borrowing money from family or friends, fifty-percent reported taking on credit card debt twenty-three percent reported taking out a mortgage or loan, and fifteen percent reported filing for bankruptcy as a result of their or their child's medical bills (Figure 4.16). This suggests that despite the increased coverage of UCD related services reported under Medicaid vs. private insurance within our sample, Medicaid recipients, who report lower household incomes both within our sample and in the general population, still experience greater financial strain when caring for a child with special health care needs.

Figure 4.16. Financial consequences of medical bills related to UCD; By insurance type (N=53)



Discussion

This study explored issues related to the access of sub-specialized medical, pharmaceutical, and support services for UCD through the lens of coverage and cost utilizing an online, self-administered parent/patient survey. The survey was developed by integrating information obtained through interviews with parents and key clinical and patient-advocate informers as well as by adapting relevant questions from the National Survey of Children with Special Health Care Needs ("SLAITS - National Survey of Children with Special Health Care Needs," n.d.) and the Commonwealth Fund Health Insurance Survey ("Biennial Health Insurance Surveys | Commonwealth Fund," n.d.).

An analysis of survey data revealed key trends in out of pocket spending, variation in medical management vs. liver transplant coverage and costs of care, notable differences in the cost and coverage experience of Medicaid covered vs. privately insured individuals affected by UCD, and significant financial strain resulting from the special health care needs of this population.

Overall cost and coverage trends

First, findings from this study suggest that coverage for amino acid supplements and medical foods/metabolic formula may be insufficient/limited for many individuals diagnosed with the disorder. Metabolic formula modified low-protein foods, and amino acid supplements are a medical necessity for individuals affected by UCD. Anecdotally, families affected by UCD have expressed concern that coverage for medical foods and supplements is limited. However, the extent of this limitation was not previously well defined in the literature. A lone 2012 survey of the parents of 305 children with inherited metabolic disease noted uneven coverage of treatment for these disorders and established the presence of a financial burden for families managing childhood metabolic illness. The survey revealed that even though nearly all children with inherited metabolic disorders had medical coverage of some type, uncovered expenses were reported for 11 percent of families purchasing medical foods, 26 percent purchasing supplements, 33 percent purchasing medical feeding supplies, and 59 percent purchasing modified low-protein foods (Berry et al., 2013b). This current study's findings align with and further define the cost and coverage gap established within this previous research by not just noting coverage and cost barriers but also estimating out of pocket costs. Like the Berry et al study, nearly all survey participants reported some form of health insurance coverage but

still noted a significant out of pocket cost burden and challenges with coverage of medically necessary services for UCD. As was seen in the Berry et al survey study, cost and coverage issues with amino acid supplements and medical foods/metabolic formula were consistently reported by survey participants. Moderate to high out of pocket expenses were reported by nearly 50 percent of the sample and issues with the cost and coverage of amino acid supplements were reported by most survey respondents. The majority of survey respondents also reported cost and coverage issues related to accessing medical foods/metabolic formula and a notable percentage of survey participants reported medical food/metabolic formula costs in excess of $1000 annually.

This study also began to define the cost burden of other forms of UCD-related care including routine physician visits, emergency medical care, medications, therapies, and even medical related travel and accommodations. Most out of pocket spending within these service categories can be characterized as moderate (less than $1000 annually) based on survey findings but for a notable minority within the survey sample (14-16 percent across various categories) out of pocket costs were reported to reach figures in excess of $1000 per category annually- some even reporting spending over $2500 or $5000 on a given form of UCD-related care within the last 12 months. In additional to these estimated out of pocket costs, many survey respondents (30-44 percent depending on the service category) reported experiencing some type of challenge related to the cost and coverage of their UCD care over their or their child's lifetime. Together, these findings suggest that some individuals affected by UCD face gaps in coverage for medically necessary aspects of their disease management and treatment and that for these individuals, out of pocket costs may rise to exceptionally high levels.

Variation in cost and coverage landscape by treatment type

This study also revealed important differences in the cost and coverage landscape of liver transplant vs. medical management for UCD, which is an aspect of the cost and coverage experience not previously addressed in the literature. Overall, survey responses demonstrated more comprehensive and generous coverage of liver transplant related medical and pharmaceutical costs when compared to these same service categories for medical management of the condition. Lower levels of out of pocket spending were noted for liver transplant related routine physician and emergency medical care when compared to out of pocket physician and emergency costs for medical management. In addition to this, no respondents reported catastrophic out of pocket payments (more than $2500) related to liver transplant pharmaceuticals while a small, but notable percentage of medically managed respondents reported markedly high (more than $2500) uncovered medication-related costs. Variation in cost and coverage between these two available interventions may have important financial implications for families who are faced with the choice to continue medical management or pursue liver transplant as a treatment for UCD. Thus, more research should be done to further characterize the coverage and cost differences noted through this study and their implications.

Variation in cost and coverage landscape by insurance type

This study also began to explore the impact of insurance coverage type on the coverage and cost experience of families affected by UCD. This analysis established a consistent pattern of less out of pocket spending, fewer reported cost and coverage concerns, and few reported cost and coverage related barriers to care among Medicaid covered respondents when compared to privately insured survey participants. These

findings align with Medicaid medical necessity policy and previously published literature on medical necessity standards used by Medicaid vs large commercial health insurers. Coverage requirements in the private insurance market differ from those in Medicaid and thus benefits within a private insurance plan are often less comprehensive than Medicaid due to more restrictive interpretations of the medical necessity standard. Previous research has found that private insurers are more likely than state Medicaid agencies to establish medical necessity standards that limit coverage to treatment and to include more stringent cost and evidence of effectiveness requirements for covered services (Fox & McManus, 2001). These policy differences may explain, at least in part, the consistent trend towards more generous coverage of UCD-related services among Medicaid recipients in the survey sample.

This trend held true across almost all cost and coverage related issues surveyed in this study. However, Medicaid participants were more likely to report being told by UCD doctors that they do not accept their insurance compared to privately insured survey respondents. This represents the only scenario in which Medicaid coverage seemed to be a barrier and not a facilitator to accessing UCD related care within the survey sample. This finding is also consistent with published trends in physician acceptance of patients by payment source and previous literature in this area, which suggests that physicians are more often unwilling to accept new Medicaid patients when compared to those who are privately insured (Decker, 2012). Medicaid recipients in the sample were also more likely to report financial consequences of high-cost care like using up all their savings, taking on credit card debt, borrowing money from family or friends, taking out a loan, or even being unable to pay for basic necessities like food, heat or rent or filing for bankruptcy.

These findings, together with this study's findings comparing out of pocket costs and coverage challenges by insurance type, suggest that despite more generous coverage of services under Medicaid, Medicaid recipients are still at greater risk of experiencing significant financial strain as a consequence of caring for a child with special health care needs. Future studies should further explore this phenomenon to better understand what may be done, outside of improved coverage and benefits, to address the financial implications of inherited metabolic disease for low-income and/or Medicaid populations.

Financial implications of UCD

In addition to the findings on costs, coverage, and their relative impacts on UCD-related care access, this study strived to more systematically describe the financial stressors that face families affected by UCD. Prior to this research, only one previous study had been published highlighting the financial stress imposed on families affected by UCD. This study collected questionnaire data from 118 families residing in the U.S. who belonged to the NUCDF. Forty-nine percent of surveyed families noted financial stress resulting from having a child with a metabolic disorder. Families highlighted concern over losing or changing insurance needed to maintain their child's health and the burden of medication and hospitalization costs (Cederbaum et al., 2001). This lone study, which was conducted over 15 years ago, established the presence of financial stressors in families affected by UCD. The current study described in this paper further characterized the nature of this burden. Survey analysis suggests that the majority of families affected by UCD face barriers to their career development by avoiding job changes to maintain insurance and/or stopping/cutting down on work to care for their or their child's health care needs.

This study also specifically addresses experiences of financial hardship due to the high-cost of UCD-related care. It establishes a high frequency of credit card debt, exhausted savings, and borrowed money among families affected by UCD, regardless of insurance status. Although lower rates of bank-loans, inabilities to pay for basic necessities, and bankruptcy were observed among the total and privately-insured samples, these events did occur with at least some frequency among all survey respondents. These findings suggest that medical costs related to UCD care are often financially destabilizing and for some, catastrophic in nature.

Limitations

The survey participant sample for this study may be biased by recruitment source and self-selection. Recruitment was conducted via NUCDF's membership network and thus, this sample may not capture the perspective of individuals who have not engaged as members with this organization. Coverage experience may be mediated, in part, by engagement with an organization like NUCDF that offers family support and guidance on these issues. Thus, the experience of individuals outside the sample may differ systematically from those that are included. Participation in the survey was also voluntary, and thus only the perspective of individuals who have self-selected to participate are reflected in this study's findings. The descriptive statistics presented in this study cannot be widely generalized to other UCD families who were either unaware of the opportunity to participate or declined participation in the research.

Data for this study was collected through self-report and is thus, vulnerable to recall bias. Given the complexity and high volume of medical, pharmaceutical and ancillary services patients with UCD utilize, respondents may have difficulty identifying

all out of pocket costs or recalling every circumstance when they encountered a challenge or barrier to acquiring or paying for treatment.

This study would be strengthened by a larger sample of Medicaid-covered and liver transplant participants. Once stratified by treatment or insurance type, sub-sample figures were vastly reduced. Although trends and patterns were identified within the available sample, subsequent research should work to validate these finding by over-sampling for both Medicaid-covered and liver transplant patients.

Finally, this study is exploratory in nature and not designed to identify any associations or establish causality between insurance type and coverage experience. It is designed instead to provide a landscape of cost and coverage issues as it relates to UCD care and may provide a basis for future inquiries.

Conclusion

This study aggregated previously uncollected information on cost and coverage of UCD related services from the perspective of the parent/patient to provide a comprehensive discussion of the payment landscape and common coverage challenges for this set of rare disorders. Although this study focuses explicitly on UCD, findings may be applicable to other types of inherited metabolic disease whose patients have similar complex medical, nutritional, pharmaceutical, and ancillary needs.

This research applied health services survey methodology to a population and field for which health services research is scarcely seen. Patients with rare diseases are generally heterogeneous, limited in numbers, and spread through a large geographic region. Thus, health services researchers rarely work to identify rare-disease subjects and

obtain sufficient survey data to establish a study of this kind. Thus, this study begins to address a gap in published literature examining costs, coverage or access issues related to UCD or other inherited metabolic disorders,

Findings from this study may also have significant policy implications. Individuals with UCD and other inherited metabolic disorders have complex medical, nutritional, pharmaceutical, and ancillary needs that are further complicated by high costs, state-to-state and insurance-based variation in coverage policy, regionalized services areas, and pharmaceutical market forces for orphan drugs. This research established a basic understanding of the cost and coverage landscape for this population and began to explore some of the implications of policy-driven cost and coverage challenges like the differences in out of pocket costs and coverage experiences by insurance type. This study also identifies disease management and treatment areas with particularly notable insufficiencies in coverage and overwhelmingly high costs. It begins to describe some of the real-life financial consequences of coverage gaps and high out of pocket medical spending in this population. Patient advocates and policy-makers may utilize this research data to help inform discussions on improvements to cost and coverage policy for rare-disease groups.

Chapter 5: Conclusion

This dissertation includes three complementary studies assessing the role of healthcare access in informing treatment choice for patients diagnosed with Urea Cycle Disorders. This section provides a summary of the key findings from these three studies as they pertain to the choice between medical management and liver transplant, a discussion of their practice and policy implications, and opportunities for future research.

Study one

The first study utilized grounded theory to construct a conceptual framework that describes the treatment decision making experience of parents whose children are diagnosed with UCD. It explored various catalysts to treatment choice and outlined the clinical, personal, social, and system factors that drive the decision between medical management and liver transplant within this rare-disease population.

Practice implications

The results from this qualitative analysis hold practice implications for physicians and other members of the patient care team. In the short-term, this framework equips providers with an evidence-based account of the patient experience so that they may adapt their individual approach to treatment counseling to better address the concerns, needs, and expectations of their patients and families. It also allows providers to anticipate those needs and be better prepared for productive family and patient interactions.

In the long-term, as more data becomes available on the relative merits of medical management vs. liver transplant and new clinical guidelines or practice parameters are developed around treatment for the condition, guideline developers may

consider integrating the qualitative evidence produced through this study. In doing so, updated guidelines and new recommendations may promote a more standardized, patient-centric approach to treatment counseling that accounts not only for advances in clinical research but also for available evidence on the patient and family experience.

The International Rare Disease Research Consortium (IRDiRC), a joint initiative between the European Commission and the U.S. National Institutes of Health, was launched in 2011 to foster international research collaboration and investment in the field of rare diseases. In 2015, the IRDiRC established a Task Force on Patient-Centered Outcome Measures (PCOMs), which published a report in 2016 highlighting the importance of PCOMs in rare disorders (International Rare Diseases Research Consortium, 2016). PCOMs are characterized by our ability to evaluate outcomes that reflect patient needs and priorities (Morel & Cano, 2017). Most current clinical research and practice is based on outcome measures that do not appropriately capture patient values. Despite growing interest in patient-centered research and care, historically, the effectiveness of most rare disease interventions has been determined by the evaluation of surrogate clinical outcomes (e.g., laboratory measures) that may not reflect the benefits that patients most value (Heneghan, Goldacre, & Mahtani, 2017). Rare disease groups, like those affected by UCD, are often characterized by significant heterogeneity, variability, small size, and geographic spread. These factors pose additional challenges to the identification of and consensus on appropriate and patient-centric outcome measurement (Arbuckle & Abetz-Webb, 2013). Published follow-up opinions building off the IRDiRC Task Force report have proposed mixed methods research as a mechanism to address these challenges and a route to the development of more patient-

centric outcome measures in rare disease (Morel & Cano, 2017). Mixed methodology can combine qualitative and quantitative analyses to more efficiently utilize data from small samples (Regnault, Willgoss, Barbic, & International Society for Quality of Life Research (ISOQOL) Mixed Methods Special Interest Group (SIG), 2017) and qualitative research can be a critical first step in constructing a deeper understanding of the patient and caregiver experience. This includes the impact of rare diseases on daily life, key burdens from the patient and caregiver perspective, and patient expectations for current and future therapies.

The treatment decision-making framework for UCD constructed through grounded theory analysis of patient and provider interviews and focus groups in study one of this dissertation begins to meet the objectives of PCOM development in rare-disease outlined by the IRDiRC. According to the IRDiRC and the U.S. Food and Drug Administration, conceptual models and a definition of patient preferences, core concepts, and values are a fundamental first step in the construction of any patient-centered or patient-reported outcome measure/instrument (International Rare Diseases Research Consortium, 2016; U.S. Food and Drug Administration, 2009). The framework developed through this dissertation research acknowledges UCD patients and caregivers as essential experts in their own condition by utilizing their shared experience to construct a description of key challenges and the main factors families consider when navigating the choice between medical management and liver transplant. This qualitative research defines what patients and caregivers value most in terms of alleviation when considering various treatments for UCD and thus, provides researchers and practitioners with a foundation for the future development of PCOMs to better evaluate and compare

the effectiveness of treatments. At present, PCOMs do not exist for UCD or most other rare inherited metabolic disorders and have not been used consistently in the rare-disease medical or research community (Morel & Cano, 2017). If developed, these outcome metrics could offer more meaningful estimations of patient benefit that resonate with patients' daily experiences, preferences, expectations, and values and thereby help reduce uncertainty over the effectiveness of treatment for UCD (Morel & Cano, 2017). Future research initiatives should consider utilizing the conceptual framework presented in this dissertation as an anchor for the development of PCOMs in UCD. Psychometric methods may be applied to convert concepts within the model into quantifiable items and assessment tools and to test new PCOM instruments in the field (Hobart & Cano, 2009; Morel & Cano, 2017).

Access to care

Results from this first study also promote access to and delivery of sub-specialized medical care as a key dimension of treatment choice, providing a basis for the inquiries examined through the subsequent two studies within this dissertation. The study concluded that, among other factors, issues related to the availability, delivery, and coverage of UCD care all have implications for treatment choice in this population.

According to the findings from this grounded theory study, the availability of high-quality long-term and emergent metabolic care, including the family's proximity to expertise in UCD and confidence in their metabolic team's ability to manage their child's disorder, was a driver of treatment choice. It also suggested that variations in care delivery are common in this population and manifest through differences in physician and institutional approach to guidance around medical management vs. liver transplant as a

treatment for the condition. The study found that physician opinion was a key driver in family decision making and thus, implied that major differences in guidance across physicians and institutions may lead to disparities in treatment. This group of qualitative findings formed the basis for the second manuscript included in this dissertation, which presented results from a GIS analysis examining the association between geographic availability of sub-specialized metabolic and transplant care and treatment choice.

Large differences in the cost and coverage experience of medical management vs. liver transplant was also highlighted as a key concept within the developed framework in paper one. High out of pocket costs related to medical management of the condition through diet and medication as well as the logistical and emotional challenges of navigating various insurance coverage barriers to care were cited as a major burden for the families interviewed under this study. Many of these same cost and coverage challenges were not encountered in pursuing transplant as treatment for UCD, which was, by all accounts, a fully covered procedure with little out of pocket cost to the families. The stark qualitative differences in cost and coverage by treatment type highlighted in this study suggest major financial implications for families choosing between medical management and liver transplant as a treatment for the condition. Since little has been published on the cost and coverage experience of families affected by UCD and other rare inherited disorders of metabolism, these findings also supported the development of the third manuscript included in this dissertation, which provides results from an exploratory patient/parent level survey on the cost and coverage landscape of UCD care and the financial implications of various cost and coverage barriers encountered by this population.

In summary, the framework developed through the first study within this dissertation demonstrates strong practice implications and also provides a robust foundation of qualitative evidence upon which studies two and three were built. These subsequent studies examined in greater depth the health care access, delivery, and coverage issues contained in the framework through application of GIS techniques, secondary quantitative data analysis, and primary survey data collection. Findings and implications from these two studies are discussed in greater detail below.

Study two

The second study, which utilized GIS methodology and regression analysis to examine the association between proximity to high-quality sub-specialized metabolic and/or liver transplant care and treatment choice, was not able to establish a statistically significant relationship between proximity (i.e., geographic access) to *any* high-quality care center and treatment status (i.e., medical management vs. liver transplant). However, this study did establish a strong and statistically significant relationship between treatment status and geographic access to certain transplant care sites known for their support of and excellence in performing liver transplant for UCD. Results from this study suggest that patients who live nearest to one of these two transplant sites are three to four times more likely, depending on the severity of their diagnosis, to undergo a liver transplant than those who live in nearest proximity to one of the five other high-quality UCD transplant centers included in the analysis. These findings suggest merit to the qualitative observation first presented in paper one: institutional variation in approach to counseling and guidance around treatment has implications for treatment choice in patients diagnosed with UCD. In more practical terms, this suggests that patients who

encounter providers who support transplant as a treatment alternative for UCD are more likely to undergo the procedure than those whose providers are less supportive of this approach, regardless of the circumstances of the patient's condition. Since both transplant and medical management are regarded, in many cases, as medically acceptable treatments for UCD, UCD is often considered a preference-sensitive disease. The essential common feature of preference-sensitive conditions is that treatment choice belongs to the patient (Wennberg, 2002). In real practice, however, medical opinion rather than patient preference tends to dominate treatment choice (O'Connor et al., 1999), as is further supported through this analysis. Thus, a key question for practice leaders in the field of inherited metabolic disease is: What can or should be done to address unwarranted variations in clinical practice? When examined together, qualitative and quantitative findings from studies one and two of this dissertation suggest that everyday practice for treatment counseling in UCD is characterized by wide variations that may have little basis in clinical science. This represents a complex but important barrier to equitable access to care for the UCD community. Thus, researchers and practitioners in the field should strive to better understand the drivers and health consequences of unwarranted variation in treatment guidance for UCD and consider implementation and evaluation of interventions or remedies aimed at addressing inter-institutional inconsistencies in practice.

Study three

The third study in this dissertation examined cost and coverage of care and treatment for UCD through the collection and analysis of primary survey data from patients and parents affected by the disorder. Findings from this study provide an

important window into a previously unexplored dimension of health care access for this population.

Key findings from this study highlighted notable differences in out of pocket cost and coverage experience between treatment types for UCD, with higher out of pocket spending and more frequently encountered coverage concerns reported under medical management of the disorder than under liver transplant. These survey results align with the qualitative findings from the first manuscript, which also suggested stark differences in coverage experience by treatment type. Medical management through diet and medication is the default care option for all individuals diagnosed with UCD. Thus, every UCD patient will participate in medical management of their condition at some point in their lifetime. Some will manage the condition through diet and medications for months as they await to grow old enough for transplant, others will continue medical management for years while they consider transplant as an alternative, and others will manage the condition through diet and medication for the duration of their life. Thus, high out of pocket costs and common coverage barriers related to medical management bear an impact on all members of the UCD community, even those that eventually choose to pursue liver transplant as treatment.

Little evidence has been published comparing the relative merits of these two treatment options. In the absence of clinical research establishing the superiority or appropriateness of one treatment method over another, both medical management and liver transplant are often considered viable alternatives for treatment of UCD. Thus, any inequities in cost and coverage by treatment type cannot hold its basis in the available clinical science. Instead, these differences are likely a consequence of a variety of

national, state, and insurance plan policies. Together, these policies create a landscape in which medical management presents a considerably higher cost and coverage burden for the patient than does liver transplant and an environment in which surgical intervention is the more financially, although not necessarily clinically prudent choice for most families. Additional research is needed to better understand the policy mechanisms driving inequities in cost and coverage for UCD. However, a brief look at existing health policy provides some insight into possible explanations for the cost and coverage disparity observed within the survey data. Some of these key policy considerations are described below.

Affordable Care Act and private insurance market reforms

The 2010 Affordable Care Act (ACA) enacted health insurance reforms and federal regulations on the individual insurance marketplace. The legislation requires insurers that sell individual health insurance to offer coverage regardless of health status, mandates coverage of preexisting conditions, prohibits insurers from changing premiums based on a person's medical history or gender, limits cost-sharing, and requires coverage of a minimum set of essential health benefits (Tolbert, 2015). However, most of the law's provisions do not apply to large and self-insured employers, who still retain a great deal of discretion in designing benefit packages, cost sharing requirements, and provider networks (UC Berkeley Labor Center, 2014). In 2016, nearly 41 percent of private-sector employers reported that they self-insured at least one of their health plans (Fronstin, 2018). In 2015, 82 percent of covered workers in firms with 1,000 to 4,999 employees and 94 percent of covered workers in firms with 5,000 or more employees were in self-funded plans (Kaiser Family Foundation, 2015). Self-insured group health plans are not

subject to most of the coverage provisions outlined in the ACA and the Employee Retirement Income Security Act (ERISA) of 1974 exempts self-funded plans from most state insurance laws, including mandated benefits and consumer protection regulations (Kaiser Family Foundation, 2015). For non-self-insured employer-sponsored plans, states continue to have sole regulation and vary in their regulatory approach and the extent to which they impose benefit mandates and other policies (Lucia et al., 2018). Thus, despite enactment of the ACA, insurance coverage under large or self-insured employers still varies substantially both within and across states.

Most individuals within the UCD survey sample for study three reported having private insurance coverage of some kind (73 percent), with the vast majority reporting coverage through an employer-sponsored insurance plan (69 percent). This is fairly consistent with other available data on insurance status for CSHCNs (Musumeci & Foutz, 2018a). Since many employers self-insure in lieu of purchasing through the insurance marketplace and other forms of employer-sponsored insurance are regulated through state, not federal, policy, it is reasonable to assume that the many individuals affected by UCD who report being insured through an employer-sponsored plan are not protected by the coverage reforms and regulations instituted through the ACA.

The ACA also contains prevention provisions, including a requirement that evidence-based preventive health care services be covered in *all* public and private health insurance plans, without cost-sharing. These provisions are the only ones that apply universally across all insurer types (Shearer, 2010). However, most of the health care services reflected in study three do not fall under the definition of preventive health care, but rather, are considered elements of treatment and management for an existing

condition. Thus, services and products related to the medical management of UCD are still vulnerable to significant variation in coverage and cost-sharing across private insurance plans.

Insurance reforms and regulations under the ACA do apply to individual and small group insurance markets to the extent that individuals, families, and employers direct purchase insurance from health insurance marketplaces. For example, the federal government sets the general standards for Essential Health Benefits within marketplace insurance plans. However, states select a benchmark plan that fits within this prescribed framework and are allotted significant flexibility in setting minimum insurance plan standards (Tolbert, 2015). According to advocates within the rare-disease community, treatments for rare disorders, like the pharmaceuticals used to medically manage UCD, are particularly vulnerable to variation in minimum essential benefit standards and often omitted from health plan benefit packages. Thus, even UCD families covered through an ACA regulated marketplace insurance plan may be forced to navigate arduous appeals processes, look for alternative non-insurance sources of coverage, or pay the full cost of treatment out of pocket.

Liver transplant, although also considered a form of treatment for UCD, is a more widely understood and utilized intervention for a variety of conditions both metabolic and non-metabolic in nature. Thus, the medical and pharmaceutical services surrounding transplant have been found to be consistently covered across both individual and group insurance markets (Center for Consumer Information and Insurance Oversight, 2011; Henry, 2012), which may explain, at least in part, the lower out of pocket costs for UCD-related liver transplant services reported by study three participants.

In a post-Affordable Care Act world, health insurance plans are also looking for different ways to manage growing health care costs. One potential tactic includes the narrowing of provider networks to shift some of the payment burden to the health services consumer. This can have a significant impact on patients with rare diseases who must seek their care from sub-specialists, often out of state, with the knowledge and expertise to appropriately manage their condition. If a specialist or hospital is removed from a UCD patient's narrowed insurance network, they may see a substantial rise in out of pocket costs related to the medical management of their condition. On the other hand, long-term care for the post-transplant patient, although also sub-specialized, is more readily accessible across many provider networks and US hospital centers.

Medicaid/CHIP benefit and cost sharing policy

Medicaid, a joint federal and state program, provides health insurance coverage for low-income children in the United States. CHIP complements Medicaid by covering uninsured children in families with incomes above Medicaid eligibility levels. As of 2017, 49 states had extended Medicaid/CHIP eligibility for children up to at least 200 percent of the federal poverty level (FPL) (Musumeci & Foutz, 2018b). According to the National Survey of Children's Health, Medicaid and CHIP covered about half (48 percent) of all children with special health care needs in 2016 (Musumeci & Foutz, 2018b). Among study three UCD survey respondents, 16 percent reported being covered by either Medicaid or CHIP. This comparatively smaller percentage is likely a result of higher household incomes within the survey sample. Study three survey findings suggested lower out of pocket costs and fewer coverage challenges across UCD related medical, pharmaceutical and ancillary services for Medicaid beneficiaries when

compared to individuals covered by private insurance. These results reflect Medicaid's comprehensive benefit policies and cost-sharing regulations. Children enrolled in Medicaid must be covered for all medically necessary care through the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit, which is intended to help low-income children access all forms of needed care (Artiga & Ubri, 2017). States are also prohibited from charging premiums for children enrolled in Medicaid with incomes under 150 percent FPL and many children enrolled in Medicaid are also exempt from most forms of cost-sharing (depending on their income level and state-specific regulation) (Artiga & Ubri, 2017; "Out-of-Pocket Cost Exemptions," n.d.). States have more flexibility in designing benefits and cost-sharing requirements for CHIP and higher-income Medicaid recipients, which may explain the moderate UCD-related out of pocket costs reported by some Medicaid beneficiaries within the survey sample. However, analyses still show that CHIP offers more comprehensive benefits and is more affordable than employer-sponsored or individual marketplace insurance plans (MACPAC, 2017). Ultimately, Medicaid and CHIP help provide children with special health care needs, like those diagnosed with UCD, with access to all medically necessary services at a reasonable out of pocket cost. Thus, Medicaid beneficiaries may be better positioned than those with private insurance to explore all available treatment options. For Medicaid/CHIP covered UCD patients, this means that the choice between medical management and liver transplant may be less clouded by coverage concerns and high out of pocket spending for UCD related-care. However, despite more generous and affordable coverage of services, Medicaid beneficiaries affected by UCD still reported experiencing significant financial strain as a result of caring for and paying for the care of

a child with special health care needs. Most notably, 43 percent of Medicaid beneficiaries who participated in the study three survey reported that they were unable to pay for basic necessities like food, heat or rent because of their child's medical bills. This was compared to 14 percent among privately insured survey respondents. Medicaid respondents consistently reported financial complications related to the cost of their child's UCD care at a higher frequency than privately insured survey participants (Figure 4.16). These findings suggest that although Medicaid coverage may reduce overall out of pocket spending and coverage barriers among UCD patients when compared to private insurance, it does not sufficiently offset the financial burden of care experienced by these lower-income families.

Medically necessary food mandates

Inconsistency in medically necessary food policy across states is another potential source of the high costs and barriers to coverage reported by survey respondents in relation to medical management of UCD. States play an integral role in ensuring access to medically necessary foods and formulas designed to meet the needs of patients affected by inherited metabolic diseases like UCD. Some states pay for and provide medical foods through health department programs and others have enacted legislation that require insurers to provide medically necessary food coverage. However, coverage policy varies substantially state to state and even in states where legislation has been enacted, various exemptions, quantity limits, and age or gender exclusions limit the true scope of coverage for medically necessary foods and formulas. In addition to this, self-insured employer-sponsored health plans, which are regulated by ERISA, are not affected by state medical food coverage mandates. On average, states regulate less than half of the

health insurance market (Claxton, Rae, Long, Damico, & Whitmore, 2018), so many UCD patients are likely to be covered by plans that are not required to comply with state legislation around medically necessary foods.

Inequities in coverage of medically necessary foods can make it difficult for UCD patients to receive insurance reimbursement for life-saving metabolic formulas and low-protein foods. These inconsistencies align closely with survey findings from paper three, which reported moderate out of pocket costs and substantial coverage barriers related to the utilization of nutritional supplements by patients with UCD. The Medical Nutrition Equity Act (MNEA- S.1194) (Casey, 2017) was introduced to Congress in May 2017. If passed, it would mandate that *all* private health insurance policies, including state-regulated or self-insured/self-funded plans, and federal health programs, including CHIP, Tricare, Medicaid, Medicare, and Federal Employee Health Benefit Plans, provide coverage for medically necessary food and vitamins for both children and adults diagnosed with inborn errors of metabolism and other specified digestive disorders. Several professional medical societies and patient advocacy groups have formed a coalition known as Patients & Providers for Medical Nutritional Equity, working to encourage passage of the federal bill. This legislation could dramatically change the landscape of nutritional benefits for insured patients with UCD and other rare conditions, regardless of their insurance type, and have a positive impact on the cost and coverage experience of accessing medical foods and formulas. It is the hope that, once published, findings from study three of this dissertation may contribute to these efforts.

Cost and coverage of orphan drugs

Finally, limited and variable prescription drug coverage for high-cost orphan drugs is another potential source of cost and coverage inequity between medical management and liver transplant treatment for UCD. The US Orphan Drug Act (ODA) of 1983 was enacted with the objective of stimulating research on rare diseases and the development of pharmaceutical products for the treatment of rare conditions. The ODA created several incentives for the pharmaceutical industry, including 7-year U.S. market exclusivity on drugs developed to treat orphan disease, defined as having a U.S. patient prevalence of less than 200,000 (Wellman-Labadie & Zhou, 2010). Since its enactment, little research has been conducted to determine the implications of ODA incentives on cost and coverage for families affected by inherited metabolic disease. Anecdotally, expensive orphan drugs are often excluded from pharmaceutical plan formularies or placed within their "specialty" tier, which may require the patient to subsidize higher co-insurance rates (Hyde & Dobrovolny, 2010; Kaiser Family Foundation, 2017). In the case of UCD, these prescriptions may cost several hundred thousand dollars annually. For example, it has been reported that Ravicti, a commonly prescribed medication for the medical management of UCD, costs nearly $800,000 per patient per year (America's Health Insurance Plans, 2016). It is important to note that pharmaceutical companies have utilized patient assistance programs (PAPs) to off-set these out of pocket costs and that many UCD patients report enrolling in PAPs to pay for high-priced medications (Hyde & Dobrovolny, 2010). However, it is unclear how many patients utilize such non-insurance coverage resources and the sustainability of PAPs as a long-term coverage solution for orphan drugs like Ravicti.

Future Research Opportunities

The study findings and implications detailed above, although discussed within the context of UCD, are likely to reflect the health care access experience of other populations affected by rare conditions where many of the same policy drivers may be at play. Thus, this dissertation project points to several opportunities for future health service research both within the UCD community and the larger field of rare disorders. The framework synthesized in the first paper provides a platform for a range of research related to the drivers of treatment choice in UCD and other rare disorders of childhood for which analogous decisions must be made between conventional therapy and other interventions. It also provides a foundation for the development of patient-centered treatment outcome measures for inherited metabolic disorders like UCD.

This research also applied mixed methodology to a population and field for which integrated qualitative and quantitative methods have been scarcely used. Patients with rare diseases are generally heterogenous, limited in numbers, and spread through a large geographic region. Thus, identifying subjects and obtaining sufficient quantitative and qualitative data to conduct mixed-methods analysis can pose a challenge, resulting in a dearth of published examples of mixed methodology in this field. This dissertation demonstrates a viable approach to conducting mixed-methods research with rare-disease populations and may be used and refined as a model for future inquiries. Studies two and three of this dissertation began to test, and through their results, support several of the key qualitative findings reported through paper one. Future research should continue to employ mixed-methods to test the validity of the concepts detailed in the framework and

to develop patient-centered outcome measures that align with the patient and caregiver experience described through the presented conceptual model.

Future research should also focus on further defining and addressing the health care access challenges for UCD and other comparable rare conditions highlighted through this dissertation. For example, additional work should be done to study unwarranted variation in treatment for UCD and other rare disorders. Studies may continue to define the extent of the problem and as a next step, implement and evaluate interventions aimed at creating more standardization in the delivery of care within the field of rare disease. This dissertation highlighted the UCDC longitudinal study as an important source of data for inquiries of this kind and demonstrated uses for nationally collected rare disease consortium data in answering research questions around health care access and delivery of services. Currently, NIH-RDCRN funds 21 consortia of rare disease ("Rare Diseases Research Groups & Studies | Rare Diseases Clinical Research Network," n.d.). These consortia may represent additional opportunities for health services related analyses that reach outside the traditional confines of clinical research (Lohr & Steinwachs, 2002).

Finally, future research should do more to understand the policy mechanisms that drive inequities in cost and coverage of UCD and other rare conditions. Findings from this dissertation demonstrate a concerning level of financial burden among families affected by UCD. More should be done to define this burden among UCD patients and other patients diagnosed with rare disorders. Researchers may consider the use of prospective data collection on out of pocket health care costs, coverage denials and appeals, and other significant financial events to better characterize the nature of the

problem. Future studies may also make use of state variation in cost and coverage policy (e.g., differences in medical food mandates) to examine the impact of these policies on out of pocket spending and other key measures of the financial burden related to medical care for rare diseases.

Ultimately, it is the hope that the research presented through this dissertation will demonstrate value in constructing a health services related research agenda that targets otherwise under-studied communities of rare and ultra-rare diseases and that these and future findings will bolster interest in addressing the access needs of this population through policy and practice reforms.

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Appendix A

Table A1. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients under the condition that the patient was diagnosed after the neonatal-period (i.e., late-onset) adjusting for patient age, sex, race, ethnicity, and income proxy (N=232)

Variable (comparison category)	Variable Categories	Odds Ratio (95%CI)	P-Value
DV: LT as treatment for UCD			
Nearest LT center (non-"gold standard" LT site)	"Gold standard" LT site	4.45 (1.08-18.42)	0.04
Disease severity (late-onset)	Neonatal-onset	21.46 (7.81-58.93)	<0.001
Nearest LT center * Disease severity	"Gold standard" LT site * Neonatal-onset	0.70 (0.12-3.93)	0.68
Patient age	1-23[α]	0.96 (0.90-1.03)	0.30
Patient sex (female)	Male	1.71 (0.79-3.67)	0.17
Patient race (white)	Asian	2.38 (0.68-8.36)	0.18
	Black	0.83 (0.19-3.69)	0.81
	Multiple races	2.47 (0.58-10.47)	0.22
Patient ethnicity (non-Hispanic)	Hispanic	1.76 (1.00-7.62)	0.05
Median income at patient zip-code ($50,000-$74,999)	<$35,000	0.72 (0.16-3.17)	0.67
	$35,000-$49,999	0.50 (0.19-1.34)	0.17
	$75,000-$99,999	0.64 (0.21-1.91)	0.42
	=>$100,000	0.48 (0.17-1.42)	0.19

[α]Continuous variable

Table A2. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients under the condition that the patient was diagnosed during the neonatal-period (i.e., neonatal-onset) adjusting for patient age, sex, race, ethnicity, and income proxy (N=232)

Variable (comparison category)	Variable Categories	Odds Ratio (95%CI)	P-Value
DV: LT as treatment for UCD			
Nearest LT center (non-"gold standard" LT site)	"Gold standard" LT site	3.10 (1.08-8.85)	0.04
Disease severity (neonatal-onset)	Late onset	0.05 (0.02-.13)	<0.001
Nearest LT center * Disease severity	"Gold standard" LT site * Late-onset	1.44 (0.25-8.14)	0.68
Patient age	1-23[α]	0.96 (0.90-1.03)	0.30
Patient sex (female)	Male	1.71 (0.79-3.67)	0.17
Patient race (white)	Asian	2.37 (0.68-8.36)	0.18
	Black	0.83 (0.19-3.67)	0.81
	Multiple races	2.47 (0.58-10.47)	0.22
Patient ethnicity (non-Hispanic)	Hispanic	2.76 (1.00-7.62)	0.05
Median income at patient zip-code ($50,000-$74,999)	<$35,000	0.72 (0.16-3.17)	0.67
	$35,000-$49,999	0.50 (0.19-1.34)	0.17
	$75,000-$99,999	0.63 (0.21-1.91)	0.42
	=>$100,000	0.48 (0.17-1.42)	0.19

[α]Continuous variable

Table A3. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients under the condition that the patient reported less than 4 episodes of hyperammonemia in their lifetime adjusting for patient age, sex, race, ethnicity, and income proxy (N=185)

Variable (comparison category)	Variable Categories	Odds Ratio (95%CI)	P-Value
DV: LT as treatment for UCD			
Nearest LT center (non-"gold standard" LT site)	"Gold standard" LT site	1.56 (0.52-4.62)	0.43
Disease control (<4 HA episodes)	≥4 HA episodes	3.26 (1.42-7.47)	0.005
Nearest LT center * Disease control	"Gold standard" LT site * ≥4 HA episodes	1.73 (0.35-8.57)	0.50
Patient age	1-23[α]	0.91 (0.85-0.97)	0.005
Patient sex (female)	Male	3.39 (1.67-6.86)	0.001
Patient race (white)	Asian	1.94 (0.54-6.88)	0.31
	Black	0.67 (0.14-3.35)	0.63
	Multiple races	3.32 (0.88-12.54)	0.08
Patient ethnicity (non-Hispanic)	Hispanic	1.12 (0.44-2.86)	0.82
Median income at patient zip-code ($50,000-$74,999)	<$35,000	1.40 (0.36-5.38)	0.63
	$35,000-$49,999	0.78 (0.31-1.95)	0.59
	$75,000-$99,999	0.60 (0.21-1.73)	0.34
	=>$100,000	0.52 (0.19-1.46)	0.22

[α]Continuous variable

Table A4. Odds of undergoing liver transplant as a treatment for UCD if nearest liver transplant center is one of two considered to deliver "gold standard" in transplant care for UCD patients under the condition that the patient reported <u>at least</u> 4 episodes of hyperammonemia in their lifetime adjusting for patient age, sex, race, ethnicity, and income proxy (N=185)

Variable (comparison category)	Variable Categories	Odds Ratio (95%CI)	P-Value
DV: LT as treatment for UCD			
Nearest LT center (non-"gold standard" LT site)	"Gold standard" LT site	2.69 (0.83-8.70)	0.10
Disease control (≥4 HA episodes)	<4 HA episodes	0.31 (0.13-0.70)	0.005
Nearest LT center * Disease control	"Gold standard" LT site * <4 HA episodes	0.58 (0.12-2.87)	0.50
Patient age	1-23[α]	0.91 (0.85-0.97)	0.005
Patient sex (female)	Male	3.39 (1.67-6.86)	0.001
Patient race (white)	Asian	1.94 (0.54-6.88)	0.31
	Black	0.67 (0.14-3.35)	0.63
	Multiple races	3.32 (0.88-12.54)	0.08
Patient ethnicity (non-Hispanic)	Hispanic	1.12 (0.44-2.86)	0.82
Median income at patient zip-code ($50,000-$74,999)	<$35,000	1.40 (0.36-5.38)	0.63
	$35,000-$49,999	0.78 (0.31-1.95)	0.59
	$75,000-$99,999	0.60 (0.21-1.73)	0.34
	=>$100,000	0.52 (0.19-1.46)	0.22

[α]Continuous variable