Published in final edited form as:

Mol Genet Metab. 2017 June ; 121(2): 119–126. doi:10.1016/j.ymgme.2017.04.007.

Hospitalizations for mitochondrial disease across the lifespan in the U.S

Shana E. McCormack, MD^{1,2}, Rui Xiao, PhD³, Todd J. Kilbaugh, MD⁴, Michael Karlsson, MD^{4,5}, Rebecca D. Ganetzky, MD⁶, Zarazuela Zolkipli Cunningham, MBChB, MRCP⁷, Amy Goldstein, MD⁸, Marni J. Falk, MD^{2,6}, and Scott M. Damrauer, MD⁹

¹Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia PA

²Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA

³Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA

⁴Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA

⁵Mitochondrial Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden

⁶Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia PA

⁷Division of Neurology, Children's Hospital of Philadelphia, Philadelphia PA

⁸Division of Neurology, Children's Hospital of Pittsburgh, Pittsburgh, PA

⁹Division of Vascular Surgery, Hospital of the University of Pennsylvania, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA & Department of Surgery, Corporal Michael Crescenz VA, Philadelphia, PA

Abstract

Importance—Mitochondrial disease is being diagnosed with increasing frequency. Although children with mitochondrial disease often have severe, life-limiting illnesses, many survive into adulthood. There is, however, limited information about the impact of mitochondrial disease on healthcare utilization in the U.S. across the lifespan.

Objectives—To describe the characteristics of inpatient hospitalizations related to mitochondrial disease in the U.S., to identify patient-level clinical factors associated with in-hospital mortality, and to estimate the burden of hospitalizations on individual patients.

Corresponding author and person to whom reprint requests should be addressed: Shana McCormack, MD, Children's Hospital of Philadelphia, Division of Endocrinology and Diabetes, 3401 Civic Center Boulevard, Suite 11NW, Philadelphia, PA 19104, Telephone: (215) 590 3174, Fax: (215) 590 3053, mccormacks1@email.chop.edu.

Disclosure statement: The authors have nothing to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Design—Cross-sectional and longitudinal observational studies.

Setting—U.S. hospitals.

Participants—Individuals with hospital discharges included in the triennial Healthcare Cost and Utilization Project (HCUP) Kids Inpatient Database (KID) and the National Inpatient Sample (NIS) in 2012 (cross-sectional analysis); individuals with hospital discharges included in the HCUP California State Inpatient Database from 2007–2011, inclusive (longitudinal analysis).

Exposure—Hospital discharge associated with a diagnosis of mitochondrial disease.

Main outcome measures—Total number and rate of hospitalizations for individuals with mitochondrial disease (*International Classification of Diseases, 9th revision, Clinical Modification* code 277.87, disorder of mitochondrial metabolism); in-hospital mortality.

Results—In the 2012, there were approximately 3,200 inpatient pediatric hospitalizations (1.9 per 100,000 population) and 2,000 inpatient adult hospitalizations (0.8 per 100,000 population) for mitochondrial disease in the U.S., with associated direct medical costs of \$113 million. In-hospital mortality rates were 2.4% for children and 3.0% for adults, far exceeding population averages. Higher socioeconomic status was associated with both having a diagnosis of mitochondrial disease and with higher in-hospital mortality. From 2007–2011 in California, 495 individuals had at least one admission with a diagnosis of mitochondrial disease. Patients had a median of 1.1 hospitalizations (IQR, 0.6–2.2) per calendar year of follow-up; infants under 2y were hospitalized more frequently than other age groups. Over up to five years of follow up, 9.9% of participants with any hospitalization for mitochondrial disease were noted to have an in-hospital death.

Conclusions and Relevance—Hospitalizations for pediatric and adult mitochondrial diseases are associated with serious illnesses, substantial costs, and significant patient time. Identification of opportunities to prevent or shorten such hospitalizations should be the focus of future studies.

Keywords

mitochondrial disease; health services research; hospitalizations

1. INTRODUCTION

Mitochondria are sub-cellular organelles that serve many critical functions, including production of energy. “Primary mitochondrial respiratory chain disease” refers to the class of disorders caused by pathogenic mutations in mitochondrial and/or nuclear DNA affecting function of the mitochondrial respiratory chain complexes. Despite substantial clinical heterogeneity, many patients with severe forms of mitochondrial disease present in infancy and childhood, thus pediatricians are often the first practitioners to encounter patients with suspected mitochondrial disease.¹ Although previously considered a rare class of disorders, recent estimates suggest that pathogenic mitochondrial and nuclear gene mutations are present in at least 1 in 4,300 adults.²

Efforts are ongoing to improve standardization of care for patients with mitochondrial disease, including the development of expert consensus guidelines.³ Many of the treatment recommendations center around the care of acutely ill patients. Despite anecdotal and survey

evidence of substantial healthcare utilization in individuals with mitochondrial disease, there are few systematic investigations of their hospitalization patterns and costs. Families have indicated that this lack of information adds to their difficulty in planning care.⁴

Therefore, the objective of the present study was to investigate the impact of hospitalizations for mitochondrial disease across the lifespan in the U.S.

2. METHODS

2.1. Study Design and Setting

- i. Cross-sectional observational study. Analyses were performed using the Kids Inpatient Database (KID, pediatric) and the National Inpatient Survey (NIS, adult) from the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ) for the year 2012.⁵ Sample weights are used to generate national estimates.
- ii. Longitudinal observational study. This analysis used the California State Inpatient Database (SID-HCUP/AHRQ), for the years 2007–2011, inclusive.⁶ This database includes all admissions for patients of all ages to civilian hospitals in California; admissions for the same individual can be tracked over time.

2.2. Human Subjects Considerations

These analyses of de-identified data from a national sample were determined by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) not to meet the criteria for human subjects research, and therefore, ongoing IRB oversight was not required (FWA0000459).

2.3. Sample Identification

Hospitalizations were classified as either including ("mitochondrial disease") or not including ("not mitochondrial disease") a specific diagnosis of mitochondrial disease as designated by ICD9-CM code 277.87 (disorder of mitochondrial metabolism). In addition, individuals with Leigh syndrome, a neurodegenerative condition in which many identified mutations affect the mitochondrial respiratory chain and/or pyruvate dehydrogenase complex⁷, may receive the non-specific ICD9 code 330.8 ("other specified cerebral degenerations of childhood"). We sought to capture details of hospitalizations for individuals with possible Leigh syndrome. In addition, we sought to compare hospitalizations with diagnostic code of 277.87 to those with other related chronic neurologic or neuromuscular conditions that are separately coded. Therefore, we performed sensitivity analyses on hospitalizations including ICD9 330.8, ICD9 334.0 (Friedreich's Ataxia, whose pathogenesis includes mitochondrial dysfunction⁸), and ICD9 359.1 (muscular dystrophy, another myopathy). Hospitalizations flagged as "neonatal" or "maternal", i.e., pertaining to childbirth, were excluded from all analyses because our focus was on hospitalizations related to illness.

2.4. Demographics

Patient age and sex at admission were noted. Since the majority of individuals with mitochondrial disease were white, population ancestry was classified as white versus non-white. As a proxy for socioeconomic status (SES), quartile classification of the estimated median income for residents in the patient's zip code was included. This value ranges from 1 to 4, going from poorest to wealthiest households.

2.5. Chronic conditions

The number of chronic conditions for each participant was included.⁹

2.6. Hospital characteristics

These included: census region, teaching status, and whether the hospital was a free-standing children's hospital (pediatric analysis only).

2.7. Hospitalizations

Outcomes examined included: whether emergency room use occurred, number of in-hospital diagnoses, principal admitting diagnoses, whether a major operation occurred, length of stay, in-hospital mortality, and total hospital costs. Total hospital costs represent costs incurred (wages, supplies, utility costs), versus charges, that reflect the amount billed. Hospital-specific cost-to-charge ratios were used to generate estimated hospital costs from the charges.

2.8. Statistical Analyses

For the cross-sectional analyses of HCUP-KIDS and HCUP-NIS hospitalizations, descriptive statistics were generated. Appropriate tests for survey data implemented in SAS (v 9.4) (surveyreg, surveyfreq) were used to compare characteristics of hospitalizations where mitochondrial disease was versus was not included. U.S. census data¹⁰ were used to generate estimates per 100,000 population.¹¹ To enrich the description of hospitalizations, frequency plots were generated with in-hospital diagnoses mapped hierarchically onto phenotypes for purposes of visualization.¹² Bivariate logistic regression for survey data was performed to identify clinical characteristics associated with in-hospital mortality. Characteristics noted to be statistically significantly associated with in-hospital mortality in bivariate analyses were then included in multivariable logistic regression analyses to determine the independence of effects. For longitudinal analysis of hospitalizations related to mitochondrial disease in California between 2007 and 2011, descriptive statistics were generated. For each individual, number of hospitalizations in each calendar year of follow up was calculated. Analyses were performed in R (v.3.2.2).

3. RESULTS

3.1. Cross-sectional analysis

Results of the pediatric cross-sectional analysis are shown in Table 1A (details in Supplemental Table 1A). In 2012, an estimated 3,200 inpatient pediatric hospitalizations in the U.S. included the ICD9 code for mitochondrial disease. Children and adolescents

hospitalized with a mitochondrial disease diagnosis were more likely to be of white, non-Hispanic ancestry, to reside in geographic areas with higher median income, and to be privately insured. Substantially more chronic conditions were noted in hospitalizations for children with mitochondrial diseases than those without (4.3 vs. 0.7, $p<0.0001$). Also, hospitalizations for children with mitochondrial diseases were more likely to occur in children's hospitals (48% vs. 20%, $p<0.0001$) and in teaching hospitals (92% versus 67%, $p<0.0001$). Characteristics of hospitalizations are shown in Table 1B (details in Supplemental Table 1B). Patients with mitochondrial diseases were more likely to be admitted via the emergency room (55% versus 45%, $p<0.0001$), incur more in-hospital diagnoses, and have longer lengths of stay. The most common admitting diagnoses reflect the chronicity of illnesses. For example, "complications of a device, implant, or graft", e.g., gastrostomy tube, ventriculoperitoneal shunt, etc., is a frequent reason for admission. Principal diagnoses stratified by age group are shown in Supplemental Table 3. Despite the severity of their illnesses, children hospitalized with mitochondrial diseases were less likely to undergo a major operative procedure (13% versus 21%, $p<0.0001$), highlighting that many of their most pressing problems are managed medically and/or by minor operative procedures. Most striking, in-hospital mortality for children with mitochondrial diseases was 2.4%, as compared to 0.4% in those without ($p<0.0001$). The median cost of a hospitalization for a child with mitochondrial disease was more than twice the cost for a child without mitochondrial disease ($p<0.0001$). In total, an estimated \$80 million in direct hospitalization costs were incurred for children with mitochondrial diseases in the U.S. in 2012.

Results of the cross-sectional analyses in the adult population are similar to those obtained in children, but also demonstrate some key differences, as seen in Tables 2A and 2B (with details in Supplemental Tables 2A and 2B). In 2012, there were an estimated 2,000 inpatient adult hospitalizations for mitochondrial disease in the U.S. The median age at admission was 34 years (IQI, 22–52 years). As a result, we selected adults of similar age range (18–53 years) to serve as comparators for this study for purposes of illustration. Adults hospitalized with mitochondrial disease were more likely to be female, of non-Hispanic white ancestry, and reside in a geographic area with a higher median income. The complexity, acuity, and nature of co-morbid illnesses related to mitochondrial disease were similar in adults and children. In-hospital mortality was also substantially higher for adults with mitochondrial diseases than those without (3.1% versus 0.9%, $p<0.001$). In total, approximately \$33 million in direct hospitalization costs were incurred for adults with mitochondrial diseases in 2012 in the U.S.

In both children and adults, we visualized the range of co-morbid in-hospital diagnoses associated with admissions related to mitochondrial diseases in Supplemental Figures 3 and 4. Notably, in both children and adults, a wide range of organ systems is affected by mitochondrial diseases. In children, gastrointestinal complaints and developmental delay are observed most frequently. In adults, gastroesophageal reflux disease (GERD) is also found, along with comorbidities noted less frequently or not at all in children, including hypertension, coronary artery disease, major depression, and tobacco use; the latter may more reflect diagnoses of adulthood rather than mitochondrial disease, although this merits further study.

The higher rate of in-hospital mortality in both children and adults hospitalized with mitochondrial disease prompted us to examine more closely risk factors within this group. First, we examined the principal diagnoses in patients where the outcome of the hospitalization was death (Supplemental Table 4). Next to mitochondrial disease itself, sepsis, respiratory failure, and epilepsy occurred most often in these patients. Next, we performed bivariate analyses of demographic and clinical factors we postulated could be associated with mortality (Table 3A). In children, we found that admission via the emergency room was associated with higher in-hospital mortality, with an odds ratio (OR) of 2.27, 95% confidence interval (CI), 1.48 4.98, $p=0.0013$. Other indices of illness severity, however, displayed different patterns. In children, having more in-hospital diagnoses (OR 0.87, 95% CI, 0.82 0.91, $p<0.0001$) and a longer LOS (OR 0.98, 95% CI, 0.98 0.99, $p<0.0001$) were associated with lower mortality, while the opposite was true in adults, i.e., more in-hospital diagnoses (OR 1.12, 95% CI, 1.02 1.23, $p=0.023$) and longer LOS (OR 1.04, 95% CI, 1.00 1.07, $p=0.04$) were associated with increased mortality. In children, non-white population ancestry was associated with reduced likelihood of in-hospital death (OR 0.49, 95% CI, 0.25 0.39, $p=0.029$), and higher socioeconomic status was associated with higher odds of in-hospital death (OR 1.42, 95% CI, 1.11 1.28, $p=0.005$). These unexpected associations were not observed in adults.

Next, multivariable regression analyses were performed to understand the independence of these effects (Table 3B). Analyses were performed separately for children and adults. In the multivariable model of pediatric admissions, presentation via the emergency room (OR 3.09, 95% CI 1.52 6.37, $p=0.0018$) and having more chronic conditions (OR 1.18, 95% CI 1.02 1.36, $p=0.029$) were each independently associated with higher mortality. Again, in children, higher socioeconomic status appeared independently associated with in-hospital mortality (OR 1.41, 95% CI, 1.08 1.84, $p=0.011$). In the multivariable regression analysis model for adults, after accounting statistically for other covariates, having more in-hospital diagnoses was associated with a reduced risk of in-hospital death (OR 0.84, 95% CI, 0.72 0.81, $p=0.03$), in contrast to the result in bivariate analysis.

3.2. Longitudinal Data (California, 2007 2011)

Results of the analyses in longitudinal data are shown in Table 4. Over these five years, 495 individuals had at least one admission with a diagnosis of mitochondrial disease (ICD9 277.87), representing 2,485 admissions in total. Patients had a median of 1.1 hospitalizations (IQR, 0.6 2.2) per calendar year of follow-up. Over the five years included, individuals who had at least one hospitalization for mitochondrial diseases spent a median of 52 days (IQR, 20 128) in the hospital. In-hospital death was noted in the last hospitalization for 9.6% of the adults and 10.0% of children. At least one “do not resuscitate directive” during any hospitalization was noted in 42% of the adults who died in the hospital, and 7.8% adults who did not die in the hospital; for children, the corresponding values were 13.3% and 3.0%.

3.3. Comparison with other Chronic Neurologic and/or Muscular Diseases

In Supplemental Table 5 we show results of similar analyses regarding hospitalizations in individuals with other cerebral degenerations of childhood (a category that includes Leigh

syndrome), Friedreich's Ataxia, and muscular dystrophy. Overall, these conditions also demonstrate a high burden of comorbidities, costs, and excess mortality.

4. DISCUSSION

In summary, we have found that in the U.S., hospitalizations for pediatric and adults with mitochondrial diseases are associated with serious illnesses and substantial costs. Approximately 3,200 pediatric and 2,000 adult hospitalizations were associated with \$113 million in direct medical costs. These may well be underestimates, as we observed in the longitudinal data set that only approximately 50% of all such admissions are coded to indicate the patient has mitochondrial disease. Additionally, although diagnostic code we used is specific to mitochondrial disorders, it does not capture all disease sub-types, and even with perfect assignment, likely underestimates true disease prevalence. Clearly, much remains to be done to examine both the sensitivity and the specificity of administrative diagnostic codes with respect to new and evolving diagnostic criteria for mitochondrial disorders.³

A significant finding of our study is that in-hospital mortality was increased ~6-fold in children and ~3-fold in adults relative to comparators without mitochondrial disease. Paradoxically, in unadjusted analyses metrics for illness severity and acuity (e.g., number of in-hospital diagnoses, length of stay) seemed associated with lower in-hospital mortality rates in children with mitochondrial diseases. The opposite pattern was observed in adults. We postulate that these differences may reflect more acute, catastrophic illnesses in children that result in death, with less time in the hospital to accumulate diagnoses, and/or less attention to recording of comorbid conditions. Indeed, in multivariable regression analyses, admission via the emergency room and having more chronic conditions, all else equal, were both independently associated with higher rates of in-hospital mortality in both children and adults. Also, in the longitudinal data set, fewer children than adults who ultimately died had a "do not resuscitate" directive. This may relate to different practices surrounding this decision-making in children as compared to adults. Indeed, a previous study found that children entering hospice care were less than half as likely as adults to have a "do not resuscitate" directive.¹³

We also observed that in children, having higher socioeconomic status was independently associated with higher in-hospital mortality. We posit that this is due to diagnostic bias. The "diagnostic odyssey" that many patients undergo can take years of testing and evaluation, much of which may not be covered by insurance.¹⁴ Thus, among the most severely ill children with the highest mortality, those from families with higher incomes are more likely to have obtained a "true diagnosis" than those from families with lower incomes before they ultimately succumb to their illness. In addition, we posit that having a higher socioeconomic status permits more in-home care for mild or moderate illnesses, thus seeking care in the hospital is reserved for the most severe illnesses, where the outcome is more likely to be in-hospital death. These findings raise important questions about access to care for the most vulnerable children with complex medical problems and few resources.

This study utilizes population-level administrative data to study healthcare utilization for individuals with mitochondrial disease; no significant evidence base exists in this important area of research currently. This is in part because large samples are required to generate sufficient numbers of affected patients. One longitudinal prospective study from Europe¹⁵ demonstrated significant annual costs related to Friedreich's Ataxia (FA), a neuromuscular disorder that impacts mitochondrial function. They found that hospitalizations contributed to approximately 20% of total direct medical costs in the UK. Perhaps more critically, the costs related to caregiver support were ~6-fold greater than the costs of hospitalizations. In future, accounting for these other costs in mitochondrial diseases will be both important and illuminating. Information about healthcare utilization may also guide the evaluation of investigational drugs to treat mitochondrial disorders. In the absence of a very clear, reproducible biomarker of mitochondrial disease¹⁶, health care utilization metrics may represent viable endpoints for clinical trial development.

Results from the present study can also be situated in an important and growing literature focused on patients with one or more chronic complex medical condition. A seminal study using the same HCUP-KIDS database found that as the number of chronic complex medical conditions increases for a given patient, so do indices of acuity and resource use during hospitalizations.¹⁷ Our findings demonstrate this phenomenon for children with mitochondrial disease, and also illustrate that these hospitalizations are similarly resource-intensive for adults with mitochondrial disease. We showed that individuals with other progressive disorders such as Friedreich's Ataxia and Muscular Dystrophy also incur high costs (Supplemental Table 5). With improved supportive care for children and increasing rates of diagnosis in older individuals, there is a need for mitochondrial disease physicians who can care for patients across the age spectrum, and/or who can collaborate in achieving the pediatric-to-adult transition.¹⁸

This study has several key strengths and limitations. The large sample size of the administrative datasets allows us to identify many admissions related to mitochondrial disorders, a significant advantage when studying a set of individually rare and likely under-diagnosed conditions. However, an important associated limitation is that the sensitivity and specificity of using the ICD9 code 277.87 to identify "true" cases of mitochondrial diseases in these administrative databases is not known. Moreover, diagnostic criteria for mitochondrial diseases are evolving¹ and consensus regarding diagnosis can be challenging to achieve.³ Despite this important limitation, in both children and adults, the comorbidities identified in the present study in association with mitochondrial disorders closely recapitulate the range of clinical problems described in curated observational studies of individuals with mitochondrial diseases across the lifespan.^{1,18} Therefore, we expect that these estimates offer plausible, if imprecise, estimates of healthcare burden related to hospitalizations for mitochondrial disorders. The true magnitude of healthcare utilization and costs likely vastly exceeds what is reported here. The advent of ICD10 codes that include greater granularity for mitochondrial disease diagnoses may help with achieving more diagnostic precision. An inherent limitation of the cross-sectional dataset is the inability to identify the same individual across multiple hospitalizations. While this is possible in the California dataset, individuals may also have moved in or out of the state during the course of the study. Thus, truly patient-specific longitudinal assessments of

healthcare burden may require prospective tracking, as may become possible with the advent of registries such as the North American Mitochondrial Disease Consortium.¹⁹ Another limitation is that the median income of the patient's zip code was used as the primary proxy for socioeconomic status, thus our intriguing findings require follow-up studies with more direct metrics. Finally, in the present study we compared participants with mitochondrial disorders to "all-comers" of similar ages for purposes of illustration. This is because the primary purpose of this initial study is to be descriptive. In the future, for example, we may compare children with mitochondrial disorders to others with chronic conditions, to enrich and contextualize our understanding of these patterns.

The severity of illness in many individuals with mitochondrial disease is such that hospitalizations at some frequency are unavoidable. However, there is likely much in the way of supportive care that can be pursued to prevent reduce their burden. Identification of risk factors for, and more importantly, strategies to help prevent, mitochondrial disease related hospitalizations needs to be the focus of continued investigation.^{20–26} Moreover, emphasis should be placed on understanding the impact of these hospitalizations on quality of life for both patients with mitochondrial disease and their families.^{27,28} It is our hope that these initial efforts to define the scope of the health care burden of mitochondrial disease in the U.S. will be followed closely by studies of best practices to optimize patients' experiences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SEM is supported by NIH DK102659. RDG is supported by NIH GM008638

Abbreviations

HCUP-NIS Healthcare Cost and Utilization Project – Nationwide Inpatient Sample

HCUP-KID Healthcare Cost and Utilization Project – Kids' Inpatient Sample

References

1. Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007; 120(6):1326–1333. [PubMed: 18055683]
2. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Annals of neurology*. 2015; 77(5):753–759. [PubMed: 25652200]
3. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2014
4. Noorda G, Hermans-Peters M, Smeitink J, et al. Mitochondrial disease: needs and problems of children, their parents and family. A systematic review and pilot study into the need for information of parents during the diagnostic phase. *Journal of inherited metabolic disease*. 2007; 30(3):333–340. [PubMed: 17508266]

5. HCUP Kids' Inpatient Database (KID). [Accessed 7/11/2016] Healthcare Cost and Utilization Project (HCUP). 2012. <http://www.hcup-us.ahrq.gov/kidoverview.jsp>
6. HCUP State Inpatient Databases (SID). [Accessed 7/11/2016] Healthcare Cost and Utilization Project (HCUP). 2007–2011. <http://www.hcup-us.ahrq.gov/sidoverview.jsp>
7. Gerards M, Sallevelt SC, Smeets HJ. Leigh syndrome: Resolving the clinical and genetic heterogeneity paves the way for treatment options. *Mol Genet Metab*. 2016; 117(3):300–312. [PubMed: 26725255]
8. Kaplan J. Friedreich's ataxia is a mitochondrial disorder. *Proceedings of the National Academy of Sciences of the United States of America*. 1999; 96(20):10948–10949. [PubMed: 10500103]
9. Perrin EC, Newacheck P, Pless IB, et al. Issues involved in the definition and classification of chronic health conditions. *Pediatrics*. 1993; 91(4):787–793. [PubMed: 8464668]
10. U.S. Census Bureau PD. Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2012.
11. Bureau USC. [Accessed 7/11/2016] <https://www.census.gov/popest/data/state/asrh/2012/SC-EST2012-AGESEX-CIV.html>
12. Carroll RJ, Bastarache L, Denny JC. R PheWAS: data analysis and plotting tools for phenome-wide association studies in the R environment. *Bioinformatics*. 2014; 30(16):2375–2376. [PubMed: 24733291]
13. Dingfield L, Bender L, Harris P, et al. Comparison of pediatric and adult hospice patients using electronic medical record data from nine hospices in the United States, 2008–2012. *J Palliat Med*. 2015; 18(2):120–126. [PubMed: 25411904]
14. McCormick E, Place E, Falk MJ. Molecular genetic testing for mitochondrial disease: from one generation to the next. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2013; 10(2):251–261. [PubMed: 23269497]
15. Giunti P, Greenfield J, Stevenson AJ, et al. Impact of Friedreich's Ataxia on health-care resource utilization in the United Kingdom and Germany. *Orphanet journal of rare diseases*. 2013; 8:38. [PubMed: 23448170]
16. Pfeffer G, Horvath R, Klopstock T, et al. New treatments for mitochondrial disease-no time to drop our standards. *Nature reviews Neurology*. 2013; 9(8):474–481. [PubMed: 23817350]
17. Simon TD, Berry J, Feudtner C, et al. Children with complex chronic conditions in inpatient hospital settings in the United States. *Pediatrics*. 2010; 126(4):647–655. [PubMed: 20855394]
18. Chinnery PF. Mitochondrial disease in adults: what's old and what's new? *EMBO molecular medicine*. 2015; 7(12):1503–1512. [PubMed: 26612854]
19. 2016. <https://www.rarediseasesnetwork.org/cms/NAMDC>
20. Berman S, Rannie M, Moore L, Elias E, Dryer LJ, Jones MD Jr. Utilization and costs for children who have special health care needs and are enrolled in a hospital-based comprehensive primary care clinic. *Pediatrics*. 2005; 115(6):e637–642. [PubMed: 15930189]
21. Chamberlain LJ, Chan J, Mahlow P, Huffman LC, Chan K, Wise PH. Variation in specialty care hospitalization for children with chronic conditions in California. *Pediatrics*. 2010; 125(6):1190–1199. [PubMed: 20439593]
22. Collier RJ, Lerner CF, Eickhoff JC, et al. Medical Complexity among Children with Special Health Care Needs: A Two-Dimensional View. *Health Serv Res*. 2016; 51(4):1644–1669. [PubMed: 26619824]
23. Kuo DZ, Berry JG, Glader L, Morin MJ, Johaningsmeir S, Gordon J. Health Services and Health Care Needs Fulfilled by Structured Clinical Programs for Children with Medical Complexity. *The Journal of pediatrics*. 2016; 169:291–296. e291. [PubMed: 26526361]
24. Nageswaran S. Respite care for children with special health care needs. *Arch Pediatr Adolesc Med*. 2009; 163(1):49–54. [PubMed: 19124703]
25. Smith AG, Andrews S, Bratton SL, et al. Pediatric palliative care and inpatient hospital costs: a longitudinal cohort study. *Pediatrics*. 2015; 135(4):694–700. [PubMed: 25802343]
26. Szilagyi PG, Shenkman E, Brach C, et al. Children with special health care needs enrolled in the State Children's Health Insurance Program (SCHIP): patient characteristics and health care needs. *Pediatrics*. 2003; 112(6 Pt 2):e508. [PubMed: 14654673]

27. Elson JL, Cadogan M, Apabhai S, et al. Initial development and validation of a mitochondrial disease quality of life scale. *Neuromuscular disorders : NMD*. 2013; 23(4):324–329. [PubMed: 23433484]
28. Senger BA, Ward LD, Barbosa-Leiker C, Bindler RC. Stress and coping of parents caring for a child with mitochondrial disease. *Appl Nurs Res*. 2016; 29:195–201. [PubMed: 26856513]

Table 1A

Demographic characteristics of hospitalizations, summary.

Hospitalizations in 2012, HCUP-KID				
	Pediatric (under 21 years), with Mitochondrial Disease		Pediatric (under 21 years), without Mitochondrial Disease	
Number of hospitalizations, In total	<i>Total</i>		<i>Total</i>	
	3,228		2,935,658	
Number of hospitalizations, by age group (years)	<i>Total (%)</i>		<i>Total (%)</i>	
<2	423 (13)		708,523 (24)	
2 – <18	2530 (78)		1,411,438 (48)	
18 – <21	275 (8.5)		815,697 (28)	
Sex and population ancestry, by age group (years)	% female (n)	% white, non-Hispanic (n)	% female (n)	% white, non-Hispanic (n)
<2	49.7 (210)	51.2 (217)	43.7 (309,977)	43.7 (309,853)
2 – <18	49.3 (1,246)	65.8 (1,665)	51.0 (720,041)	46.2 (651,874)
18 – <21	56.2 (154)	61.0 (168)	76.0 (620,164)	46.8 (381,848)
Number of chronic conditions, by age group	<i>Median (IQR)</i>		<i>Median (IQR)</i>	
<2	3.8 (2.5, 5.5)		0 (0, 0.8)	
2 – <18	4.3 (2.7, 6.2)		0.7 (0, 1.9)	
18 – <21	4.8 (3.2, 6.8)		0.2 (0, 1.6)	
Median household income for participant zip code (quartile, higher = higher income)	<i>Median (IQR)</i>		<i>Median (IQR)</i>	
	2.3 (1.2, 3.2)		1.6 (1.0, 2.7)	
Expected primary payer	<i>Percentage in category (n)</i>		<i>Percentage in category (n)</i>	
Medicaid	37.0 (1194)		52.7 (1,548,473)	
Private, Including HMO	55.5 (1,791)		37.9 (1,113,639)	
Self-pay	1.6 (53)		3.8 (111,667)	
No charge/other	5.9 (188)		5.2 (154,313)	
Hospital characteristics				
Geographic region	<i>Total (%)</i>		<i>Total (%)</i>	
Northeast	587 (18)		512,699 (17)	
Midwest	817 (25)		654,462 (22)	
South	1059 (33)		1,139,573 (39)	
West	766 (24)		628,924 (21)	
Type	<i>Total (%)</i>		<i>Total (%)</i>	
Children's hospital	1,561 (48)		584,938 (20)	
Not a children's hospital	1,667 (52)		2,350,720 (80)	
Teaching Status	<i>Total (%)</i>		<i>Total (%)</i>	
Teaching hospital	2,967 (92)		1,979,759 (67)	
Not a teaching hospital	261 (8.1)		955,899 (33)	

IQR = inter-quartile interval. Values in bold text are statistically significantly different between individuals with and without mitochondrial disease.

Table 1B

Hospitalization characteristics, outcomes, costs, and charges, summary.

Hospitalizations in 2012, HCUP-KID				
	Pediatric (under 21 years), with Mitochondrial Disease		Pediatric (under 21 years), without Mitochondrial Disease	
Emergency room (ER) use	<i>Percentage in category (n)</i>		<i>Percentage in category</i>	
% with ER use	54.9 (1772)		45.3 (1,329,463)	
Number of in-hospital diagnoses, by age group(years)	<i>Median (IQI)</i>		<i>Median (IQI)</i>	
<2	9.4 (6.3, 14.1)		2.8 (1.5, 5.0)	
2 – <18	9.0 (6.0, 13.3)		3.1 (1.6, 5.3)	
18 – <21	9.8 (6.5, 13.5)		3.9 (2.2, 6.1)	
Principal admitting diagnosis, 5 most common	<i>Diagnosis</i>	<i>% of total (n)</i>	<i>Diagnosis</i>	<i>% of total (n)</i>
	Other nutritional,endocrine, metabolic ^I	12.5 (403.2)	Mood disorders	5.5 (160,664)
	Epilepsy	11.6 (374.0)	Pneumonia	4.5 (130,796)
	Complication of device; implant or graft	6.7 (215.1)	Asthma	4.4 (128,011)
	Pneumonia	5.2 (166.5)	Bronchitis	4.2 (124,068)
	Fluid/electrolyte disorders	4.5 (145.3)	Delivery-related	3.2 (93,927)
Major operating room procedure?	<i>Percentage (n)</i>		<i>Percentage (n)</i>	
Yes	13.4 (434)		20.7 (607,259)	
Length of stay	<i>Median (IQI)</i>		<i>Median (IQI)</i>	
	3.1 (1.4, 7.1)		1.9 (1.0, 3.6)	
In-hospital death?	<i>Percentage (n)</i>		<i>Percentage (n)</i>	
Yes	2.4 (77)		0.4 (11,943)	
Hospital costs	<i>Median (IQI)</i>		<i>Median (IQI)</i>	
	\$9,037 (\$4,346, \$20,728)		\$4,240 (\$2,474, \$8,206)	

IQI = inter-quartile interval.

^I Includes the diagnosis of mitochondrial disease itself.

Values in bold text are statistically significantly different between individuals with and without mitochondrial disease.

Table 2A

Patient and hospital characteristics, adult hospitalizations, summary.

Hospitalizations in 2012, HCUP-NIS		
	Adults (18 years and older), with Mitochondrial Disease	Adult (18–53 years), without Mitochondrial Disease
Number of hospitalizations, In total	<i>Total</i>	<i>Total</i>
	1,935	8,459,353
Age (years)	<i>Median (IQI)</i>	<i>Median (IQI)</i>
	35.6 (23.0, 52.5)	41.5 (31.3, 48.1)
Sex	<i>% female (n)</i>	<i>% female (n)</i>
	62.5 (1,210)	51.4 (4,345,732)
Population ancestry	<i>% white, non-Hispanic (n)</i>	<i>% white, non-Hispanic (n)</i>
	80.6 (1,450)	61.1 (4,899,721)
Number of chronic conditions	<i>Median (IQI)</i>	<i>Median (IQI)</i>
	5.87 (3.90, 7.77)	2.99 (1.32, 5.07)
Median household income for participant zip code (quartile, higher = higher income)	<i>Median (IQI)</i>	<i>Median (IQI)</i>
	2.16 (1.07, 3.26)	1.66 (1.00, 2.73)
Expected primary payer	<i>Percentage in category (n)</i>	<i>Percentage in category (n)</i>
Medicaid	19.4 (375)	23.9 (2,017,352)
Private, Including HMO	40.1 (775)	39.5 (3,328,675)
Self-pay	3.4 (65)	13.8 (1,164,906)
Medicare	33.9 (655)	15.4 (1,300,065)
No charge/other	3.4 (65)	7.4 (622,420)
Hospital characteristics	<i>Total (%)</i>	<i>Total (%)</i>
Geographic region		
Northeast	600 (31)	1,699,748 (20)
Midwest	490 (25)	1,888,638 (22)
South	520 (27)	3,293,309 (39)
West	325 (17)	1,578,313 (19)
Teaching Status	<i>Total (%)</i>	<i>Total (%)</i>
Teaching hospital	1,310 (68)	4,565,669 (54)
Not a teaching hospital	625 (32)	3,894,339 (46)

IQI = inter-quartile interval. Values in bold text are statistically significantly different between individuals with and without mitochondrial disease.

Table 2B

Hospitalization characteristics, outcomes, costs, and charges, summary.

Hospitalizations in 2012, HCUP-NIS				
	Adults (21 years and older), with Mitochondrial Disease		Adult (21 years and older), without Mitochondrial Disease	
Emergency room (ER) use	<i>Percentage in category (n)</i>		<i>Percentage in category (n)</i>	
% with ER use	68.2 (1,320)		62.3 (5,270,361)	
Number of in-hospital diagnoses, by age group (years)	<i>Median (IQI)</i>	<i>Range</i>	<i>Median (IQI)</i>	<i>Range</i>
	11.5 (8.1, 15.3)	2 – 34	6.7 (3.8, 10.4)	0 – 60
Principal admitting diagnosis, 5 most common	<i>Diagnosis</i>	<i>% of total (n)</i>	<i>Diagnosis</i>	<i>% of total (n)</i>
	Other nutritional, endocrine, metabolic ^I	17.1 (66)	Mood Disorder	6.6 (112,038)
	Epilepsy	6.7 (26)	Schizophrenia	3.2 (53,716)
	Complication of device; implant or graft	6.7 (26)	Skin infection	3.0 (51,559)
	Sepsis	4.9 (19)	Diabetes mellitus	2.9 (49,836)
	Other gastrointestinal	3.4 (13)	Sepsis	2.7 (46,100)
Major operating room procedure?	<i>Percentage (n)</i>		<i>Percentage (n)</i>	
Yes	13.4 (260)		29.0 (2,453,866)	
Length of stay	<i>Median (IQI)</i>		<i>Median (IQI)</i>	
	3.59 (1.60, 7.90)		2.41 (1.15, 4.59)	
In-hospital death?	<i>Percentage (n)</i>		<i>Percentage (n)</i>	
Yes	3.1 (60)		0.9 (79,370)	
Hospital costs	<i>Median (IQI)</i>		<i>Median (IQI)</i>	
	\$8,695 (\$4,799, \$16,884)		\$6,536 (\$3,779, \$11,850)	

IQI = inter-quartile interval.

^I Includes the diagnosis of mitochondrial disease itself.

Values in bold text are statistically significantly different between individuals with and without mitochondrial disease.

Table 3A

Bivariate analyses, risk factors for mortality during hospitalizations where mitochondrial disease was noted, stratified by pediatric versus adult age.

Hospitalizations in 2012, HCUP-KID and HCUP-NIS				
	Pediatric (< 21 years), with Mitochondrial Disease		Adult (18 years), with Mitochondrial Disease	
Factor	Unadjusted OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value
Age (per year increase)	1.05 (0.97, 1.13)	0.24	1.02 (1.00, 1.07)	0.06
Male sex	0.89 (0.53, 1.49)	0.65	1.20 (0.37, 3.85)	0.76
Non-white population ancestry	0.49 (0.25, 0.93)	0.029	2.20 (0.66, 7.38)	0.20
Number of chronic conditions	0.84 (0.76, 0.93)	0.0007	1.10 (0.90, 1.33)	0.35
Median household income for participant zip code	1.42 (1.11, 1.82)	0.0050	0.85 (0.48, 1.51)	0.58
Medicaid insurance	0.75 (0.43, 1.31)	0.31	1.40 (0.37, 5.35)	0.62
Emergency room use	2.72 (1.48, 4.98)	0.0013	0.93 (0.27, 3.14)	0.91
Number of in-hospital diagnoses	0.87 (0.82, 0.91)	< 0.0001	1.12 (1.02, 1.23)	0.023
Major operating room procedure	0.49 (0.27, 0.90)	0.021	1.30 (0.27, 6.19)	0.74
Length of stay (per day increase)	0.98 (0.98, 0.99)	< 0.0001	1.04 (1.00, 1.07)	0.04
Hospital Characteristics				
Geographic region				
Northeast	reference		reference	
Midwest	0.84 (0.316, 2.241)	0.71	3.76 (0.37, 38)	0.87
South	0.86 (0.307, 2.406)	0.80	4.76 (0.51, 44)	0.52
West	0.98 (0.353, 2.718)	0.80	7.80 (0.85, 72)	0.10
Non-children's hospital	0.84 (0.460, 1.530)	0.57	-	-
Non teaching hospital	1.61 (0.375, 6.873)	0.52	0.41 (0.09, 1.90)	0.25

Factors indicated in bold text demonstrated a statistically significant association with in-hospital mortality during hospitalizations where mitochondrial disease was noted (i.e., OR>1 corresponds to increased risk of in-hospital death, OR<1 corresponds to decreased risk of in-hospital death). OR = odds ratio; CI = confidence interval.

Table 3B

Multivariable logistic regression analysis of in-hospital mortality during hospitalizations where mitochondrial disease was noted, stratified by pediatric versus adult age.

	Pediatric (< 21 years), with Mitochondrial Disease		Adult (≥ 18 years), with Mitochondrial Disease	
Factor	<i>Adjusted OR (95% CI)</i>	<i>p-value</i>	<i>Adjusted OR (95% CI)</i>	<i>p-value</i>
Age (per year increase)	1.00 (0.94, 1.08)	0.84	0.96 (0.93, 1.00)	0.05
Non-white population ancestry	0.57 (0.29, 1.13)	0.11	0.58 (0.19, 1.78)	0.34
Number of chronic conditions	1.18 (1.02, 1.36)	0.03	1.33 (0.93, 1.88)	0.12
Median household income for participant zip code	1.41 (1.08, 1.84)	0.01	1.11 (0.64, 2.02)	0.67
Emergency room use	3.09 (1.52, 6.28)	.002	1.46 (0.38, 5.72)	0.58
Number of in-hospital diagnoses	0.82 (0.78, 0.88)	< 0.0001	0.84 (0.72, 0.98)	0.03
Major operating room procedure	1.14 (0.56, 2.32)	.73	1.29 (0.23, 7.35)	0.77
Length of stay (per day increase)	1.00 (0.99, 1.02)	.60	0.98 (0.95, 1.00)	0.10

Factors indicated in bold text demonstrated a statistically significant association with in-hospital mortality during hospitalizations where mitochondrial disease was noted (i.e., OR>1 corresponds to increased risk of in-hospital death, OR<1 corresponds to decreased risk of in-hospital death). OR = odds ratio; CI = confidence interval.

Table 4

Longitudinal Trends in Hospitalization in California between 2007 and 2011, inclusive.

California SID		
	Individuals with at least one hospitalization associated with mitochondrial disease	
Number of individuals, total	495	
Age group at initial hospitalization (years)	<i>Total</i>	<i>Percent</i>
<2	68	14%
2 – <18	230	46%
18 – <65	176	36%
65 +	19	4%
Sex and population ancestry, by age group (years)	<i>% female (n)</i>	<i>% white, non-Hispanic (n)</i>
<2	47% (32)	23% (15)
2 – <18	46% (104)	38% (80)
18 – <65	61% (105)	61% (100)
65 +	58% (11)	79% (15)
Number of chronic conditions, by age group (years), at initial hospitalization	<i>Median (IQI)</i>	<i>Range</i>
<2	4 (2 – 6)	0 – 10
2 – <18	3 (2 – 6)	1 – 10
18 – <65	5 (3 – 7)	1 – 14
65 +	5.5 (5 – 6.5)	4 – 11
Expected primary payer, at initial hospitalization	<i>Percentage in category (n)</i>	
Medicaid	40% (200)	
Private, Including HMO	42% (207)	
Medicare	10% (51)	
No charge/other	8% (37)	
Length of Stay (days), for all hospitalizations	<i>Median (IQI)</i>	<i>Range</i>
	4 (2 – 8)	0 – 268
In-Hospital Mortality (%), for all hospitalizations	<i>Percentage (n)</i>	
	2% (49)	
Number of admissions per participant per year of follow-up, by age group (years) *	<i>Median (IQI)</i>	<i>Range</i>
<2	1.9 (0.9 – 2.9)	0.2 – 12
2 – <18	1.1 (0.6 – 2.0)	0.2 – 36
18 – <65	1.1 (0.6 – 2.0)	0.2 – 12
65 +	1.1 (0.8 – 2.6)	0.3 – 5.1
Estimated hospitalization costs per year of follow-up, by age group at initial hospitalization (years) **	<i>Median (IQI)</i>	<i>Range</i>
<2	\$ 36,069 (14,472 – 95,093)	\$ 999 – 385,708
2 – <18	\$ 15,018 (6,128 – 44,255)	\$ 444 – 1,791,876

California SID		
	Individuals with at least one hospitalization associated with mitochondrial disease	
18 – <65	\$ 15,495 (5,797 – 31,977)	\$ 457 – 325,860
65 +	\$ 10,423 (5,397 – 33,899)	\$ 1,564 – 115,199

IQI = inter-quartile interval.

* Difference across age groups in hospitalization frequency is statistically significant, $p=0.014$ by Kruskal-Wallis test.

** Difference across age groups in hospitalization costs is statistically significant, $p<0.0001$ by Kruskal-Wallis test.