I, A Rang, Kim M.S., hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Discontinuing Enzyme Replacement Therapy in Patients with Lysosomal Storage Diseases due to Significant Clinical Decline

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Discontinuing Enzyme Replacement Therapy (ERT) in Patients with Lysosomal Storage Diseases (LSDs) due to Significant Clinical Decline

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Abstract

Enzyme replacement therapy (ERT) is considered the most effective and promising treatment for patients with lysosomal storage diseases (LSDs). Since ERT has been available for a relatively short amount of time, scientific focus has been on how effectively the replacement enzyme works. Few studies have discussed discontinuing ERT and those that have focus on the clinical effects of discontinuation. The purpose of this study was to learn the experiences, thoughts, attitudes, and reported behaviors of healthcare providers related to discontinuation of ERT in patients with severe forms of LSDs who experience significant clinical decline. Moreover, this study assessed how healthcare providers define significant clinical decline in this patient population. A survey was sent out to healthcare professionals through the Metab-L and the National Society of Genetic Counselors’ (NSGC) listservs. A total of 81 responses were used in the final analysis. The most commonly selected feature describing significant clinical decline was persistent vegetative state (58/74; 78.38%). Cognitive decline was a factor as well, especially when comparing two hypothetical patient scenarios that were provided. One quarter of participants had previously recommended discontinuing ERT due to significant clinical decline with nearly 90% of families actually opting to discontinue. Recommending discontinuation of ERT correlated with healthcare providers’ number of years of experience and genetic counselors were less likely to discuss the option with the patient/family compared to the physician population. One of the reasons that genetic counselors listed for this was that recommending discontinuation of therapy was outside their scope of practice. In conclusion, there are healthcare providers discussing the option of discontinuing ERT in cases with significant clinical decline, especially those with more years of experience. Persistent vegetative state and cognitive decline play a role when considering discontinuation of the therapy, though decision should always come with full involvement of the patient and family as well as healthcare team. The roles of genetic counselors in this situation need to be considered in light of their organizational situation and the definition of genetic counseling developed by the NSGC.

Keywords: Enzyme Replacement Therapy (ERT), Discontinuing Enzyme Replacement Therapy; Lysosomal Storage Diseases (LSDs), Significant Clinical Decline, Genetic Counseling
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**Background**

The lysosomal storage diseases (LSDs) are a group of more than 50 inborn errors of metabolism which result from defects of specific lysosomal enzymes, lysosomal membrane proteins, or transporters. Undigested macromolecules in the lysosomes including sphingolipids, glycogen, mucopolysaccharides, and glycoproteins progressively accumulate in cells of most tissues (Desnick et al., 2012; Jurecka et al., 2012). Enzyme replacement therapy (ERT) was first suggested as a treatment for patients with LSDs in 1964 (Deduve, 1964), and clinical trials for ERT by intravenous (IV) infusion for several LSDs began in the early 1970s. These early trials confirmed the feasibility of ERT and in 1991, ERT became commercially available for Gaucher disease (Rosenberg, 1991). Today, FDA approved products exist not only for Gaucher disease, but also for Fabry disease, Mucopolysaccharidosis (MPS) I, II, IVA and VI, and Pompe disease. There are ongoing clinical trials for other LSDs (Desnick et al., 2012), including MPS IIA and Lysosomal Acid Lipase Deficiency that may also benefit from ERT.

After the safety and effectiveness in treating type I Gaucher disease with ERT was established, scientific focus in the last decade has been on how effectively the replacement enzyme works (Beutler, 2004; Burrow et al., 2007; Connock et al., 2006; de Ru et al., 2011; Desnick et al., 2012; Muenzer et al., 2012; Wraith, 2006). Although ERT is the most promising therapy for patients with LSDs, it is not a cure, and it only slows down the progression of the disease. Traditional ERT is unable to cross the blood-brain barrier; therefore, ERT is not able to treat neurological symptoms which are present in many LSDs (Desnick et al., 2012). At some point, disease progression may make it difficult to ascertain if the ERT is helping the patient. Also, regardless of its medical benefits, ERT is a time consuming and expensive process which requires patients and their families to take on a significant burden. Treatment occurs weekly or biweekly, depending on the disease and is lifelong process. If the patient does not respond well to ERT or if there is significant clinical decline after many years of treatment, patients, family members, and healthcare providers might consider discontinuing ERT when it appears to be no longer effective.
Significant Clinical Decline

To date, there are few publications that address discontinuing ERT because of a patient’s significant clinical decline. Among the patients with Gaucher disease that Elstein et al (2000) described, one patient had reactive arthritis and three patients had pulmonary hypertension during ERT which led them to withdraw from the therapy. However, the purpose of the study was not to explore the reasons of discontinuation nor to describe significant clinical decline, but to evaluate the clinical responses after the withdrawal.

Hospice literature does discuss treatment failure and imminent clinical decline, although it is not specific for patients with LSDs. Miller et al (2012) reported three pediatric patients with progressive diseases who required hospice care due to clinical decline. Their decline included profound cognitive impairment, hypotonic cerebral palsy, intractable seizures, feeding entirely via gastrostomy tube, inability to move, ventilator-dependency with severe neuropathic pain and feeding intolerance. One of the ways that Travis et al (2005) approached a patient’s decline was described as “... focus on incremental treatment failures that signal the need for the care team to transition the person from active curative care to palliation and end-of life (EOL) care.” These treatment failures that they described included weight loss, repetitive falls, recurrent incontinence, and increased dependency in personal care. The authors also mentioned decreased cognitive functioning that is not treatable or reversible, uncontrollable persistent or recurrent infections, declining immune functioning, skin breakdown, failure to meet desired therapeutic goal, and lose of interest in living as contributing to clinical decline.

Discontinuing ERT

Case reports and studies of interrupting or discontinuing ERT in patients with LSDs have focused mostly on the clinical effects after discontinuation (Anbu et al., 2006; Elstein et al., 2000; Grinzaied et al., 2002; Wegrzyn et al., 2007). Several studies have described and discussed the limitations of ERT, other possible/upcoming treatment options and the guidelines that should be developed in order to meet the treatment goals. Muenzer et al (2012) proposed treatment guidelines for ERT in severe Hunter syndrome in order to help guide decisions about initiation and
discontinuation of the therapy. This is important because the neurological decline in Hunter syndrome cannot be stopped or reversed with ERT. The authors emphasized that the decision of initiating and discontinuing ERT should be individualized based on realistic expectations of the benefits and risks of treatment.

The few studies that discussed reasons for discontinuation have listed the reasons broadly such as infusion reaction, financial constraints, and personal concerns. Anbu et al (2006) described about a 21 year old female with MPS I H/S (intermediate Hurler-Scheie syndrome) who became pregnant after about 80 weeks of treatment with laronidase and discontinued ERT due to the uncertainty about fetal effects. She could not receive ERT immediately post-partum because of financial reasons. Grinzaid et al (2002) reported four patients with Gaucher disease who discontinued ERT due to patient and/or family’s request, cost, and concern about future insurability. Elstein et al (2000) described the withdrawal of ERT in fifteen patients with Gaucher disease in Israel with reasons of unspecified personal concerns, desire to serve in the military, political/financial constraints and clinical deterioration including reactive arthritis and pulmonary hypertension.

Purpose of Study
This study focused on the reasons for discontinuing enzyme replacement therapy in patients with lysosomal storage diseases, especially in the presence of significant clinical decline. We expect to expand the discussion that Muenzer et al (2012) addressed with Hunter syndrome to the LSDs for which ERT is currently available. Specifically we sought to identify the experiences, thoughts, and attitudes of healthcare providers relative to their reported behaviors involving discontinuation of ERT in patients with the following LSDs – Gaucher disease type II, Gaucher disease type III, non-transplanted MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome) and Pompe disease (all types). Also, we assessed how healthcare providers define significant clinical decline in patients with LSDs.

Methods

Participants and Procedures
This cross-sectional study involved surveying a sample of healthcare providers – physicians, genetic counselors, and nurses – who see patients with certain lysosomal storage diseases (LSDs) in the United States and other countries through the National Society of Genetic Counselors (NSGC) and Metab-L listserv. Among the LSDs described above, Gaucher disease type I and Fabry disease were excluded because the physical and/or cognitive symptoms are typically not as severe as the other conditions. Thus, they were considered too difficult to assess significant clinical decline. This study was approved by the Institutional Review Boards (IRB) at Cincinnati Children’s Hospital Medical Center and the University of Cincinnati.

**Questionnaire**

An online questionnaire (appendix 3) was developed by the primary investigator with input from the research advisory committee (RAC) members. The questionnaire contained a total of 28 questions. Skip logic was applied throughout the survey in order to guide the participants to specific questions based on their previous responses. The online questionnaire was piloted for face validity with a small group of genetic counselors and one physician who were then ineligible for participation in the actual study. The survey was accompanied by a cover letter (appendix 1 and 2) explaining the purpose of the study and how to participate. Waiver of documentation of informed consent was received from the IRB.

The questionnaire sought participants’ demographic information including job title, gender, age, city and/or state they practice, years of practice, number of patients following, and number of patients discontinued enzyme replacement therapy (ERT). Participants who ever had a patient with certain LSDs were eligible to continue the questionnaire, but if not, they were skipped to the vignette section. For those who were eligible, questionnaire asked how they define *significant clinical decline* in patients with certain LSDs. Specific clinical features from clinical experience and a literature search were listed and based on that information, participants could select in the list and/or were able to expand their thoughts. Furthermore, questionnaire asked participants their experience regarding discontinuing ERT in patients with certain LSDs. There were also two vignettes about hypothetical
patient case scenarios and related multiple choice and open-ended questions about whether to discuss the option of discontinuing ERT or not in each case (Table 1).

The qualitative data which were unable to be categorized throughout the questionnaire such as *I checked one of boxes ONLY because your survey would not let me continue without doing so* were excluded. Also, repetitive comments that were already chosen in close-ended answer and irrelevant comments were excluded in the final analysis.

**Data Collection**

Data were collected with SurveyMonkey®, an online survey tool. An invitation that contained a link to the survey was emailed to potential participants (appendix 1). Reminder emails were sent three weeks and five weeks after the initial emailing (appendix 2). The duration of the survey started on September 10th, 2013 and ended on November 5th, 2013.

**Data Analysis**

All survey responses (n=122) were collected electronically through SurveyMonkey®. The software that was used for the data analysis was SAS V9.3 (SAS institute, Cary, NC). Descriptive statistics for variables measured is provided as a frequency and percentages. Association between measured outcomes (question 13, 14, 15, 21, 22, and 27) and demographic variables were examined using a chi-square test. For open-ended data analysis, the first author independently coded the responses after downloading it from the SurveyMonkey®. The coded data was confirmed with the other authors, and discrepancies in coding were discussed and reconciled.

**Results**

**Demographic Information**

Among all survey responses (n=122), incomplete responses that only contained demographic information (n=28), wrong population (n=7), and not enough data to analyze (n=6) were removed from the final analysis. Therefore, 81 responses were analyzed. Demographics of healthcare providers who participated in this study were 54 (66.67%) genetic counselors, 22 (27.16%) physicians and five (6.17%) others, which included one medical science liaison (MSL) and four nurses (Table 2). Seventy of 81 participants (86.42%) were female and 52 (64.19%) were between the ages of 25-44. Locations
of respondents were sorted according to the six National Society of Genetic Counselors (NSGC) regional categories with creation of a “Region 7” for the participants from Canada and other areas outside the USA. Large number of participants (68.83%) was from regions 2, 3, and 4. No correlation of participants’ questionnaire responses with their practice locations was identified in the data analysis.

**Characteristics of Participants**

Among 81 participants, 74 (91.36%) people reported having at least one patient with one of the LSDs included in this study. There were 7 people (8.64%) with no experience seeing patients with LSDs, and each of them skipped to the vignette section of the questionnaire.

Among those 74 people who were eligible to continue the questionnaire, the majority of the respondents (30/74; 40.5%) followed patients with LSDs for 1-5 years (Chart 1). The highest average number of patients seen in a year was either 1-5 patient(s) or more than 20 patients (Chart 2) and the number of patients currently on ERT is close to these numbers of patients that respondents see in a year (Chart 3).

**Significant Clinical Decline**

The most commonly selected answer associated with significant clinical decline was persistent vegetative state which 58 (78.38%) out of 74 people selected (Table 3); however, there was no significance in the answer combinations among nine different clinical features that were provided in the question. Written comments that we received from 17 participants were coded thematically with a yield of four major themes (Table 4).

**Discontinuing ERT**

Thirty six of the 74 eligible participants indicated they had patients who had discontinued ERT. Selecting from multiple choice options, inconvenience for the patient and/or caregiver and infusion-associated reaction were selected as the most common reasons for discontinuing ERT outside of significant clinical decline by 16 participants (44.44%) each. Other responses were lack of insurance (10/36; 27.78%), financial reasons (10/36; 27.78%), and none of the above (5/36; 13.89%). Respondents could also provide open-ended comments, and those were coded thematically (Table 5). Written comments that were coded into "Death" were confusing because it was not specified whether
it was an accidental death or just mentioning that the patients continued ERT until death; therefore, we excluded in the analysis.

Among the 74 respondents with experience seeing patients with LSDs, 17 (25%) of them said that they had recommended discontinuing ERT due to significant clinical decline in their patients (Chart 4). Ten (58.82%) of them had recommended discontinuing ERT to 1-2 patient(s) and six (35.29%) of them had recommended it to 3-4 patients. One participant had 5-6 patients for whom she had suggested discontinuation. Fifteen participants (88.24%) responded that the patient actually followed through by discontinuing ERT; all 15 reported that they would make the same recommendation again in the future. In the two situations where discontinuation did not occur, patient/family preference overrode the recommendation but those two people indicated they would still recommend discontinuing ERT if patients show significant clinical decline. Fifty one participants (75%) had no experience with discontinuing ERT. The majority (25/51; 49.02%) of people reported that none of their patients had significant clinical decline (Tables 6).

Comparison between physicians and genetic counselors

There was a significant difference (p=0.011) between physicians and genetic counselors in their experience recommending discontinuation of ERT for the patients who showed significant clinical decline (Chart 4). Ten out of 22 physicians (45.45%) have recommended discontinuing ERT for patients with certain LSDs due to significant clinical decline, whereas only five of the 41 genetic counselors (12.20%) had made such recommendations. The remaining 36 genetic counselors (87.80%) reported that they do not have experience recommending discontinuation of therapy. Six (27.27%) genetic counselors answered that the reason for them to not recommend discontinuing ERT was because it is outside the scope of practice (Table 7).

How often people discuss discontinuing ERT

Healthcare providers with less experience were less likely to recommend discontinuing ERT compared to people who have more than 10 years of experience (p=0) (Chart 5). There was also a significant difference (p=0.005) between how often healthcare providers discuss discontinuing ERT amongst themselves and their years of practice (Chart 6). Healthcare providers with six or more years
of experience tended to discuss discontinuing ERT with their colleagues more “often” or “always” compared to less experienced group that did not select “often” or “always” at all.

**Vignettes**

Seventy three of 81 participants answered questions associated with the first vignette, and 67 out of 81 participants answered questions associated with the second vignette.

In the first vignette, 57 of 73 people (78.08%) said that they would discuss discontinuing ERT with the patient’s family. The most common reason was *poor quality of life and/or burden to the family and the patient* (27/55; 49.09%) (Table 8). The most common clinical issues that contributed to participants’ decision to recommend discontinuing ERT were that the patient *required full time care for all activities of daily living* (38/57; 66.67%) and *cognitive impairment* (27/57; 47.37%) (Table 9). For those who selected not to discuss discontinuing ERT (16/73; 21.92%), the most common response was because it *still had benefits* (6/13; 46.15%) (Table 10).

In the second vignette, 39 of 67 participants (58.21%) responded that they would discuss the option of discontinuing ERT with the patient’s family. The most common reason was *to inform and discuss the option of discontinuing ERT* (23/38; 60.53%) (Table 11). Clinical features that mostly influenced participants’ decision of discontinuing ERT were *respiratory failure* (29/39; 74.36%) and the *requirement of full time care for all activities of daily living* (24/39; 61.54%) (Table 12). The most common reasons for not discussing discontinuation of ERT (28/67; 41.79%) were *normal cognitive function* (10/25; 40%) and *still having benefits for physically and/or emotionally* (10/25; 40%) (Table 13). Clinical aspects that mostly affected people’s decision of not discontinuing ERT for the patient in vignette 2 was *normal cognitive function* (20/28; 71.43%) (Table 14).

**Discussion**

To our knowledge, this is the first study to assess the reasons healthcare professionals provide for their reported behaviors involving discontinuation of ERT in patients with the following LSDs: Gaucher disease type II, Gaucher disease type III, non-transplanted MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome) and Pompe disease (all types).
Participants identified multiple conditions that defined “significant clinical decline” for them. Seven out of nine possible choices were selected by more than 50% of respondents. The majority of respondents identified persistent vegetative state (58/74; 78.38%) as a component of significant clinical decline. The other selected choices were requires full time care for all activity, cognitive decline, loss of ability to talk, tracheostomy and/or ventilator use, loss of ability to walk, and persistent seizures. This highlights the breadth of issues that make up “significant clinical decline” for practitioners. All of the clinical descriptions contribute to clinical decline, but as some participants mentioned in additional written comments throughout the survey, a global consideration of all the issues facing a patient must be included in assessing clinical decline and whether it counts as significant. Although we focused on the LSDs that have relatively severe symptoms, disease course and progression can be very different. As some of the participants commented, significant clinical decline may depend on each patient and disease.

By providing two hypothetical vignettes, we were able to better understand healthcare providers’ thoughts on discontinuing ERT. The first vignette was about a 13 year old boy with the severe type of Hunter syndrome and the second one was about a 10 year old girl with advanced Pompe disease. They both are on ERT and have clinical symptoms associated with their disease. Cognitive decline seemed to play a role when thinking about discontinuing the therapy. The boy with Hunter syndrome showed cognitive impairment whereas the girl with Pompe disease does not have it. There were more healthcare professionals who selected to talk about discontinuing ERT with the boy with Hunter syndrome and the clinical reasons for that was requires full time care and cognitive impairment. As one of the respondents noted in written comment about the girl with Pompe disease, “…given normal cognitive status, it isn’t fair to have that discussion without in some way taking into account the wishes of a 10 year old.” It means that it is important to consider the patient’s overall wellness and what the treatment means to her when she has ability to make those decisions. Forty percent of people noted that the girl with Pompe disease is still having benefits physically and/or emotionally. This implies that healthcare providers may be hesitant to talk about removing the therapy for patients who have normal cognitive function because the patients may participate in decision
making process directly which can be uncomfortable discussion to make. More discussion is needed in order to better understand healthcare providers’ comfort level of discussing treatment options such as discontinuing therapy related to patient’s cognitive status.

Respondents were asked about their personal experience with recommending discontinuation of ERT due to significant clinical decline. One quarter of participants had made the recommendation to discontinue ERT. Of those families whose healthcare provider recommended discontinuing ERT, almost 90% of them did opt to discontinue. Though the numbers we surveyed are small, this indicates that some healthcare providers are discussing the option of discontinuing ERT, while others are not. We did not assess if families were satisfied with stopping ERT; however, providers seemed satisfied since they indicated they would make same decision again if they faced a same situation in the future.

Among three quarter of participants who have not recommended discontinuing ERT, almost a half indicated that none of their patients had experienced significant clinical decline. About one quarter of participants who were all genetic counselors indicated that making such recommendations was outside the scope of their practice. This explains a part of the reasons that genetic counselors were less likely than physicians to recommend discontinuing ERT. In some organizations, there might be a clear delineation of roles so that genetic counselors do not participate in decision making about medical treatment such as ERT or it might indicate that “recommending discontinuation of ERT” is a task the medical doctor must perform during their clinical interaction with the patient. This issue highlights a need to consider how individual genetic counselors define their role, in light of their organizational situation and in light of the definition of genetic counseling developed by the NSGC (Resta, 2006). Job descriptions for genetic counselors differ among institutions and how much genetic counselors become involved in a decision making process for patient care differs as well. Some institutions require more independence, whereas some settings limit their involvement. Many genetic counselors practice as part of a team, where they would collaborate with physicians and other providers prior to coming to any conclusions about discontinuing ERT.

A decision should always come with full involvement of the patient and family. As Muenzer et al (2012) suggested, the goals and expectations for treatment should be discussed prior to the start
of therapy; it is important to keep family apprised of all options including the option of no treatment, so that when the time comes, the patient and/or family should not be surprised by the discussion.

When the discussion happens, it is important to consider the whole picture, including length of time on ERT, disease progression, and family dynamics/desires. Although it was a small number of people, it is important to note that 15 out of 17 families were in agreement when discontinuing ERT was brought up to them as an option. While Muenzer et al (2012) developed guidelines for initiation and discontinuation of ERT for patients with Hunter syndrome, guidelines for other LSDs that currently have ERT as a treatment option should be developed.

This study also showed that recommending cessation of ERT correlates with healthcare providers’ number of years of experience. More experienced healthcare providers tended to discuss the option of discontinuing ERT more often with patients and/or families, and they were more likely to discuss it with colleagues as well. There can be a lot of contributing factors for this trend such as healthcare providers who practiced longer may have seen more long term outcomes of ERT or come across with this kind of situation more often compared to those who practiced for a relatively short amount of time. Also, providers that follow patients with chronic diseases such as LSDs follow the same patients for many years and build a strong rapport with the family. This relationship may provide different perspectives when it comes to patient care and discussing discontinuation of the therapy.

Some of the written comments that we have collected very well described some of the limitations of this study and suggested interesting points of view. One such comment was “it’s not as definitive as “yes/no” for most of these things. In general, as with any medical treatment, it is when the burden of ERT outweighs the benefit. The decision to stop ERT should be part of a general conversation about end-of-life management. Perhaps the better metric is I would consider a decision to move to a comfort care/hospice management protocol as significant in the decision to end ERT.”

Another written comment we received suggested a model of patient care that could be followed: “Our lysosomal physician may review with a family that in his clinical opinion that the difficulties of ERT (time, mediport access, traveling with a medically fragile child) may possibly outweigh the potential
benefits and discuss the possibility of discontinuing ERT. However, this is always done in conjunction with our supportive care/palliative care team who along with the genetic counselor helps the family articulate their goals for care (i.e. quality of life, quantity of life, etc.). This leads to more discussion and ultimately the family’s decision whether or not to continue with ERT.”

There are several limitations in this study. The primary investigator and research advisory committee members who formulated the questionnaire may have brought bias to the study by limiting the answers in certain way that the investigator wants to be answered. Also, although we clearly stated that we were only including certain LSDs, there is a possibility that the respondents thought about their patients with Gaucher disease type I or Fabry disease when they answered questions. Also, there is a possibility that participants answered differently not based on what they truly believe or how they have acted, but by the way they felt others might want them to respond. Lastly, we are aware that the disorders we are studying are quite rare. It is possible that respondents from the same center may be referring to the same patients in their responses. However, we sought to assess the participant’s experiences, thoughts, and attitudes, and we anticipated finding differences in opinions about discontinuing ERT among different healthcare providers even if they had seen the same patients.

**Conclusions**

In conclusion, this study showed that some healthcare providers are discussing the option of discontinuing ERT in cases with significant clinical decline, especially those providers with more years of experience. Although many clinical symptoms altogether play a big role for healthcare providers considering the option of discontinuing the therapy, persistent vegetative state and cognitive decline were the most important factors. Reasons for discomfort with discussing and/or offering this option deserve further exploration.

Some genetic counselors are uncomfortable discussing discontinuation of ERT because they think it is not in their scope of practice. This concept should be discussed and evaluated at the clinic level and also at a national level such as in the NSGC Special Interest Group for metabolic and lysosomal storage diseases.
References


Appendices

Appendix 1: Cover letter sent out for the first time.

**Discontinuing Enzyme Replacement Therapy (ERT) in Patients with Lysosomal Storage Diseases (LSDs) due to Significant Clinical Decline**

My name is A Rang Kim and I am a genetic counseling student at the University of Cincinnati. I am inviting you to participate in a research survey as part of my Master’s thesis. I value your opinion and your specialization in the field of lysosomal storage diseases.

The purpose of this study is to learn about the experiences and the thoughts, attitudes and behaviors of healthcare providers relative to discontinuation of enzyme replacement therapy (ERT) in patients with certain lysosomal storage diseases (LSDs) due to significant clinical decline. **This study focuses on the following disorders: Gaucher disease type II, Gaucher disease type III, MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome) and Pompe disease (all types).**

The data collected in this study will be analyzed and published in order to identify the reasons given by healthcare providers for stopping ERT. Additionally, we seek to define significant clinical decline.

Participation in this study is voluntary, and your response will be kept confidential. If you are willing to share your thoughts and experiences, please follow the link below. Completion of the questionnaire will take approximately 5 to 10 minutes. This study has been approved by the Institutional Review Boards (IRB) at Cincinnati Children’s Hospital Medical Center and at the University of Cincinnati.

Please follow the link to access the survey: [https://www.surveymonkey.com/s/GYC6Y7T](https://www.surveymonkey.com/s/GYC6Y7T)

If you have any questions or concerns regarding this study, please feel free to contact me by email at a.rang.kim@cchmc.org or my research advisor Lisa Berry, MS, CGC, in the Division of Human Genetics, Cincinnati Children’s Hospital Medical Center at lisa.berry@cchmc.org.

Thank you for your time and participation.

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Appendix 2: Cover letter sent out for the second and third time.

REMINDER:

Discontinuing Enzyme Replacement Therapy (ERT) in Patients with Lysosomal Storage Diseases (LSDs) due to Significant Clinical Decline

My name is A Rang Kim and I am a genetic counseling student at the University of Cincinnati. I am inviting you to participate in a research survey as part of my Master’s thesis. I value your opinion and your specialization in the field of lysosomal storage diseases.

The purpose of this study is to learn about the experiences and the thoughts, attitudes and behaviors of healthcare providers relative to discontinuation of enzyme replacement therapy (ERT) in patients with certain lysosomal storage diseases (LSDs) due to significant clinical decline. This study focuses on the following disorders: Gaucher disease type II, Gaucher disease type III, MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome) and Pompe disease (all types).

The data collected in this study will be analyzed and published in order to identify the reasons given by healthcare providers for stopping ERT. Additionally, we seek to define significant clinical decline. Participation in this study is voluntary, and your response will be kept confidential. If you are willing to share your thoughts and experiences, please follow the link below. Completion of the questionnaire will take approximately 5 to 10 minutes. This study has been approved by the Institutional Review Boards (IRB) at Cincinnati Children’s Hospital Medical Center and at the University of Cincinnati.

Please follow the link to access the survey: https://www.surveymonkey.com/s/GYC6Y7T

If you have any questions or concerns regarding this study, please feel free to contact me by email at a.rang.kim@cchmc.org or my research advisor Lisa Berry, MS, CGC, in the Division of Human Genetics, Cincinnati Children’s Hospital Medical Center at lisa.berry@cchmc.org.

Thank you for your time and participation.

A Rang Kim
Genetic Counseling graduate student, Class of 2014
University of Cincinnati Genetic Counseling Program
Cincinnati Children’s Hospital Medical Center, ML 4006
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Email: a.rang.kim@cchmc.org
Appendix 3: Questionnaire

1. What is your area of medical practice?
   - ☐ Physician (M.D. or D.O.) (Skip to question 2)
   - ☐ Genetic counselor (Skip to question 3)
   - ☐ Other – please describe: _______________ (Skip to question 3)

2. What is your specialty?
   (Drop down box – applied from American Board of Medical Specialties)

3. What is your gender?
   - ☐ Male
   - ☐ Female

4. Which category below includes your age?
   - ☐ 20-24
   - ☐ 25-29
   - ☐ 30-34
   - ☐ 35-39
   - ☐ 40-44
   - ☐ 45-49
   - ☐ 50-54
   - ☐ 55-59
   - ☐ 60 and above

5. In what city and state do you see patients with LSDs?
   (The city should be typed in by the participants and the drop down list for the states will be provided)

6. Have you ever had a patient with any of the following disorders: Gaucher disease type II, Gaucher disease type III, non-transplanted MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome), or Pompe disease (all types)?
   - ☐ Yes (Continue the survey)
   - ☐ No (Skip to vignette part)
The following questions pertain only to the diagnoses of: Gaucher disease type II, Gaucher disease type III, non-transplanted MPS type I (Hurler syndrome), MPS type II (Hunter syndrome), MPS type VI (Maroteaux-Lamy syndrome) or Pompe disease (all types).

7. For how many years have you followed patients diagnosed with above listed LSDs?
   - Less than one year
   - 1-5 years
   - 6-10 years
   - More than 10 years

8. Approximately how many patients with above listed LSDs do you see, on average, in a year?
   - 1-5 patient(s)
   - 6-10 patients
   - 11-15 patients
   - 16-20 patients
   - More than 20 patients

9. Among your patients with LSDs listed above, approximately how many are currently on ERT?
   - None
   - 1-5 patient(s)
   - 6-10 patients
   - 11-15 patients
   - 16-20 patients
   - More than 20 patients

10. Have you ever had patients with LSDs listed above who discontinued ERT?
    - Yes (Skip to question 11)
    - No (Skip to question 12)

11. Among those patients who discontinued ERT, what was the reason(s) other than significant clinical decline? (Select all that apply) (Next question will be question 12)
    - Lack of insurance
    - Financial reasons
    - Inconvenient (too far to travel for infusions/caregiver time away from work)
    - Infusion associated reactions
    - None of the above
    - Other: ____________________________
12. As you may know, some patients undergoing ERT for LSDs listed above experience clinical decline that you might consider as “significant.” When thinking about patients in this situation, **how do you define significant clinical decline** in patients with LSDs listed above? (Select all that apply)

- Loss of ability to walk
- Loss of ability to talk
- Cognitive decline
- Persistent vegetative state
- Persistent of seizures
- Chronic pain
- Tube feeding (no or limited oral feeding)
- Tracheostomy and/or ventilator use
- Requires full time care for all activities of daily living
- If you wish to expand your answer, please use the textbox below:

13. Have you ever recommended discontinuing ERT for any patients with above listed LSDs who showed significant clinical decline according to your definition?

- Yes (Skip to question 14)
- No (Skip to question 19)

14. For how many patients have you recommended discontinuing ERT?

- 1-2 patient(s)
- 3-4 patients
- 5-6 patients
- 7-8 patients
- 9-10 patients
- More than 10 patients

15. Have you ever actually discontinued ERT for a patient?

- Yes (skip to question 16)
- No (skip to question 17)

16. Based on your experience discontinuing ERT, would you ever make the same decision again in a similar situation? (will skip to question 20 after answering yes or no)

- Yes
- No

17. Why have you **NOT** discontinued ERT?

- Members of the medical team were opposed to the recommendation.
- Patient/patient’s family declined the option to discontinue ERT.
- The patient died before the decision could be carried out.
- Other: ________________________________
18. In your current practice, would you still recommend discontinuing ERT for patients with LSDs who show significant clinical decline?  
(This question is only for the participants who answered “No” to 15 and proceeded to 17)  
☐ Yes  
☐ No

19. Why have you not recommended discontinuation of ERT? Choose the response that is most applicable to most of your cases.  
(This question is only for the participants who answered “No” to 13, and after answering it will skip to question 20)  
☐ None of my patients had significant clinical decline.  
☐ I never thought of the option/idea of discontinuing ERT for patients with LSDs.  
☐ I cannot recommend discontinuing ERT because it is the standard care and the only available treatment option for these patients.  
☐ Discontinuation of ERT is not consistent with my ethical standards.  
(Please explain: )  
☐ Others: __________________________________________

20. How often have you discussed with colleagues the option of discontinuing ERT in patients with LSDs? (Everyone will answer this question except for the participants who answered “No” to question 6)  
☐ Never  
☐ Rarely  
☐ Sometimes  
☐ Often  
☐ Always
Vignettes
Two hypothesized situations are provided below. Each vignette contains three questions.

Vignette 1. Patient A is a 13-year-old male with Hunter syndrome who was diagnosed at age 3. He has been on ERT for 7 years, and travels an hour to the hospital every week for his infusion. He does not experience infusion reactions. Over the years, it has become clear that Patient A has the severe neurological form of Hunter syndrome. His current symptoms include cognitive impairment, hearing loss, joint stiffness and he is now non-verbal. Recently, he lost the ability to walk and he now requires full time care for all activities of daily living. Patient A is able to eat/drink by mouth and his respiratory status is compromised but does not yet require tracheostomy.

21. Would you discuss the option of discontinuing ERT with this patient’s family?
   ☐ Yes (Skip to question 23 after answering to question 22)
   ☐ No (Skip to question 24 after answering to question 22)

22. Please specify the reason(s) why you choose to or choose not to discuss the option of discontinuing ERT with the family.

23. What clinical aspect(s) have mostly affected your decision of discontinuing ERT?
   (Select all that apply)
   ☐ Cognitive impairment
   ☐ Hearing loss
   ☐ Joint stiffness
   ☐ Non-verbal
   ☐ Loss of the ability to walk
   ☐ Requires full time care for all activities of daily living
   ☐ Compromised respiratory status
   ☐ Other: ___________________________________

24. What clinical aspect(s) have mostly affected your decision of continuing ERT?
   (Select all that apply)
   ☐ No infusion reactions
   ☐ Eat/drink by mouth
   ☐ Respiratory status is compromised but does not yet require tracheostomy
   ☐ Other: ___________________________________
**Vignette 2.** Patient B is a 10-year-old female with Pompe disease who was diagnosed at 8 months of age. She has been on ERT since her diagnosis and travels an hour to the hospital for her infusion every 2 weeks. She does not experience any infusion reactions and her antibody titers are low. Her current symptoms include respiratory failure, severe hypotonia, speech difficulties, feeding difficulties and hypertrophic cardiomyopathy. She is no longer able to walk and has a tracheostomy and is ventilator dependent. She requires full time care for all activities of daily living and receives most of her nutrition from a G-tube. Her cognitive function is normal.

25. Would you discuss the option of discontinuing ERT with this patient’s family?
   □ Yes (Skip to question 27 after answering to question 26)
   □ No (Skip to question 28 after answering to question 26)

26. Please specify the reason(s) **why you choose to or choose not to** discuss the option of discontinuing ERT with the family.

27. What clinical aspect(s) have mostly affected your decision of **discontinuing** ERT?
   (Select all that apply)
   □ Respiratory failure – has a tracheostomy and is ventilator dependent
   □ Severe hypotonia
   □ Speech difficulties
   □ Feeding difficulties
   □ Hypertrophic cardiomyopathy
   □ No longer able to walk
   □ Requires full time care for all activities of daily living
   □ Receives most of her nutrition from a G-tube
   □ Other: ______________________________

28. What clinical aspect(s) have mostly affected your decision of **continuing** ERT?
   (Select all that apply)
   □ No infusion reactions
   □ Low antibody titers
   □ Normal cognitive function
   □ Other: ______________________________
# Tables and Figures

## Table 1. Vignettes

<table>
<thead>
<tr>
<th>Vignette</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vignette 1</strong></td>
<td>Patient A is a 13-year-old male with Hunter syndrome who was diagnosed at age 3. He has been on ERT for 7 years, and travels an hour to the hospital every week for his infusion. He does not experience infusion reactions. Over the years, it has become clear that Patient A has the severe neurological form of Hunter syndrome. His current symptoms include cognitive impairment, hearing loss, joint stiffness and he is now non-verbal. Recently, he lost the ability to walk and he now requires full time care for all activities of daily living. Patient A is able to eat/drink by mouth and his respiratory status is compromised but does not yet require tracheostomy.</td>
</tr>
<tr>
<td><strong>Vignette 2</strong></td>
<td>Patient B is a 10-year-old female with Pompe disease who was diagnosed at 8 months of age. She has been on ERT since her diagnosis and travels an hour to the hospital for her infusion every 2 weeks. She does not experience any infusion reactions and her antibody titers are low. Her current symptoms include respiratory failure, severe hypotonia, speech difficulties, feeding difficulties and hypertrophic cardiomyopathy. She is no longer able to walk and has a tracheostomy and is ventilator dependent. She requires full time care for all activities of daily living and receives most of her nutrition from a G-tube. Her cognitive function is normal.</td>
</tr>
<tr>
<td>Variable</td>
<td>Levels</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic counselor</td>
</tr>
<tr>
<td>Physicians</td>
<td>Clinical Genetics (MD)</td>
</tr>
<tr>
<td></td>
<td>Clinical Biochemical Genetics</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Not provided</td>
</tr>
<tr>
<td>Others*</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td></td>
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<tr>
<td>25-29</td>
<td></td>
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<td>55-59</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td></td>
</tr>
<tr>
<td><strong>Locations</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Region 1</td>
</tr>
<tr>
<td></td>
<td>Region 2</td>
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<td>Region 6</td>
</tr>
<tr>
<td></td>
<td>Region 7</td>
</tr>
<tr>
<td></td>
<td>Not provided</td>
</tr>
</tbody>
</table>

* Others: one medical science liaison (MSL) and four nurses

** Modified NSGC region categories (Region 7 was created to include Canada and Other countries outside the USA)

Region 1: CT, MA, ME, NH, RI, VT, CN
Region 2: DC, DE, MD, NJ, NY, PA, VA, WV, PR, VI
Region 3: AL, FL, GA, KY, IA, MS, NC, SC, TN
Region 4: AR, IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, OK, SD, WI
Region 5: AZ, CO, MT, NM, TX, UT, WY
Region 6: AK, CA, MI, ID, NV, OR, WA
Region 7: International, including Canada
Table 3. Features that affect healthcare providers when defining *Significant Clinical Decline* in patients with certain LSDs

<table>
<thead>
<tr>
<th>Responses</th>
<th>Frequency (*n=74)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Close-ended answers (Select all that apply)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>58</td>
<td>78.38</td>
</tr>
<tr>
<td>Requires full time care for all activity</td>
<td>51</td>
<td>68.92</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>50</td>
<td>67.57</td>
</tr>
<tr>
<td>Loss of ability to talk</td>
<td>45</td>
<td>60.81</td>
</tr>
<tr>
<td>Tracheostomy and/or ventilator use</td>
<td>43</td>
<td>58.11</td>
</tr>
<tr>
<td>Loss of ability to walk</td>
<td>41</td>
<td>55.41</td>
</tr>
<tr>
<td>Persistent seizures</td>
<td>39</td>
<td>52.70</td>
</tr>
<tr>
<td>Tube feeding (no or limited oral feeding)</td>
<td>30</td>
<td>40.54</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>27</td>
<td>36.49</td>
</tr>
</tbody>
</table>

* Seventy four respondents participated in this question and they were able to select multiple answers.
Table 4. Significant clinical decline in patients with certain LSDs free response themes

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quote</th>
<th>Frequency (*n=17)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depends on each patient and disease</td>
<td>This is a patient specific question and must consider the patient's disease state at the start of ERT, as well as the items listed above. In addition, the patient's subjective response to therapy should be considered.</td>
<td>6</td>
<td>31.58</td>
</tr>
<tr>
<td>Downhill trend / disease progression</td>
<td>Something that is stabilized, for instance, inability to talk or [tracheostomy], is not as big as a problem by itself unless it is part of a downhill trend.</td>
<td>4</td>
<td>21.05</td>
</tr>
<tr>
<td>Loss of skill / functionality</td>
<td>I would consider the decline to be significant if they are losing important skills that they once had. The way this question is worded is difficult to answer; all of the features listed above are significant disabilities in my opinion, but if they have ALWAYS had pain, then &quot;chronic pain&quot; isn't technically part of their decline.</td>
<td>2</td>
<td>10.53</td>
</tr>
<tr>
<td>Patient's perception about decline</td>
<td>Significant decline, in part, is also driven more by patient perception than provider assessment.</td>
<td>1</td>
<td>5.26</td>
</tr>
</tbody>
</table>

* Seventeen respondents provided written comments that were classified into multiple themes. Three comments were excluded in the final analysis due to repeating multiple choice answers that they already selected.
Table 5. Reasons for discontinuing ERT other than significant clinical decline free response themes

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quote</th>
<th>Frequency (*n=15)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy / No benefit</td>
<td>Did not feel that the ERT was beneficial</td>
<td>7</td>
<td>41.18</td>
</tr>
<tr>
<td>Personal reasons</td>
<td>Patient lost interest in therapy</td>
<td>5</td>
<td>29.41</td>
</tr>
<tr>
<td>Psychological reasons</td>
<td>Anxiety surrounding the infusion setting and process</td>
<td>2</td>
<td>11.76</td>
</tr>
<tr>
<td>Drug shortage</td>
<td>Drug shortage</td>
<td>1</td>
<td>5.88</td>
</tr>
</tbody>
</table>

* Fifteen respondents provided written comments that were classified into multiple themes. One comment was excluded in the final analysis due to repeating multiple choice answers that they already selected.
### Table 6. The reasons for not recommending discontinuation of ERT

<table>
<thead>
<tr>
<th>Response</th>
<th>Frequency (n=51)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of my patients had significant clinical decline</td>
<td>25</td>
<td>49.02</td>
</tr>
<tr>
<td>I never thought of the option/idea of discontinuing ERT for patients with LSDs</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>I cannot recommend discontinuing ERT because it is the standard care and the only available treatment option for these patients</td>
<td>4</td>
<td>7.84</td>
</tr>
<tr>
<td>Discontinuation of ERT is not consistent with my ethical standards</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>*Other</td>
<td>21</td>
<td>41.18</td>
</tr>
<tr>
<td>Not provided</td>
<td>1</td>
<td>1.96</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>51</td>
<td>100</td>
</tr>
</tbody>
</table>

* People who selected other were able to expand their answers in a box. Although 21 people selected "other," there were 22 responses in the box we provided (see Table 7).
<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quote</th>
<th>Frequency (*n=22)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outside the scope of practice as a GC</td>
<td>I am a genetic counselor and this is outside of my scope of practice.</td>
<td>6</td>
<td>27.27</td>
</tr>
<tr>
<td></td>
<td>While some of my patients have had profound neurological progression and may be technology dependent (mainly feeding tube), many of our patients experience decrease frequenting of URIs and other illnesses that can further compromise the patient's health while on ERT. Therefore, if ERT is having this effect, staying on ERT improves overall quality of life.</td>
<td>5</td>
<td>22.73</td>
</tr>
<tr>
<td>Still has benefit</td>
<td>We did have a patient almost discontinue re: significant side effects from ERT. She has been doing better on fewer infusions. I find that patients reassess what a decline means to their quality of life and whether or not ERT is helpful to them.</td>
<td>4</td>
<td>18.18</td>
</tr>
<tr>
<td>Use of other treatment or other method</td>
<td>I have discussed this option with parents, however, all of the parents whose children had been receiving and had benefitted from ERT did not want to discontinue therapy; thus, it did not get to the point of a formal recommendation to discontinue.</td>
<td>3</td>
<td>13.64</td>
</tr>
<tr>
<td>Patient/family desired to continue ERT</td>
<td>The patient told us that he wanted to discontinue, and we supported that decision.</td>
<td>3</td>
<td>13.64</td>
</tr>
<tr>
<td>Patient/family decided to discontinue ERT on their own</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Twenty two respondents provided written comments that were classified into multiple themes. Some comments were excluded due to irrelevance to the question.
Table 8. The reasons people choose to discuss the option of discontinuing ERT with the family (Vignette 1).

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quote(s)</th>
<th>Frequency (*n=55)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor quality of life/burden to the family and the patient</td>
<td>It appears as though his parents may want permission for them to enjoy the rest of their time with their son without having to drive to and from the hospital for infusions that most likely are not helping anymore so they may have even more time with their son.</td>
<td>27</td>
<td>49.09</td>
</tr>
</tbody>
</table>
| Discuss the option of discontinuing ERT and the outcome | • As they are the primary caregivers and the most suffered individuals from the child current status. For me, in chronic disease parents are doctors of the child.  
• They should always be informed about the alternatives to therapy which include no therapy.                          | 20                | 36.36           |
| Disease progression                              | Neurological symptoms will worsen and ERT is not preventing worsening of somatic symptoms.                                                                                                                    | 15                | 27.27           |
| Lack of efficacy/no benefit                      | ERT in this situation is not really helping, other than making the parents feel as if they are doing something. In a cost benefit analysis, overall the cost is greater than the benefit.                        | 11                | 20.00           |
| Cognitive decline                               | Mostly his cognitive impairment                                                                                                                                                                                | 1                 | 1.82            |

* Fifty five respondents provided written comments that were classified into multiple themes. One comment was excluded in the final analysis due to irrelevance to the question.
Table 9. Clinical aspects that have mostly affected people's decision of discontinuing ERT in patient A

<table>
<thead>
<tr>
<th>Content</th>
<th>Frequency (*n=57)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires full time care for all activities of daily living</td>
<td>38</td>
<td>66.67</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>27</td>
<td>47.37</td>
</tr>
<tr>
<td>Compromised respiratory status</td>
<td>22</td>
<td>38.60</td>
</tr>
<tr>
<td>Loss of the ability to walk</td>
<td>19</td>
<td>33.33</td>
</tr>
<tr>
<td>Non-verbal</td>
<td>12</td>
<td>21.05</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2</td>
<td>3.51</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>1</td>
<td>1.75</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>36.84</td>
</tr>
</tbody>
</table>

* Fifty seven respondents participated in this question and they were able to select multiple answers.
Table 10. The reasons people choose NOT to discuss the option of discontinuing ERT with the family (Vignette 2).

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quotes</th>
<th>Frequency ((*n=13))</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still have benefits</td>
<td>Patient is not at the end of life. Still may have some quality of life</td>
<td>6</td>
<td>46.15</td>
</tr>
<tr>
<td>Outside the scope of practice as a genetic counselor</td>
<td>It is not my job. I am a genetic counselor not an MD, and I would always advise a patient to discuss medication options with their doctor.</td>
<td>4</td>
<td>30.77</td>
</tr>
<tr>
<td>Family objections</td>
<td>I would be [concerned] the family would object and then think I wanted to &quot;harm&quot; their child.</td>
<td>3</td>
<td>23.08</td>
</tr>
</tbody>
</table>

* Thirteen respondents provided written comments that were classified into multiple themes.
Table 11. The reasons people choose to discuss the option of discontinuing ERT with the family.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quotes</th>
<th>Frequency (*n=38)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform/discuss the option of discontinuing ERT</td>
<td>Patient's situation is not likely to improve. Family should be able to participate in treatment decision at this point.</td>
<td>23</td>
<td>60.53</td>
</tr>
<tr>
<td>Poor quality of life</td>
<td>Quality of life may be worse with ERT than without it.</td>
<td>10</td>
<td>26.32</td>
</tr>
<tr>
<td>No benefit</td>
<td>At this point in her disease, her progression is so far advanced and ERT does not appear to be working any longer.</td>
<td>9</td>
<td>23.68</td>
</tr>
<tr>
<td>Disease progression</td>
<td>It appears as though she is declining physically from her disease. She has been on ERT since 8 months of age and is now 10 so she's been receiving treatment for almost 10 years. It may be better for the family to prepare for the passing of their child and to try to make her as comfortable as possible when that time comes.</td>
<td>9</td>
<td>23.68</td>
</tr>
<tr>
<td>Burden to the patient and the family</td>
<td>Again, there is this issue of possible treatment related burdens to the patient and family. It would be important to understand the family and patient's goals for her care and for her life. Does ERT help of hinder those goals?</td>
<td>2</td>
<td>5.26</td>
</tr>
</tbody>
</table>

* Thirty eight respondents provided written comments that were classified into multiple themes.
<table>
<thead>
<tr>
<th>Content</th>
<th>Frequency (*n=39)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure - has a tracheostomy and is ventilator dependent</td>
<td>29</td>
<td>74.36</td>
</tr>
<tr>
<td>Requires full time care for all activities of daily living</td>
<td>24</td>
<td>61.54</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>16</td>
<td>41.03</td>
</tr>
<tr>
<td>Receives most of her nutrition from a G-tube</td>
<td>13</td>
<td>33.33</td>
</tr>
<tr>
<td>Severe hypotonia</td>
<td>10</td>
<td>25.64</td>
</tr>
<tr>
<td>No longer able to walk</td>
<td>9</td>
<td>23.08</td>
</tr>
<tr>
<td>Feeding difficulties</td>
<td>7</td>
<td>17.95</td>
</tr>
<tr>
<td>Speech difficulties</td>
<td>4</td>
<td>10.26</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>17.95</td>
</tr>
</tbody>
</table>

* Thirty nine respondents participated in this question and they were able to select multiple answers based on their reasoning.
Table 13. The reasons people choose NOT to discuss the option of discontinuing ERT with the family (Vignette 2).

<table>
<thead>
<tr>
<th>Theme</th>
<th>Example Quotes</th>
<th>Frequency (*n=25)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cognitive function</td>
<td>… Given that cognition is not affected, I would not be able to justify not extending her life.</td>
<td>10</td>
<td>40.00</td>
</tr>
<tr>
<td></td>
<td>If the patient has been stable for a number of years with these clinical symptoms, why choose now to discontinue therapy. Why not at an earlier age? If the patient is declining in health in any way or if it is obvious that we are doing things to the patient and not for the patient, then that is the time to consider discontinuation of therapy. If the child is cognitively normal and can undergo developmental testing and or psychological evaluation and they are happy with the way their care is going then we continue status quo.</td>
<td>10</td>
<td>40.00</td>
</tr>
<tr>
<td>Still have benefits (physically and/or emotionally)</td>
<td>I do not have significant experience with ERT and would leave this discussion to the geneticist.</td>
<td>4</td>
<td>16.00</td>
</tr>
<tr>
<td>Outside the scope of practice as a genetic counselor</td>
<td>We would discuss increasing dosage of ERT.</td>
<td>2</td>
<td>8.00</td>
</tr>
<tr>
<td>Consider other options (increasing dose)</td>
<td>… ERT is standard of care, well-supported for use in Pompe</td>
<td>1</td>
<td>4.00</td>
</tr>
<tr>
<td>ERT is standard care</td>
<td>The antibody [titer] is low</td>
<td>1</td>
<td>4.00</td>
</tr>
<tr>
<td>Low antibody titer</td>
<td>… I am concerned the family would interpret it as me wanting [to] withhold treatment and &quot;harm&quot; their child.</td>
<td>1</td>
<td>4.00</td>
</tr>
</tbody>
</table>

* Twenty five respondents provided written comments that were classified into multiple themes.
Table 14. Clinical aspects that mostly affected people's decision of NOT discontinuing ERT in patient B

<table>
<thead>
<tr>
<th>Content</th>
<th>Frequency (*n=28)</th>
<th>Percentages (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cognitive function</td>
<td>20</td>
<td>71.43</td>
</tr>
<tr>
<td>No infusion reactions</td>
<td>9</td>
<td>32.14</td>
</tr>
<tr>
<td>Low antibody titers</td>
<td>9</td>
<td>32.14</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>28.57</td>
</tr>
</tbody>
</table>

* Twenty eight respondents participated in this question and they were able to select multiple answers.
Chart 1. Number of years that respondents followed the patients with LSDs

<table>
<thead>
<tr>
<th>Number of years</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>15</td>
</tr>
<tr>
<td>1-5 years</td>
<td>30</td>
</tr>
<tr>
<td>6-10 years</td>
<td>14</td>
</tr>
<tr>
<td>More than 10 years</td>
<td>15</td>
</tr>
</tbody>
</table>
Chart 2. Average number of patients with LSDs that respondents see in a year
Chart 3. Number of patients with LSDs currently on ERT
Chart 4. Different trend between Physicians and Genetic Counselors who recommended discontinuing ERT for the patients who showed significant clinical decline

- **Physicians:** 10 Yes, 12 No
- **Genetic Counselors:** 5 Yes, 36 No
- **Other:** 2 Yes, 3 No
Chart 5. Comparison between the years of practice and recommending discontinuation of ERT
Chart 6. How often healthcare providers (n=64) discuss discontinuing ERT in patients with certain LSDs

<table>
<thead>
<tr>
<th>Frequency Duration</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 10 years</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6-10 years</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1-5 year(s)</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Less than one year</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>