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## Exploration Of Patient Attitudes Toward Receiving Incidental Diagnoses Of Lysosomal Storage Disorders Through Expanded Carrier Screening

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EXPLORATION OF PATIENT ATTITUDES TOWARD RECEIVING  
INCIDENTAL DIAGNOSES OF LYSOSOMAL STORAGE DISORDERS THROUGH  
EXPANDED CARRIER SCREENING

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May 2020

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## **Abstract**

The increased prevalence of expanded carrier screening (ECS) has made it possible for individuals to receive incidental diagnoses of genetic conditions through prenatal or preconception screening that was originally intended to assess risk for genetic conditions in future offspring. The inclusion of genetic conditions with variable expressivity and late-onset phenotypes, such as certain lysosomal storage disorders, have increased the likelihood that this type of screening will result in an incidental diagnosis. Four participants from the lysosomal storage disorders program at NYU Langone Health were interviewed to elicit their psychological reaction to incidental diagnoses of Gaucher Disease Type 1, Fabry Disease and Late-onset Pompe Disease. Relevant themes include the quality of explanation of the diagnosed genetic condition, availability of support from medical providers, and consequences of the condition on aspects of daily living. Overall, participants believed that expanded carrier screening gave important information and recommended that providers responsible for ordering ECS or explaining results offer an appropriate level of education and compassion to their patients. Their responses reveal room for improvement in pre-test counseling, disclosure of incidental diagnoses, patient education during post-test counseling and referral services within the role of the genetic provider.

**KEYWORDS:** expanded carrier screening, incidental diagnosis, lysosomal storage disorder, attitudes, patient perspective, psychosocial, adult-onset, late-onset, asymptomatic

## Introduction

Panel tests that analyze many genes at once have changed the terrain of carrier screening, increasing the efficiency and affordability of genetic testing and expanding the options available to patients. Carrier screening assists individuals and couples in determining their risk for having a pregnancy affected by an autosomal recessive or X-linked condition, and has traditionally been offered according to individuals' ethnicity or family history as recommended by professional societies such as the American College of Obstetricians and Gynecologists (The American College of Obstetricians and Gynecologists, 2017). In recent years, expanded carrier screening (ECS) has become an option to assess genetic risks. Unlike traditional screening, it is offered regardless of ethnicity or family history and allows patients to uncover their reproductive risk for hundreds of conditions simultaneously.

The breadth of conditions tested by expanded carrier screening poses both challenges and benefits to patients and providers. One of these challenges is the risk of an incidental diagnosis, where an individual who receives carrier screening finds that he or she has a genetic diagnosis of one of the conditions included on a carrier screening panel. Because many ECS panels now include conditions for which there can be medical consequences to carriers, these incidental diagnoses are becoming more common (Wong, Lizarin, & Haque, 2016) and pose unique obstacles for pre- and post-test counseling. A significant number of disorders that are included on ECS panels have reduced penetrance, variable expressivity and late-onset phenotypes, and providers often have difficulty in addressing these phenotypic nuances during pre-test counseling (Janssens et al., 2017). Not all providers who offer carrier screening are genetics professionals, and some studies have shown that providers can have insufficient knowledge about the genetic

implications of carrier status, appropriate referrals after a positive screening results, and guidelines regarding carrier screening (Qureshi, 2006; Darcy et al., 2012).

### ***Current state of ECS, risks and benefits***

There is currently much variation in the way laboratories approach carrier screening in terms of the method of testing, number of conditions included, types of inheritance associated with the conditions, and types of result reporting. In a survey of 16 expanded carrier screening providers in 2018, Chokoshvilli, Vears and Borry found that there was great variability in the number of genetic conditions included, which ranged from dozens to over 1000. Laboratories used different types of sequencing even when testing for the same disease; while most of them provided targeted genotyping for screening cystic fibrosis, some offered complete gene sequencing and copy number variation (CNV) analysis. Among the laboratories who offered targeted sequencing, the number of allele positions analyzed ranged from 28 variants to over 600, and laboratories often used a combination of these testing strategies in their analysis. In addition to autosomal recessive diseases, some providers offer screening for X-linked and autosomal dominant conditions, such as Fragile X Syndrome and familial hypercholesterolemia, which increase the probability of returning positive results that have health implications for the individual being screened. Some laboratories reported only pathogenic or likely pathogenic variants while others provided information on variants of uncertain significance. Even though all laboratories included in the study provided screening for cystic fibrosis, spinal muscular atrophy and maple syrup urine disease type 1B, there were no consistent criteria by which other conditions were selected for inclusion in these panels (Chokoshvilli, Vears & Borry, 2018).

ECS poses both advantages and limitations to patients. Testing for a larger number of conditions independent of ethnicity can reveal positive carrier status for conditions that are not anticipated based on an individual's family history or ethnic background, providing additional benefit to the patient in making family planning decisions for conditions they were otherwise unaware of. In a study of 23,453 individuals across ethnicities, 24% were found to be carriers for at least one of 108 genetic disorders (Lazarin et al., 2013). Another study of 4,232 infertility patients who underwent ECS through a single panel that screened for 100 conditions showed that 29.4% carried at least one condition, as opposed to 8.5% that would have been identified if carrier screening were offered only based on ethnicity (Peysers et al., 2019). Current sequencing techniques allow for multiple analyses to be performed on the same sample without a proportional increase in sequencing costs, allowing individuals to make informed reproductive decisions using a broader pool of genetic information. The increased likelihood of screening positive on ECS panels can help improve the public's knowledge of carrier status and possibly decrease stigma for such a phenomenon (Kraft et al., 2019).

The breadth and complexity of ECS can make it challenging for patients to understand the methodology behind ECS and the implications of its results. For example, 30% of a sample of Dutch patients surveyed about their opinions regarding ECS were under the impression that a positive carrier status for a recessive condition signifies that they would experience symptoms of the condition, even though this is not the case for carriers of most diseases. Additionally, participants often misunderstood the nature of autosomal recessive conditions, indicating that they did not feel a need to undergo carrier screening when they had no family history of any genetic condition (Nijmeijer et al., 2019). Interviews of women receiving expanded carrier screening as a part of their prenatal care revealed confusion between ECS and other types of

prenatal testing, such as screening for Down Syndrome (Rothwell et al., 2017). Another complication of carrier screening in general is that it is often offered by non-genetics professionals such as obstetricians, who are not necessarily familiar with its benefits and limitations. An online survey of 156 obstetricians on their knowledge about screening for cystic fibrosis demonstrated that although most of them knew about screening guidelines, 17% did not interpret results correctly and 43% could not provide statistics for carrier frequency, screening sensitivity and residual risk (Darcy et al., 2012).

### ***Incidental diagnosis through ECS***

Within the broad range of conditions that are included on ECS, it is increasingly likely for individuals undergoing ECS to receive an incidental diagnosis. In a retrospective study of 23,453 participants who underwent ECS via genotyping, 78 individuals tested homozygous or compound heterozygous for recessive conditions that have variable expressivity or late-onset phenotypes, prominent among them hemoglobinopathies, cystic fibrosis and Gaucher Disease (Haque et al., 2016). The fact that many individuals are asymptomatic at the time of incidental diagnosis complicates patient education, as does the need to balance reproductive risks with adult health management (Lazarin et al., 2013). There is concern that asymptomatic individuals incidentally diagnosed through ECS may face undue psychological burden and seek unnecessary medical care if they never manifest symptoms of a low-penetrance or variably expressed condition. The need for diagnostic testing to confirm ECS results adds further inconvenience and burden to the patient experience (Wienke et al., 2014).

### ***Expert recommendation regarding ECS***

Given the discrepancy in curation of ECS panels, the American Association of Obstetrics and Gynecology (ACOG) has developed recommendations for designing such panels in a way that encourages clinical utility. The ACOG committee proposed a carrier frequency of at least 1/100 for conditions to be tested in ECS panels, and designated a number of additional criteria to be met: a “well-defined phenotype” which has been extensively studied in literature; significant negative impact on cognitive or physical function that decreases life quality; the availability of medical or surgical procedures used to treat the condition; ability for the condition to be diagnosed prenatally in order for the mother to take preventative or ameliorative action; and early onset. The committee discourages the inclusion of diseases that have late-onset phenotypes and emphasizes the continued importance of assessing individuals’ reproductive genetic risk based on personal and family history (The American College of Obstetricians and Gynecologists, 2017).

Opinions differ as to the effectiveness of these recommendations in producing clinically useful results. Ben-Shachar et al. argue that the 1/100 carrier frequency is too conservative and would prevent a significant portion of individuals undergoing ECS from discovering their carrier status. It maintains that the increased yield of ECS outweighs the burden it places on public health costs (Ben-Shachar et al., 2019). Lazarin et al. also remark that while carrier screening guidelines recommended by organizations like ACOG and the American College of Medical Genetics and Genomics (ACMG) are effective at discovering carriers in certain ethnic groups, they still miss the majority of carriers for most genetic conditions (Lazarin et al., 2013). On the other hand, Grody, Cutting and Watson assert that ACOG recommendations should be observed because they adequately enforce carrier screening test quality. Using cystic fibrosis as an

example, the authors argue that expanding the number of loci tested in *CFTR* beyond the 25 that were strongly recommended by ACOG and ACMG led to high false positive rates, low positive predictive value, and low marginal returns on additional costs used for sequencing more loci. They state that competition between laboratories to include more loci becomes arbitrary and drives out smaller laboratories who offer good quality testing but a smaller number of loci (Grody, Cutting, & Watson, 2007).

### *Attitudes toward ECS*

Few studies have investigated patient attitudes towards expanded carrier screening, but some investigations reveal the psychosocial experience of patients who have undergone traditional carrier screening. Overall, patients viewed carrier screening positively. A majority of patients reported feeling relief or satisfaction after finding out their negative carrier status, and many did not change their health behavior or health coverage as a result of carrier screening. Most patients experienced no or low levels of anxiety throughout the screening process, and some individuals appreciated the convenience of screening for multiple conditions with a single blood draw (Kraft et al., 2018). Negative reactions to carrier screening included feeling psychological distress during sequential screening of individuals' partners after one partner was discovered to be a carrier for a particular condition. In a structured interview of 10 women who underwent carrier screening in Australia, many participants stated that they did not expect to receive a positive result, and experienced anxiety while waiting for their partners' results. Because most of these participants were already pregnant, the implications of positive results were more dire as they signaled the possibility of termination. Most of the participants recognized that carrier screening was voluntary and did not feel pressured to undergo it, although

many participants mentioned that they agreed to the screening out of convenience, as it did not require another blood draw in addition to the one needed for their other laboratory tests (Beard et al., 2016).

Providers also hold different opinions in regard to the benefits, limitations and best practices regarding expanded carrier screening. In a sample of 16 European geneticists, the majority agreed on the way expanded carrier screening should be presented to patients: ideally it would be in a preconception setting to maximize individuals' capacity for reproductive decision making and offered in a way that does not coerce patients to undergo testing. They also agreed on the importance of appropriate post-test counseling, emphasizing that couples should have access to a detailed explanation of the relevant genetic condition, consultation with a specialist of the condition, and opportunities to meet with individuals who have the condition. In terms of pre-test counseling, providers disagreed on the level of detail that should be offered to patients about the characteristics of the conditions that would be screened. Some preferred a generalized consent with no mention of specific conditions while others preferred to categorize conditions based on characteristics like severity. The geneticists also disagreed on whether expanded carrier screening should be offered exclusively to couples or include individuals as well. Some geneticists oppose offering expanded carrier screening to individuals for the purpose of excluding future partners with whom they can have a high-risk pregnancy, while others approve of using ECS for partner selection. Several participants approved of ECS due to the fact that many individuals with family histories of genetic conditions seek carrier screening to rule out their own risk (Janssens et al., 2017).

Cho, et al. also investigated the opinions of several focus groups of genetics professionals on ECS, and some participants highlighted further challenges to expanded carrier screening.

Because many of the conditions included on ECS are rarer than the ones included on traditional screening, some participants noted that obstetric providers who are familiar with traditional screening may not be prepared for positive results that may be returned for rare genetic conditions, and that positive results may warrant referral to a geneticist or genetic counselor for further evaluation. Other participants emphasized the importance of clarifying limitations of ECS during pre-test counseling, including the fact that ECS does not screen for aneuploidies, and that a negative ECS result does not necessarily mean a risk-free pregnancy or a complete ruling out of carrier status for genetic conditions included in the testing (Cho et. al., 2013).

### ***Lysosomal Storage Disorders***

Lysosomal storage disorders (LSDs) are a group of about 50 disorders, some of which are commonly screened for on expanded carrier screening panels. In general, LSDs are characterized by a build-up of substrate in the lysosomes; organelles that aid in the digestive system of the cell (Germain, 2010). Often, LSDs are caused by enzymatic deficiency or deficiency of other types of proteins that help enzymes digest their target substrates. All together these disorders have a prevalence of less than 1 in 7000 live births (Wasserstein et al., 2019). Usually, early-onset forms are most severe with rapid onset of disease, and late-onset forms have milder, more slowly progressive symptoms (Freeze, Kinoshita, & Schnaar, 2017). An increasing number of patients with mild forms of lysosomal storage disorders are being diagnosed via expanded carrier screening. Three LSDs that have been incidentally diagnosed by carrier screening are outlined in more detail.

Gaucher disease is an autosomal recessive LSD caused by two pathogenic variants in the *GBA* gene which results in deficiency of the enzyme  $\beta$ -glucocerebrosidase, and accumulation of

the glycolipid, glucocerebroside, within the lysosome (Freeze, Kinoshita, & Schnaar, 2017). This disorder takes three forms which are differentiated by a severity and impact on the central nervous system. In general, all types of Gaucher disease have some degree of bone disease, anemia, platelet deficiency and hepatosplenomegaly. Gaucher disease type 1 (GD1) is more common and is characterized by the lack of progressive neurodegenerative disease and central nervous system disease.

GD1 can be diagnosed by assessing the enzyme activity level of  $\beta$ -glucocerebrosidase in leukocytes or through molecular genetic testing for pathogenic variants in the *GBA* gene. GD1 has a frequency of approximately 1 in 57,000 births making it the most common LSD. It is shown to be more frequent in Ashkenazi Jewish (1 in 855), Spanish, Portuguese, Swedish, Greek, and Albanian populations due to a founder effect. Observed prevalence of patients with GD1 is much lower than expected based on carrier frequency, suggesting that this is a low-penetrance disease (Zuckerman et al., 2007). Notably, homozygosity or compound heterozygosity for the common variants N370S and R496H often produce mild symptoms or no symptoms at all (Zeid et al., 2020).

Currently, GD1 is managed through intravenous enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). ERT provides a recombinant enzyme to overcome the digestive block in the lysosomes. SRT is an oral treatment that aims to decrease the production of glucocerebroside, allowing for the patient's residual enzyme to be able to adequately break down the remaining substrate. Individuals who do not receive regular ERT or SRT may experience complications that necessitate splenectomies, blood transfusions, and joint replacement surgeries (Biegstraaten et al., 2016). In general, these therapies are extremely

effective, though costly, an approximate \$200,000 annually in the United States per patient (Zuckerman et al., 2007).

Pompe disease is a rare, often fatal, autosomal recessive condition also referred to as Glycogen Storage Disease Type II (GSD II) (Cupler et al., 2012). It is caused by two pathogenic variants in the *GAA* gene which causes a deficiency of acid alpha-glucosidase enzyme and a buildup of glycogen in the cell (Lin et al., 2017). Pompe disease symptoms include progressive muscle weakness and respiratory insufficiency (Cupler et al., 2012). This disease presents in two forms, infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD), generally distinguished by age of onset and the involvement of cardiomyopathy – a common cause of death within the first year of life for IOPD patients (Lin et al., 2017).

Pompe disease is part of the Recommended Uniform Screening Panel (RUSP) list as one of the conditions that the Secretary of the Department of Health and Human Services recommends states include in newborn screening programs (NBS). Pompe disease can be diagnosed through molecular genetic testing or measurement of residual acid alpha-glucosidase enzyme activity. Molecular genetic testing is preferred; however, enzyme testing might be helpful for testing asymptomatic individuals who have been diagnosed through ECS (Winchester et al., 2008). In the United States, the frequency of Pompe disease is approximately 1 in 40,000. However, studies from Israel, Taiwan, and NBS in some regions of the United States report higher frequencies such as 1 in 25,000 in California. This NBS study also showed that the frequency of IOPD (approximately 1 in 250,000) was much lower than the frequency of potential LOPD (approximately 1 in 37,500) (Tang et al., 2020).

Enzyme replacement therapy can increase quality of life and slow progression of the disease. Treatment of LOPD also involves physical and respiratory therapy to increase muscle

and lung strength. ERT is an established treatment option during pregnancy and should be considered (Koyunca et al., 2017). Long-term effects of treatment have not yet been studied, but in general, patients are susceptible to premature death usually due to the effects of respiratory muscle weakness (Winchester et al., 2008).

Fabry disease is a rare X-linked condition caused by a pathogenic variant in the *GLA* gene that results in accumulation of globotriaosylceramide in lysosomes, due to reduced activity of the enzyme alpha-galactosidase A (Biegstraaten et al., 2016). Classical Fabry disease presents as a multisystem disease which usually begins to show in childhood or adolescence and causes crises of burning pain in the hands and feet (acroparesthesia), angiokeratomas, sweating abnormalities, kidney disease, cataracts and other eye issues. Classical and non-classical Fabry disease are differentiated by percent of enzyme activity. Heterozygous females typically develop milder symptoms with a later age of onset than males, but some have symptoms as severe as affected males due to skewed X-inactivation and other unidentified mechanisms (Germain, 2010).

Fabry disease can be diagnosed through identifying alpha-galactosidase A enzyme deficiency in males, although this testing is not diagnostic in females. Diagnosis can be made or confirmed through molecular genetic testing and identification of a hemizygous *GLA* pathogenic variant in males and a heterozygous *GLA* pathogenic variant in females (Biegstraaten et al., 2016). Reported incidences in the general population range from 1 in 476,000 to 1 in 117,000. These numbers may underestimate the true prevalence though, as NBS studies have shown much higher incidences such as 1 in ~3,100 in Italy and 1 in 1,500 in Taiwan (Spada et al., 2006; Lin et al., 2009).

Fabry disease is managed by using a team of specialists to treat symptoms as they arise and to regulate pain management. Experts recommend that enzyme replacement therapy be used although long-term use has not been proven to continuously help manage symptoms (Biegstraaten et al., 2016). In heterozygous females, life threatening manifestations have been seen including cardiac ischemia, cerebrovascular accidents, hypertension, dysrhythmias, and renal insufficiency (Wang et al., 2007). Death from Fabry disease usually occurs from complications of renal disease, cardiac disease, and cerebrovascular disease.

Incidental diagnosis on carrier screening of patients without prior symptoms of a late-onset disease presents challenges in determining ongoing surveillance and when to consider initiation of treatment. It also presents psychosocial challenges for the patient faced with an unexpected diagnosis, particularly during pregnancy. With the exception of select case reports, this phenomenon of incidental diagnosis is not yet studied in the area of late-onset genetic conditions on ECS, and thus there is much to be learned regarding the impact of this event on patients, conduction of medical surveillance and treatment decisions, and on the wider healthcare system. Qualitative study of the patient experience in this scenario has not yet been completed, presenting a novel opportunity. This study aims to provide qualitative insight on the patient experience so that relevant providers in this area may gain valuable knowledge for their practice, and to bring attention to this phenomenon.

## **Methods**

### *Participants*

A total of 12 patients receiving care at the New York University Lysosomal Storage Disorders Program who received an incidental diagnosis of a late-onset lysosomal storage

disorder on preconception or prenatal expanded carrier screening met criteria for participation. These individuals included 3 males and 8 females who ranged in age from 25 to 39 years. One patient was excluded because they discontinued care at this facility. The sub-investigator contacted the remainder of the patients about participation in the study, four of whom indicated interest, completed and returned consent forms, and engaged in structured interviews with study staff. IRB approval was obtained from the NYU School of Medicine.

### *Materials*

This study consists of a one page quality of life scale (QoLS) questionnaire and a guided interview by audio call. The recordings were transcribed and sent back to the participants for review. The questions included in the interviews elicited responses for three periods in the patient's experience with incidental diagnosis: initial experience with ECS, the period directly after incidental diagnosis, and the current period after they established care with a specialty clinic in regards to their diagnosis.

### *Procedure*

Participants were recruited from the clinical practice of the principal investigator and the sub-investigator. Participants were identified by Epic data review of new patients seen in the clinical practice between September 1st, 2015 and October 1, 2019, diagnosed with a late-onset LSD. Recruitment took place over the phone and email where an electronic copy of the consent forms, QoLS, and available time slots for the audio interview were emailed to the participant. The interview portion of the study took place by audio call on the web conference platform Cisco

WebEx by a study staff member located in a private remote location. Participants completed a structured interview regarding their experience of diagnosis and access to medical care.

The PI and the sub-I had access to Epic data for clinical care and the following data points and Protected Health Information (PHI) from Epic were used for research: Name, phone number, and email were used for study recruitment and communication, and LSD disease diagnosis, gender, and age (documented as a 5 year age range e.g. 20-24 years) were used for analysis.

This study conducted preliminary qualitative data analysis. Analyses described individual data by drawing on themes in participant responses and presenting limited quotes of direct participant responses. Data was described according to type of participant diagnosis, time period since receiving the diagnosis, whether patient received pretest counseling about incidental diagnoses, and whether the diagnosis was received in the context of prenatal or preconception care, but these groups were not expected to achieve statistical significance in light of the small study size. Answers to QoLS questions were summarized quantitatively using average scores for each participant, average scores across each question and range among scores for each question. Trends among participant satisfaction scores were evaluated qualitatively.

## **Results**

Four interviews were conducted with female participants who have been incidentally diagnosed with Gaucher Disease Type 1, Late-onset Pompe Disease and Fabry Disease. Three participants received ECS for preconception purposes, and one received ECS prenatally. Interviews lasted between 25-45 minutes.

Six main categories emerged from the participants' responses: 1) quality of explanation of ECS prior to testing, 2) quality of health education during results disclosure, 3) emotional response to first knowledge of incidental diagnosis, 4) impact of diagnosis on quality of life, 5) impact of specialized care on experience with diagnosis, and 6) current attitude about ECS.

Themes from each category are elucidated below, as well as main trends from patient responses to the Quality of Life Surveys (QoLS). QoLS responses and participants' demographic information are summarized in Tables I and II, respectively.

### ***Explanation of ECS prior to testing***

A common theme among participant responses was that the participants recalled not receiving significant education on the specifics of ECS, for example the conditions that would be included in the testing panel and the types of results that can return. None of them remember having received formal pre-test counseling. Much of the participants' knowledge of ECS prior to testing was reportedly from their past experiences; they had either heard of other people in their community who underwent a similar type of test, or they heard about genetic screening through word-of-mouth. All participants expressed that they never expected to receive a positive result, especially one that indicated that they were diagnosed with a genetic condition themselves. One participant stated that there were some educational materials that were included with her direct-to-consumer testing kit, but that she did not read them carefully. She remembered thinking that the testing process was simple and knowing some details about the test beforehand, such as variation in severity of conditions covered, because many people in her community undergo ECS. Both participants who received ECS during their appointment at fertility clinics stated that they had no choice about genetic testing as they recall it was presented as a mandatory procedure

during their evaluation. One of these participants said that she did not know that a genetic test had been ordered for her, although she reported that she was not in a place to pay attention to any information about ECS due to impatience to initiate the *in vitro* fertilization process. Several participants stated that they received their results in a stepwise process; for example, an initial email disclosing the results followed by a phone call, or an initial email followed by an in-person appointment to discuss the results.

### ***Quality of health education during results disclosure***

All participants received their ECS results either through their ordering physician, a genetic counselor, or a combination of both. Regardless of the type of provider that disclosed the results, their perceived level of knowledge about the incidentally diagnosed condition heavily influenced participants' satisfaction with their explanation. The participants were concerned with several aspects of their diagnosis: the clinical features of the disorder itself, how it would impact them, and resources for dealing with the diagnosis. Participants were dissatisfied with providers who they felt were not knowledgeable about the diagnosis and who could not provide details about prognosis and treatment. According to several participants, their providers admitted that they knew little about the genetic condition that was diagnosed. Participants were also dissatisfied when they felt a lack of ability to provide referrals to specialty clinics or to resources that could help them manage their diagnosis. Several participants said that they were left to their own devices in regards to finding follow-up care, and they either turned to the internet or their insurance company to look for specialty providers. Participants also reported utilizing the internet to find more information about their genetic condition, which often led to increased anxiety when they learned about serious or life-threatening symptoms. Participant 1 stated that

she was satisfied with her results disclosure and that it was straightforward for her to initiate next steps in her care because she recalled being given a thorough explanation of her genetic condition and a referral to an appropriate specialty clinic.

### ***Feelings upon initial news of incidental diagnosis***

All participants recalled feeling surprised at their incidental diagnosis. Participant 2 said “I was upset, I was disappointed, I was concerned, I was confused, I was worried” upon hearing her results. Two participants expressed a degree of denial about their results due to their absence of symptoms. Participant 3 reported hoping that she was misdiagnosed, and Participant 1 reported having to take some time before the reality of her diagnosis could sink in. Several participants expressed a level of confusion that did not resolve after speaking with their diagnosing provider, because they still felt anxious after their providers’ explanations. One participant said that she felt afraid because she thought that she could develop symptoms at any moment or die at a much younger age than she had expected.

### ***Impact of diagnosis on quality of life***

The degree to which each participant felt that their diagnosis affected their everyday lives depended mostly on the nature of follow-up activities and their plans regarding pregnancy. One participant stated that her diagnosis did not significantly affect her quality of life until she began to undergo enzyme replacement therapy. She cites difficulty with time management, financial challenges and juggling of multiple responsibilities as factors that decrease her quality of life. Several participants, including one who was asymptomatic, said that getting insurance coverage for their condition is a major concern, both in terms of paying for treatment and of being able to

get supplemental insurance coverage with a pre-existing condition. Both participants 1 and 4 report experiencing difficulty with getting their treatments covered under their health insurance plans. Participant 3 said that her diagnosis compelled her to purchase life and disability insurance--something she had been delaying--in case she needed it in the future. She said that she expected pushback from the insurance company due to having a known genetic condition, and was pleasantly surprised that she was able to purchase the insurance that she wanted. The participants who are currently asymptomatic stated that their diagnosis does not significantly influence their everyday activities and relationships. However, they reported feeling anxiety and uncertainty about the future since it is difficult to predict when, if ever, symptoms would appear.

One participant who was diagnosed while pregnant said that she became more cautious about her pregnancy and elicited extra professional help for the birthing process that she would not have done otherwise. She also reported needing to follow up with different specialists due to the fact that pregnancy increases the risk of symptoms. Both participants who were diagnosed while undergoing or preparing to undergo fertility procedures said that their treatment was delayed or complicated by their diagnosis. Participant 2 said that could not continue until she had received medical clearance from a specialist for her condition, and participant 4 stated that she underwent a second round of preimplantation genetic testing before proceeding with her pregnancy, which increased her treatment costs.

A positive effect that stemmed from incidental diagnoses in this cohort was that several of the participants' relatives received diagnoses themselves through cascade testing, some of whom are currently receiving treatment for significant symptoms. One participant's brother was reported to have symptoms all his life that did not lead to a diagnosis until the participant underwent ECS and identified the probable cause. That participant stated that her incidental

diagnosis improved her relationship with her brother because she now has greater concern for his health.

### ***Impact of specialized care on diagnosis***

All participants indicated that having access to a doctor who specializes in the rare diseases with which they were diagnosed was helpful. The participants who were dissatisfied with the initial explanation of their results remembered feeling less anxious and more informed after they met with a specialist who was familiar with their condition. One participant said that the doctor was the resource she would depend on the most should she develop symptoms of her condition. All participants appreciated thorough explanation of the treatment options available, and one person said that she liked the doctor's dedication to research because it made her hopeful for better treatment in the future. Multiple participants felt that their needs were being heard and addressed by the doctor, which was important to them.

Participants mentioned a few other resources that were helpful to them, including a patient advocacy group dedicated to their genetic condition, a case manager at the pharmaceutical company prescribing enzyme replacement therapy, and the internet at large. Participant 3 said that she was only able to find a specialist after contacting a support line at a patient advocacy website dedicated to Pompe disease. She stated that advocates working for this group also connected her to other people with the same diagnosis and informed her of community events and resources. Participant 1 said her case manager was her most helpful resource because she supports her emotionally and helps coordinate her treatments. Several participants turned to the internet for information regarding their diagnosis, which was not always a successful strategy. However, one participant said that she was able to get most of the

information needed online, which was crucial because she felt that the provider who disclosed the results to her did not provide enough explanation.

### ***Current attitude about ECS***

All participants reported that they would undergo ECS again if they had the choice, because they believed that expanded carrier screening gave important information. Several participants stated that ECS should be offered to everyone. Participant 1 added that she recommends individuals pursue carrier screening that includes a comprehensive list of conditions, because she knew of carrier screening options that would not have included the condition with which she was diagnosed. All participants advised providers disclosing ECS results to be knowledgeable about the conditions in which they are educating their patients, and be prepared to provide resources, such as pamphlets or referrals to patient groups. One participant also expressed a desire for the provider to demonstrate compassion during results disclosure. One participant remarked that it would be helpful for providers to recommend ECS to women who are considering getting pregnant as carrier screening has the most impact for reproductive decision making during the preconception period. She also advised providers to educate individuals undergoing ECS on the possibility of incidental diagnosis, as she did not recall being educated about this possibility prior to testing.

Despite the confusion and difficulty that sometimes accompanied their experiences surrounding incidental diagnosis, several participants stated that they appreciated ECS for giving information that was useful not only for pregnancy, but for personal health purposes as well. One participant stated that she “would rather [have known] about it now than not know about it”.

### *QoLS answers*

The *QoLS* consists of 16 questions to which participants scored a number from 1-7, 1 indicating the lowest satisfaction with the area of life assessed by the question and 7 indicating the highest. Each participant's scores were averaged across all questions; the average score among participants for each question was calculated as well as the range among participant scores for each question. Among the three participants who returned their surveys, their average reported scores were 5.9, 5.5 and 5.5 across all questions, between mostly satisfied (a score of 5) and pleased (a score of 6). No participants scored lower than 4 (mixed) to any question. The questions that elicited the lowest average scores among all participants were numbers 8, 10, 12 and 15 (average scores of 4.33, 5, 5 and 5 respectively). These questions asked about participating in organizations/public affairs, understanding the self, expressing the self creatively, and participating in active recreation. Notably, there was no range in participant responses for questions number 10 and 12 (self-understanding and self-expression). The questions that elicited the highest average scores among all participants were numbers 5 and 16 (average scores of 6.67 for both questions). These questions pertained to the participants' satisfaction with relationships to spouses or significant others and level of independence. There was a range of 1 for both responses among participants' scores. Other questions that featured high average scores among all participants were numbers 1, 3, and 6 (all scores of 6.33), which asked about material comforts, family relationships and relationships with close friends, respectively. There was a range of 1 in the responses for each of these questions. Responses to 6 out of 16 questions had a range of 2, and responses to 1 out of 16 questions had a range of 3. The questions that had greater range in response tended to ask about day-to-day activities, such as

working, studying, or doing leisure activities. Having and rearing children also elicited a range of 2.

Overall, participant satisfaction with the categories mentioned on the questionnaire are moderate to high, with more variation (score range of 2-3) in responses to the categories that depend on individual circumstances, such as work, time and/or resources with which to do leisurely, civic or educational activities, and having or raising children. Participants reported the highest levels of satisfaction with their independence, material comfort, and close relationships, and there was low discrepancy in the participants' ratings of these categories (score range of 0-1). No participants rated themselves as actively dissatisfied with any category of life elicited by the questionnaire. The participants had different experiences in terms of pregnancy, but all of them reported that they were "mostly satisfied" to "delighted" in terms of having children and childcare. The participants reported that they were "mostly satisfied" or "pleased" with their health, including the ones who were exhibiting symptoms and undergoing treatment at the time of the interview.

**Table I. QoLS Answers**

scale is designated as follows: 7-Delighted; 6-Pleased; 5-Mostly satisfied; 4-Mixed; 3-Mostly dissatisfied; 2-Unhappy; 1-Terrible

Category	Participant 1 scores	Participant 2 scores*	Participant 3 scores	Participant 4 scores	Average score for question	Range
1. Material comforts home, food, conveniences, financial security	7	-	6	6	6.33	1
2. Health - being	6	-	6	5	5.67	1

physically fit and vigorous						
3. Relationships with parents, siblings & other relatives-communicating, visiting, helping	7	-	6	6	6.33	1
4. Having and rearing children	6	-	5	7	6	2
5. Close relationships with spouse or significant others	7	-	6	7	6.67	1
6. Close friends	6	-	6	7	6.33	1
7. Helping and encouraging others, volunteering, giving advice	5	-	5	7	5.67	2
8. Participating in organizations and public affairs	4	-	5	4	4.33	1
9. Learning-attending school, improving understanding, getting additional knowledge	6	-	4	5	5	2

10. Understanding yourself - knowing your assets and limitations - knowing what life is about	5	-	5	5	5	0
11. Work - job or in home	7	-	5	5	5.67	2
12. Expressing yourself creatively	5	-	5	5	5	0
13. Socializing - meeting other people, doing things, parties, etc	6	-	6	4	5.33	2
14. Reading, listening to music, or observing entertainment	7	-	5	4	5.33	3
15. Participating in active recreation	5	-	6	4	5	2
16. Independence, doing for yourself	6	-	7	7	6.67	1
Participant's average score	5.9	-	5.5	5.5	-	-

\*Participant 2 did not return her QOLS to the study team.

**Table II. Participant demographics**

Participant number	Age at time of diagnosis	Time since incidental	ECS ordered by	Diagnosis	Method of results
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	(years, presented as a 5 year range)	diagnosis			disclosure/provider type
1	25-29	2.5 years	Self, through direct-to-consumer site	Gaucher Disease Type 1	Email, then over the phone with a genetic counselor
2	35-39	6 months	Fertility doctor	Gaucher Disease Type 1	In person, physician
3	35-39	4 years	OBGYN	Late-Onset Pompe Disease	In person, physician and genetic counselor
4	30-34	4 months	Fertility doctor	Non-classical Fabry Disease	Email, then in person with a physician

### **Discussion**

The advent of expanded carrier screening over 10 years ago has made determining reproductive risk for individuals and couples more widespread. In this study, we assessed the psychological outcomes of receiving an incidental diagnosis from ECS. Until this study, qualitative insight on the patient experience of receiving an incidental diagnosis from ECS had not yet been investigated.

### ***Practice implications***

Ensuring adequate pre-test counseling is an important process for any type of genetic testing, especially ECS because of the extensive number of diseases it may entail. The informed

consent process should address the results a patient may receive, including incidental diagnosis (Janssens et al., 2017). Perceived lack of quality informed consent was highlighted in our study by the patients' confusion upon receiving a diagnosis, especially in the absence of any prior symptoms. The subjects in this study valued the information given to them through ECS. They reported emotional distress from the time they were first disclosed the results until they were able to speak with a LSD specialist. Adequate pre-test counseling may have better prepared them psychologically for this type of result by preparing them for the unexpected. We recommend that providers offering ECS discuss incidental diagnoses as part of the informed consent process.

A common theme noted in this pilot study was that individuals were more satisfied when they received additional support and resources. The level of knowledge of the provider who disclosed results to the patients heavily influenced initial patient satisfaction, with greater knowledge resulting in higher satisfaction. Without satisfactory knowledge from their provider, many individuals used the internet as their primary resource for information. This leaves the potential for emotional distress and misinformation. Adequate counseling and information about a diagnosis could prevent patients from relying on online sources for medical information. Specifically, patients requested details about the impact of the disease, resources for dealing with the diagnosis, and details about prognosis and treatment. Patients found that patient advocacy groups, a case manager from the pharmaceutical company providing enzyme replacement therapy, insurance companies, labs, and the internet at large served as resources when there was insufficient information given by their provider. We suggest that clinics that offer ECS also offer resources such as pamphlets of information for late-onset diseases commonly found in ECS, medical counseling by professionals familiar with the specific disease, such as referral to a

genetic counselor, and have a plan in place to refer out to specialists in the area who treat and manage these conditions.

All subjects interviewed reported that they did not experience symptoms prior to their diagnosis. Some patients with LSDs may be asymptomatic or mildly symptomatic throughout their lifetime which can complicate patient education, reproductive risk, and adult health management (Lazarin et al., 2013). Patients in this study expressed feelings of denial and uncertainty about their future health. In the absence of symptoms and without adequate information initially given, it was difficult for patients to understand their disease and how it would affect their finances, personal lives, and time management. This highlights that incidental diagnoses are difficult for patients to adjust to, which providers should take into consideration if encountered in their practice. After meeting with an LSD specialist, the same patients reported feeling more capable and equipped to handle their diagnosis. Without adequate medical counseling prior to and after testing, ECS may cause unnecessary anxiety for patients.

Despite the issues experienced by the participants in this study, the subjects reported that they would have testing again if offered and that they would recommend testing to others in their community. The patient's expressed that the knowledge gained through ECS was useful information for their personal health, their reproductive health, and their families. We suggest that providers who offer ECS ensure that their clinics offer satisfactory pre-test counseling, ample resources for information on late-onset conditions, and be prepared to refer patients to specialists for their disease, particularly those with a high frequency in founder populations, such as Gaucher Type 1 in the Ashkenazi Jewish population, or non-classical Fabry disease in the Taiwanese population.

### ***Study limitations***

One limitation of this study is the small sample size (N=4). One way that this could be addressed is to recruit individuals from multiple LSD clinics. Patients should be recruited from multiple ethnic backgrounds and countries when possible in order to discern differences in the experiences of individuals that have arrived at their incidental diagnoses who have alternative ethnic, socioeconomic and cultural backgrounds than those represented in this study sample. It would also be helpful to know if differences in accessibility and quality of healthcare in different parts of the US and the world affect individuals' outlook on incidental diagnoses. In addition to eliciting recruitment from other LSD centers, patients could be recruited from centers that see patients who have been incidentally diagnosed with additional late-onset or low-penetrance diseases commonly placed on ECS panels.

Secondly, although we utilized the QoLS to assess the psychosocial experience of the participants numerically, it is difficult to correlate their answers on the survey to the outcomes that they spoke about related to incidental diagnosis. It is possible that some question categories are significantly related to the participants' experience of incidental diagnoses while other categories are not at all related. The scores could be affected by other life factors that this study does not address, as well as individual characteristics affecting mood, outlook on the future, resilience and adaptation. Because there are no QoLS responses taken in the peri-diagnostic period with which to compare the current QoLS assessments, it is also difficult to determine whether participants' satisfaction with life has changed in the intervening time using this quantitative method.

### ***Research recommendations***

In future studies, it would be valuable to include a control group of adult patients that have been diagnosed with late-onset LSDs based on symptoms and compare their diagnosis experience with that of individuals diagnosed from ECS. Another avenue for future research would be to ask whether or not the patient's partner was tested. There were varying degrees of anxiety surrounding future pregnancies for the patients. It would be valuable to know whether or not their knowledge about the risk of their children having this disease was the cause for this concern or lack of concern.

If including QoLS in future studies, it would be helpful to ask participants specifically about the effect of their incidental diagnosis on any areas of the questionnaire that have particularly high or low scores so as to determine how the scoring relates specifically to the patient's experience of incidental diagnosis. If the QoLS is not incorporated, it may be helpful to add additional detail to the interview script eliciting categories such as childcare, ability to participate in public and private activities, and material comfort in order to elicit how satisfaction in these categories has changed over time.

This pilot study provides initial insight into the importance of pre- and post-test counseling for ECS. Satisfactory pre-test counseling for ECS should include a clear discussion of the possibility of incidental diagnosis of late-onset conditions. Disclosing the diagnosis should be accompanied by ample support, information, and resources. Likewise, post-test counseling should resolve uncertainty and anxiety by supplementing the patient with resources and referrals to specialists for their condition. The growing use of ECS will bring about more incidental diagnoses and the importance of satisfactory pre- and post-test counseling must be implemented for the psychosocial and personal health benefit of the patient.

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