FEASIBILITY OF REQUIRING INFANTS TO BE SCREENED AND TREATED FOR LYSOSOMAL STORAGE DISORDERS

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BACKGROUND

The Oregon State Public Health Laboratory of the Oregon Health Authority screens all infants born in Oregon for more than forty disorders of body chemistry that can result in profound disability or death unless they are detected and treated before symptoms begin (ORS 433.285-295). Oregon's panel of newborn screening disorders is established in OAR 333-024-0210 and does not currently include any lysosomal storage disorders (LSDs) (Appendix).

Senate Bill 284

Senate Bill 284 of the 77th Legislative Assembly directed the Oregon Health Authority to conduct a study to assess the feasibility of requiring infants to be screened and treated for LSDs and to report the results of this study to the Legislative Assembly:

SECTION 1. (1) As used in this section, "lysosomal storage disorder" means Krabbe disease, Pompe disease, Gaucher disease, Fabry disease, Niemann-Pick disease or any other inherited metabolic disorder resulting from a defect in lysosomal functionality.
(2) The Oregon Health Authority shall conduct a study related to infants who have a lysosomal storage disorder and assess the feasibility of requiring infants born in this state to be screened and treated for lysosomal storage disorders. The authority shall report the results of the study to the Legislative Assembly, in the manner provided for in ORS 192.245, on or before March 1, 2015.

SECTION 2. Section 1 of this 2013 Act is repealed on March 2, 2015.

Lysosomal Storage Disorders

There are at least 50 known LSDs, which are a type of "lipid storage disease", described by the National Institutes of Health as follows: "…a group of inherited metabolic disorders in which harmful amounts of fatty materials (lipids) accumulate in various cells and tissues in the body. People with these disorders either do not produce enough of one of the enzymes needed to break down (metabolize) lipids or they produce enzymes that do not work properly. Over time, this excessive storage of fats can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen, and bone marrow."[1]

The symptoms of LSDs vary depending on the nature of the material that accumulates as well as the tissues where it accumulates, which in turn is determined by which of the many lysosomal enzymes is defective. Many of the LSDs primarily affect the nervous system (brain), whereas others affect mostly the liver and spleen and have no neurologic symptoms. Treatment for LSDs is based on the use of various approaches to replace the missing enzyme, which may include intravenous enzyme infusions, or transplants of bone marrow or other tissues. Early attempts at gene therapy are being used experimentally for some of the disorders.

LSD NEWBORN SCREENING IN THE U.S.

The Recommended Uniform Screening Panel (RUSP)

The U.S. Secretary of Health and Human Services decides which disorders are included in the Recommended Uniform Screening Panel for all U.S. infants, based on analysis and advice from the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

(SACHDNC). The RUSP defines the standard of practice for State newborn screening programs, and Oregon is in compliance for all metabolic disorders.

Disorders can be added to the RUSP through a formal review process that considers all available medical and scientific evidence. Anyone may nominate a disorder for the RUSP by submitting the necessary supporting information to the SACHDNC. The Committee then conducts a comprehensive evidence-based review of the benefits and feasibility of newborn screening, and decides whether to advise the Secretary that the disorder should be added to the Panel.[2] To be recommended for the RUSP, a disorder must be detectable by a valid and practical laboratory test, treatable with currently available and effective therapies, and medically severe enough that diagnosing it in newborns will yield benefits that outweigh the financial and societal costs of screening.

There are currently 31 disorders on the RUSP, but none of them are LSDs.[3] Eleven disorders have been nominated to the SACHDNC since its work began in 2008. Two of these (Critical Congenital Cyanotic Heart Disease and Severe Combined Immunodeficiency) were recommended favorably by the SACHDNC and then added to the RUSP by the Secretary. Four LSDs have been nominated for addition to the RUSP, including three (Niemann-Pick Disease, Krabbe Disease, and Fabry Disease) that were reviewed but not recommended to the Secretary. The fourth LSD, Pompe Disease, was recommended for inclusion on the RUSP in June 2013 but final approval by the Secretary is still pending.[4]

Test Selection and Predictive Value

Newborn screening is performed in two stages that begin with an initial screening test, followed by a confirmatory test for all initially positive samples.

The initial screening method must have very high "sensitivity", meaning that virtually 100% of infants with a disorder will be identified (i.e., no "false negatives"). However, because of the nature of laboratory testing, any test with100% sensitivity will also yield some "false positive" test results in infants who do not actually have the disorder.

Next, second tier confirmatory testing is used to distinguish which of the positive initial screening results are true positives (the infant has the disorder) versus false positives. So, confirmatory tests are more specific than screening tests, but they are also more complex and expensive, and they often require the collection of another blood sample and/or additional diagnostic procedures.

Therefore, when selecting an initial screening test, there must be a balance between achieving 100% sensitivity to detect all affected infants, while not producing too many false positive results. False positive screens can generate an unmanageable number of confirmatory tests and medical consultations, as well as anxiety, expense, unnecessary medical procedures, and stigmatization of infants.

To assure this balance, an initial screening test must have an acceptable "Positive Predictive Value" (PPV); i.e., the probability that a positive test result is correct. For example, for a screening test with a 75% PPV, positive results are correct three-fourths of the time. In contrast, if a test has a 5% PPV this means that positive results will be incorrect 95% of the time, meaning that for every affected infant correctly identified, another 19 infants and their families will be subjected to the negative consequences of a false positive result. Most initial newborn screening tests should have a PPV in the range of 50%. A lower PPV means that a

test has limited value to distinguish between affected and unaffected infants in a practical and cost-effective manner.

LSD Newborn Screening in Other States

As of December 31, 2014 five states have laws mandating newborn screening for LSDs. The number of disorders varies from state to state as shown below.[5,6]

	Fabry	Gaucher	Krabbe	MPS I*	MPS II*	Niemann-Pick	Pompe
Illinois	√	√	√	√	√	√	√
Missouri	√	√	√	√		√	√
New Jersey	√	√	√	√	√	√	√
New Mexico	√	√	√			√	√
New York			√				

*MucopolysaccharidosisTypes I and II

Relevant LSD Legislation

Illinois: SB 1566 was signed into law on November 5, 2007 requiring the State of Illinois Newborn Screening Program to screen for five LSDs (Fabry, Gaucher, Krabbe, Niemann-Pick and Pompe). In August 2011, legislation (SB1761) required the addition of Mucopolysaccharidoses (MPS) Types I and II.[7]

Missouri: HB 716, the Brady Alan Cunningham Newborn Screening Act, signed into law in July 2009, mandated screening for Fabry, Gaucher, Krabbe, Niemann-Pick and Pompe.[7]

New Jersey: Emma's Law, S-1999/A-2708, signed into law in January 2012, required screening for Krabbe, Pompe, Gaucher, Neimann-Pick and Fabry.[8] MPS I and II are mandated if/when they are added to the RUSP.[9]

New Mexico: HB 201, signed into law in March 2010, mandated screening for Fabry, Gaucher, Krabbe, Neimann-Pick and Pompe as soon as screening is feasible. None of these five disorders have yet been added to the New Mexico screening panel.[7]

New York: Universal newborn screening for Krabbe began in 2006, following the issuance of an executive order by the Governor. In 2009, legislation (S6656/A979) was introduced requiring the addition of Pompe, Fabry, Niemann-Pick and Gaucher.[10] New York is currently conducting a pilot study to evaluate technical aspects, as well as the ethical, legal, and social issues associated with newborn screening for these additional four disorders.[5]

Pending LSD Legislation

California: April 2014 amendment to SB 1072 requires the expansion (until January 1, 2018) of statewide newborn screening to include Krabbe and MPS I.[11]

Maryland: Lily's Law, HB 111, introduced in January 2014, requires the addition of Krabbe, Pompe, Gaucher, Neimann-Pick, Fabry and MPS-I.[12]

Pennsylvania: Hannah's Law, was passed by the Senate in October 2014 and currently awaiting the Governor's signature. This legislation mandates screening for Krabbe, Fabry, Gaucher, Pompe, Niemann-Pick and MPS I.[13]

LSD project

Washington: The Washington Newborn Screening Program has been piloting Fabry Disease screening for several years but does not include Fabry in its official panel of disorders.[5] The program is currently collaborating with a University of Washington researcher (in conjunction with PerkinElmer) to develop a multiplex assay for nine LSDs utilizing tandem mass spectrometry (MS/MS).[14] Data from this project are not yet available.

Laboratory Screening for LSDs

As reported to the Oregon Senate Committee on Health Care and Human Services in February 2013, there is still no U.S. Food and Drug Administration (FDA)-approved laboratory method for LSD screening of dried blood spot specimens. Each state that is currently attempting LSD screening has independently developed and validated its own method, as required for a "Laboratory Developed Test" by the FDA.

Two methods are utilized by newborn screening programs to test for LSDs: tandem mass spectrometry (MS/MS) and microfluidics, as shown in the table below.

Illinois	Tandem mass spectrometry (MS/MS)
Missouri	Microfluidics
New Jersey	MS/MS
New York	MS/MS
Washington	MS/MS (method development pilot project)

MS/MS is used in all U.S. newborn screening laboratories (including Oregon's) to detect several types of disorders (e.g., amino acid, fatty acid oxidation). Theoretically, the existing MS/MS protocol could be expanded to include LSD screening. However, detecting LSDs requires separate dedicated MS/MS instruments and cannot simply be added onto the existing test regimen because of the higher pressures used in LSD screening. These take a greater toll on the instrument seals, thereby requiring more frequent maintenance, causing instrument failure, and leading to delays in reporting of test results for all disorders.[15] Each additional MS/MS instrument costs approximately $300,000.

Microfluidics for LSD screening was introduced by Advanced Liquid Logic in 2010. The company established pilot projects with Illinois in November, 2010 and Missouri in January, 2012.[15] Due to technical problems, Illinois suspended microfluidics screening and converted to MS/MS. Missouri continues to utilize microfluidics on a developmental basis. Advanced Liquid Logic, purchased by Illumina in July 2013, is now providing the microfluidics technology through a newly formed company, Baebies, which currently offers a four-plex test (Pompe, Fabry, Gaucher, MPS I) and a two-plex test (Pompe/Biotinidase). Krabbe, Neimann-Pick and MPS II additions are expected in 2015.[16] Performance data are preliminary and do not yet meet the standards of predictive value needed for a screening test (below).

LSD Screening Results/Cases Identified

Illinois: 16,300 specimens tested for six disorders (Krabbe, Fabry, Pompe, Niemann-Pick A/B, Gaucher, and MPS-I); 1,300 specimens tested for five disorders (Fabry, Pompe, Niemann-Pick A/B, Gaucher, and MPS-I)[15]

	Fabry	Gaucher	Krabbe	MPS I	Niemann-Pick	Pompe
Number initially positive	5	4	8	17	1	12
Follow-up confirmed positive	0	1	0	0	1	0
Follow-up confirmed negative	4	3	5	10		7
Follow-up Results Pending	1			2	3	
Other Resolutions:						
Pseudo-deficiency			1	5	1	
Carrier			2		1	

Information received on the sensitivity, specificity, and positive predictive value (PPV) for Illinois indicates 100% sensitivity (based on proficiency testing for Krabbe and Pompe), and 99.7% specificity (45 false positives in 16,300 specimens). However, the PPV was only 4.2% (i.e., only two of 47 initially positive results were confirmed positive on follow-up)[15]

Missouri: Microfluidics pilot/implementation phase totals to date, presented 12/16/14.[17] Total Samples screened: 174,636 (≈149,500 infants)

Disorder	Screen positives	Confirmed Disorders	Conditions of unknown significance or onset	Pseudo-deficiencies	Carriers	False Positives	Pending	Lost to Follow-up	Positive Predictive Value (PPV)
Pompe	76	13	3	13	13	26	7	1	17.1%
Gaucher	19	1	2	0	2	13	0	1	5.2%
Fabry	99	37	7	0	0	41	9	5	37.4%
MPS-I	42	1	0	21	2	11	7	1	2.4%

New Jersey: The validation and pilot for the five originally mandated LSDs will be initiated in the second half of 2015, so NJ does not yet have any data to share.[18]

New York: Previous information received from the NY Newborn Screening Program indicated that they had screened approximately 1.5 million newborns for Krabbe. Two hundred eighty-six of these were initially positive and five of these had been confirmed as infantile onset cases.[19] This indicates a PPV of 1.7%. A recent request for more updated information has not yet elicited a response.

Costs of LSD Screening:

Detailed cost data are not available since most states are still working in a pilot screening mode. However, Illinois will be raising its fees by $21 per sample, and New Jersey by approximately $50 per sample to cover LSD implementation (assuming that $10 of the $60 increase, described below, is for SCID). For comparison, Oregon currently charges $32 per sample to screen for all 40+ disorders.

Illinois: Two different rounds of legislation added LSD testing. The first mandated testing for five LSDs and raised the newborn screening fee from $59 to $78. The second round of legislation added MPS I, MPS II, and Severe Combined Immunodeficiency (SCID) and increased the fee by $8 for SCID and $2 per additional LSD. The current fee is $88 per specimen, and the fee will increase to $90 when LSD testing is expanded statewide.[15]

New Jersey: The current newborn screening fee is $90.00 per initial specimen. A fee increase has been proposed to cover the addition of LSDs and SCID (which was implemented with no fee increase) that is expected to be implemented at the end of 2015. The fee will increase to $150.00 which covers laboratory, follow-up and health service grants to regional centers.[18]

LSD TREATMENT

Krabbe Disease

Krabbe disease is a rare (incidence estimated at 1 in 100,000 births) neurodegenerative disorder known as a leukodystrophy, which results from an inherited deficiency of a lysosomal enzyme called galactocerebrosidase. Symptoms usually begin within the first 6 months of life, but some patients don't present until adolescence or even adulthood. In infants the most common initial symptoms include excessive crying, irritability, poor growth, abnormal muscle tone and arrest of normal neurologic development (motor skills, language). The only available treatment for early infantile onset Krabbe disease is hematopoietic stem cell transplantation (HSCT). However, HSCT is associated with a significant risk of both morbidity and mortality (10% mortality rate), and therefore it is essential that the procedure be limited to infants with early onset disease. There is currently no way to determine when or even if symptoms will develop in infants identified via newborn screening. The difficulties this poses are best illustrated by the experience of the state of New York, which started universal newborn screening for Krabbe disease in 2006.

Based on prior studies it was expected that 90% of patients identified by newborn screening in New York would develop symptoms during infancy, and therefore be candidates for HSCT.[20] However, after 4 years of screening they found that the majority of children identified had remained clinically unaffected. So far they have been unable to identify any means of predicting which children will develop symptoms during infancy, and which will remain asymptomatic for many years. Because HSCT is most effective if performed before symptom onset, the inability to predict which infants are at highest risk has significantly complicated the decision-making regarding the follow up of these children. Evidence that in most cases HSCT merely attenuates the progression of the disease, but does not prevent it, further complicates the follow up of these infants.[21,22] The uncertainties regarding symptom onset as well as the lack of definitive therapy has raised ethical questions about newborn screening for Krabbe disease.[23] In its report recommending against the inclusion of Krabbe disease on newborn screening panels the SACHDNC noted several issues related to treatment, including: a) a need for consensus about the case definition of what constitutes Early Infantile Krabbe Disease, and b) the need for more information about the specific benefits of Hematopoietic Stem Cell Transplant (HSCT) to treat patients and what mutations would benefit most from HSCT.[24]

Pompe Disease

Pompe disease (also known as Glycogen Storage Disease Type 2 or acid maltase deficiency) is an inherited disorder with an incidence of about 1 in 40,000 births. It is caused by a deficiency of the lysosomal enzyme acid α-glucosidase, which results in the accumulation of glycogen (a storage from of glucose) in the heart, muscles, nerves, and other tissues. The infantile onset form of Pompe disease results in heart failure and profound generalized muscle weakness that begins in the first few months of life and progresses rapidly, usually leading to death by 2 years of age. There are also childhood, juvenile, and adult onset forms of Pompe disease, which have less impact on the heart but lead to generalized muscle weakness that eventually leads to respiratory failure requiring mechanical ventilation.

Enzyme replacement therapy (ERT) for Pompe disease was approved by the FDA in 2006. Patients receive intravenous (IV) infusions of the missing enzyme (acid α-glucosidase) every two weeks, which reduces the accumulation of heart and muscle glycogen. ERT can reverse and/or prevent the heart failure that normally leads to infant death in Pompe disease, and can improve muscle function, but does not completely eliminate symptoms. Unlike untreated children with infantile Pompe disease, some children that receive ERT will learn to walk independently, and acquire other motor skills not previously possible. Nonetheless, over time the surviving infants have been found to develop profound weakness of leg, hip, facial and neck muscles.[25] Approximately 50% of surviving treated infants require assisted ventilation due to impaired function of respiratory muscles and the nerves that control them.[26] Cognitive function in surviving infants receiving ERT is at the lower end of the normal range.[27] Evidence suggests that early treatment for the infantile form of Pompe disease improves health outcomes.[28] Whether pre-symptomatic treatment leads to better outcomes for childhood or adult onset forms of Pompe disease is unknown. ERT must be given for the life of the patient or until a definitive treatment such as gene therapy is available. Due to its relatively recent FDA approval (2006), information on the long-term outcome of infants receiving ERT for Pompe disease is lacking. Among the reasons stated by the SACHDNC in its October 2008 report recommending against inclusion of Pompe disease on newborn screening panels was that "No rigorous cost or cost-effectiveness data were identified in the systematic review".[24] Citing the publication of additional data and advances in screening and treatment for Pompe disease, in May 2012 the Advisory Committee accepted a nomination to re-review Pompe disease and recommended it for inclusion in the RUSP. A final decision from the Secretary of Health & Human Services regarding whether to include Pompe disease in newborn screening panels is pending.

Gaucher Disease

There are three sub-types of Gaucher disease (GD), which all result from reduced function of the lysosomal enzyme acid β-glucosylceramidase. The most common is type 1, which is characterized by enlargement of the liver and spleen, anemia, nose bleeds / easy bruising due to reduced platelets, bone pain, osteoporosis, and growth failure but no neurologic involvement. Type 1 GD affects 1 in 500 to 1,000 people of Ashkenazi Jewish heritage, and 1 in 50,000 to 100,000 in the general population. Type 2 Gaucher Disease is a rapidly progressive neurodegenerative disorder that results in death by 3 years of age. It is less frequent than type 1 GD, with an incidence of approximately 1 in 100,000. Symptoms of type 3 GD are intermediate between those of types 1 and 2, and include slowly progressive neurologic problems such as incoordination, mental deterioration, and seizures. The incidence is estimated at 1 in 50,000 live births.

The diagnosis of GD can be made via measurement of enzyme activity or DNA testing. In some cases DNA testing will allow prediction of whether or not neurologic symptoms will develop, but often no prediction can be made. Gaucher disease was the first LSD for which ERT was developed. Since its FDA approval in 1991 there have been many studies that have demonstrated its efficacy in type 1 GD, preventing or reversing liver and spleen enlargement, anemia, bleeding and bruising, growth failure and bone disease.[29] In contrast, ERT does not prevent the rapidly progressive neurologic symptoms in patients with type 2 GD, and its efficacy in preventing the later onset of neurologic symptoms in type 3 GD is uncertain. The lack of a definitive way to predict the likelihood of neurologic symptoms in pre-symptomatic patients makes it difficult to determine whether an individual patient should receive ERT. Uncertainties regarding treatment also arise in patients with type 1 GD, many of whom will not develop significant symptoms until adulthood. It is recommended that patients identified pre-symptomatically or with only mild symptoms be monitored regularly, and that ERT be initiated only when considered clinically necessary. Though most would agree that the presence of significant bone disease or growth failure are indications for initiation of ERT, there is a lack of consensus with regards to other symptoms and the need for initiation of therapy with ERT.[30]

Fabry Disease

Fabry disease results from deficient activity of the lysosomal enzyme α-galactosidase, and has an incidence of 1 in 40,000 to 60,000 births. Symptoms include periodic pain crises in the extremities (hands and feet), sweating abnormalities and heat intolerance, abdominal pain, kidney failure, heart disease, and cerebrovascular disease (stroke). Without treatment abdominal and extremity pain typically begin in childhood or adolescence, with kidney and heart disease developing by age 20-30, and death by 40-50. Fabry disease is inherited as an X-linked disorder, which means that it primarily affects males, though females frequently have problems with pain and heart disease that begin in adulthood.

In 2003 the FDA approved ERT for Fabry disease based on the demonstration that it reduced the amount of abnormal storage material accumulating in lysosomes in the kidney and other tissues. In subsequent studies it has been shown that ERT slows the progression of the kidney, heart and cerebrovascular disease but does not stop it completely. It is unknown whether initiation of treatment with ERT prior to the development of kidney or other damage will prevent it from occurring. At the present time ERT is typically not begun until late childhood or adolescence in males, and in the 20s or later in females. However, there are no clear evidence-based guidelines for when to initiate ERT in patients with Fabry disease. A 2013 Cochrane review of ERT for Fabry disease noted a lack of robust evidence supporting its long-term efficacy.[31] The SACHDNC recommended against the inclusion of Fabry disease in newborn screening panels based largely on issues related to treatment, including "…a) variable and possible late onset (>10 years) of the disease; b) unclear if those at highest risk of serious symptoms can be discerned in newborns; c) the lack of published data of preventive treatment early in life; d) some risk of immunologic response to enzyme replacement therapy; and e) the need for a prospective study of screening and therapeutic intervention to demonstrate the benefit of newborn screening for Fabry Disease".[24]

Niemann-Pick Disease

Niemann-Pick disease (NPD) is a LSD that result from deficient activity of acid sphingomyelinase. There are two forms of NPD, type A (NPD-A) is a fatal disorder of infancy characterized by progressive enlargement of the liver and spleen that is typically noticed by 3 months of age. This is followed by progressive growth failure, muscle weakness, and loss of neurologic function leading to a complete loss of contact with the environment and death by 2-

3 years of age. In contrast, most patients with NPD type B (NPD-B) have little or no neurologic involvement and survive into adulthood. However, there are many patients whose symptoms lie somewhere between these extremes, many of who will develop liver, cardiac, and lung disease.[32] Although NPD is found in all populations, NPD-A occurs more frequently among individuals of Ashkenazi Jewish ancestry (~1 in 40,000). The incidence of NPD-A and NPD-B in all other populations is estimated to be 1 in 250,000.

The earlier onset and neurologic symptoms associated with NPD-A is generally believed to be the result of a more severe deficiency of acid sphingomyelinase activity in comparison to NPD-B patients. However, there is overlap, and prediction of whether an infant will have NPD-A or NPD-B is not always possible. DNA mutation analysis may help predict symptoms but not in all cases. Infants with both NPD-A and NPD-B can be identified via newborn screening. A third form of Niemann-Pick disease (type C; NPD-C) is caused by a different gene than types A and B, and cannot be identified via newborn screening, therefore treatment options for NPD-C will not be discussed.

Currently there are no known treatments for NPD-A. Hematopoietic stem cell transplantation has been attempted but found to be uniformly unsuccessful. Outcomes of HSCT have been somewhat better in patients with NPD-B though it is uncertain whether the potential benefits outweigh the risks.[32] Treatment related concerns were among the reasons provided by the SACHDNC for its recommendation against inclusion of NPD on newborn screening panels, including: a) discerning type A from B is not always possible to help predict the phenotypic range of those children who will be identified through population-based screening; b) no published studies are available to show the efficacy of treatment in humans especially for those most likely to benefit early in life; c) no FDA approved treatment currently exists; and d) the need for pilot studies of the newborn screening test and treatment protocols.[24] An industry sponsored (Genzyme Corporation) phase 1 clinical trial to test the safety of enzyme replacement therapy (ERT) for NPD-B is currently underway. However, based on the experience with other forms of ERT, FDA approval, if granted, is likely to take many years (>5).

Cost of Treatment for LSDs

Enzyme replacement therapy is available for Fabry, Gaucher, and Pompe diseases, and in clinical trials for Niemann-Pick disease type B. It is given every two weeks via IV infusion, which is done in hospital or outpatient infusion centers, or at home. In either case a skilled infusion nurse is necessary for administration of the ERT. The annual cost of ERT, including personnel and ancillary expenses is approximately $250,000 to $300,000 for an adult. Dosage is based on body size and as a result drug costs are lower for children, though ancillary and personnel expenses are not significantly different.

Hematopoietic stem cell transplant is the only therapy available for Krabbe disease. The estimated cost for a pediatric HSCT at OHSU / Doernbecher Children's hospital is $490,000. This cost includes all facility and professional charges, pre-transplant work-up, donor search and testing, acquisition of cells, transplant inpatient stay, and 90 days of follow-up. OHSU requires a deposit of the entire estimated amount prior to services being provided. If actual charges are less the excess will be refunded. If actual charges are greater than the amount deposited the patient/responsible party must pay that additional amount.

ETHICAL CONSIDERATIONS IN NEWBORN SCREENING FOR LSDs

The symptoms of all LSDs span a broad spectrum of severity. The ability to predict the type and severity of symptoms in an asymptomatic newborn is difficult, and in some cases nearly impossible. In both Gaucher and Niemann-Pick diseases the severe subtypes associated with progressive neurologic degeneration have no treatment, and in infantile onset Krabbe disease treatment slows neurologic regression but it does not prevent it. Since the most severe forms of LSDs are usually associated with the most significant reduction in enzyme activity, the patients most likely to be identified via newborn screening are those for whom treatment has the least to offer. This is in stark contrast to conditions such as phenylketonuria, the first disorder for which newborn screening was developed more than 50 years ago, in which the availability of an acceptable (i.e. effective) treatment for patients identified by newborn screening was deemed a necessary criterion.[33]

Even in the absence of a beneficial treatment there are possible benefits to the diagnosis of an infant with a LSD via newborn screening, including elimination of the long diagnostic odyssey that parents often endure as they seek the cause for their child's symptoms. However, the identification of newborns with disorders for which no effective treatment exists also presents significant challenges for parents, families, and their caregivers. An example is the ''vulnerable child syndrome'' (parental over-protection of a child in the absence of symptoms) that can result when a family has an asymptomatic child but is aware of the high likelihood of the future onset of severe symptoms and a shortened lifespan.[34] Data are lacking on whether the avoidance of a diagnostic odyssey provides greater benefit to parents than the stress and anxiety associated with a diagnosis for which there is no treatment. All of these issues make it very difficult to find a balance between the benefit derived from identification of the treatable subtypes, and the harm associated with finding the untreatable subtypes of LSDs.[35]

In the evidence review conducted for the SACHDNC on the merits of inclusion of Krabbe disease on newborn screening panels the authors concluded their review with the following statement: "Therefore, we advocate that any screening for Krabbe disease be conducted within the framework of a research protocol. Enrollment of those with a positive newborn screen into registries and prospective clinical trials will be essential to addressing critical gaps such as the impact of a positive screen on families, including harms related to the uncertainty of diagnosis and the neurologic outcomes for those who receive early treatment. Until fundamental issues regarding screening, diagnosis, and treatment are resolved, the Advisory Committee would be unlikely to reconsider whether to recommend that all states should screen for Krabbe disease".[36] Such concerns are applicable to many of the LSDs, not just Krabbe disease. Several states have now begun evaluations of newborn screening for LSDs, and it is hoped that data derived from these experiments will provide a foundation of evidence that other states (including Oregon) can utilize as they develop their own approaches to newborn screening for LSDs.

SUMMARY

Newborn screening for LSDs is still developmental. There is no FDA-approved laboratory screening method for newborn dried blood spots for any LSD and the few states that are attempting LSD screening have experienced only limited success. The predictive value of positive screening tests is unacceptably low – ranging from 1.7% to 37.4% - which means that the overwhelming majority of positive initial test results are wrong. This large number of false positives generates anxiety and expense for infants' families, as well as unnecessary medical procedures and costs.

With current technologies, the cost per screening test for LSDs is quite high compared with other newborn screening disorders. Ideally, each infant could be screened for several LSDs simultaneously in a single test to lower the unit cost per disorder, but this is not yet possible. However, one state (Washington) is trying to develop a multiplex MS/MS method to screen for nine LSDs simultaneously and Missouri's microfluidics pilot project also shows promise as a multiplex assay.

Treatment options for LSDs are still experimental and costly. Several attempts have been made to treat LSDs using hematopoietic stem cell transplantation and enzyme replacement therapy, but none have proven consistently successful over the long term. However, several clinical trials are underway and some new treatments have shown promising early results.

Ethical and governance issues for LSD screening are similar to those for all other disorders on the newborn screening panel. The RUSP review process sets the U.S. standard for evaluating any disorder based on the available scientific and medical evidence; i.e., a valid and practical laboratory test, effective treatment, and benefits that outweigh the financial and societal costs of screening. So far, only one of the four LSDs nominated for addition to the RUSP has been recommended (Pompe Disease) and this recommendation has not been accepted by the Secretary of HHS since it was brought forward in June, 2013.

If effective, LSD newborn screening and treatment could prevent devastating disease and death for a number of infants, and hopefully this will be possible in the near future. However, at present the combination of inaccurate screening methods, little or no effective treatment, and high costs for both screening and treatment, make LSD newborn screening infeasible for Oregon.

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APPENDIX: OREGON NEWBORN SCREENING DISORDER PANEL

Testing for Metabolic Diseases

333-024-0210

Infants Tested for Metabolic Diseases

Every infant born in Oregon on or after May 1, 2014, shall be tested for at least the following congenital disorders by the state public health laboratory:

(1) Cystic fibrosis (CF).

(2) Endocrine disorders:

(a) Congenital hypothyroidism (CH); and

(b) Congenital adrenal hyperplasia (CAH).

(3) Galactosemia (GALT).

(4) Hemoglobin disorders:

(a) Sickle cell disease (Hb S/S);

(b) Sickle cell/beta thalassemia (Hb S/A); and

(c) Sickle cell/hemoglobin C disease (Hb S/C).

(5) Metabolic disorders:

(a) Amino acid disorders:

(A) Homocystinuria (HCY);

(B) Phenylketonuria (PKU); and

(C) Tyrosinemia (TYR).

(b) Biotinidase deficiency;

(c) Fatty acid oxidation disorders:

(A) Carnitine uptake defect (CUD);

(B) Carnitine/acylcarnitine translocase deficiency (CT);

(C) Carnitine palmitoyl transferase deficiency (CPT), Types I and II;

(D) Glutaric acidemia, Type II (GA-II);

(E) Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD);

(F) Medium-chain acyl-CoA dehydrogenase deficiency (MCAD);

(G) Short-chain acyl-CoA dehydrogenase deficiency (SCAD);

(H) Trifunctional protein deficiency (TFP); and

(I) Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD).

(d) Organic acid disorders:

(A) Beta-ketothiolase deficiency (BKT);

(B) Glutaric acidemia, Type I (GA-I);

(C) Isobutryl-CoA dehydrogenase deficiency (IBG);

(D) Isovaleric acidemia (IVA);

(E) Malonic aciduria (MAL);

(F) Maple syrup urine disease (MSUD);

(G) Methylmalonic acidemia (MMA);

(H) Propionic acidemia (PA);

(I) 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency (2M3HBA);

(J) 2-Methylbutyryl CoA dehydrogenase deficiency (2MBG);

(K) 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG);

(L) 3-methylcrotonyl-CoA carboxylase deficiency (3-MCC);

(M) 3-methylglutaconyl-CoA hydratase deficiency (3MGA); and

(N) Multiple carboxylase deficiency (MCD).

(e) Urea Cycle Disorders:

(A) Arginase deficiency (ARG);

(B) Argininosuccinate lyase deficiency (ASA); and

(C) Citrullinemia, Type I (CIT I).

(6) Other disorders as defined by Oregon Health Authority.

(7) Severe combined immunodeficiencies (SCID).

Stat. Auth.: ORS 433.285

Stats. Implemented: ORS 433.285

Hist.: HD 18-1981(Temp), f. & ef. 9-11-81; HD 3-1982, f. & ef. 2-25-82; HD 17-1983, f. & ef. 10-12-83; HD 10-1986, f. & ef. 6-11-86; HD 28-1994, f. 10-28-1994, cert. ef. 11-1-94; OHD 15-2002, f. & cert. ef. 10-4-02; PH 30-2004(Temp), f. & cert. ef. 9-17-04 thru 3-13-05; PH 37-2004, f. & cert. ef. 12-7-04; PH 11-2014, f. 4-15-14, cert. ef. 5-1-14

Oregon Health Authority

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