The Role of Genetic Counseling in Pompe Disease After Patients Are Identified Through Newborn Screening

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abstract

An important part of the coordinated care by experienced health care teams for all Pompe disease patients, whether diagnosed through newborn screening (NBS), clinical diagnosis, or prenatal diagnosis, is genetic counseling. Genetic counseling helps families better understand medical recommendations and options presented by the patient’s health care team so they can make informed decisions. In addition to providing important information about the inheritance and genetic risks, genetic counseling also provides information about Pompe disease and available treatments and resources and should be offered to families with an affected child and all adults diagnosed with Pompe disease. Although the need for genetic counseling after a positive newborn screen for Pompe disease is recognized, the role that genetic counseling plays for both families of affected patients and health care teams is not fully understood. Consistent best genetic counseling practices also are lacking. The guidance in this article in the “Newborn Screening, Diagnosis, and Treatment for Pompe Disease” supplement is derived from expert consensus from the Pompe Disease Newborn Screening Working Group. It is intended to help guide genetic counseling efforts and provide a clear understanding of the role for families or carriers of Pompe disease identified through NBS; explain special considerations (eg, diagnosis of late-onset Pompe disease before the appearance of symptoms) and the impact and implications associated with a diagnosis (eg, determination of genetic risk and carrier status and preconception counseling); and provide health care teams caring for patients with a framework for a standardized approach to genetic counseling for patients and at-risk family members.

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Ms Atherton analyzed and interpreted the data, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Day-Salvatore analyzed and interpreted the data and critically reviewed and revised the manuscript; both authors approved the final manuscript as submitted; both authors are members of the Pompe Disease Newborn Screening Working Group and have experience in newborn screening and in treating and caring for patients with Pompe disease; and both authors provided input and reviewed and approved the content for all articles of the supplement.

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DOI: https://doi.org/10.1542/peds.2016-0280F

Accepted for publication Mar 8, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1088-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

The guidelines/recommendations in this article are not American Academy of Pediatrics policy, and publication herein does not imply endorsement. 2017;140(s1):e20160280F
Once a patient is diagnosed as having Pompe disease, coordinated care by a team of clinicians experienced in treating patients with the disease and continued communication within the team is needed. Genetic counseling is an important component of a patient’s care and can be a source of much-needed key information about the disease for the families of patients that will help them make informed medical and personal decisions. Genetic counseling should be offered to all families with an affected child and all adults diagnosed with Pompe disease either through newborn screening (NBS), clinical diagnosis, or prenatal diagnosis. In addition to providing information about the genetic risks and inheritance of Pompe disease, genetic counseling can be a valuable source of information about the natural history of the disease as well as available treatments and resources that can help patients and their families.

Recognizing the important role that NBS plays in identifying infants with serious and, unless diagnosed early, often potentially fatal illnesses, the National Society of Genetic Counselors in the United States strongly supports screening all newborns for the panel of disorders recommended by the US Secretary of Health and Human Services on the Recommended Uniform Screening Panel (RUSP), with the exception of cases where parents make an informed decision to decline or opt out of screening after being thoroughly educated on NBS. Although the need for genetic counseling after a positive NBS result for Pompe disease is recognized, there is a lack of clear understanding of what genetic counseling can provide for both families of affected patients and health care teams, as well as a lack of consistent best counseling practices.

Counseling may be even more critical in cases where the phenotype is difficult to predict, pseudodeficiency alleles and/or variants of uncertain significance are present, or the potential exists for 2 different phenotypes in offspring if 1 parent is affected with late-onset Pompe disease (LOPD) and the partner is a carrier for a pathogenic variant that could result in classic infantile-onset Pompe disease (IOPD).

The recommendations provided in this article are derived from the expert consensus from the Pompe Disease Newborn Screening Working Group. They are intended to help guide genetic counseling efforts for the families of patients or carriers of Pompe disease identified through NBS and provide physicians and health care teams caring for patients with Pompe disease with a framework for a standardized approach to genetic counseling for the patient and at-risk family members. Because individual patient needs and available resources vary, the Working Group stresses that these differences must be taken into account. Treating physicians and genetic counselors need to consider the guidelines presented in this article as overall guidance that should be tailored as needed and as is appropriate when developing individual recommendations for patients and families.

These guidelines and recommendations do not necessarily reflect the policy of the American Academy of Pediatrics, and publication herein does not imply endorsement.

Genetic counseling also may not be available in all geographic locations. In these instances, genetic counseling may be provided by the treating physician or another care team member, such as a nurse practitioner or registered nurse, who is knowledgeable about Pompe disease and related genetic counseling aspects. State NBS follow-up programs typically have a list of consultants; alternatively, GeneTests (www.genetests.org/clinics/) lists clinical services, including genetic counseling, by state and country. Telegenetics is an additional means for providing genetic counseling. Telegenetics collectively includes telemedicine, which typically refers to remote clinical services and tends to be patient-centric (eg, patient and provider interactions through videoconferencing or telephone), and telehealth, which is broader and more encompassing and can refer to nonclinical services (eg, health care–provider training and education, patient/family education, and team meetings) in addition to clinical services. Telegenetics is especially valuable for underserved areas where services are limited or not available and for locations that pose geographic barriers and therefore restrict or limit access to specialized care. Many states are amenable to telegenetic services and suggest them as an option for genetic counseling. Where genetic counseling may not be offered, the availability of telegenetics should be investigated.

THE GENETICS OF POMPE DISEASE

Pompe disease is inherited in an autosomal recessive manner. The parents of an affected individual are assumed to be obligate heterozygotes carrying a single copy of an acid α-glucosidase (GAA) pathogenic variant or deletion in the majority of cases. Confounding factors in counseling may include undisclosed donor egg/sperm, uniparental disomy, the rare chance of germ-line mosaicism or de novo variant, and nonpaternity.

Each full sibling of an individual with Pompe disease at conception has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier of Pompe disease. When an at-risk sibling is confirmed to be unaffected, their chance of being a carrier of Pompe disease is 2 out of
3. Half-siblings have a 50% chance of being a carrier of Pompe disease.

The sibling phenotype concordance in classic IOPD is high. Classic IOPD is the most severe form of Pompe disease, with symptoms presenting before 12 months of age with cardiomyopathy. Phenotype discordance (ie, onset, course, and severity) has been observed within and between families with identical GAA genotypes of patients presenting with non-classic IOPD (patients presenting with symptoms before the age of 12 months but without cardiomyopathy) and patients with LOPD (patients with symptom onset after 12 months of age), indicating that other factors (eg, environmental and epigenetic) may modify the clinical course in patients.

Children with classic IOPD have not historically survived to adulthood to reproduce, although the availability of enzyme replacement therapy (ERT) may improve their fitness and prolong their survival. All of the offspring of an individual with Pompe disease are obligate heterozygotes (carriers) for a pathogenic variant in GAA, although they may inherit different alleles. If an individual with Pompe disease has a child with another individual with Pompe disease, all of their children will have Pompe disease. The phenotype may vary depending on the GAA variants involved. Likewise, individuals with Pompe disease who have a child with someone who is a carrier will have a 50% chance with each pregnancy to have a child with Pompe disease. Again, the phenotype could be variable and depend on the GAA variants that are inherited.

THE ROLE OF GENETIC COUNSELING IN NBS

Education for families and patients regarding NBS and Pompe disease is essential. Families need to understand the issues they will face depending on whether the diagnosis is IOPD or LOPD. Genetic counseling plays an important role here for patients and their families. With proper genetic counseling based on individual situations, families will be provided with important information and a better understanding of the medical recommendations and options presented to them that will help them make informed and sometimes difficult choices and adapt to the risk or condition identified through NBS. The role of the genetic counselor is to also help the family understand the medical management and treatment/nontreatment recommendations presented to the family by the treating provider so families can be involved in making the best decision possible for their child.

NBS and LOPD: Special Considerations for Genetic Counseling

Although there are general considerations applicable to all patients diagnosed with Pompe disease on NBS, there are issues unique to those found to have LOPD. With the advances in NBS technologies in Pompe disease came the ability to identify patients with LOPD before symptoms appear. Unlike patients with classic IOPD, these patients can remain asymptomatic for years and traditionally are not diagnosed clinically until onset of signs and/or symptoms that present as late as the second to sixth decade of life. These asymptomatic patients are sometimes referred to as “patients in waiting” because they have a future health risk for Pompe disease identified through NBS, but have not presented yet with clinical manifestations and therefore have no immediate health impact and no indication for initiation of ERT. Although a diagnosis of LOPD on NBS may be stressful and unsettling, a benefit of having a confirmed diagnosis is that patients and their families will be spared the “diagnostic odyssey” experienced by so many patients with LOPD after the onset of symptoms of this rare disease. A confirmed diagnosis is especially important because of the availability of a specific treatment for Pompe disease. A diagnosis of LOPD through NBS impacts families and raises a number of ethical and practical considerations as well as long-term implications that can and need to be addressed and explained appropriately by genetic counselors and geneticists who are part of the patient’s management team. Genetic counseling can help answer questions and provide much-needed information and rationales for recommendations made by the patient’s health care teams for families of LOPD patients.

Impact and Implications of a Diagnosis of Pompe Disease

Once a patient is diagnosed with either IOPD or LOPD through NBS, family members also are made aware of their own health and reproductive risks. Family members who are at an increased risk of being a carrier should be informed of the family history of Pompe disease as well as any genetic testing results that are available. Carrier testing of at-risk family members is most informative when the variants are known within a family. Enzyme testing is not a reliable method to assess for carrier status. Variant analysis is necessary to confirm carrier status. Heterozygotes (carriers) for Pompe disease appear to be asymptomatic, although this supposition may change as our knowledge of the disease continues to increase. Carrier testing should be offered to at-risk family members who are of a legal age to provide informed consent for genetic carrier testing. Carrier testing of minors is not recommended unless there is a concern that the individual has Pompe disease. Siblings of an affected individual should be offered targeted testing for the familial pathogenic...
variants identified if there is any question as to their health status so that morbidity and mortality can be reduced by early diagnosis of Pompe disease in affected individuals and initiation of treatment with ERT. This testing is especially important and recommended for siblings of asymptomatic newborns diagnosed with LOPD who also may have LOPD but have not exhibited any symptoms or in whom manifestations have not been recognized due to the typical low index of clinical suspicion associated with Pompe disease. Identification of carriers is likely to occur through NBS for Pompe disease. If carriers are identified while trying to rule out Pompe disease, the family should be notified of these results so that the parents can undergo carrier testing to determine if they are at an increased risk of having a child with Pompe disease. Full GAA gene sequencing for Pompe disease carrier testing should be offered to any partner of an individual who is found to be a carrier of Pompe disease. Genetic counseling is important to inform couples of their risk of having an affected child with Pompe disease. Determination of genetic risk, carrier status, and discussion of preimplantation/prenatal testing options should be completed before achieving a pregnancy. For couples who are both found to be carriers of Pompe disease, prenatal diagnosis is available by using DNA-based methodologies through chorionic villus sampling or amniocentesis. Both disease-causing alleles of an affected family member must be identified for prenatal testing to be informative. Results of prenatal testing cannot predict the age of onset, clinical course, or degree of disability in non-classic IOPD or LOPD. Other considerations for preconception genetic counseling can include discussion about in vitro fertilization with preimplantation genetic diagnosis, donor egg/sperm, and adoption. New and emerging technologies, such as noninvasive prenatal screening by using cell-free fetal DNA that arises from the placenta and can be extracted from a maternal blood sample, may advance in the future and could provide a noninvasive alternative to prenatal diagnosis for identifying at-risk fetuses with Pompe disease. Discussions with a genetic counselor regarding available technologies for the prenatal diagnosis of Pompe disease are important moving forward given the marked improvement in genetic testing technologies in the 21st century.

ACKNOWLEDGMENTS
The members of the Pompe Disease Newborn Screening Working Group (in alphabetical order) are as follows: Andrea M. Atherton, MS, CGC, Children’s Mercy Hospital (Kansas City, MO [time of the study]); Andrea Atherton, MS, CGC, Children’s Mercy Hospital (Kansas City, MO [current affiliation]); Olaf Bodamer, MD, PhD, Boston Children’s Hospital (Boston, MA); Barbara K. Burton, MD, Northwestern University Feinberg School of Medicine, and Ann & Robert Lurie Children’s Hospital (Chicago, IL); Debra Day-Salvatore, MD, St. Peter’s University Hospital (New Brunswick, NJ); Roberto Giugliani, MD, PhD, Hospital de Clínicas de Porto Alegre and Federal University of Rio Grande do Sul (Porto Alegre, Brazil); Wuh-Liang Hwu, MD, PhD, National Taiwan University Hospital, and National Taiwan University College of Medicine (Taipei, Taiwan); Simon A. Jones, MBChB, BSc, MRCPCH, St. Mary’s Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, University of Manchester (Manchester, UK); Priya S. Khishnani, MD, Duke University (Durham, NC); David F. Kronn, MD, New York Medical College, Valhalla, NY; Kimitoshi Nakamura, MD, PhD, Kumamoto University (Kumamoto, Japan); Torayuki Okuyama, MD, PhD, National Center for Child Health and Development (Tokyo, Japan); C. Ronald Scott, MD, University of Washington (Seattle, WA); and Kathryn J. Swoboda, MD, Massachusetts General Hospital (Boston, MA). We thank Zsuzsanna Devecseri, MD, MBA, Joan Keutzer, PhD, and Susan E. Sparks, MD, PhD, of Sanofi Genzyme for critical review of the manuscript and Marianne B. Zajdel of Sanofi Genzyme for medical writing support.

ABBREVIATIONS
ERT: enzyme replacement therapy
GAA: acid α-glucosidase
IOPD: infantile-onset Pompe disease
LOPD: late-onset Pompe disease
NBS: newborn screening

FUNDING: Sanofi Genzyme (Cambridge, MA) facilitated and provided financial support for the meeting of the Pompe Disease Newborn Screening Working Group to discuss and develop the recommendations provided in all articles comprising the “Newborn Screening, Diagnosis, and Treatment for Pompe Disease” guidance supplement and paid for editorial writing support for the supplement. The recommendations and opinions expressed in this article and in all others in the Supplement are those of the authors based on their clinical expertise and experience and do not necessarily reflect those of Sanofi Genzyme.

POTENTIAL CONFLICT OF INTEREST: Andrea Atherton, MS, CGC, received honoraria and reimbursement for travel as a consultant and member of the speakers bureaus for Sanofi Genzyme and Shire when she was an employee of Children’s Mercy Hospital (Kansas City, MO); she currently is a full-time employee of Shire. Debra Day-Salvatore, MD, received travel reimbursement and honoraria from Sanofi Genzyme.
REFERENCES


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Pediatrics 2017;140:S46
DOI: 10.1542/peds.2016-0280F

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*Pediatrics* 2017;140;S46
DOI: 10.1542/peds.2016-0280F

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