Newborn screening (NBS) for Pompe disease is done through analysis of acid α-glucosidase (GAA) activity in dried blood spots. When GAA levels are below established cutoff values, then second-tier testing is required to confirm or refute a diagnosis of Pompe disease. This article in the “Newborn Screening, Diagnosis, and Treatment for Pompe Disease” guidance supplement provides recommendations for confirmatory testing after a positive NBS result indicative of Pompe disease is obtained. Two algorithms were developed by the Pompe Disease Newborn Screening Working Group, a group of international experts on both NBS and Pompe disease, based on whether DNA sequencing is performed as part of the screening method. Using the recommendations in either algorithm will lead to 1 of 3 diagnoses: classic infantile-onset Pompe disease, late-onset Pompe disease, or no disease/not affected/carer. Mutation analysis of the GAA gene is essential for confirming the biochemical diagnosis of Pompe disease. For NBS laboratories that do not have DNA sequencing capabilities, the responsibility of obtaining sequencing of the GAA gene will fall on the referral center. The recommendations for confirmatory testing and the initial evaluation are intended for a broad global audience. However, the Working Group recognizes that clinical practices, standards of care, and resource capabilities vary not only regionally, but also by testing centers. Individual patient needs and health status as well as local/regional insurance reimbursement programs and regulations also must be considered.
Delays in the clinical diagnosis of Pompe disease are frequent due to the rarity of the disorder, its heterogeneous clinical presentation, and overlap of signs and symptoms with other neuromuscular disorders. These delays range from a few months in patients with classic infantile-onset Pompe disease (IOPD) to many years in patients with late-onset Pompe disease (LOPD). A published analysis of data from 1003 patients in the Pompe Registry reported diagnostic delays of 1.4 months in patients with classic IOPD, 12.6 years among non-classic infantile and juvenile patients, and 6 years for patients with LOPD. With the availability of enzyme replacement therapy (ERT) with alglucosidase alfa (recombinant human acid a-glucosidase [rhGAA]) for Pompe disease and new treatments on the horizon, timely and accurate diagnosis can lead to early initiation of ERT before the onset of irreversible pathologic changes. Classic IOPD is rapidly progressive, and any delay can have a negative impact on outcomes. Even in cases of LOPD that are considered to be in the early stages of the disease clinically, there often is significant damage to the muscles as noted by studies such as whole-body MRI and muscle ultrasound. Thus, any delay in treatment initiation can be significant, even for cases that are felt to be identified early or those in which the patients appear to be in good clinical condition.

NEWBORN SCREENING AND POMPE DISEASE

In March 2015, the US Secretary of Health and Human Services decided to adopt the Advisory Committee on Heritable Disorders in Newborn and Children recommendation to add Pompe disease to the Recommended Uniform Screening Panel (RUSP). Early detection of patients with classic IOPD and initiation of ERT have clear benefits as seen in these patients in reports from the newborn screening (NBS) pilot program in Taiwan, when compared with patients with classic IOPD diagnosed clinically, where delays in diagnosis clearly lead to a more guarded prognosis. With LOPD, patients diagnosed early in the presymptomatic phase of the disorder will benefit from avoiding the many years of diagnostic odyssey they follow after they present with signs and symptoms of LOPD. Patients identified through NBS can be started on ERT when there is early evidence of disease progression.

NBS for Pompe disease is done through analysis of GAA enzyme activity in dried blood spots (DBSs). If levels of GAA are found to be normal, then the patient is classified as unaffected and no additional testing is required or performed. If the GAA levels are below established cutoff values, molecular testing of the GAA gene may be performed on second-tier screening.

Here, 2 algorithms for confirmatory testing that will confirm or refute a diagnosis of Pompe disease are provided, based on whether DNA sequencing is performed by the NBS laboratory (Figs 1 and 2). The confirmatory testing discussed includes recommended clinical and laboratory procedures. The recommendations for confirmatory testing after a positive NBS result and the 2 algorithms were developed by the Pompe Disease Newborn Screening Working Group, a group of international experts on both NBS and Pompe disease.

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

WHAT CONSTITUTES A DIAGNOSIS OF POMPE DISEASE?

Ideally, a diagnosis of Pompe disease is confirmed in a patient with decreased GAA activity in the blood (leucocytes, DBSs, isolated lymphocytes) or another tissue with the presence of 2 known pathogenic GAA variants in trans. A probable diagnosis of Pompe disease can be made if there is decreased enzyme activity, but molecular studies are ambiguous due to the presence of molecular variants of unknown significance (VUS). In IOPD, the presence of clinical findings of Pompe disease in the presence of decreased enzyme activity is a confirmation of diagnosis. In cases of LOPD where there is confirmed decreased enzymatic activity, patients will need to be managed closely for the development of signs or symptoms of disease, even when molecular changes are known because there is considerable variation in how and when patients will present.

Sometimes in patients suspected to have LOPD, only 1 pathogenic variant is found along with low GAA activity. In these cases, if the low GAA level is not due to a pseudodeficiency allele, which can cause low GAA activity measured in enzyme assays, but is not associated with Pompe disease, then measuring GAA activity in another sample (eg, blood, fibroblasts, or muscle biopsy tissue) may be necessary to confirm a diagnosis.

Nomenclature for classifications of patients with Pompe disease has been problematic, confusing, and used inconsistently and variably in the published literature and within the medical community. Pompe disease must be considered as a continuum of disease that varies by age of onset, symptoms, organ involvement, and degree of muscle involvement and pathology. The subtypes of Pompe disease are not always clearly delineated based on age at presentation because of the heterogeneous nature of the disease. Clinical presentation and manifestations, therefore, also must be carefully considered and...
evaluated when classifying diagnosed patients.

**IOPD**

Throughout this article, classic IOPD will be used to describe infantile-onset patients with cardiomyopathy. The signs and symptoms in patients with symptom onset at ≤12 months of age typically include prominent cardiac involvement (cardiomegaly/hypertrophic cardiomyopathy), progressive muscle weakness and hypotonia, delays in motor development, respiratory distress, feeding problems, and failure to thrive.4,8–11 Patients with classic IOPD have absent or low GAA activity in DBS or lymphocyte specimens. In skin fibroblast assays, classic IOPD patients have <1% activity.4 In patients with classic IOPD, there is minimal variability in the clinical phenotype as is seen and expected across the rest of the Pompe disease spectrum.4,12 For most patients, follow-up testing will be done by DBS or lymphocyte/leukocyte assay.13 Few will have a skin biopsy as follow-up testing.

**LOPD**

In older children and adults (age of onset of symptoms at >12 months), significant cardiac involvement is usually not observed, and in the vast majority, there is no cardiac involvement. However, cardiac involvement in the form of cardiac hypertrophy and heart rhythm disturbances, such as supraventricular tachycardia or Wolff-Parkinson-White can develop over time. The most prominent manifestation in LOPD is progressive muscle weakness (neck, trunk, arms, legs, and diaphragm).9,14,15 It must be recognized that there are other clinical presentations for patients with LOPD.16 Patients with LOPD generally have GAA enzyme activity levels that are 2% to 40% of normal values in skin fibroblasts.9,17,18 Although unexpectedly low GAA activity levels <1% have also been noted in adults with Pompe disease,17 GAA activity levels >1% generally have not been noted in patients with classic IOPD. Some patients have symptom onset at ≤12 months of age but without cardiomyopathy. These patients are often referred to as having “non-classic” IOPD.9,15,19

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**FIGURE 1**

Diagnostic algorithm for Pompe disease with DNA sequencing as part of the NBS laboratory protocol. Modified from the New York Mid-Atlantic Consortium for Genetic and Newborn Screening Services (NYMAC) Pompe Disease NBS Symposium 2013. a Obtain as a baseline for monitoring response to treatment; can also be postponed until a definitive diagnosis is obtained. b The diagnosis of LOPD based on enzymatic and molecular analyses remains a clinical challenge, because these patients by definition will be normal at the time of diagnosis. Patients will need to be followed closely for the development of clinical signs and symptoms; however, currently, we do not know if all patients with enzymatic and molecular variants suggesting LOPD will actually go on to develop disease. Patients with low GAA activity and molecular variants in trans previously identified in patients with LOPD will be at very high risk of developing LOPD, although patients with low GAA activity and molecular variants not previously identified have less certain clinical outcomes. There are also patients with low GAA activity above the range seen in previous LOPD patients with VUS (not a pseudodeficiency allele) who will need to be followed for possible LOPD. In situations where greater ambiguity exists, analysis in another tissue, as noted, may help to more clearly delineate the patients’ disease status. c Includes VUS with borderline low GAA activity.
Cardiac involvement can occur, however, in some of these cases. Hypertrophic cardiomyopathy, once thought to be limited only to patients with classic IOPD is being reported in patients who do not fall into the classic IOPD category. In this article, LOPD will be used for all patients diagnosed with Pompe disease other than those with classic IOPD and includes patients with onset of symptoms at ≤12 months of age without cardiomyopathy or with cardiac involvement (non-classic infantile-onset disease) and juvenile and adult patients traditionally classified as LOPD.

COMPONENTS OF SECOND-TIER CONFIRMATORY TESTING

Enzyme-Based Assays
Biochemical assays used to demonstrate deficient GAA enzyme activity are the standard methods used to confirm a diagnosis of Pompe disease. These assays measure GAA enzyme activity in blood, cultured skin fibroblasts, or muscle biopsy specimens. Each has associated benefits and drawbacks. Because availability and standard practice are variable across different geographic regions, not all methods may be options for all laboratories. Factors that need to be considered when evaluating the results of GAA enzymatic activity testing include the presence of a pseudodeficiency allele that can alter the residual enzyme level in a screened infant and the possibility that the assay conditions and procedures may not be optimal, leading to false-positive results. It is therefore essential that molecular genetic analysis be done to confirm or rule out a diagnosis of Pompe disease in the presence of low GAA activity and to ensure that treatment with ERT is not started in patients without a confirmed molecular diagnosis. Recommendations for good laboratory practices for biochemical genetic testing and NBS have been published by the Centers for Disease Control and Prevention and should be consulted.

Blood Assays
Advances in diagnostic capabilities and laboratory methodology that measure GAA activity in blood (eg, enzyme assays by using DBSs, purified lymphocytes, and mixed leukocyte assay methods) have been developed. These assays are less invasive, more rapid, and easier to standardize than diagnostic methods measuring enzymatic activity in other tissues that have been used in the past. DBS samples are more stable than whole-blood samples. Measuring GAA activity in DBS samples is therefore valuable for the diagnosis of Pompe disease. Recent results have supported its reliability and sensitivity. Many laboratories offer lymphocyte assay of GAA from whole-blood specimens. The sampling, shipping, and handling requirements of the testing laboratory must be followed carefully for these samples. However, enzymatic analysis is not sufficient to confirm a diagnosis. A molecular test is needed to confirm the diagnosis made by GAA activity.

Skin Fibroblast Assays
Measuring enzyme activity in skin fibroblasts has long been the gold standard for measuring GAA activity. It is important to note that enzymatic analysis, for example, in lymphocytes, is generally less specific than results obtained with skin fibroblasts, and so there can be a “gray zone” of enzyme activity where one cannot differentiate classic IOPD from LOPD.

FIGURE 2
Diagnostic algorithm for Pompe disease without DNA sequencing as part of the NBS laboratory protocol. When pathogenic variants are detected, parental DNA analysis is recommended to confirm presence of variants in trans. Blood-based assays include DBSs, purified lymphocytes, and mixed leukocyte assay methods. Obtain as a baseline for monitoring response to treatment; can also be postponed until a definitive diagnosis is obtained. Need to ensure assay is being done in a laboratory with appropriate enzyme assay experience and capabilities and that the patient has not received a blood transfusion or other interventions that would result in normal GAA enzyme levels.
Skin fibroblasts also allow for determination of the cross-reactive immunologic material (CRIM) status. However, with the availability of molecular testing and its ability to predict CRIM status, the skin fibroblast assay is not needed in most cases. Skin biopsy should only be considered as a second-tier diagnostic tool when indeterminate results have been obtained by other methods and when a patient has 1 variant and low enzyme activity in blood and assay of enzyme activity in another tissue is needed to confirm a diagnosis. The time required to culture skin fibroblasts to obtain enough material for adequate enzyme assay can be 4 to 6 weeks, which is too long to allow early initiation of treatment in classic IOPD and limits the usefulness of this test in the infantile setting.

Muscle Biopsy Assays

GAA activity can also be measured in fresh muscle tissue obtained by biopsy. Histologic examination may reveal the abnormal glycogen accumulation that is typical of the disease. Although it provides reliable results, muscle biopsy is no longer recommended for confirmatory testing because it is invasive and adds unnecessary discomfort for patients. The related risks associated with the need for anesthesia also must be considered, particularly in infants who have classic IOPD. Because of the variable and heterogeneous muscle involvement, muscle histology cannot be used as a sole method of diagnosis, particularly for the juvenile or adult patient in whom the extent of glycogen accumulation is less and more variable than in the patient with IOPD. If muscle biopsies are done, it is important that they are handled by laboratories with experience with Pompe disease and with capabilities to perform appropriate histologic analyses and recognize potential hallmarks of the disorder, such as the Glycogen Storage Disease Laboratory of the Duke University Biochemical Genetics Laboratory. Detailed information about sample requirements, testing, and shipping can be found at https://pediatrics.duke.edu/divisions/medical-genetics/biochemical-genetics-laboratory/glycogen-storage-disease-laboratory.

Non-Enzyme-based Confirmatory Methods

Genotyping/Variant Analysis

Variant analysis of the GAA gene is essential for confirming the biochemical diagnosis of Pompe disease. A diagnosis is usually confirmed by documentation of 2 known pathogenic variants in trans identified through full gene sequencing. In some instances, however, only 1 variant is detected because the second variant could be a deletion or duplication or could reside in a promoter region or deep in the intron. In these cases, it is necessary to use other methods to confirm a diagnosis, such as measuring GAA enzymatic activity in another tissue. This is especially important in patients with LOPD. Although current genetic testing is a reliable means for identifying IOPD patients, data for patients with LOPD or not affected by the disease are less certain. Many new genotypes are being identified through NBS with unclear phenotypes, making it difficult to determine the percentage of cases not correctly identified through molecular genetic testing. Only close and continued follow-up will help to resolve these cases. Variant analysis is particularly important in confirmatory testing for detecting a pseudodeficiency allele or alleles, which can produce misleading low levels of GAA activity and lead to false-positive results. Confirmatory testing is especially important among the Asian population in which the GAA pseudodeficiency allele is seen at a higher frequency (up to 4%) compared with white populations. Confirmation of variants in trans requires parental testing to confirm the phase of the variants. In cases of classic IOPD, prediction of CRIM status is possible with genotyping alone in close to 92% cases. The nature and site of the 2 variants in the GAA gene typically predict a patient’s clinical course. Sometimes, only 1 previously identified variant is found coupled with a novel, unclassified sequence VUS, thus complicating the diagnosis of Pompe disease. More than 400 pathogenic variants have been identified, in addition to numerous polymorphisms and VUSs in the GAA gene. Pseudodeficiency alleles have also been described. A database with a list of these variants (the Pompe Center Mutation Database, Erasmus Medical Center, Rotterdam, Netherlands) can be found at http://cluster15.erasmusmc.nl/klgn/pompe/mutations.html. Additionally, a database listing GAA gene variants (Duke Children’s Hospital and Health Center) identified in CRIM-negative patients with Pompe disease is available at https://pediatrics.duke.edu/sites/pediatrics.duke.edu/files/field/attachments/GAA_mutation_database.pdf. The lists continue to expand each year as new variants are identified.

The role of gene sequencing in NBS continues to expand. One laboratory with DBS sequencing capabilities can now have target turnaround times (TATs) of 2 to 3 days. Variant analysis can be done at the same time as the DBS is retested for GAA activity measurement to serve as a second-tier screening test. Consistency has been demonstrated between measurements of GAA activity in DBSs and gene sequencing results. The latter is important for identification of pseudodeficiency allele(s) and determination of CRIM status so that appropriate follow-up can be planned and unnecessary screening avoided.

A TAT of 2 to 3 days for sequencing is necessary to
avoid delays in initiating treatment in cases of classic IOPD, for which hypertrophic cardiomyopathy is usually present by birth. A fast TAT is especially important in states where GAA sequencing is not part of the NBS second-tier test. Parents should provide informed consent for testing because nonpaternity can be detected through molecular genetic testing. Depending on the geographic location, written consent may be required.

**Laboratory Analyses**

In addition to measuring GAA enzyme activity and gene sequencing, there are a number of serum enzyme biomarkers that are indicative of tissue damage, including creatine kinase (CK), CK-MB, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), and urine biomarkers, including urine glucose tetrasaccharide (Glc4), that can be helpful when trying to establish a diagnosis in a patient with a positive NBS result for Pompe disease.13,39 However, clinicians need to bear in mind that although helpful diagnostically, these findings are not specific to Pompe disease and individually have limited prognostic value.

**Serum CK**

Serum CK is uniformly elevated in patients with classic IOPD and in children and juveniles with symptomatic Pompe disease and therefore is an important part of confirmatory testing. CK elevation is a sensitive although nonspecific marker of muscle damage.22,40,41 For example, in the NBS setting, CK levels may be falsely elevated as a result of trauma associated with birth. A more significant elevation is usually found in patients with classic IOPD.42 Elevated CK levels may be the only manifestation in patients with “asymptomatic” LOPD, but data on the age at which CK levels rise in symptomatic patients are lacking at this time. However, normal CK values do not exclude a diagnosis of LOPD39 because ~5% of patients with LOPD have normal CK levels.22,40,41

**Other Serum Enzymes**

AST, ALT, and, to a lesser extent, lactate dehydrogenase serve as serum enzyme biomarkers of muscle damage in Pompe disease. AST levels typically are higher than those of ALT. As is true of CK, levels of these enzymes occasionally may be within normal limits in patients with LOPD.13

**Urine Hexose Tetrasaccharide**

Glc4 has been found to be elevated in both urine and plasma in patients with Pompe disease. Measurements in urine are more reliable and easier to obtain for follow-up. Glc4 can also be measured in urine as the total hexose tetrasaccharide (Hex4) fraction, a breakdown product of glycogen. Here, Glc4 measurements will be reported as Hex4. Hex4 serves as a useful biomarker of glycogen storage, which is helpful in assessing severity and overall disease burden and may be useful as an adjunctive diagnostic biomarker in infants with a positive newborn screen. Levels of excretion are higher in infants and those with significant disease burden and are correlated with muscle biopsy glycogen content. Hex4 is also useful for monitoring the clinical response to treatment.13,43 Although also elevated in other glycogen storage disorders, diagnostically, Hex4 is close to 100% sensitive in identifying patients with classic IOPD. This was confirmed by Chien et al44 who reported baseline urinary Hex4 concentrations in patients with classic IOPD, LOPD, and a pseudodeficiency allele identified through NBS in Taiwan. Baseline Hex4 was not elevated in the LOPD and GAA pseudodeficiency cohorts but was elevated in the patients with classic IOPD. Negative results therefore may be helpful in ruling out the diagnosis of classic IOPD when combined with results of enzyme assays. Increases in Hex4 are often noted to precede muscle weakness and, as such, Hex4 is a sensitive marker of disease activity in patients. However, careful assessments by a trained physical therapist can often capture subtle changes that are missed by motor milestone assessments. Patients with LOPD who eventually need treatment tend to have Hex4 levels at the upper level of normal or above, suggesting that Hex4 levels, combined with other laboratory results (such as CK, AST, and ALT) and the patient’s clinical picture can be useful in cases of LOPD.

**Cardiac Evaluation**

Assessments for cardiac involvement (eg, cardiomegaly and cardiomyopathy) are necessary for diagnosis of patients with classic IOPD and for distinguishing them from patients with LOPD (including non-classic IOPD). Components of the cardiac evaluation should include an electrocardiogram (ECG) and echocardiogram (ECHO). Where cardiac evaluation is not immediately available, a chest radiograph looking for an enlarged cardiac shadow may be a useful initial evaluation. Although not typically seen in patients with LOPD, cardiac involvement is starting to be found more frequently in patients who do not have classic IOPD.4,45,46 Typical findings during cardiac evaluation for Pompe disease are summarized in Table 1. If cardiomyopathy is present at the initial evaluation, this confirms the infant has classic IOPD, and CRIM status should be determined as quickly as possible before initiation of ERT. If the results of the cardiac evaluation are normal, then the diagnosis of LOPD is more likely, although some patients with non-classic IOPD have developed cardiomyopathy after several months.19–21 Therefore, patients with low enzyme activity will have to be
TABLE 1 Cardiac Evaluations and Findings

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Characteristic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic IOPD</strong></td>
<td><strong>LOPD</strong></td>
</tr>
<tr>
<td>ECG</td>
<td>Large and tall QRS complex</td>
</tr>
<tr>
<td></td>
<td>Some have short PR interval</td>
</tr>
<tr>
<td></td>
<td>Delta wave due to WPW, or other aberrant pathways</td>
</tr>
<tr>
<td>ECHO</td>
<td>Cardiac involvement always detected.</td>
</tr>
<tr>
<td></td>
<td>in NBS, LVM/LVMI may be just above the ULN; therefore, if LVM/ LVMI is normal, but there is a high suspicion of involvement, a follow-up ECHO is needed</td>
</tr>
<tr>
<td></td>
<td>Evidence of significant hypertrophic cardiomypathy</td>
</tr>
<tr>
<td>Reduced left ventricular function (ie, EF and SF) in later stages; hyperdynamic state usually seen in initial stages</td>
<td>Increased LVMI</td>
</tr>
<tr>
<td>Increased LVM/LVMI and LVOT obstruction</td>
<td>Reduced left ventricular function (ie, EF and SF) as cardiac disease progresses</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Enlarged cardiac shadow</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td></td>
</tr>
</tbody>
</table>

EF, ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; SF, systolic fraction; ULN, upper limit of normal; WPW, Wolff-Parkinson-White.

managed closely for onset of cardiac involvement.

**POMPE DISEASE DIAGNOSTIC ALGORITHM WITH DNA SEQUENCING AS PART OF NBS LABORATORY PROTOCOL**

The algorithm in Fig 1 provides recommendations for the stepwise diagnostic evaluation that should be followed when mutation analysis/ DNA sequencing is available as part of the NBS laboratory protocol. Recommended evaluations based on a combination of low GAA activity and the presence or absence of GAA variants is provided. When followed, this algorithm will lead to 1 of 3 diagnoses:

- Classic IOPD
- LOPD (for all patients with a confirmed diagnosis who are not classified as having classic IOPD, and includes patients with non-classic IOPD and with LOPD)
- No disease/not affected/carrier/pseudodeficiency.

**POMPE DIAGNOSTIC ALGORITHM WITHOUT DNA SEQUENCING AS PART OF NBS LABORATORY PROTOCOL**

The algorithm in Fig 2 provides recommendations for the stepwise diagnostic evaluation that should be followed when variant analysis/ DNA sequencing is not available as part of the NBS laboratory protocol. For NBS laboratories that do not have DNA sequencing capabilities, the responsibility for obtaining sequencing of the GAA gene will fall on the referral center. Typically, the results of sequencing will not be available as quickly in this setting. A TAT of 2 to 3 days for sequencing results is ideal. The clinicians responsible for the follow-up of patients in these settings should consider contacting laboratories that have experience with GAA gene sequencing and pathogenic variants to explore faster TATs in light of the crucial need for quick results. The diagnosis of classic IOPD cannot be delayed by waiting for the sequencing result. Therefore, cardiac evaluation, ideally by chest radiograph, ECG, and ECHO, must be performed to detect classic IOPD immediately. Where cardiac evaluation capabilities are limited, valuable information can be obtained from just a chest radiograph and ECG. Blood GAA activity needs to be measured to confirm GAA deficiency.

**SUMMARY**

The objective of the initial patient evaluation after a positive NBS result is to establish or refute the diagnosis of Pompe disease and to categorize patients accurately. Once these are established, it is then up to the clinicians to determine whether the patient should be referred for immediate treatment with ERT or should go into follow-up without treatment. Clearly patients with classic IOPD should be referred for treatment with ERT. All other patients should be managed closely, especially by monitoring the attainment of motor milestones for any evidence of delays that may signify the onset of clinical LOPD.

**The Main Challenges**

The recommendations for confirmatory testing and initial evaluation provided in this article for a broad global audience are based on the clinical experience and expertise of the members of the Pompe Disease Newborn Screening Working Group, who are involved in the screening and care of patients with Pompe disease and who are all coauthors on sections in this NBS guidance supplement. However, the Working Group recognizes that clinical practices, standards of care, and resource capabilities vary regionally and by testing centers. Confirmatory testing recommendations need to be in harmony with state or regional protocols, which are dependent on local resources. Also, individual patient needs and health status must be considered along with local/ regional insurance reimbursement.
programs and regulations. Therefore, the recommendations should serve as guidance rather than as set or standard practices. Understandably, adaptations will be needed and expected based on region-specific practices and capabilities.

Pompe disease is a continuum of disease, and our knowledge about it continues to improve as new information becomes available in both the clinical and laboratory settings. Therefore, the recommendations provided here are based on our current knowledge and experience. Because we are currently in a dynamic phase in the field of NBS and lysosomal storage disorders, recommendations will likely change as we learn more about Pompe disease and as technology advances and innovations occur over time. Thus, we expect the need to revisit and revise these recommendations as appropriate in the next 3 to 5 years.

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ABBREVIATIONS

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CK: creatine kinase
CRIM: cross-reactive immunologic material
DBS: dried blood spot
ECG: electrocardiogram
ECHO: echocardiogram
ERT: enzyme replacement therapy
GAA: acid α-glucosidase
Glc₄: glucose tetrasaccharide
Hex₄: hexose tetrasaccharide
IOPD: infantile-onset Pompe disease
LOPD: late-onset Pompe disease
NBS: newborn screening
TAT: turnaround time
VUS: variant of unknown significance

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The Initial Evaluation of Patients After Positive Newborn Screening:
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