Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum

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abstract

After a Pompe disease diagnosis is confirmed in infants identified through newborn screening (NBS), when and if to start treatment with enzyme replacement therapy (ERT) with alglucosidase alfa must be determined. In classic infantile-onset Pompe disease, ERT should start as soon as possible. Once started, regular, routine follow-up is necessary to monitor for treatment effects, disease progression, and adverse effects. Decision-making for when or if to start ERT in late-onset Pompe disease (LOPD) is more challenging because patients typically have no measurable signs or symptoms or predictable time of symptom onset at NBS. With LOPD, adequate, ongoing follow-up and assessments for onset or progression of signs and symptoms are important to track disease state and monitor and adjust care before and after treatment is started. Because numerous tests are used to monitor patients at variable frequencies, a standardized approach across centers is lacking. Significant variability in patient assessments may result in missed opportunities for early intervention. Management of Pompe disease requires a comprehensive, multidisciplinary approach with timely disease-specific interventions that target the underlying disease process and symptom-specific manifestations. Regardless of how identified, all patients who have signs or symptoms of the disease require coordinated medical care and follow-up tailored to individual needs throughout their lives. The Pompe Disease Newborn Screening Working Group identifies key considerations before starting and during ERT; summarizes what comprises an indication to start ERT; and provides guidance on how to determine appropriate patient management and monitoring and guide the frequency and type of follow-up assessments for all patients identified through NBS.

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Pompe disease is a progressive disorder with considerable variation in age of presentation, severity, and rate of progression. It is clear that the health status of patients with symptomatic disease is expected to worsen over time if left untreated. However, the outcomes of patients with asymptomatic disease diagnosed through newborn screening (NBS) cannot be accurately determined and patients will require ongoing follow-up, thus underscoring the need for continued evaluation and close monitoring of all patients diagnosed with Pompe disease after an abnormal newborn screen. Treating the underlying cause of Pompe disease involves replacement of the deficient or missing enzyme (acid α-glucosidase [GAA]) to restore GAA activity to allow it to complete its function. Enzyme replacement therapy (ERT) with alglucosidase alfa (recombinant human GAA [rhGAA]) is the only specific treatment approved for Pompe disease at this time (alglucosidase alfa is marketed as Lumizyme within the United States and as Myozyme outside of the United States and is approved in >70 countries).[1,2] Although treatment with alglucosidase alfa is life-saving, it needs to be recognized that it is not curative. It is administered through biweekly, and occasionally weekly, lifelong infusions. It must be emphasized that ERT comprises 1 aspect of care. A multidisciplinary approach is needed to ensure that other aspects of the disease are addressed.

Once a diagnosis of Pompe disease is confirmed in infants identified after an abnormal newborn screen, the next step is to determine whether to start treatment with ERT or delay treatment pending the appearance of objective signs and symptoms. Regardless of age of onset and severity, all patients with Pompe disease should be monitored prospectively.[3,4]

For patients diagnosed with classic infantile-onset Pompe disease (IOPD), that is, onset of symptoms at ≤12 months of age with cardiomyopathy, treatment with ERT should be initiated as soon as possible after a diagnosis is confirmed and cross-reactive immunologic material (CRIM) status, which is indicative of a patient's level of endogenous GAA enzyme protein, is determined. After CRIM status is known, immune tolerance induction (ITI) can be started as recommended for patients who are CRIM negative (ie, patients who completely lack the endogenous GAA enzyme).[5] In classic IOPD, infants present with cardiomyopathy at birth or shortly thereafter and often have additional systemic involvement. The positive response to early treatment with ERT in patients with classic IOPD as well as the rest of the clinical spectrum underscores the rationale for NBS[6–15] and reinforces the need to start ERT as early as possible before irreversible pathology occurs.[3] Once ERT begins, regular and routine follow-up is necessary to assess the effects of treatment on the patient's health status, monitor for any adverse effects from treatment, and assess for disease progression. Testing for the development of antibodies and monitoring the occurrence of infusion-associated reactions (IARs) will allow appropriate intervention at the earliest opportunity.[16] ITI is an important factor related to ERT that can impact patients' responses to treatment and outcomes and will be discussed in detail.

The challenge, however, lies with the decision-making for patients with late-onset Pompe disease (LOPD), which in this article will be used to include all patients who do not fall into the category of classic IOPD, namely, all patients with symptom onset at ≤12 months of age and typically without cardiomyopathy (non-classic IOPD), and those traditionally considered LOPD, namely, patients with onset of disease at >12 months of age. Because these patients typically have no measurable signs or symptoms, clinical manifestations, or predictable onset of symptoms at NBS, clinicians are faced with deciding when and if to start ERT. The definition of LOPD is also broad and includes infants who present as early as the first year of life typically without cardiac hypertrophy, although cardiac involvement can occur in some cases.[17] This cohort typically has more rapidly progressive disease than older patients with LOPD given the early onset of symptoms, yet these patients previously remained undiagnosed for long periods of time.[5] Although the benefits of starting ERT early have been reported in patients with LOPD,[15,18–24] additional studies are needed that can guide when to initiate ERT in these patients.

Because of the variable and unpredictable onset of symptoms in patients, there is a need for close follow-up and monitoring for patients with LOPD diagnosed via NBS. The significant delays between onset of symptoms and diagnosis that are common among patients across the disease spectrum, especially for patients with LOPD,[15,25] will clearly be reduced with expansion of NBS initiatives. The timely follow-up of neonates and infants with Pompe disease, as with many other inborn errors of metabolism, is critical to the ultimate success of any NBS program.

A wide variety of clinical evaluations and tests are currently in use for monitoring at variable frequencies all patients with Pompe disease. However, the lack of a standardized approach across centers has resulted in significant variability in terms of how and when patients are assessed that may result in missed opportunities for early intervention. A consensus regarding ideal standardized assessments

for patients across the spectrum of disease phenotypes should help guide both patients and physicians in the optimal follow-up regimens to minimize burden while maximizing care outcomes. Patients with Pompe disease, regardless of whether they are identified via NBS, require coordinated medical care and follow-up throughout their life spans.

In this article, which is part of the "Newborn Screening, Diagnosis, and Treatment for Pompe Disease" guidance supplement, the Pompe Disease Newborn Screening Working Group identifies key aspects to be considered before starting ERT and during treatment; summarizes what comprises an indication to start ERT, especially in LOPD patients; and provides guidance on how to determine the appropriate management and monitoring of patients based on their diagnoses and clinical manifestations. The Working Group also provides additional expert consensus to help guide the frequency and type of follow-up assessments for patients identified through NBS. In providing these recommendations, it is the goal of the Pompe Disease Newborn Screening Working Group to provide a standardized framework for the diagnosis, management, and follow-up of patients for physicians and health care teams managing patients with Pompe disease. The Working Group recognizes that individual patient needs and available resources must be taken into account and therefore advises treating physicians and health care teams to consider the guidelines presented in this article as a framework when developing individual follow-up programs. The Working Group also recognizes that the guidelines will need to be updated on a regular basis as our understanding increases.

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

TABLE 1 Presenting Signs and Symptoms by Symptom Class Among Patients With Classic Infantile-Onset Pompe Disease (IOPD)[15,25,26,28–33]

Most Common Symptoms in Classic IOPD in the Clinical Setting
Cardiovascular
Cardiomegaly
Hypertrophic cardiomyopathy
Congestive heart failure
Rhythm disturbances
SVT often a presenting feature
Respiratory
Respiratory distress, frequent pneumonia, or upper respiratory infections
Sleep apnea
Respiratory failure
Weak cry
Wet cough
Neurologic/musculoskeletal
Hypotonia (floppy baby)
Generalized muscle weakness (most severely affecting proximal muscles)
Neck (poor head control)
Trunk muscles
Proximal muscles (upper and lower extremities affected equally)
Distal muscles (lower slightly more affected than upper)
Developmental delay
Absent or delayed motor milestones or regression
Hypertrophy and firmness of calf muscles
Poor reflexes (in the later stages of the disease)
Facial myopathy with open mouth posture and tongue protrusion
Gastrointestinal
Hepatomegaly (in setting of CHF)
Failure to thrive
Poor suck, feeding and swallowing difficulties
Macroglossia
Other
Hearing deficit

CHF, congestive heart failure; SVT, supraventricular tachycardia.

PRESENTING SIGNS AND SYMPTOMS

The signs of disease progression may be subtle and overlooked, especially in patients with LOPD.[15,25–28] Waiting for more obvious symptoms to develop or telling the patient and/or the patient's family to come back when symptoms become evident will most likely have a negative impact on the potential treatment benefit for that patient. For patients with classic IOPD on ERT, monitoring for the appearance of new symptoms and improvement or worsening of existing symptoms is important for evaluating treatment response. The presenting symptoms most commonly reported in patients with both classic IOPD and LOPD (including non-classic IOPD) are listed in Tables 1 and 2. Although these symptoms represent those most frequently reported as the first signs and symptoms, they are by no means an exhaustive list for either group. There also may be overlap between groups. Furthermore, it must be understood that this list is based on findings in cases identified clinically and not in the NBS setting. Cardiomyopathy, however, is the 1 distinguishing symptom that must always be present at presentation or within the first few days to the first few months of life to be considered classic IOPD.

A primary challenge in the management of patients with Pompe disease identified through NBS is how to appropriately and consistently manage asymptomatic patients

because there may be a long delay to onset of initial signs and symptoms. These patients are at risk for being lost to follow-up after screening, particularly those who have not yet shown clinical manifestations, but who may or would exhibit subclinical findings of Pompe disease when properly evaluated. Ideally, a default mechanism for follow-up should be established once a diagnosis is made through NBS. Immediate referral to an appropriate multidisciplinary subspecialty clinic is the best way to ensure appropriate and coordinated care after the initial diagnosis. Such referral is especially important because, in many areas, primary care physicians do not have the experience or resources to appropriately and effectively manage patients with Pompe disease.

INITIAL CONSIDERATIONS: A MULTIDISCIPLINARY APPROACH TO TREATING THE DISEASE AS WELL AS THE MANIFESTATIONS

The management of Pompe disease requires a comprehensive multidisciplinary approach encompassing strategies that include appropriate and timely interventions that are disease-specific to target the underlying disease process and symptom-specific manifestations.[40] Clinical experience with treating and managing the disease is important. Care is a collaboration across multiple specialties and can include specialists in inherited metabolic diseases, developmental pediatrics, cardiology, pulmonology, neurology, anesthesiology, urology, immunology, and nutrition. Patients will often require early intervention with physical, occupational, and speech therapy, and should be evaluated early for these needs. Genetic counseling is needed for new families. Overall coordination of care across disciplines and continued oversight of the care and management by a clinician who is experienced in treating patients and knowledgeable about the disease itself, potential complications, and the nuances of treatment are essential. Telemedicine also can play a part in monitoring and care coordination of patients and is recommended especially in geographic locations where resources and facilities with experience in the care of patients with Pompe disease are limited. Most importantly, the treatment of any patient with Pompe disease, as with other inherited metabolic diseases, needs to be tailored to the individual patient. Management guidelines for patients across the disease spectrum have been published for various parts of the world.[3,4,41] Clinicians should also refer to these guidelines when treating patients with Pompe disease.

Most NBS programs do short-term follow-up of babies with a positive newborn screen until the diagnosis is confirmed or excluded. Decisions on treatments and long-term follow-up of patients are the responsibility of the clinical specialist. In the United States, the clinical specialist is usually the medical geneticist. In Pompe disease, monitoring of patients to determine when to initiate ERT is

TABLE 2 Presenting Signs and Symptoms by Symptom Class Among Patients With Late-Onset Pompe Disease (LOPD)[15,27,28,34–39]

Most Common Symptoms in LOPD
Respiratory
Respiratory insufficiency/distress
Sleep apnea (OSA, sleep hypoventilation)
Shortness of breath after exercise
More frequent respiratory challenges in supine versus upright position (indicative of early involvement of diaphragm)
Weak cough
Respiratory muscle weakness (including diaphragm, intercostal, and accessory muscles)
Neurologic/musculoskeletal
Delayed milestones
Muscle weakness
Limb-girdle weakness
Proximal muscles (lower extremities affected much more often than upper extremities)
Distal muscles (mainly lower extremities affected)
Neck muscles
Trunk muscles
Exercise intolerance
Myalgia
Ambulation difficulties
Scoliosis
Low back pain
Fatigue
Muscle wasting (especially proximal muscles)
Rigid spine syndrome
Ptosis
Gastrointestinal
Lingual weakness
Chewing and swallowing difficulties/aspiration pneumonia/oropharyngeal dysphagia
Poor weight gain
Difficulty maintaining weight
Macroglossia
Lingual weakness
Cardiovascular/vascular
Cardiomegaly (uncommon)
Left ventricular hypertrophy (occasionally)
Heart rhythm disturbances
Dilation of ascending aorta
Brain aneurysms (often involving basilar artery)
Other
Asymptomatic elevated CK levels

OSA, obstructive sleep apnea.

critical. The follow-up of Pompe disease is lifelong and is closely related to disease severity.

TREATMENT WITH ERT WITH ALGLUCOSIDASE ALFA IN POMPE DISEASE: WHEN TO START AND SPECIAL CONSIDERATIONS

The availability of ERT with alglucosidase alfa and the development of new therapies for Pompe disease make early diagnosis necessary so that treatment can be started before irreversible damage has occurred. An accurate confirmation of diagnosis is essential because treatment is a lifelong commitment. It is therefore equally important to avoid unnecessary treatment in patients with incomplete diagnostic workups who may not have Pompe disease at all, may be carriers, or have pseudodeficiency.

Delays in diagnosis of any length postpone the start of ERT, which is detrimental to long-term outcomes.[6,8,9,42] In classic IOPD, disease progression is rapid and fatal by 2 years of age without timely initiation of ERT.[3,40] As our knowledge of Pompe disease has increased, our approach to treating these very young, sick patients has changed. The Taiwan NBS program demonstrated that patients with classic IOPD identified through NBS and therefore started on ERT early in life maintained improved motor function.[43,44] Outcomes were investigated among a cohort of patients with classic IOPD from the Taiwan NBS program to see if starting ERT early (at ~10 days of age) influenced clinical outcomes.[45] ERT was started at a mean age of 11.92 days in the study cohort. Results showed that starting ERT even a few days earlier may lead to better long-term outcomes, supporting the need for the earliest possible identification of patients with classic IOPD. A number of other studies found that early initiation of treatment resulted in improved rates of ventilator-free and long-term survival, improved and/or reversal of cardiac abnormalities, improved motor function, and improved cardiac and skeletal muscle response.[7,8,11,14] In the past, initiation of ERT within the first 6 months of age was considered ideal for a favorable response to ERT. We have subsequently learned that children treated within this time frame, although alive, have severe long-term sequelae.[46,47] We now recognize that initiation of treatment should be done in a timely manner because the disease is rapidly progressive in patients with classic IOPD and is best when started within the first days of life rather than within the first few months.

The initial health status and condition of the patient at diagnosis rather than chronological age alone most influences the outcomes of treatment.[48] The best clinical response is seen in patients who have less muscle pathology because affected muscles from patients with more pathology due to progression of the disease may not respond adequately to ERT. This effect on response, coupled with individual patient heterogeneity, can affect the rate of disease progression and creates a narrow therapeutic opportunity for patients with classic IOPD.[48] The most noticeable benefit of ERT in patients with classic IOPD has been on cardiac muscle.[9] Left ventricular mass, left ventricular mass index, and cardiac function as measured by ejection fraction and shortening fraction are improved in most patients. Most notably, the cardiac muscle response to ERT appears to be good regardless of the stage of the disease at the start of treatment.[49] Although the response in skeletal muscle has been more variable, the best response has been seen in patients treated early before irreversible muscle damage occurs. Clinical response to ERT can be influenced by a number of factors, including the extent of muscle damage at the start of ERT, the muscle fiber type affected, CRIM status, immune response, and other pathology, such as autophagic processes and the presence of mitochondrial involvement.[48,50,51] The immune response seen most commonly in CRIM-negative IOPD patients and a subset of CRIM-positive cases can lead to the development of high and sustained anti-human recombinant alpha glucosidase (anti-rhGAA) immunoglobulin G (IgG) antibody titers, which leads to a poor clinical response. This factor appears to be independent of the muscle pathology at the time of treatment initiation.

There is considerable variability in response to treatment, and the long-term outcome of ERT is unfolding, which adds to the challenges associated with effectively and appropriately treating patients. Our knowledge continues to improve as young patients are now surviving into adolescence because of early initiation of ERT, and a new natural history has emerged. In patients who present with LOPD, the course of disease is typically less aggressive. However, there is an inevitable accumulation of glycogen in tissues and other pathology.[52,53] Left untreated, the disease causes deteriorating respiratory and motor function and progressive disability that increase the risk of needing ambulatory (wheelchair use) and ventilator support.[40] In patients with Pompe disease, long-term treatment with ERT may improve functionality and quality of life and stabilize progression in many patients.

As the new natural history emerges, there is growing evidence of effects of the disease in other organs not previously recognized, such as involvement of the eye, bladder, gastrointestinal tract, and blood vessels. Histopathologic examination of tissue samples from patients with classic IOPD and LOPD has revealed

multiple organ involvement that is consistent with the nonskeletal muscle manifestations of the disease.[48] Clinicians need to be aware of new manifestations of Pompe disease that will require additional treatment considerations. Follow-up and monitoring of patients with LOPD comprise the most complex part of the screening program. The current problem mainly centers on how to manage patients without overt signs or symptoms of Pompe disease who are diagnosed through NBS and how to monitor these patients to ensure that treatment is initiated as soon as there is evidence of clinical pathology.

The Importance of CRIM Status in ERT

Determination of CRIM status as early as possible should be the goal, ideally at the time of the initial referral from the NBS laboratory for patients with classic IOPD.[54–57] CRIM status determination is critical to patient classification and prediction of response to treatment. Although patients who have residual GAA protein are classified as CRIM-positive and those who completely lack the enzyme are classified as CRIM-negative, CRIM status should not be viewed as an either/or phenomenon. Rather, it should be seen as a continuum because CRIM status alone does not accurately predict the antibody response to ERT.

Fast and reliable methods for determining CRIM status are essential because it will lead to more rapid and early treatment decisions and improved clinical outcomes for patients with classic IOPD. A number of methods are available. CRIM status is recognized by anti-GAA antibodies on Western blot analysis.[57,58] Although Western blot analysis of skin fibroblasts is a reliable method for determining CRIM status in patients with classic IOPD, it is invasive, and results can take several weeks. In most cases, when the pathogenic variants are already known, CRIM status can be predicted by *GAA* variant analysis alone. At this time, CRIM status can be accurately predicted by the underlying genotype in ~92% of cases. A blood-based assay for determining CRIM status has been developed recently and has produced reliable results in the majority of cases as confirmed by Western blot from skin fibroblasts and variant assays.[57,59] Results can be obtained quickly, usually within 2 to 3 days. Limitations of the assay, however, are the amount of blood required and the need for specialized tubes for collection of the blood sample and for testing to be done in specialized laboratories with appropriate capabilities. In patients who are CRIM-negative, deletion, nonsense, and frameshift pathogenic variants are associated with undetectable levels of enzyme protein, the development of high levels of neutralizing antibodies to ERT, and adverse clinical outcomes. A combination of 2 such pathogenic sequence variants (ie, multiexon deletion, nonsense, and frameshift variants) indicates CRIM-negative activity on either blood or skin Western blot analysis.[58] In CRIM-positive patients, although missense pathogenic sequence variants can cause classic IOPD, some GAA enzyme protein is usually detected, and these variants typically are not associated with the development of antibodies during ERT. Missense pathogenic variants may also be present in CRIM-negative patients in some instances depending on the location of the change.[55] In-frame deletion pathogenic variants are predictive of a CRIM-positive status.[58] Although an assay is available to determine CRIM status for patients whose CRIM status cannot be determined on the basis of molecular analysis alone,[57,59] availability of testing is likely to change. It therefore is recommended that NBS laboratories that are performing the screening be considered as a resource to find laboratories that have the capabilities for this assay. Currently, CRIM status is not determined on Western blot alone, but rather from a combination of information from Western blot and pathogenic variant analysis status .[60] As stated earlier, CRIM status can be given in situations of known pathogenic variants previously reported without the need for a Western blot. However, declaring CRIM status based on results of Western blot alone is concerning and can result in the wrong classification of CRIM status, given that the latter needs to be done in a laboratory with significant clinical experience. There are a number of laboratories in the United States and Europe that currently have the capabilities to perform Western blot analyses to determine CRIM status. The number will increase as more facilities acquire the capabilities and experience needed to perform these analyses.

CRIM-negative patients are not immunologically tolerant to GAA and typically develop high levels of antibodies against rhGAA. These patients seroconvert quickly after initiation of ERT and develop high and sustained anti-rhGAA IgG antibody levels, which neutralize the efficacy of ERT, leading to clinical decline that is similar to that seen in untreated patients. Therefore, it is critical to consider if immune modulation via an ITI therapy is needed at the time of the initiation ERT in these cases.[60] The persistence of the high and sustained antibody titers (HSATs) for periods of time rather than the absolute levels of the titers influences clinical outcomes, thus underscoring the need for ITI as early as possible.[61] Approximately 25% to 30% of classic IOPD patients are CRIM-negative.[9,55,56] This distribution varies between different ethnicities of the world (eg, patients in Taiwan: 0%[6,44]; the United States: 25%–30%[55,56]; and Brazil: >30%[62]) and thus needs to be recognized so that ITI recommendations can be tailored accordingly.

CRIM-positive patients typically have low antibody titers and better clinical outcomes than CRIM-negative patients. Some CRIM-positive patients may develop a low, transient titer response, and ITI is not needed because these patients usually are immunologically tolerant of rhGAA. These patients have a favorable response to treatment. However, a subset of CRIM-positive patients (~30% of patients with classic IOPD and 10% of patients with LOPD[63]) develop high and sustained anti-rhGAA IgG antibody titers and will have a clinical decline similar to that seen in CRIM-negative patients.[54,61,64] In retrospect, these patients also would benefit from ITI in the naive setting. It is important to recognize that early treatment does not prevent immune response. Cases (both CRIM-positive and CRIM-negative) have been reported where treatment was started before 1 month of age, and yet patients developed HSATs.[55] ITI protocols are being developed for CRIM-positive cases that could allow all CRIM-positive patients to be treated with ITI and thus reduce the risk of HSATs and poor outcomes.

DIAGNOSIS VERSUS CLINICAL FEATURES AND WHEN TO START TREATMENT

Genotyping is strongly recommended not only to help confirm the diagnosis, but also to help predict when treatment should be started and possible outcomes, including immune responses to treatment. It is recommended that ERT should not be initiated until the results of sequence variant analysis are available to confirm the diagnosis of Pompe disease and the CRIM status has been determined. Identification of pathogenic variants will help avoid unnecessary initiation of ERT in patients with false-positive screening results, including those who have a pseudodeficiency allele. To ensure that ERT is initiated in a timely manner for patients with classic IOPD, the need for a quick turnaround time for results, ideally 2 to 3 days, cannot be overemphasized and must be clearly communicated and confirmed with laboratories performing the molecular analyses.

Classic IOPD

The need for early initiation of ERT is the same for all patients with classic IOPD. General recommendations as to when to start ERT in patients based on CRIM status are provided in this section and in the accompanying algorithm (Fig 1).

CRIM-Positive Patients

In CRIM-positive patients with classic IOPD, ERT should be started as soon as possible after a diagnosis has been confirmed and CRIM status determined. After ERT is initiated, CRIM-positive patients should have their antibody titers monitored closely (see "Recommendations for Follow-up and Assessment Schedule: Patients With Classic IOPD Who Are CRIM-Positive and CRIM-Negative").

CRIM-Negative Patients

Although there is a subset of patients who may not do well despite early initiation of ERT, such as those who are treated with ERT as monotherapy, the clinical benefits are maximal when ERT is started early and when ITI is started at the same time.[5,65] The immune response can be prevented by ITI in these patients who otherwise would develop HSATs. Although early initiation of ERT and ITI is necessary for the prevention of irreversible pathology and disease progression, this does not necessarily lead to low or no antibody formation or completely prevent an immune response in some cases. Therefore, anti-rhGAA IgG titers will need to be monitored closely. Prophylactic ITI started at the time of ERT initiation for all CRIM-negative patients is currently recommended and justified.[55,66] More will be learned about early initiation of ERT and the role of ITI with more widespread use of NBS programs as more patients are identified and treated early.

Recommendations for Immune Modulation

Although the recommendations for ITI discussed in this article are based on the Pompe Disease Newborn Screening Working Group's current knowledge and clinical experience, immune modulation may be considered for other patients at the discretion of the treating physician. The Working Group recommends that immune modulation be done in all CRIM-negative and high-risk CRIM-positive patients. Ideally, ITI should be started when ERT is started because ITI is more likely to be successful when started at the onset of ERT.[55]

Protocols and recommendations for ITI have been developed and published.[5,67] Immune modulation should be targeted with agents that act to eliminate proliferating B cells and T cells.[68,69] Successful ITI has been achieved, and results are encouraging with regimens of rituximab, methotrexate, and/or immunoglobulin (intravenous immunoglobulin [IVIG]), which may play a strong role in immune modulation and prevent the deleterious immune response against alglucosidase alfa.[5,16,54,67] The Working Group recommends an ITI regimen that combines rituximab, methotrexate, and intravenous immunoglobulin based on published results indicating that it appears safe and efficacious. A clinical algorithm with recommendations outlining steps for the management of CRIM-negative patients with IOPD and initiation of this ITI regimen has been developed by Banugaria et al[5] and can be used to minimize delays between determining CRIM status and starting ITI concurrently with ERT. If there is B-cell recovery and a patient continues to have low

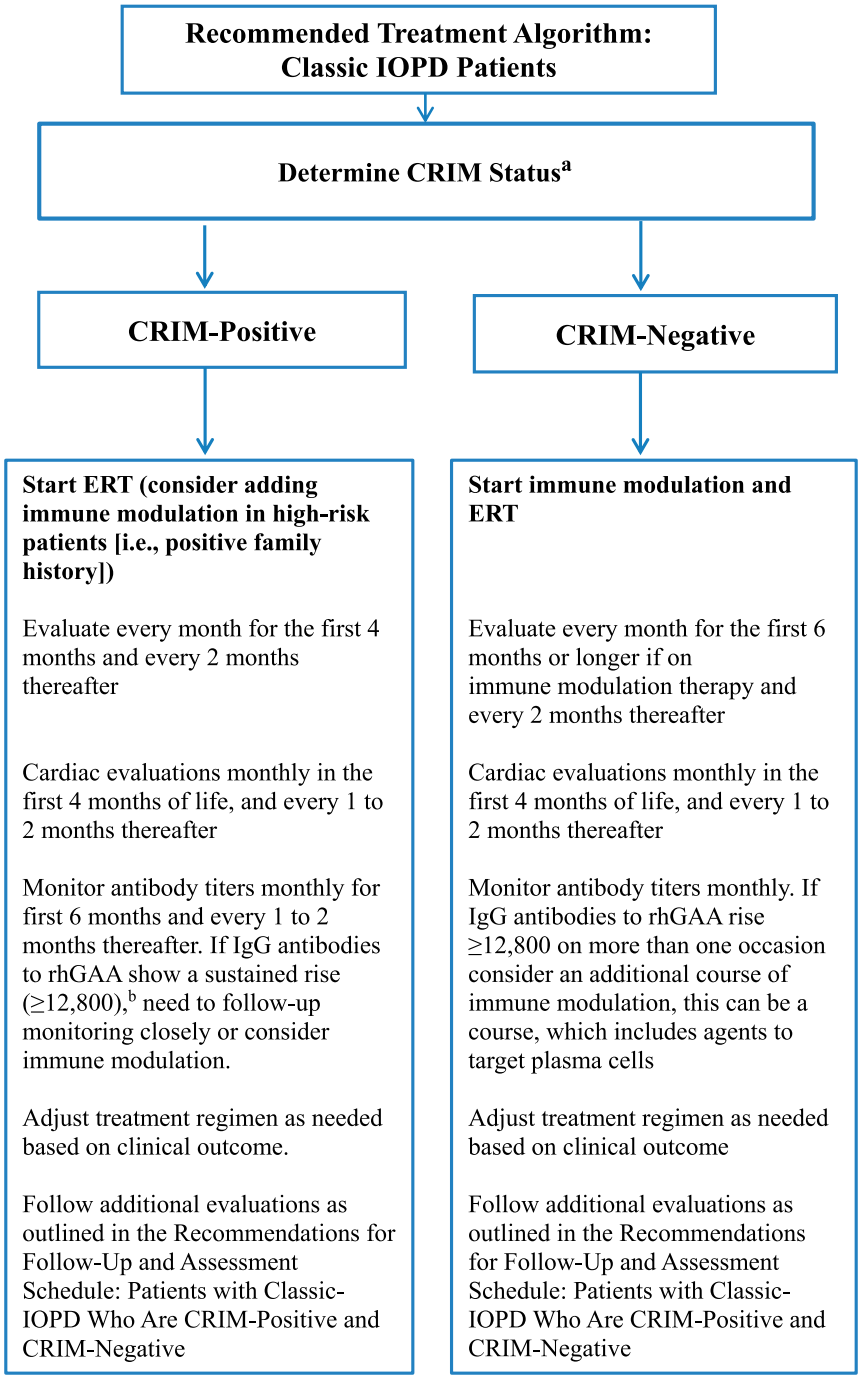

FIGURE 1

Recommended treatment algorithm for patients with classic IOPD in year 1. [a] See "The Importance of CRIM Status in ERT." [b] See prescribing information for alglucosidase alfa.[1,2]

or no antibodies, then immune modulation is likely successful. In a small number of cases, tolerance is not achieved. Other ITI regimens, for example, those using methotrexate only, are currently being developed and investigated.[60,69,70]

When planning ITI, there are a number of factors and potential challenges that need to be addressed and resolved so that patients who need ITI can receive it. The availability of ITI components and resources may be an issue in some cases. For example, rituximab is not available in all parts of the world. Also, the availability of physicians experienced in ITI and properly equipped treatment facilities can vary significantly in different geographic regions, thus limiting patient access to needed care. The risk of infection for patients is also an important factor that needs to be considered and properly handled for patients undergoing ITI, especially in developing countries. Antibody testing is currently available at no extra cost to patients through Sanofi Genzyme (Cambridge, MA).

If there is some exposure to ERT, then it is important to monitor anti-rhGAA IgG titers monthly to detect if the patient has seroconverted and if anti-rhGAA IgG titers are increasing. Differences in the amount of ITI needed have been seen between ERT-naive patients and patients who are already receiving ERT, with the latter needing a more extensive ITI protocol of a prolonged duration.[67] Close monitoring is needed for all patients on ERT regardless of whether they are on ITI so that if antibody formation occurs and the titers are of significance (rising titers or HSATs), it is detected and managed as early as possible (see "Recommendations for Follow-up and Assessment Schedule: Patients with Classic IOPD Who Are CRIM-Positive and CRIM-Negative").

In 1 study, patients with classic IOPD were stratified into 3 groups based on their anti-rhGAA antibody titer levels:

- HSAT: anti-rhGAA IgG antibodies measured ≥51 200 on ≥2 occasions;
- Sustained intermediate titer: anti-rhGAA IgG antibodies ranged from 6400 to 25 600;
- Low-titer: anti-rhGAA IgG antibodies remained <6400 throughout the course of ERT.

All but low-titer levels were associated with poor clinical outcomes.[55] In

another study, 5 patients with antibody titer levels ≥12 800 at week 12 had an average increase in clearance of alglucosidase alfa of 50%, suggesting neutralization of enzyme uptake or activity in this cohort.[1,42]

If antibody formation can be prevented early, then the chance of success and good clinical outcomes for patients is improved. Successful ITI has changed the natural course of the patients who are CRIM-negative and improves survival.[5,60]

For CRIM-positive patients who need ITI, the full regimen used for CRIM-negative patients is currently being used, and follow-up should be similar to that for CRIM-negative patients. For all CRIM-positive patients not initiated on ITI, measurement of anti-rhGAA IgG titers should be done monthly to detect antibody formation as early as possible to avoid delays in ITI initiation if needed.

Once successful immune modulation is completed, all patients should be monitored routinely for antibody formation and B-cell recovery. If antibody titers continue to increase, patients should be further immune modulated as/if needed regardless of CRIM status. Recommendations for ITI will be revisited and revised as needed as we learn more in clinical settings.

RECOMMENDED SCHEDULES OF ASSESSMENTS

Once a diagnosis of Pompe disease has been confirmed in patients identified through NBS, patients can be classified into 1 of 4 groups based on their symptom-onset category and CRIM status (for patients with classic IOPD): (1) classic IOPD patients who are CRIM-negative (completely lacking the endogenous GAA enzyme); (2) classic IOPD patients who are CRIM-positive (have some endogenous GAA enzyme); (3) symptomatic LOPD (including non-classic IOPD) patients; and (4) asymptomatic LOPD patients. This classification helps providers choose the most appropriate schedule of recommended assessments as well as treatment for each group. It is important to evaluate these patients carefully to be able to correctly classify them into these 4 groups.

Recommended schedules of assessments that were developed for each group based on this classification of patients will be presented. Special treatment considerations relevant to each group specifically as well as for all patients across the disease spectrum also will be discussed.

Each care guideline in this article includes specific recommendations by the Pompe Disease Newborn Screening Working Group based on their knowledge and collective expertise at the time of publication. These recommended schedules and treatment considerations will undoubtedly be revised as needed and when appropriate. Members of the Working Group and the broader health care community who manage patients with Pompe disease gather information through follow-up and monitoring of patients. The Pompe Registry Recommended Schedule of Assessments[71] was used in this article as a template for follow-up recommendations because it includes core assessments that have proved helpful in monitoring disease progression in clinical practice. The Working Group revised and customized the recommendations considered most appropriate for each of the 4 groups of patients. The recommendations may be used as a guide for clinicians as they move through the treatment and follow-up of patients for the first 5 years after diagnosis and are by no means intended to replace good clinical judgment.

Recommendations for Follow-up and Assessment Schedule: Patients With Classic IOPD Who Are CRIM-Positive and CRIM-Negative

Infants found to have classic IOPD have severe symptoms and rapid progression, so they must be closely managed, especially for cardiac problems. Their care should be coordinated across a multidisciplinary team led by a clinician who has expertise in managing Pompe disease, including all of the associated manifestations of this multisystem disorder. This team can include primary care doctors; neuromuscular, physiatry, pulmonary, cardiology, and developmental specialists; nurses; physical, occupational, and speech therapists; nutritionists; genetic counselors; and others as needed.[3,4,26] Additional guidelines for the management and coordinated care of infants with a confirmed diagnosis of classic IOPD have been published and should be consulted when caring for these very young, sick infants.[3,4]

Table 3 contains the Pompe Disease Newborn Screening Working Group's recommendations for the frequency of assessments for patients identified through NBS with classic IOPD who are either CRIM-positive or CRIM-negative. For patients with classic IOPD already receiving ERT, the recommended schedule of comprehensive assessments and follow-up by body system regardless of CRIM and ITI status is based on the clinical status of the patient and his or her respective needs.

Late-Onset Pompe Disease (LOPD)

In cases of LOPD, which in this article includes all patients not classified as classic IOPD, it will be necessary to wait for measurable clinical signs and symptoms pointing to the onset of Pompe disease before initiating ERT. Determining the appropriate frequency and methods of clinical monitoring and what comprises an indication to start treatment poses significant challenges for LOPD patients diagnosed through NBS.[15] The Taiwan NBS pilot program as well as the Missouri screening experience have provided some insights.

TABLE 3 Classic Infantile-Onset Pompe Disease (CRIM-Negative and CRIM-Positive): Recommended Follow-up Schedule and Assessments for Patients

	Assessment Time Point and Frequency				
	Initial Newborn Referral	2–4 wk of Age	Monthly to 4 mo of Age	Every 2 mo (4–12 mo of Age)	Every 3–6 mo[a] (>12 mo of Age)
Initial enrollment					
Demographics	X	—	—	—	—
Diagnosis (GAA and variants)	X	—	—	—	—
CRIM status[b]	X	—	—	—	—
General patient monitoring					
Medical Hx	X	X	X	X	X
Clinical follow-up	X	X	X	X	X
Physical examination	X	X	X	X	X
Ht/Wt/HC/BMI	X	X	X	X	X
CK/CK-MB, HCO_3	X	X	X	X	X
Urine Hex_4	X	X	X	X	X
Clinical assessments					
Chest radiograph	X	—	—	—	—
ECG (PR, QRS, QTc, WPW)	X	X	X	X	X
ECHO (LVMI, EF, SF)	X	X	X	X	X
Audiology	X (BAER)	—	—	X	X
Developmental assessments[c]	X	—	X	X	X
Treatment evaluations					
ERT antibodies (CRIM-negative)[d,e]	X[f]	X[f]	X	X	X
ERT antibodies (CRIM-positive)[g,e]	X[f]	X[f]	X	X	X
Videofluoroscopic swallow study	X	—	X[a]	X[a]	X[a]
Pulmonary evaluation	X	—	X[a]	X[a]	X[a]
Motor status	X	—	—	—	X
Early intervention	—	—	—	X	—
Cardiac evaluation	X	X	X	X	X

A change in clinical status may indicate a need for additional intervention. For patients who are on ITI, laboratory assessments for safety of the ITI regimen, including ALT, AST, and complete blood count, should be done. BAER, brainstem auditory-evoked response; CK-MB, CK myocardial band; ECG, electrocardiogram; EF, ejection fraction; HC, head circumference; HT, height; Hx, history; LVMI, left ventricular mass index; SF, shortening fraction; WPW, Wolff-Parkinson-White; —, not applicable.

[a] As clinically indicated.

[b] Varies with patient's genotype.

[c] Denver; Bailey; TIMP; AIMS; Gross Motor Function Measure-88; CHOP INTEND. Videotaping can be done and used to assess patients.

[d] Rise in antibodies of >25 600 may indicate a need for immune modulation.

[e] Antibody titer levels indicating a need for immune modulation are based on antibody testing done by Sanofi Genzyme, Cambridge, MA.

[f] Should be measured before treatment initiation at initial evaluation or at 2–4 wk.

[g] Rise in antibodies of >12 800 may indicate a need for immune modulation.

Currently, the majority of patients diagnosed with LOPD through NBS have not been started on ERT. Treatment has been initiated in a subset of patients, including those with 1 splice site mutation, in the first year of life.[43,44,72] It is, of course, recognized that the cohort in Taiwan is unique. IOPD patients are CRIM-positive and the LOPD cases lack the common Intervening Sequence (IVS) splice site pathogenic variant (c.-32-13T>G), the variant generally seen in up to 70% of cases of LOPD in the white population in heterozygosity.[40,44,73,74] Thus, the experience from Taiwan, although helpful, does not fully address the issues in the United States. There are some cases of LOPD with the IVS variant that present in the first year of life. These patients need to be monitored closely during the first year. To our knowledge, to date, there have been no published cases of patients with cardiomyopathy with IVS splice site variants, and clinicians need to keep this in mind. Furthermore, over time, we will likely recognize that there are unique characteristics within the cases of Pompe disease identified in other parts of the world, similar to the clinical experience with Gaucher disease. The outcome and need for ERT in LOPD patients diagnosed through NBS will require continued long-term follow-up. Historically, patients with LOPD do not start ERT until they are diagnosed clinically, which can occur anywhere between the first and sixth decade of life. It is not always clear when their first signs or symptoms of Pompe disease manifested and, therefore, if their clinical outcomes would be different if they were treated with ERT earlier. However, these patients had signs and symptoms of disease before treatment, and so the same outcome is not expected for the new cohort of patients identified through NBS. Based on data from the Pompe Registry, many patients with LOPD have symptoms for >10 years before a diagnosis of Pompe disease is confirmed.[75] An earlier diagnosis would likely result in improved outcomes for these patients.

Although data on the effects of ERT on clinical outcomes in these patients may be limited, initial evidence does indicate that the best morphologic results from ERT may be achieved when treatment is started while patients have measurable signs of disease, but are still clinically asymptomatic.[53] Additional studies are needed to support or refute these findings.

Recommendations for Follow-up and Assessment Schedule: Symptomatic LOPD (Including Non-classic IOPD) Patients

Because Pompe disease is a multisystem disease, symptomatic patients (including non-classic IOPD patients) should be evaluated for the impact of the disease on their growth, cardiac, pulmonary, musculoskeletal, and developmental status. Multispecialty care, comprising the same providers as those needed for patients with classic IOPD, is recommended for symptomatic LOPD patients as well.

Patients with symptom onset at ≤12 months of age without cardiac involvement need to be monitored regularly. Although progression during the first year of life is variable, with some patients presenting during that time, follow-up is important in this cohort, even for those without overt signs and symptoms in the first year of life, because they can develop significant multisystemic involvement during the first few years of life that could benefit from early initiation of treatment. Education of pediatricians involved in the primary care of these patients is important so they can clinically monitor patients for signs and symptoms of disease progression and make referrals to other specialists as needed. In some areas and geographic regions, Web-based programs and learning seminars are available through state or local chapters of organizations, such as the American Academy of Pediatrics, that can be valuable sources for updated information about state and regional NBS programs and learning about and raising awareness of Pompe disease. Participation in such programs where available is strongly recommended for health care teams as a means for learning how to effectively monitor and manage patients diagnosed with LOPD through NBS. Appropriate timing of follow-up assessments is key for these patients (Table 4).

If a patient has no problems at the 1-month reassessment, then follow-up at 3 months and every 3 months during the first year is recommended. Once treatment is started, close monitoring of patients' responses to ERT and development of antibodies and need for ITI is essential (see "Starting or Not Starting ERT in Patients with LOPD Based on Assessment Results").

Recommendations for Follow-up and Assessment Schedule: Asymptomatic LOPD Patients

Recommendations for the follow-up and assessments of patients who have been diagnosed with Pompe disease but who are asymptomatic are provided in Table 5. For patients identified with LOPD during NBS but without apparent clinical manifestations, check-ups at 3 months of age and every 3 months are recommended during the first year and then every 3 to 12 months as clinically warranted (Table 5). Among members of the Pompe Disease Newborn Screening Working Group, there has been a trend for asymptomatic patients to be seen for evaluation on an annual basis at the specialty center with intervening evaluations by the patient's pediatrician, thus minimizing the clinical burden to the family.

STARTING OR NOT STARTING ERT IN PATIENTS WITH LOPD BASED ON ASSESSMENT RESULTS

We know from clinical experience that signs and symptoms appear in patients with Pompe disease at different times. The appropriate time or age at which to start ERT in patients who have no objective signs or symptoms of the disease is the source of much discussion.[52] Although data on the effects of ERT on clinical outcomes in these patients may be limited, initial evidence does indicate that the best morphologic results from ERT may be achieved when treatment is started while patients have the first measurable signs of disease, such as increasing CK and hexose tetrasaccharide (Hex_4) levels, and subtle signs of the disease, such as involvement of muscles/muscle groups typically noted in LOPD, but are still clinically asymptomatic.[53] Additional studies are needed to support or refute these findings.

With LOPD, the goal is to start treatment at the earliest signs of disease progression. Because Pompe disease is a disease continuum, the severity of signs and symptoms of LOPD and the extent to which they affect individual patients are highly variable. Although the decision-making process of when to start treatment in symptomatic and asymptomatic LOPD patients identified through NBS can vary based on individual patients and circumstances and on discussions between clinicians and individual patients and/or families, general recommendations as to when to start ERT in patients based on the stage and severity of Pompe disease and findings from assessments are provided in the algorithm in Fig 2.

The general recommendations provided are intended to help with deciding if and when to start ERT in the subgroups of patients identified to have LOPD through a NBS program. Recommendations are based on the current collective experience and expertise of the Pompe Disease Newborn Screening Working Group as well as on current published guidelines.[41] As more

TABLE 4 Symptomatic Late-Onset Pompe Disease (LOPD): Recommended Follow-up Schedule and Assessments for Patients

	Assessment Time Point and Frequency				
	Initial Newborn Referral	1 mo	Monthly (up to 4 mo of Age)	Every 3 mo (4–12 mo of Age)	Every 3–6 mo[a] (>12 mo of Age)
Initial enrollment					
Demographics	X	—	—	—	—
Diagnosis (GAA and variants)	X	—	—	—	—
General patient monitoring					
Medical Hx	X	X	X	X	X
Clinical follow-up	X	X	X	X	X
Physical examination	X	X	X	X	X
Ht/Wt/HC/BMI	X	X	X	X	X
CK/CK-MB/HCO_3	X	X	X	X	X
Urine Hex_4	X	X	X	X	X
Clinical assessments					
Chest radiograph	X	—	—	—	X
ECG	X	X	X[b]	X[b]	X
ECHO[c]	X	—	X[b]	X[b]	X
Audiology	X (BAER)	—	—	—	X
Developmental assessments[d]	X	—	—	—	X
Treatment evaluations					
ERT antibodies	—	—	X	X	X
Whole-body MRI/ultrasound	—	—	X[b]	X[b]	X[b]
Swallow study	—	—	X[b]	X[b]	X
Pulmonary evaluation	—	—	X[b]	X[b]	X
Motor status	—	—	—	—	X
Early intervention	—	—	—	X[b]	X
Cardiac evaluation[c]	—	—	X[b]	X[b]	X

LOPD includes non-classic IOPD as well as traditional LOPD. Initial assessments as for asymptomatic Pompe patients (see Table 5). BAER, brainstem auditory evoked response; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; HC, head circumference; Ht, height; Hx, history; —, not applicable.

[a] Varies with patient's genotype.

[b] As clinically indicated.

[c] For patients with IVS splice site variant in heterozygosity, an initial ECHO cardiogram and follow-up at 6 months of age are recommended. If normal, the frequency of ECHO evaluations can be reduced and eliminated after 6 months for patients with the IVS splice site variant in heterozygosity because the variant may be cardioprotective.

[d] Denver; Bailey; TIMP; CHOP INTEND; AIMS; Gross Motor Function Measure-88. Videotaping can be done and used to assess patients.

information regarding the course and effect of long-term treatment with ERT for patients with LOPD becomes available, these recommendations will be revised.

ADDITIONAL TREATMENT CONSIDERATIONS AND RATIONALE FOR SPECIFIC FOLLOW-UP RECOMMENDATIONS

Pompe disease is a multisystem disease and progression can occur even while patients are on ERT. Therefore, physicians need to consider treatments and interventions as needed for other symptoms and disease manifestations and any potential factors that can be associated with these. They also need to understand the rationale for general assessment recommendations for all patients identified through NBS so that they can appropriately treat and manage patients already on ERT as well as patients who are not on ERT and start or not start treatment in patients based on good clinical judgment. Although general recommendations can be made, follow-up also depends on the patient's specific genotype and known associations for milder or more severe forms of disease. Alternative schedules for follow-up can be developed based in part on the risk category stratification of individual patients based on their genotype.

Cardiac

Because there is extensive cardiac involvement in patients with classic IOPD and variable involvement reported in some patients with LOPD, a cardiologist should assess if there is a need for cardiac medications, which is typically the case in patients with classic IOPD, where even in the first week of life, there may be cardiac manifestations that require additional medical intervention. However, there have been anecdotal unreported cases of sudden death in a few patients with Pompe disease that could be related to sudden arrhythmias. Therefore, caution must be used when considering prescribing drugs for patients that can reduce blood pressure, such as β-blockers, as well procedures requiring anesthesia that also may lower blood pressure in patients.[3] Cardiac outcomes in the emerging phenotype of IOPD patients whose survival has increased due to ERT should be considered. Although heart muscle thickness may improve

TABLE 5 Asymptomatic LOPD: Recommended Follow-up Schedule of Assessments

	Assessment Time Point and Frequency							
	Initial Newborn Referral	1 mo of Age	3 mo of Age	6 mo of Age	9 mo[a] of Age	12 mo of Age	Every 3–12 mo[b] (1–3 y of Age)	Annually[c] (After 3 y of Age)
Initial enrollment								
Demographics	X	—	—	—	—	—	—	—
Diagnosis (GAA and variants)	X	—	—	—	—	—	—	—
General patient monitoring								
Medical Hx	X	X	X	X	X	X	X	X
Feeding/swallowing	X	X	X	X	X	X	X	X
Clinical follow-up	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Ht/Wt/HC/BMI	X	X	X	X	X	X	X	X
CK	X	X	X	X	X	X	X	X
Urine Hex_4	X	X[d]	X	X	X[d]	X	X	X
Clinical assessments								
Chest radiograph	X	—	—	—	—	—	—	—
ECG	X	X[a]	X[a]	X[a]	—	X	X[a]	X
ECHO	X	—	X[a]	X[a]	—	X	X[a]	X
Audiology	X (BAER)	—	—	—	—	X	X	X
Developmental assessments[e]	X	X	X	X	X	X	X	X

Any change in status may indicate a need for additional evaluation or treatment. BAER, brainstem auditory evoked response; ECG, electrocardiogram; HC, head circumference; Ht, height; Hx, history; —, not applicable.

[a] Varies with patient's genotype.

[b] As clinically indicated.

[c] For milder genotypes.

[d] If CK levels are elevated at these assessment time points.

[e] Denver; TIMP; CHOP INTEND.

with ERT, we do not know about the development of heart rhythm abnormalities. Arrhythmias have been reported to have developed while patients were on ERT. Physicians need to be mindful of these possibilities while treating patients.[76]

Because cardiac involvement in the form of hypertrophic cardiomyopathy is present in all patients with classic IOPD, cardiac evaluations and follow-up should be overseen by a pediatric cardiologist, ideally one experienced in caring for Pompe patients. In some cases of classic IOPD, 24-hour cardiac monitoring is necessary.[3,29] Cardiac outcome in long-term infantile survivors also needs to be considered. Although these patients have reduced or normalized heart muscle thickness with the initiation of ERT, we do not fully understand the long-term implications on cardiac outcomes, particularly with regard to heart rhythm abnormalities. Therefore, patients should be regularly monitored at follow-up visits.[3,32] Brain natriuretic peptide, a marker of cardiac involvement, can also be considered for ongoing patient monitoring.[77]

The IVS splice site variant (c.-32-13T>G) is a common variant found in patients with LOPD. If 1 variant found in patients with LOPD is the IVS splice variant, then there is less of a chance of cardiac involvement. Patients with this variant in heterozygosity generally do not have hypertrophic cardiomyopathy, but may have rhythm disturbances and some cardiac hypertrophy. Therefore, in patients with IVS in heterozygosity, an initial echocardiogram (ECHO) and follow-up at 6 months of age are recommended. If results are normal, the frequency of ECHO evaluations can be reduced and eliminated after 6 months for patients, unless clinically indicated.

Respiratory/Pulmonary

Early treatment with ERT generally improves respiratory performance in patients and reduces the need for ventilatory support.[7,8] Patients who are CRIM-positive and have low antibody titers seem to do better over time with ERT and typically have not required long-term respiratory support. Long-term data on the cases diagnosed clinically and by NBS are still unfolding. CRIM-negative patients who have not been immune modulated to ERT are more likely to require invasive ventilation and die despite being treated with ERT. Overall, patients diagnosed through NBS and treated before the onset of symptoms should be less likely

to require long-term pulmonary support. However, clinicians still need to implement aggressive strategies for management of pulmonary infections and proper pulmonary hygiene.

Pulmonary evaluations should be done routinely and as clinically indicated. Although pulmonary function testing, such as spirometry, is important for assessing and monitoring respiratory function, such testing is difficult and cannot be done in infants.[3,30,31,33] Evaluations should focus on assessing the patient's respiratory status and physical signs of respiratory insufficiency. Measuring and monitoring serum bicarbonate (HCO_3) are recommended because these levels give an idea of pulmonary status, with persistent elevated levels indicating carbon dioxide retention.[3,30,31,33]

Gastroenterology

Feeding difficulties and swallowing dysfunction are often among the first presenting symptoms and can lead to failure to thrive in patients with classic IOPD. Therefore, patients should be assessed for the need for feeding tubes. Parents should be questioned about the infant sweating and showing signs of fatigue during feedings, which can be suggestive of cardiac compromise.[37]

In asymptomatic patients, feeding and swallowing difficulties often are present and may go undetected or overlooked as presenting symptoms of disease.[36,38] An abnormal swallow reflex can be an early marker of involvement for LOPD. Swallowing dysfunction on videofluoroscopic swallow study may be one of the earliest signs of disease progression and should be evaluated routinely. Appropriate intake of calories is important, and input from a dietician with experience in nutritional counseling of patients with Pompe disease is therefore also recommended for all patients.

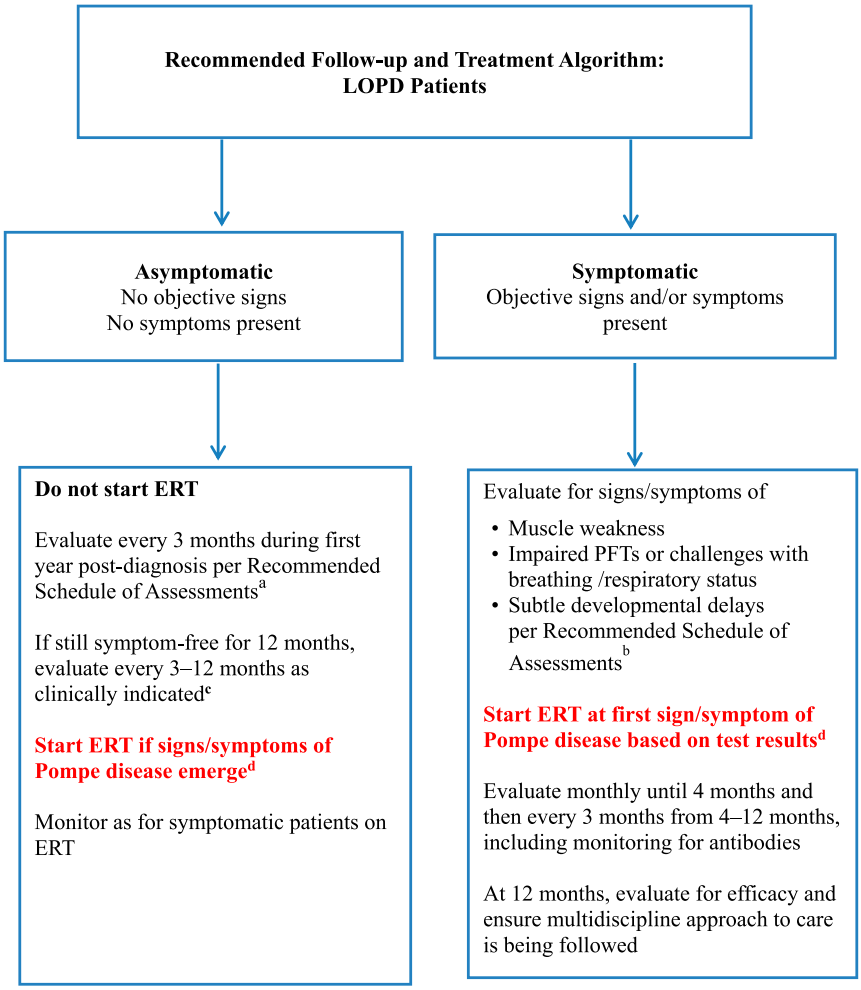

FIGURE 2
Recommended follow-up and treatment algorithm for patients with LOPD based on the presence or absence of symptoms. PFT, pulmonary function test. [a] See Table 5. [b] See Table 4. [c] If no concerns emerge and the patient remains clinically stable during the first 12 months, then evaluations can be spaced out accordingly, but are not to exceed 12-month intervals. If the results of evaluations raise questions or concerns, then closer follow-up will be needed. Parents of patients are asked to return if they have any concerns or questions of their own. [d] Based on decisions made after discussions between clinicians and individual patients and/or families.

Audiology

Hearing loss or impairment is common. It can be present shortly after birth in some patients and can contribute to developmental delays if not identified and managed proactively. Consultations with otolaryngology specialists are recommended. Patients should be tested for the type, amount, and origin of hearing loss, and auditory function should be monitored regularly.[78] Hearing loss or impairment also can be a subtle early manifestation of LOPD in asymptomatic patients.

Neuromuscular/Motor/Developmental

Motor function testing should be done as clinically indicated and available. In the first year of life, regular follow-up is recommended.

In asymptomatic patients, if nothing is found during the first year, then the risk is low, and a wait-and-see approach can be taken. Whole-body MRI or ultrasound of muscles may be informative in patients with Pompe disease, particularly in patients with LOPD. Quantitative whole-body MRI can be used to assess muscle involvement in patients with LOPD and may be more sensitive than physical examination for detecting abnormalities in various muscle groups frequently affected in Pompe disease.[79] Muscle involvement as detected on MRI may, in some cases, also indicate potential benefit of ERT initiation. However, sedation may pose a risk for patients and therefore may limit the frequency or feasibility of recommended MRI evaluations. Thorough physical therapist assessments that test for developmental delays or achievement of milestones should be done before the age of 12 months. If no delays are detected, then assessments every 6 months are recommended after 12 months of age. During all follow-up evaluations, it is important to look for signs as well as symptoms, thus underscoring the importance of close evaluations by physical therapists experienced with Pompe disease who will be more apt to notice subtle findings that are indicative of disease in LOPD patients.

Motor function testing is also particularly important to assess in apparently asymptomatic patients. A panel of tests that can be used to assess motor function and its progression in Pompe patients is available (Table 5). The Pompe Pediatric Evaluation of Disability Index is good for weak patients, but may not be appropriate for more mildly affected patients.[80] The Denver Developmental Screening test and Alberta Infant Motor Scale (AIMS) are helpful in assessing motor milestones. Abnormalities in these tests can pick up more subtle signs of a potential impact of disease progression on motor development. Both the Test of Infant Motor Performance (TIMP) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) are also useful tools for evaluating and predicting motor performance in infants at high risk for poor motor performance.[81–84]

Cognitive Measures

Assessing cognitive measures is also recommended. A full battery of developmental assessments should be done as indicated.

Immunology

Patients who have low antibody titers and have initiated treatment with ERT early are likely to do better over time with ERT. Patients who need to undergo ITI to prevent or suppress the antibody response to ERT with alglucosidase alfa (rhGAA) tend to respond more poorly and ultimately require invasive ventilation or die prematurely if not treated with ITI.[54] For patients with classic IOPD who are CRIM-positive, close monitoring of antibody titers should be performed monthly or as is considered appropriate by the treating physicians. CRIM-negative patients tend to develop HSATs, so appropriate monitoring for antibodies is essential. An ITI protocol, as discussed in the "Recommendations for Immune Modulation" section, should be used if needed, and the appropriate monitoring for antibodies continued (Table 3). Once ITI is completed, continued monitoring for antibodies is necessary and further ITI should be started as/if needed, or if patients do not respond adequately to the first course of ITI. Early detection of high antibody titers followed by successful ITI can improve ERT treatment outcomes.

Laboratory and General Assessments

For patients who present clinically during the first year of life but do not have cardiac involvement, creatine kinase (CK) levels should be monitored because elevated CK levels indicate an increased risk for disease progression in young patients. CK may not be elevated at the baseline assessment but may be elevated at a later time. The total Hex_4 fraction of glucose tetrasaccharide in urine is a helpful biomarker of glycogen accumulation and resulting tissue damage and disease severity in patients with Pompe disease.[39] In a follow-up study of patients from the Taiwan NBS program, there was a good correlation between the levels of Hex_4 excreted in urine and clinical manifestations in patients with LOPD. Although the elevations were subtle in some cases, in a number of the LOPD cases, the levels of Hex_4 were either elevated or at the upper limit of normal, prompting consideration of initiating ERT.[35] Therefore, it is recommended that Hex_4 be assessed routinely at all scheduled evaluations if available and feasible.

In asymptomatic patients, increases in CK, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urine Hex_4 may be early signs of disease progression even before symptoms manifest. Therefore, CK blood levels should be monitored routinely. In patients with true late-onset disease, CK levels oftentimes are normal at birth when they are first screened or at baseline when a diagnosis is confirmed and then are elevated at later time points, so regular monitoring of CK levels is warranted. However, CK levels need

to be interpreted carefully within the appropriate clinical context because levels can be affected by a number of factors (eg, race).[3,85] CK levels should be assessed when the patient reports muscle pain or discomfort or muscle weakness is noted to help assess for disease progression. Elevated levels of Hex_4 can be a useful means of assessing glycogen accumulation and, therefore, disease progression severity in patients with Pompe disease.[35,39] Close monitoring of Hex_4 over time, especially during the first year of life, is warranted and recommended in patients with LOPD who may present with clinical manifestations during the first year of life. Although an increase in Hex_4 at any 1 time point should not be considered significant enough to result in a change in care for a patient, it does warrant closer follow-up and monitoring.

Optional additional laboratory evaluations include liver function tests and measurements of lactate dehydrogenase levels. Liver function test elevations (AST and ALT) often are remarkable in Pompe disease compared with those seen in other neuromuscular diseases. The muscle pathology associated with Pompe disease can lead to the release of muscle enzymes, including the transaminases AST and ALT. Clinicians need to be mindful that elevated AST and ALT levels in patients with Pompe disease should not be misinterpreted as being secondary to liver disease, but rather as indicative of the underlying muscle involvement.[3] BMI also should be assessed regularly because some children do not gain lean body mass at appropriate rates.

For patients on ITI, laboratory assessments need to be done to monitor the safety of the ITI regimen. These assessments can include ALT, AST, complete blood count, and others based on the medications used in the regimen.

Intravenous Access and Central Line Placement

In all patients receiving ERT, it is essential that stable intravenous access be maintained throughout the infusions, which can last 5 to 6 hours for some patients. In patients with IOPD especially, obtaining peripheral intravenous access can be difficult and cause unnecessary discomfort for the patient. As a result, most newly diagnosed patients with IOPD should be considered for central line placement. An implantable port can and should be considered if the patient is stable and at no anesthesia risk. The patient's family should be instructed carefully on its management. Only experienced personnel should access these lines because there is an increased risk of infection in patients with indwelling catheters.

IARs

Physicians caring for patients with Pompe disease also need to consider the possibility of having to manage adverse reactions, such as IARs, in addition to immune responses during ERT. They should consult the prescribing information for alglucosidase alfa and published reports for additional information about the risks and management of these types of reactions.[2,42,67,86,87]

Dosing Flexibility

As is the case with some other lysosomal storage disorders (eg, Gaucher disease), the Pompe Disease Newborn Screening Working Group strongly recommends that there be some leeway in the guidelines for the dosing of alglucosidase alfa in patients with Pompe disease to reflect the current paradigm of care and frequent use in clinical settings of off-label dosing strategies that are sometimes necessary. The dosing instructions in the prescribing information for alglucosidase alfa (Myozyme and Lumizyme)[1,2] are specific (20 mg/kg every 2 weeks) and do not specifically recommend the dosing flexibility that is sometimes prescribed in clinical practice based on expertise, experience, and the individual response of each patient. Dose adjustments may be needed due to an inadequate response to the recommended dosage.[88] Clinicians treating patients need flexibility and should be allowed to have choices as needed. There is growing evidence that some patients may benefit from higher or more frequent dosages (eg, higher doses have been shown to improve the outcomes in muscle tissues and in cases of ptosis), which is particularly relevant for patients who experience continued clinical decline despite ERT or who initially responded well to ERT but who begin to decline and start to show progressive weakness and diminished health while on their current ERT regimen.[88,89] A new phenotype among patients with classic IOPD resulting from increased long-term survival has emerged because of ERT, and raises the question of whether the current approved dosage of alglucosidase alfa may need to be adjusted because it eventually may no longer be sufficient. Clinicians also need to assess whether early treatment with ERT in patients diagnosed through NBS will change the phenotype with fewer residual deficits. Alternative ERT regimens and new treatment approaches may need to be considered for some patients to

maintain continued clinical benefit of treatment.[46,88–90]

Cost of Treatment

The cost of any treatment is affected by the number of patients who are prescribed the treatment and varies based on individual situations. Orphan drugs to treat rare diseases are used by far fewer patients than what are considered as typical pharmaceutical drugs that may be used by hundreds of thousands or even millions of patients. Only a few thousand people worldwide receive ERT with alglucosidase alfa. The manufacturing of ERTs through recombinant DNA technology is a highly complex, resource-intensive, and time-consuming endeavor.

The cost of treatment, although a necessary consideration for the health care teams involved in the care of patients with Pompe disease, is not within the scope of this work; however, it has been the collective experience of the Pompe Disease Newborn Screening Working Group that the cost of ERT does not influence the decision to start treatment or restrict patients' access to ERT and that patients with Pompe disease who require ERT have not been denied treatment because of cost.

SUMMARY

The need for the initiation of early treatment underscores the importance of NBS for Pompe disease given the poor treatment responses for patients with classic IOPD treated after a late clinical diagnosis. For patients with LOPD, it remains to be seen how this cohort of patients will benefit from early diagnosis. Clearly, the diagnostic odyssey frequently experienced by this group of patients will be avoided. Based on avoiding a delay in diagnosis alone, an improved prognosis should be expected. Asymptomatic infants identified through NBS can be monitored closely and ERT started immediately or at the first sign or symptom indicative of clinical progression of the disease. Determining the most appropriate frequency and methodology for clinical monitoring and follow-up and how to use such data to determine when to start therapy poses significant challenges for the effective implementation of NBS in the LOPD population. Ongoing assessments can help to ensure that ERT, if indicated, begins in a timely and proactive fashion.

Because Pompe disease is on the Recommended Uniform Screening Panel (RUSP), treatment has been agreed by consensus to be beneficial in NBS settings. Pompe disease, especially classic IOPD, is a progressive disorder with considerable heterogeneity. Outcomes of treatment, therefore, cannot be guaranteed, so it is important to monitor patient response to treatment on an ongoing basis and to review treatment plans based on these findings. Decisions regarding treatment and options are made based on thoughtful, informative discussions that occur between physicians and families of these affected infants.

The full benefits of NBS for Pompe disease will only be realized by consistent follow-up and appropriate stratification of patients. The guidelines provided in this article for follow-up of patients across the entire clinical spectrum of Pompe disease are meant as a starting point. Additional modifications will be based on the reassessment of outcomes data as they become available and published. Our goal for NBS initiatives for Pompe disease worldwide is to help to ensure timely therapeutic intervention to reduce the morbidity and mortality associated with this progressive, disabling disease. The long-term follow-up and careful reporting of Pompe disease identified through NBS will be a vital documentation of the NBS program and will provide us with valuable information and increased knowledge as the natural history of the disease changes.

We hope the recommendations provided in this article will facilitate consistent and thorough clinical evaluations and approach to care for patients and allow for the collection of data elements necessary to additionally optimize patient outcomes. Regional and disease registry programs are valuable sources of important clinical information. The Pompe Registry, an observational program (sponsored by Sanofi Genzyme), is the largest repository of clinical data for patients with Pompe disease. Participating physicians who enroll patients can access and share de-identified patient data. Participation in the Pompe Registry and adding clinical data for patients are strongly encouraged and recommended for all physicians involved in the care of patients with Pompe disease (www.registrynxt.com/). The Newborn Screening Translational Research Network (NBSTRN) is an important resource for accessing and sharing data for clinicians involved in NBS. The mission of the NBSTRN is to "improve the health outcomes of newborns with genetic or congenital disorders by means of an infrastructure that allows investigators access to robust resources for newborn screening research." Information about the NBSTRN can be found at www.nbstrn.org. The National Institutes of Health support initiatives that encourage investigators and clinicians to use common data elements when compiling

and reporting data from clinical research and for patient registries. The intent is to improve the overall quality of data and allow and facilitate comparison and combination of data from different sources. Information about National Institutes of Health–supported common data elements and available tools and resources to assist investigators with improved data collection can be found at www.nlm.nih.gov/cde/.

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ABBREVIATIONS

AIMS: Alberta Infant Motor Scale
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK: creatine kinase
CRIM: cross-reactive immunologic material
ECHO: echocardiogram
ERT: enzyme replacement therapy
GAA: acid α-glucosidase
HCO_3: serum bicarbonate
Hex_4: hexose tetrasaccharide
HSAT: high and sustained antibody titer
IAR: infusion-associated reaction
IgG: immunoglobulin G
IOPD: infantile-onset Pompe disease
ITI: immune tolerance induction
LOPD: late-onset Pompe disease
NBS: newborn screening
NBSTRN: Newborn Screening Translational Research Network
rhGAA: recombinant human acid α-glucosidase
TIMP: Test of Infant Motor Performance

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Management of Confirmed Newborn-Screened Patients With Pompe Disease Across the Disease Spectrum

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