The Recommended Schedule of Assessments represents the core Pompe disease-related assessments that assist in the evaluation of a patient's disease progression over time. Physicians will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up.

### Patient Information
- Demographics
- Diagnosis (Enzyme Assay, DNA analysis)
- Medical History

### General Patient Monitoring\(^a\)
- Clinical Follow-up
- Pregnancy Status (females of childbearing potential only)

### Physical Examination\(^b\)
- Height/Length, Weight, Head Circumference\(^a\)
- Blood Pressure, Heart Rate

### Laboratory Tests\(^c\)
- Hematology/Biochemistry
- Urinalysis

### Clinical Assessments
- Chest X-Ray
- Spine X-Ray
- DXA scans\(^d\)
- Electrocardiogram
- Echocardiogram
- Auditory Examination
- Pulmonary Function Test

### Cognitive and Developmental Assessments (as age appropriate)
- Denver Developmental Screening Test II\(^f\)
- Bayley Scales of Infant and Toddler Development II\(^f\)
- Modified Leiter International Performance Scale – Revised\(^g\)

### Neuroimaging
- MRI, or CT Scan

### Motor Assessments (as age appropriate)
- Gross Motor Function Measure – 88 Item
- Pompe Pediatric Disability Index
- Motor Milestones Checklist
- Motor Functional Activities\(^h\)
- Walton & Gardner-Medwin Scale\(^i\)
- Arm and Leg Functional Tests\(^k\)
- Hand-Held Dynamometry\(^j\)
- Six-Minute Walk Test\(^l\)
- Manual Muscle Testing (Medical Research Council Scale)\(^g\)

### Quality-of-Life Outcomes
- Medical Outcomes Study 36-Item Short Form, Version 2\(^j\)
- Fatigue Severity Scale
- Rotterdam Handicap Scale – 9 Item

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\(^a\) General monitoring assessments include: development/neurology; ophthalmology; auditory, respiratory, cardiovascular, gastrointestinal/hepatic, renal, and musculoskeletal/motor systems, as appropriate and as well as smoking status. For patients less than 2 years of age, height/length, weight, and head circumference should be measured every 3 months. For patients 2 years of age or older, height/length and weight only should be measured every 6 months. Recumbent length should be measured in patients less than 3 years of age; standing height should be measured in patients 3 years of age or older.

\(^b\) Hematology/biochemistry and urinalysis include the following: ALT, AST, serum albumin, total bilirubin, BUN, CK, CK-MB, serum creatinine, Factor VII, LDH, PT, PTT, urine creatinine, urine protein, HEX4.

\(^c\) A DXA scan should be performed every 24 months in patients with a negative initial assessment, and every 12 months in patients who had any sign of osteopenia at the initial assessment.

\(^d\) If the patient's DDST-II scores are not within normal range upon enrollment, the DDST-II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. At the final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^e\) If the patient's DDST-II scores are not within normal range upon enrollment, the DDST-II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. At the final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^f\) Bayley II should be conducted in patients less than 42 months of age, if the DDST-II suggests developmental delay at the time of enrollment. The Bayley II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. The final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^g\) For patients 42 months of age or older at the time of Registry enrollment whose DDST-II scores suggest developmental delay, the Leiter-R should be administered, and should be re-administered yearly until the patient reaches 20 years of age, which is the maximum age for the test. The subsequent administration of the Bayley III, prior to a patient turning 20 years of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^h\) If a patient's DDST-II scores are not within normal range upon enrollment, the DDST-II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. Bayley II should be administered every 6 months until the patient reaches 6 years of age, if the DDST-II suggests developmental delay at the time of enrollment. The Bayley II should be administered every 6 months until the patient reaches 6 years of age, if the DDST-II suggests developmental delay at the time of enrollment. The Bayley II should be administered every 6 months until the patient reaches 6 years of age, if the DDST-II suggests developmental delay at the time of enrollment.

\(^i\) Bayley II should be conducted in patients less than 42 months of age, if the DDST-II suggests developmental delay at the time of enrollment. The Bayley II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. Bayley II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. The final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^j\) A DXA scan should be performed every 24 months in patients with a negative initial assessment, and every 12 months in patients who had any sign of osteopenia at the initial assessment.

\(^k\) If a patient's DDST-II scores are not within normal range upon enrollment, the DDST-II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. The final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

\(^l\) If a patient's DDST-II scores are not within normal range upon enrollment, the DDST-II should be administered every 6 months until the patient reaches 42 months of age, which is the maximum age for the test. The final administration of the Bayley III, prior to a patient turning 42 months of age, the Leiter-R should be administered at the same visit to establish the correlation between the scores of the 2 tests.

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SANOFI-GENZYME
Pompe disease: Assessments to Consider

The following is a detailed listing of available testing procedures for the monitoring of Pompe disease progression. Derived from a composite of recommendations for both IOPD and LOPD, these assessments are presented as examples of evaluations you may consider based on your clinical judgment.

General Patient Monitoring

Clinical follow-up
Pregnancy (applies to females of childbearing age)

Physical Exam
Height/Weight/Head circumference/PP
• Failure to thrive and other growth delays can be seen in patients with Pompe disease due to gastrointestinal problems like dysphagia, gastrointestinal reflex, and feeding/chewing and swallowing difficulties

Laboratory Tests
Blood tests
• A battery of blood tests for baseline including CK, ALT, AST, and LDH

Urine test
• HEX4 (glucose tetracarboxylic)-Elevated urinary HEX4 has been identified in patients with Pompe disease with an almost 100% sensitivity in identifying infantile-onset Pompe disease. It is recommended as an ancillary diagnostic test. It also has been shown to correlate with response to ERT.

Reference ranges for urinary HEX4:

<table>
<thead>
<tr>
<th>Age range</th>
<th>HEX4 reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6 months</td>
<td>&lt; 20 mmol/mmol creatinine</td>
</tr>
<tr>
<td>&gt;6 months to 1 year</td>
<td>&lt; 14.0 mmol/mmol creatinine</td>
</tr>
<tr>
<td>&gt;1 year to 3 years</td>
<td>&lt; 8.3 mmol/mmol creatinine</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>&lt; 3.0 mmol/mmol creatinine</td>
</tr>
</tbody>
</table>

Clinical Assessments

Chest x-ray
• The chest x-ray is to assess left ventricular hypertrophy (LVH) due to cardiac involvement and/or diaphragm elevation related to diaphragm muscle involvement
• Normal CXR will not show any abnormalities

Spine x-ray
• Evaluate thinning bones and pathologic fractures
• Evaluate for kyphoscoliosis, one of the most severe secondary effects of muscular insufficiency
• Normal spine x-ray will not show any significant abnormalities
• Spine x-ray is simple and inexpensive, may require further diagnostic imaging tests if abnormal

DXA scans
• Bone abnormalities such as osteopenia and osteoporosis can be seen with patients with Pompe disease

Electrocardiogram (ECG)
• Cardiac issues occurring in Pompe disease include cardiomyopathy, heart failure, and arrhythmia
• ECG may reveal a shortened P-R interval, and, in some cases, Wolf-Parkinson-White syndrome
• A normal ECG will have no arrhythmic abnormalities
• Dynamic ECG (cardiac Holter) to monitor any arrhythmic episodes

Echocardiogram (ECHO)
• Cardiac issues occurring in Pompe disease include cardiomyopathy, heart failure, and arrhythmia
• Cardiac ECHO to measuring left ventricular function and ejection fraction (EF) and left ventricular mass index (LVMI) to assess cardiomyopathy
• A normal ECHO will have a normal EF (normal 55%-75%)

Pulmonary function test
• In adults, as spirometry testing in standing or sitting and lying positions

• Forced expiratory volume, 1 sec (FEV1)
• Maximal inspiratory pressure (MIP)
• Maximal expiratory pressure (MEP)
• Normal ranges will vary on age, gender, and height
• Forced vital capacity (FVC)

Audiometry exam
• Hearing loss has been recognized in infantile-onset Pompe disease due to involvement of the cochlea (rare) or conductive apparatus (common) or both
• Newborn hearing exam and annual pediatric hearing exam should be performed
• Testing should include behavioral assessment when possible, otoacoustic emissions, tympanometry, and Auditory Evoked Potentials (ABR, or BAER) using air and bone conducted stimuli
• Pulse oximetry and capnography

Neuroimaging

MRI or CT scan
• Vascular anomalies have been reported in adult patients with Pompe disease

• Risk of aneurismal hemorrhages of basilar, internal carotid, and cerebralis media arteries, which can lead to severe neurologic deficits

• Designed for adults 19 to 79 years

Cognitive and Developmental Assessments

Infantile-onset Pompe disease (IOPD)
• Directly administered test; designed to screen expressive and receptive language, gross motor, fine motor, and personal social skills; results in risk category (normal, questionable, abnormal)
• Designed for ages 0 to 12 months

Bayley Scales of Infant and Toddler Development III
• Directly administered test; series of 6-item sets screening basic neurologic functions; receptive functions (visual, auditory, and tactile input); expressive functions (oral, fine, and gross motor skills); and cognitive processes; results in risk category (low, moderate, high risk)
• Designed for ages 0 to 12 months

Late-onset Pompe disease (LOPD)
• Directly administered test; designed to screen expressive and receptive language, gross motor, fine motor, and personal social skills; results in risk category (normal, questionable, abnormal)
• Designed for ages 1 to 6 years

Bayley Scales of Infant and Toddler Development III
• Directly administered test; series of 6-item sets screening basic neurologic functions, receptive functions (visual, auditory, and tactile input); expressive functions (oral, fine, and gross motor skills); and cognitive processes; results in risk category (low, moderate, high risk)
• Designed for ages 3 to 24 months

Motor Assessments

Motor Gross Function Measure – 88 item
• A standardized system with levels, representing the degrees of limitation of gross motor function

Pompe Pediatric Disability Inventory (POMPE PEDI)
• A valid instrument to assess and monitor the functional changes of children employing a dichotomous scoring system of mobility and self-care
• Designed for ages 6 months and over

Motor milestones checklist
• Motor developmental milestones are defined as average (50th percentile) motor function for an age group
• Includes areas of gross motor, fine motor, and self-help skills
• Designed for ages 1 month to 6 years

Motor functional activities
• Timing the performance of standard tests and repeating at regular intervals to assess current status, focuses mostly on the strength of the lower extremities, trunk, and pelvic muscles
• Designed for walking age and beyond as applied to muscular dystrophy

Arm and leg functional tests
• Timing the performance of standard tests and repeating at regular intervals to assess decline or stabilization

Walking and Gardner-Medwin scale
• Assessment of functional severity graded from stages 0 to 10 (0-normal)
• Reliable qualitative scale that is mainly used to describe motor function in everyday activities as applied to neuromuscular disorders

Handheld dynamometry
• A handheld dynamometer is a simple and reliable instrument, which produces quantitative and reproducible data for monitoring muscle strength in patients with Pompe disease

 Six-Minute Walk Test (6MWT)
• Provides a measure of the functional exercise level required to undertake daily physical activities
• Designed for ages 4 and up
• 6MWT in a healthy adult is reported to range from 400 m to 700 m
• 6MWT in healthy children ages 4 to 11 years is reported from 383 m to 512 m

Manual muscle testing
• The most common method of evaluating the strength of separate muscle groups is using manual muscle testing

• Evaluates the ability of a patient to move against gravity and resistance

• Uses a rating scale from 1 to 5 (5-normal)

Peabody Developmental Motor Scales–2nd Edition
• A standardized test to evaluate both fine and gross motor skills in children
• Consists of two subsets: grasping and visual-motor integration (age range: 1-20)
• A fine motor quotient is derived by adding the 2 subset scores and then converting them into a quotient

• Designed for ages 0 to 71 months

Quality of Life/Health Outcomes

Short Form 36 (SF-36) Health Survey
• A multipurpose questionnaire designed to evaluate the general health status of a person

• There are normative values and definitions for each subscale

• Designed for ages 14 years and above

Fatigue Severity Scale (FSS)
• A 9-item scale with a 7-point Likert rating to assess fatigue with a high inter reliability

Rotterdam 9-item Handicap Scale
• Specifically developed to assess the level of independent participation in daily life activities among patients with neuromuscular disorders

• Designed for adults 19 to 79 years

References: