Pompe Disease

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REVIEW
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Recommendations for Infantile-Onset and Late-Onset Pompe Disease: An Iranian Consensus

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- Local guidelines; required or not?

Is a local guideline for pompe required?

Special conditions in Iran:

Lab results are time wasting.

- Muscle biopsy is not easily accessible everywhere
- Antibody measurement not accessible
- CRIM status not accessible

Classification

- Infantile Onset Pompe Disease (IOPD)

  Classic/Non-classic
- Late Onset Pompe Disease (LOPD)

Classic IOPD

Severe Hypotonia

Rapidly progressive muscle weakness

Hypertrophic cardiomyopathy

Feeding difficulties

The symptoms are presented at roughly 3 months of age

Classic IOPD

- Death happens at the age of 6–9 months.
- 10% of patients live older than 18 months.

Non-classic IOPD

- less common
- Manifesting in the first year of life
- Muscle weakness without cardiomegaly
- Residual enzyme activity of below 20%.
- The onset of symptoms is much later (around half of these patients do not manifest until 4–11 months)
- Deteriorates more slowly than the classic IOPD patients.

When should we consider pompe disease?

Neurologic/Musculoskeletal

- ✓ Marked muscular hypotonia
- ✓ Delayed motor milestones
- ✓ Poor head control
- ✓ Facial weakness with open mouth posture and tongue protrusion
- ✓ Generalized muscle weakness mostly involving proximal and truncal muscles (rapidly progressive)
- ✓ weakness of distal muscles, calf hypertrophy
- ✓ diminished reflexes may be observed.

Respiratory

- Sleep apnea
- Cough, usually wet
- Respiratory distress
- Upper and lower respiratory infections
- And eventually respiratory failure

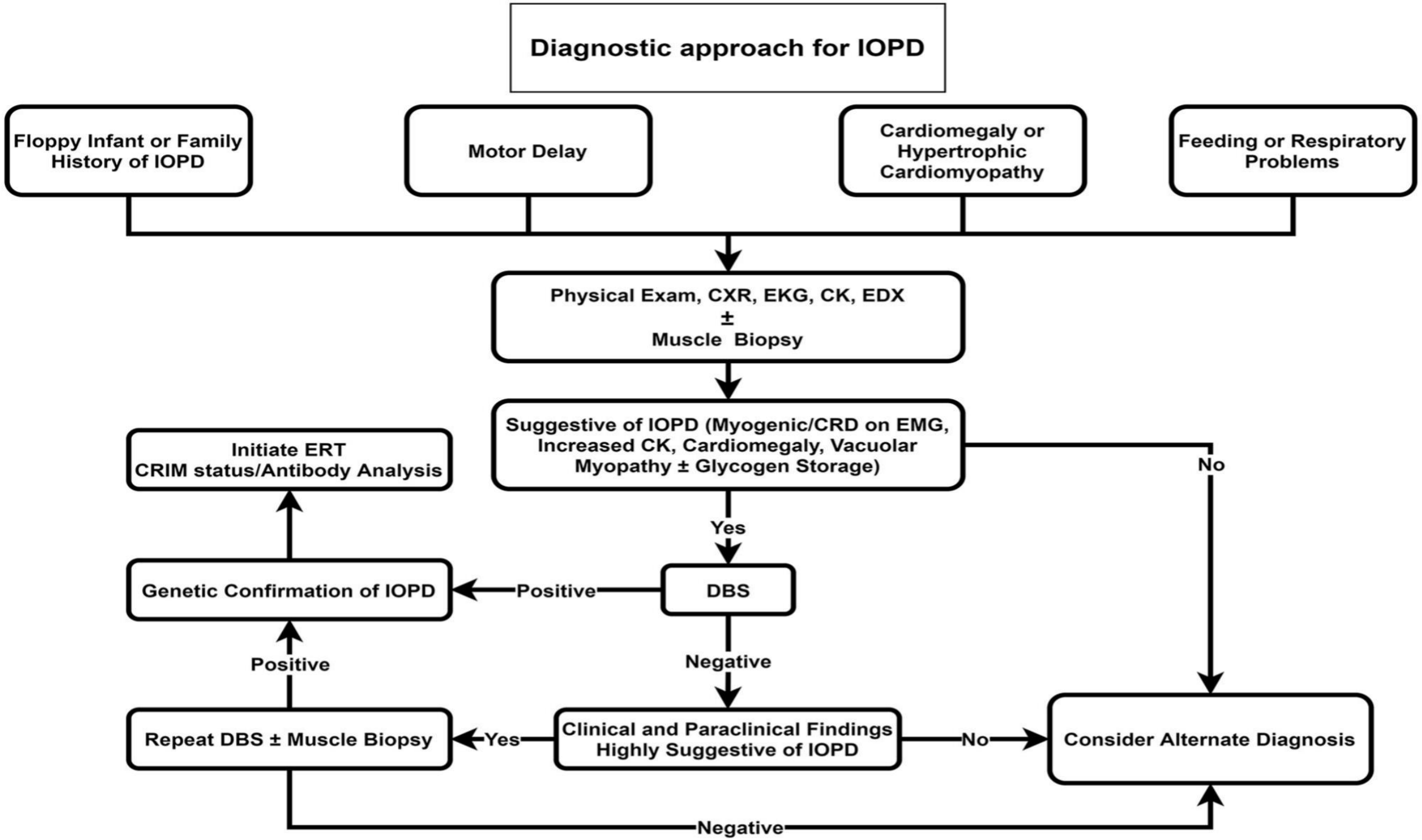
Cardiovascular

- ✓ Cardiomegaly
- ✓ Hypertrophic cardiomyopathy
- ✓ rhythm disturbances such as supraventricular tachycardia
- ✓ Congestive heart failure
- ✓ The systolic dysfunction in IOPD usually occurs after 5 months of age.

Gastrointestinal

- ✓ Hepatomegaly (CHF)
- ✓ Feeding and swallowing difficulties
- ✓ Macroglossia (tongue's muscle fibers infiltrating with glycogen)
- ✓ Poor sucking
- ✓ Failing to thrive

Diagnostic approach

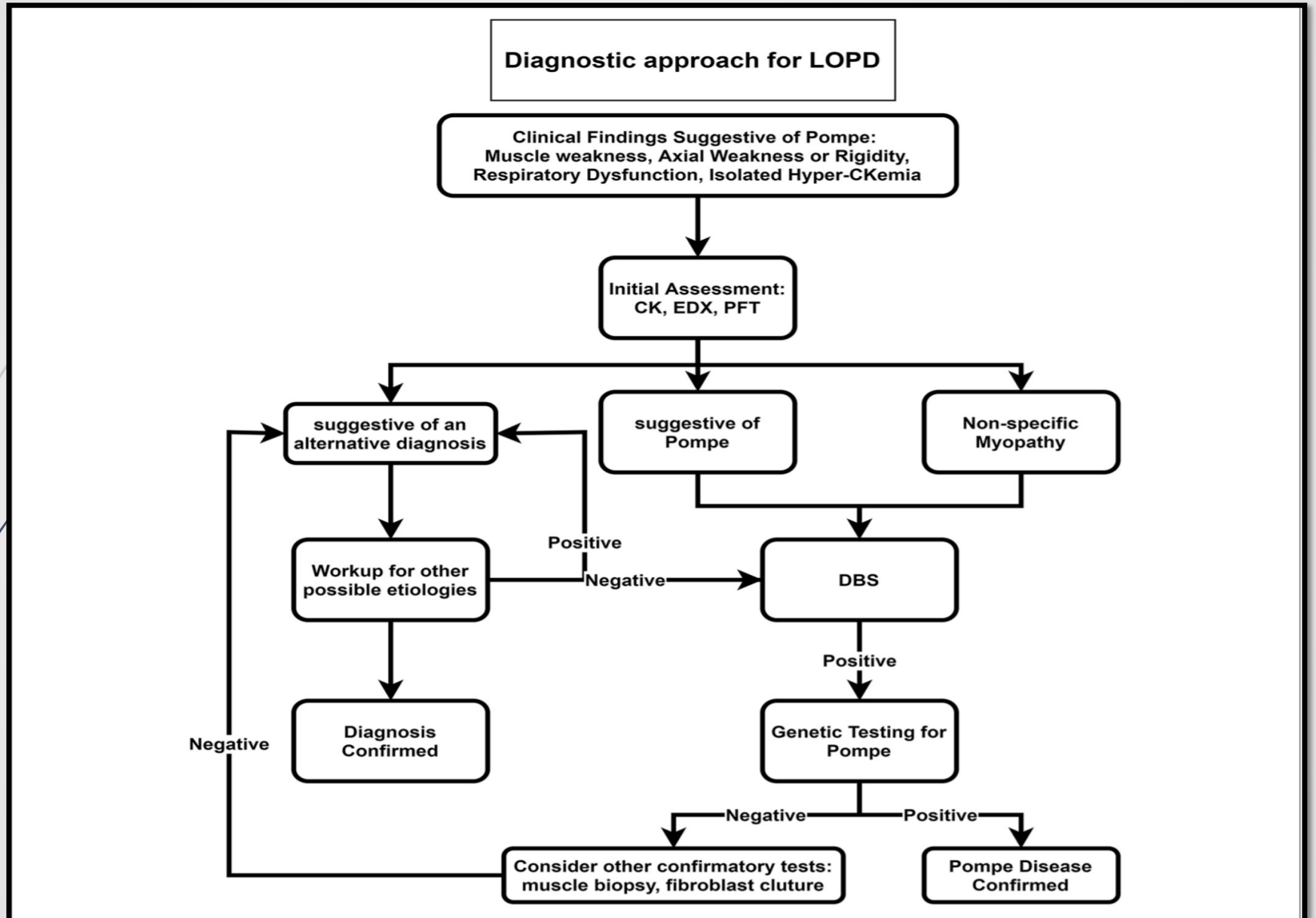

Diagnostic approach for IOPD
Floppy Infant or Family History of IOPD
Motor Delay
Cardiomegaly or Hypertrophic Cardiomyopathy
Feeding or Respiratory Problems
Physical Exam, CXR, EKG, CK, EDX
±
Muscle Biopsy
Suggestive of IOPD (Myogenic/CRD on EMG, Increased CK, Cardiomegaly, Vacuolar Myopathy ± Glycogen Storage)
No
Yes
DBS
Positive
Genetic Confirmation of IOPD
Initiate ERT
CRIM status/Antibody Analysis
Negative
Clinical and Paraclinical Findings Highly Suggestive of IOPD
No
Consider Alternate Diagnosis
Yes
Repeat DBS ± Muscle Biopsy
Positive
Negative

DIAGNOSTIC ALGORITHM

- DBS should be suggested as the initial investigation for:
- All floppy infants
- Infants with a positive family history of Pompe disease
- Cardiomegaly, hypertrophic cardiomyopathy,
- Feeding or respiratory problems

DIAGNOSTIC ALGORITHM

- Positive DBS: genetic testing for Pompe disease
- Negative DBS, but clinical and paraclinical findings highly suggestive of IOPD: repeating DBS or muscle biopsy if it was not performed before.


Diagnostic approach for LOPD
Clinical Findings Suggestive of Pompe:
Muscle weakness, Axial Weakness or Rigidity,
Respiratory Dysfunction, Isolated Hyper-CKemia
Initial Assessment:
CK, EDX, PFT
suggestive of an alternative diagnosis
suggestive of Pompe
Non-specific Myopathy
Workup for other possible etiologies
Positive
Negative
DBS
Positive
Diagnosis Confirmed
Negative
Genetic Testing for Pompe
Negative
Positive
Consider other confirmatory tests: muscle biopsy, fibroblast cluture
Pompe Disease Confirmed

DIAGNOSTIC ALGORITHM

late-onset patients:

DBS for all patients with

- muscle weakness, axial weakness, or rigidity, especially if accompanied by respiratory dysfunction

Or

- Isolated hyperCKemia

DIAGNOSTIC ALGORITHM

late-onset patients:

- After positive DBS, genetic testing is recommended
- If genetic testing is negative, confirmatory tests such as muscle biopsy or fibroblast culture are recommended.

Muscle MRI in Pompe disease

- Specially spine extensors and pelvic girdle involvement
- It could be used as a biomarker for the patients' follow-up.
- Whole-body MRI may be beneficial in measuring muscle involvement, at baseline, and recording disease progression

Muscle biopsy

Classic IOPD:

- Prominent vacuolar myopathy
- Periodic acid–Schiff stain shows prominent glycogen excess in almost all muscle fibers.
- Periodic acid–Schiff plus diastase stain reveals the digestion of all glycogen content .
- Acid phosphatase stain would show reactivity in cytoplasmic vacuoles and indicates their lysosomal origins.

Definite Diagnosis

Genetic Study

Autosomal recessive

DIFFERENTIAL DIAGNOSIS

Classic IOPD:

- Danon disease
- Fatty acid oxidation disorders
- Mitochondrial disorders. Mitochondrial complex 1 deficiency
- Spinal muscular atrophy type 1
- Congenital muscular dystrophies
- Congenital myopathies

DIFFERENTIAL DIAGNOSIS

LOPD:

- limb-girdle muscular dystrophies,
- Myotonic dystrophy type 2
- Facioscapulohumeral muscular dystrophy
- Duchenne and Becker muscular dystrophies
- congenital muscular dystrophies

DIFFERENTIAL DIAGNOSIS

LOPD:

- Myofibrillar myopathies
- Congenital myopathies
- Metabolic myopathies
- Mitochondrial myopathies
- Polymyositis with or without fibromyalgia
- Rigid spine syndrome
- spinal muscular atrophies II and III
- Myasthenia gravis, and congenital myasthenic syndromes

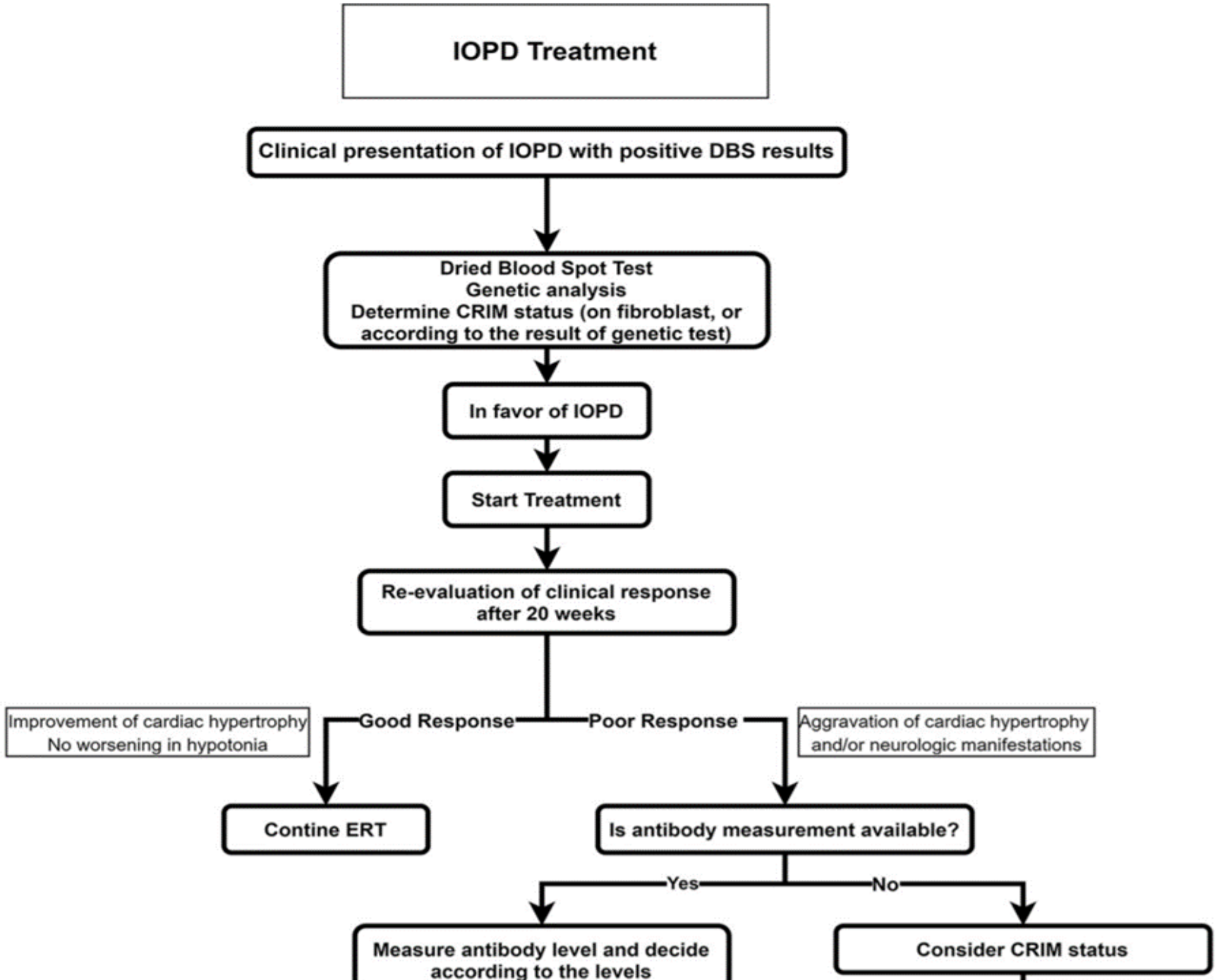
Treatment

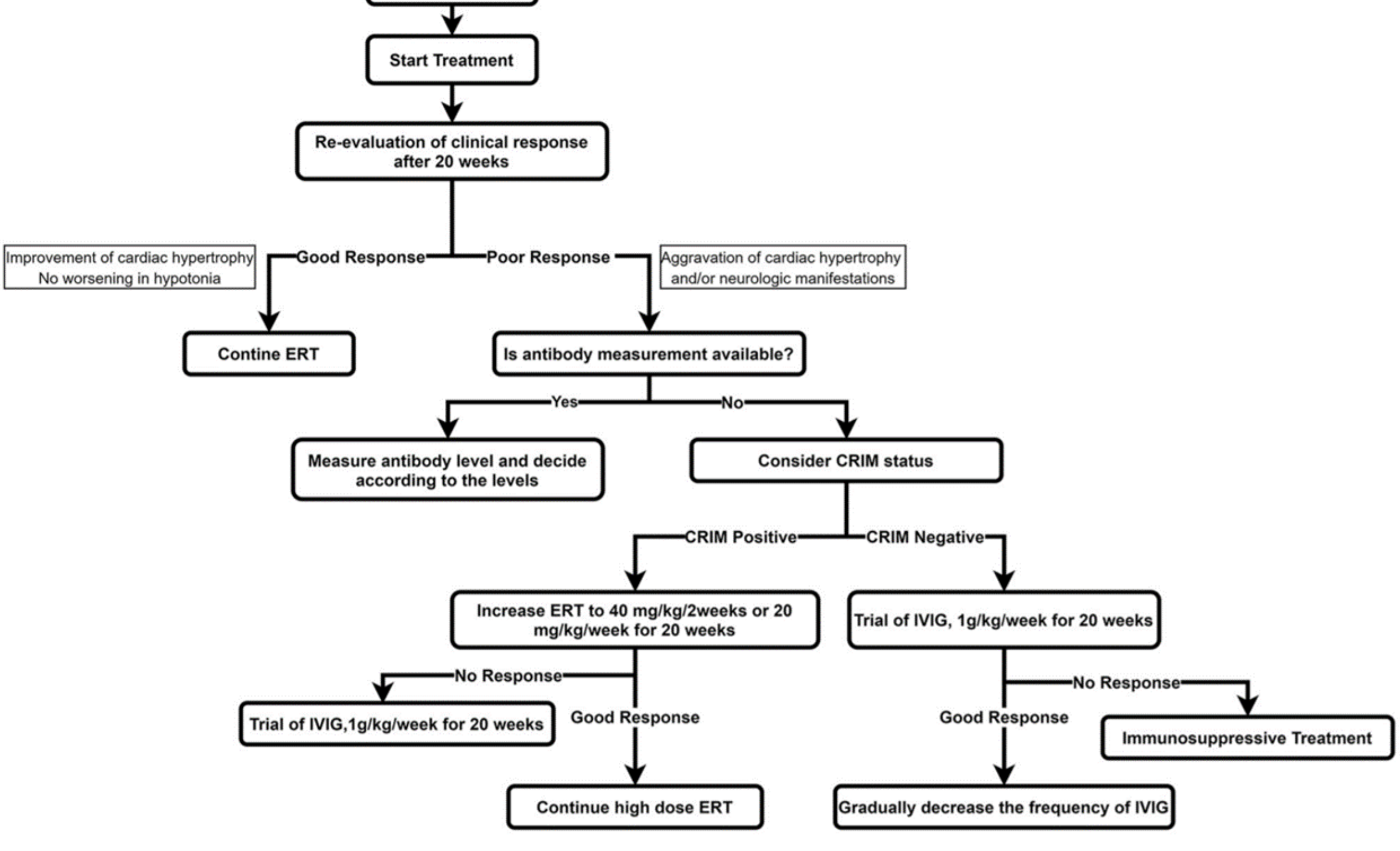
Infantile-Onset Pompe Disease

- Treatment with alglucosidase alfa (Myozyme) should be started immediately after positive DBS results or genetic confirmation.
- ERT may be started in patients with typical cardiorespiratory symptoms if the enzyme is deficient in DBS, even before seeing the genetic result .

Infantile-Onset Pompe Disease

- Usual recommended dose: 20 mg/kg alglucosidase alfa every other week
- a recent study showed that patients treated with higher doses and more frequent injections had a better outcome such as motor, respiratory, and biochemical markers


IOPD Treatment
Clinical presentation of IOPD with positive DBS results
Dried Blood Spot Test
Genetic analysis
Determine CRIM status (on fibroblast, or according to the result of genetic test)
In favor of IOPD
Start Treatment
Re-evaluation of clinical response after 20 weeks
Improvement of cardiac hypertrophy
No worsening in hypotonia
Good Response
Poor Response
Aggravation of cardiac hypertrophy and/or neurologic manifestations
Contine ERT
Is antibody measurement available?
Yes
No
Measure antibody level and decide according to the levels
Consider CRIM status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Measure antibody level and decide according to the levels
Consider CRIM status
CRIM Positive
CRIM Negative
Increase ERT to 40 mg/kg/2weeks or 20 mg/kg/week for 20 weeks
Trial of IVIG, 1g/kg/week for 20 weeks
No Response
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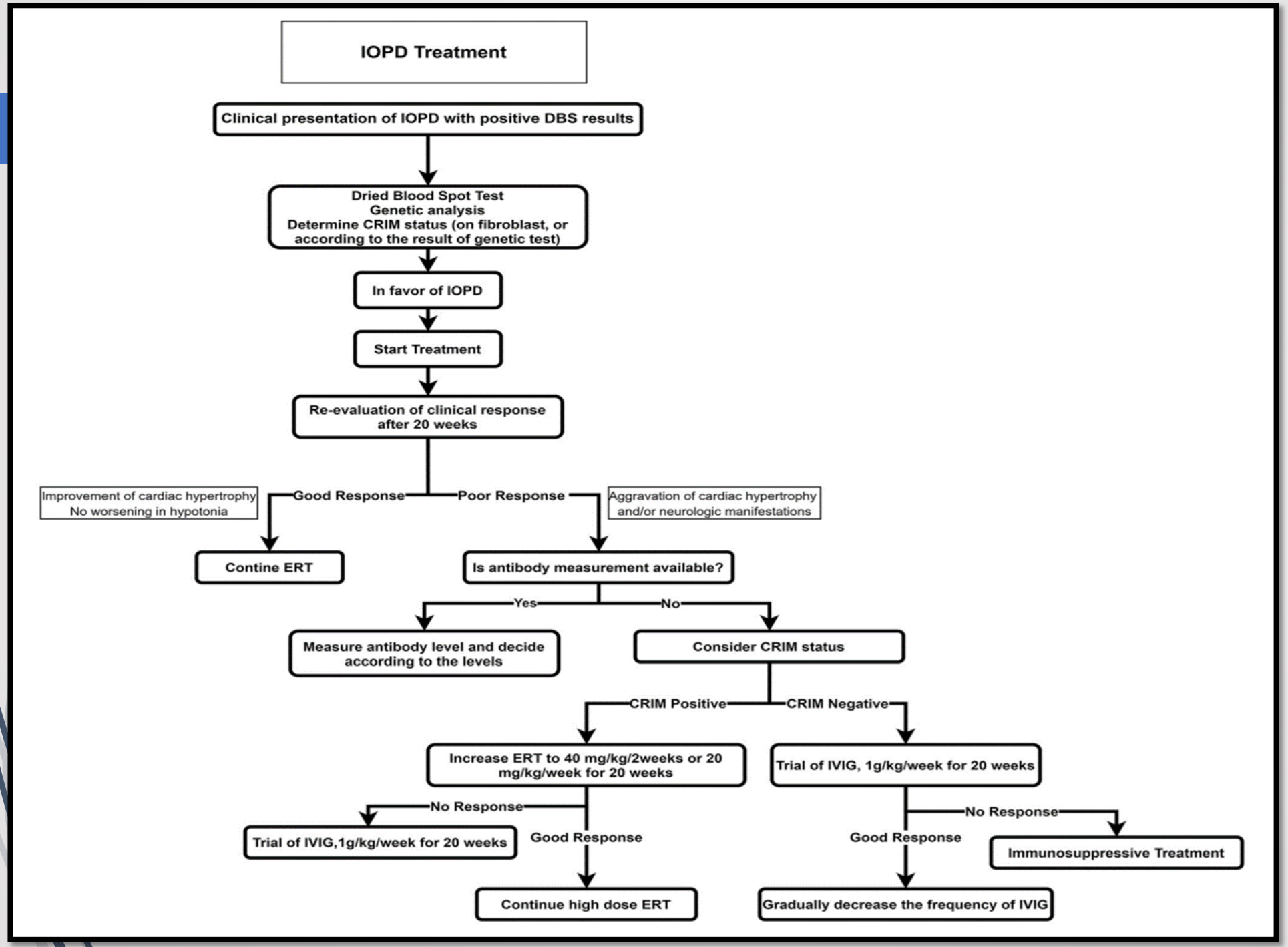
Good Response
No Response
Good Response
Immunosuppressive Treatment
Continue high dose ERT
Gradually decrease the frequency of IVIG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Cross-Reactive Immunologic Material (CRIM)

- The patients are divided into two groups according to CRIM status:
- Complete absence of GAA by Western blot method, they are classified as CRIM-negative, and
- Patients with detectable GAA protein are classified as CRIM positive .

Cross-Reactive Immunologic Material (CRIM)

- Most CRIM-negative patients on ERT have a worse prognosis because of emerging anti-rhGAA IgG antibodies.
- Some cases of CRIM-positive patients also build antirhGAA IgG antibodies such as CRIM-negative patients with an unfavorable prognosis.

Before starting ERT

- A baseline evaluation of the cardiac, respiratory, and neurologic systems and developmental milestones
- cross-reactive immunologic material (CRIM) status should also be determined (if accessible).

Before starting ERT

- If CRIM test is not available, its status should be suggested according to the mutation.
- Alternatively, the anti-myozyme antibody should be measured, if accessible.

- The first courses of ERT should be administered in an equipped pediatric center with excellent expertise on IOPD.
- Severe life-threatening adverse effects such as cardiac arrest and cardiovascular collapse are more common in patients with an acute or severe disease than in other patients.
- ERT must be postponed in patients with acute infections, fever, or other critical illnesses.
- If the condition is continued, we recommend that ERT be done in an equipped center with an expert team for resuscitation

- Patients are classified into three subclasses according to anti-rhGAA IgG antibody titers :
- High and sustained antibody titer, defined as antibody titer > 51,200 on samples at least 6 months on ERT;
- sustained intermediate titer, defined as titers of ≥12,800 and <51,200 within 12 months on ERT;
- low titer, defined as antibody titers of <12,800 during 1 year on ERT.

Prophylactic immunomodulation to manage CRIM-negative status:

- Including rituximab, methotrexate, rapamycin, mycophenolate, and intravenous immunoglobulins in various combinations .
- The usually proposed regime includes rituximab 375 mg/m2 weekly for 4 weeks, followed by maintenance therapy, methotrexate 0.5 mg/ kg every week, and intravenous immune globulin 0.5 g/kg every 4 weeks
- More effective, with lower adverse effects

Nutritional and Gastrointestinal Evaluation

- pay attention to the patient's exercise and nutrition.
- We suggest a high-protein and low-carbohydrate nutrition diet and exercise therapy.
- In patients with a motor disability that prevents regular daily activities, the total energy consumption by food must be reduced to evade obesity.
- Pompe patients should be assessed regularly for nutritional deficiencies (protein, vitamin D, other vitamins)

Nutritional and Gastrointestinal Evaluation

- The jaw muscles' fatigue, increased risk of aspiration, and the compensatory use of muscle proteins.
- So speech therapy and swallowing techniques are recommended.
- Other gastrointestinal symptoms include dysphagia, gastroesophageal reflux, gastroparesis.
- Videofluoroscopic swallowing assessment is recommended to assess patient condition, especially for aspiration risk.

FOLLOW-UP for IOPD

- We recommend that the patients be visited by the physician every 3 months
- The time interval may be modified based on the patient's clinical status. A closer follow-up is required for patients with cardiac diseases.
- CK and liver function tests should be measured every 6–12 months

TABLE 3 | Recommended follow-up and assessment in classic infantile Pompe disease (CRIM-positive and CRIM-negative).

	Assessment time point and frequency				
	Initial referral	**2–4 weeks of age**	**Monthly to 4 months of age**	**Every 2 months (4–12 months of age)**	**Every 3–6 months (>12 months of age)**
Clinical assessments					
Feeding/swallowing	■		■	■	■
Chest X Ray	■				
Electrocardiography	■		■	■	■
Echocardiography	■		■	■	■
Holter cardiac monitoring	■		■	■	■
Auditory	■				
Developmental assessments	■	■	■	■	■
Treatment evaluations					
ERT antibodies (CRIM-negative)	■	■	■	■	■
ERT antibodies (CRIM-positive)	■	■	■	■	■
Pulmonary evaluation	■		■	■	■

Motor Functions

- Difficulties associated with getting in and out of bed
- Meal preparation and eating
- Toileting, bathing
- Ambulation (10-m walking test or 6-minute walk test), Walton and Gardner-Medwin score, GSGC group tests (G = gait by walking for 10 meters, S = climbing four steps on a Stair, G = Gower's maneuver, C = rising from a Chair)
- Falls
- Dressing

Respiratory and Cardiac Functions

- Shortness of breath on exertion
- Orthopnea
- Morning headaches
- Sleep symptoms (Apnea, snoring, paroxysmal nocturnal dyspnea)
- Muscle pain and fatigue
- Palpitations

Speech and swallowing difficulties

- Choking during swallowing
- Dysarthria

FIGURE 6 | A minimum clinic visits inquiries for each session.

Low Bone Mineral Mass

- Annual dual-energy X-ray absorptiometry bone mineral density assessment for LOPD child or adult wheelchair or ventilator-dependent patients .
- If necessary, add calcium, vitamin D, and bisphosphonates to the patient's regimen.

Respiratory Outcome:

- Pulmonary function tests (FVC, MIP, and MEP at the upright and supine positions)
- Polysomnography


Thank you
for your
attention