Pompe Disease

CME Course 2023 -2024

Topic and Faculty

This CME course will discuss when to test for and how to diagnose Pompe disease in those with muscle weakness. The faculty members of the course are

- Tahseen Mozaffar, MD: neurologist and professor at the University of California, Irvine.
- Jordi Diaz Manera, MD PhD: neurologist and professor at Newcastle University, UK.

Part 1. Pompe Disease Overview

When was Pompe disease first described

Pompe is not an old disease. It was described for the first time in 1930 by Dr. Johannes Pompe on an autopsy of a seven-month-old girl. He found the heart was enlarged and it contained massive amounts of glycogen. This was the first description of what would be now known as infantile Pompe disease. For the next 50 years, Pompe was only considered to be something that happened in infants until it was described in adults.

What is the disease mechanism

There are many terms that have been used to describe Pompe disease. The biochemical diagnosis is glycogen storage disease type II or GSD type II. There's also, in the neurology literature, the acid maltase deficiency. That's been the prevailing term for at least the late onset version of the disease. We can discuss whether it's an appropriate term or not, but now the unified terminology that we use is Pompe disease. Pompe disease is a lysosomal storage disorder. There is a deficiency of a crucial enzyme called Acid Alpha Glucosidase, also known as GAA, which leads to accumulation of glycogen in the lysosome. This is a recessive disease, so you need two mutations. The gene is on the long arm of chromosome 17. There are more than 300 different mutations that have been described in GAA that may be responsible for Pompe disease. Some of them are more common and we will talk about that briefly.

What are the two forms of Pompe disease

There are two different forms of Pompe disease. There is a much rarer infantile onset disease which presents usually within a few months or a year of birth or sometimes at birth. Anything after one year of age is considered late onset Pompe disease. The infantile onset form (IOPD) has predominantly cardiac manifestations. The children present with either signs of cardiac failure or failure to thrive. Chest X-ray shows massive cardiomegaly. They also happen to have muscle weakness and they need to be treated right away to save life.

There is a much more common late onset version. Roughly about two thirds of the patients present with late onset form, at least in the parts of the world where there is a large Caucasian population. This is more common than IOPD and it can present at any time, so any time after age of one, but often presenting in the teenage or early adulthood. It is a progressive skeletal myopathy.

What are the epidemiology data on Pompe disease

The mean age of disease onset is 29 years. The classical incidence figures that we were taught in school was 1 in 40,000, based on work from the Netherlands as well as work that was described from the New York State in the US. As I said the late onset version is more common and the traditional incidence figure was 1 in 57,000. If you combine both forms of the disease in the US, the frequency was estimated to be 1 in 40,000.

All of these are changing because of newborn screening. Pompe is one of the diseases included in the newborn

screening program in the US and we are constantly revising these frequency data. There are certain populations which are at much higher risk. African Americans tend to have genetic mutations in GAA much more frequently. We know that in the Southeast Asian population, especially Taiwanese population, there's a much higher incidence. There is also a higher incidence in the Netherlands in the Dutch population.

What are the characteristic findings in Pompe disease

The muscle weakness, proximal greater than distal, is what we typically see in Pompe disease. So it looks pretty much like any other limb girdle muscular dystrophy. There is electrical activity that suggests membrane irritability on electromyography (EMG). Classically you see myotonic discharges in the paraspinal muscles, which is quite classic for Pompe disease. The EMG pattern is generally myopathic, so there are brief motor unit potentials with small amplitude and short duration. Nerve conduction is normal, but another diagnostic clue is the evidence for diaphragmatic insufficiency. When you measure the forced vital capacity in a seated position as well as in a supine position, oftentimes there is a greater than 10% drop going from seated to supine, and that is highly suggestive of diaphragmatic insufficiency. You can see the same thing on inspiratory pressure. So maximum inspiratory pressure is going to be reduced, often below -60cm of H2O. That is a good clue that we are dealing with pneumatic insufficiency. Creatine kinase can be normal. Often times it is elevated and can be as high as 15 times upper limit of normal. But it's not unusual to also see normal CK as well.

What does histopathology show in Pompe disease

The typical histopathology shows evidence for glycogen storage. If you look at the right panel, the pink slide, there are fibers that are full of glycogen. These are diffusely present throughout the muscle, not just in the subsarcolemmal position which is more characteristic of McCardle's disease or other glycogen storage disease. In this particular case, you have diffuse involvement of the muscle and then when you either use a stain which shows glycogen or combine it with acid phosphatase which is to look for lysosomal dysfunction, there is the muscle fibers light up. This is suggestive of lysosomal dysfunction in these muscles.

Now when you do semi thin sections, the panel on the left shows increased amount of glycogen in the muscle fibers. The right panel shows electron microscopy findings and you can see both free as well as lysosomal bound glycogen and autophagic material in the muscle, suggesting there is glycogen disorder with excessive amount of glycogen. It's also suggesting that there is a autophagic defect that happens in this disease.

This is from the mouse models of Pompe disease where there is a gradual autophagic buildup. There are double membranes with autophagosomes and undigested cytosolic materials that are really ugly looking. These are suggestive of autophagic debris.

What is the pathophysiology of Pompe disease

There is progressive expansion of glycogen filled lysosomes in multiple tissues. The skeletal muscle and the cardiac muscle are most affected both in the infantile as well as in the late onset disease. There is an abnormal autophagy with autophagic buildup. This was described by Dr. Andrew Engel in the 1970s. More recently, Dr. Nina Rabin at the NIH has shown it in the mouse muscle models as well that there is autophagic buildup, there is loss of contractility and muscle mass, and there is abnormal trafficking and delivery of the recombinant enzyme in the muscle.

So in Pompe disease, the gradual glycogen buildup leads to autophagic defect, which then results in protein aggregation. But also there are the results of energy deficit and deficit in some of the signaling pathways in the muscles, especially the mTORC pathway. This results ultimately in muscle atrophy, muscle loss, and muscle damage. All of this can directly link to the gradual buildup of glycogen in the lysosome. For the enzyme to work effectively, it has to be an acidic environment, which is what lysosomes provide. If you look at the panel on the right, these are muscles from Pompe dysfunction.

Why do we need to catch the disease early

Here you can see on the left it's all green, which means that there is hardly any autophagic buildup. But on the right, there are markers of autophagy that are very prominent and very clearly suggesting there is an autophagic defect. Pompe is a progressive disease. There is progressive accumulation of glycogen. There is progressive replacement of muscle tissue and buildup of lysosomal defect. The point that I want to make from this

slide is that there is a point of no return. So you want to catch the disease early, you want to treat the disease early beyond a certain point. Most of the glycogen now is going to be in the cytoplasm. You lose the acidic environment and ultimately it will be replaced by fat and scar tissue and they will not be any possibility of treating this muscle.

What is late onset Pompe disease (LOPD)

I want to mention the work by Dr. Andrew Engel from the Mayo Clinic, who described what he called acid maltase disease in late onset disease. These were adults that looked like to have muscular dystrophy and other myopathies. He showed that their muscle had a deficiency of acid maltase, which we now know what he was referring to was GAA. As I mentioned, this is the more common manifestation of Pompe disease as opposed to the infantile onset, which is early onset, and that the prevalence is about 1% in our tertiary neuromuscular clinics.

What is the prevalence of LOPD in neuromuscular clinics

This is a study that was done by my group along with 12 other centers in the US. We screened 921 patients presenting with proximal muscle weakness, isolated hyperCKemia, or neck flexor weakness, we found 1% of these patients had LOPD. Similar work has been done in Europe, in England and Germany, as well as in Spain and other countries in Europe. Very similar prevalence data has come out of those studies as well.

What is the clinical picture of LOPD

The clinical spectrum of LOPD is much broader than initially recognized. The onset of symptoms can be at any age, ranging from infancy to adulthood. Limb-girdle muscle weakness is the cardinal feature. There is also very, very common respiratory insufficiency that can be picked up by bedside pulmonary function testing. There are less familiar features, especially ptosis and bulbar weakness. Scapular winging is quite common in our clinic population, 65% of the patients have scapular winging, so that's a very helpful clue. Also, axial muscle weakness is very common, patients can present with neck drop or camptocormia, which is axial weakness. I particularly find infraspinatus muscle weakness very common. Even in cases where there is not a frank scapular winging, you may see infraspinatus weakness.

So as I mentioned, proximal muscle weakness is the most common. These patients often present with ambulation defects or difficulties. They can sometimes present with upper extremity weakness more than lower extremity weakness, which happens in about 13%. Exertional dyspnea, especially shortness of breath after exercise is also very common. Certain patients may present with distal muscle weakness as well.

What is the pattern of muscle weakness and how does it impact life

Although it's not been uniformly studied in the past, the disease does affect your quality of life. There is reduction in leisurely activities. It impairs mobility both indoors and outdoors. It impairs domestic tasks.

There was a study from the UK as well as Germany on the pattern of weakness. It showed that about 12% of patients will present with isolated hyperCKemia. They don't have any clear evidence for muscle weakness. The more common pattern is hyperCKemia, generalized limb girdle pattern muscle weakness, and ventilation defect, which accounts for about 61%. So if you see a combination of these three, think very highly of Pompe disease and you're going to be right most of the time. But it can present with shoulder muscle weakness predominantly or pelvic muscle weakness predominantly or ventilation defect as well.

As I mentioned, there is a reduction of quality of life affecting all domains. The Dutch group showed very convincingly that the disease affects quality of life. There is an increase in mortality and most of it comes from the respiratory involvement. There is not much of cardiac involvement in the late onset version, but it is a prominent feature in infantile. In adults, it's mainly the respiratory dysfunction that drives the mortality. If the patient requires wheelchair, that may also predict higher mortality.

What are the treatment advances made recently

There are now multiple drugs available for disease modification. The disease was first described in 1932. In 1954, Dr. Khoury described the biochemical defect. The first clinical trial was conducted in 1973. In 2006, FDA approved an enzyme replacement therapy. More recently, a second enzyme replacement therapy has been approved.

There are two recent clinical trials. The COMET trial showed efficacy of avalglucosidase compared to the traditional alglucosidase. The PROPEL trial showed effectiveness of cipaglucoside along with miglustat. Both of these have been published in Lancet neurology. There are currently three different gene therapy trials that are ongoing for this disease, and a number of other companies have plans to do gene therapy trials, most of them using AAV virus as the transporter. There is plan for one gene therapy that uses Lentivirus approach as well.

Part 2. Diagnostic Approach

Why is it important to avoid diagnostic delay in Pompe disease

What is clear from all the papers that have been published in the in recent years, including data from registries and retrospective data collected in clinics, is that there is a significant delay in the diagnosis of Pompe disease which is fatal. In infantile cases, patients can die if they are not treated early. In patients with late onset disease, delayed diagnosis can lead to an irreversible impairment. We know that patients with late onset Pompe disease develop significant morbidity because of the permanent weakness if not treated. I think there are enough evidence suggesting that Pompe disease should be chased in clinics. There is also something important to mention. Pompe is a treatable disease. With recent advances in therapies and with new opportunities in terms of clinical trials for patients, we need to look for this disease in clinics.

Dr. Krishnani presented data from a large cohort of patients with infantile and adult onset Pompe disease. It showed that in infantile onset Pompe disease, patients started to show symptoms at 2 months of age. They were diagnosed around four months of age and the diagnosis gap was 1.5 months. In late onset Pompe disease, the delay was between 6 to 12 years from onset of symptoms to the diagnosis. The delay in diagnosis was variable depending on the symptom that patients present. The delay is longer when patients started with non-respiratory or non-musculoskeletal symptoms. In some cases, the delay was up to 20 years.

What are the differential diagnoses of Pompe disease

The differential diagnosis of late onset disease includes many other neuromuscular disorders ranging from muscular dystrophies, inflammatory myopathies, congenital myopathies, other metabolic conditions, to diseases that are outside the muscle such as motor neuron diseases or neuromuscular junction disorders.

The most important differential diagnosis for me is the limb-girdle muscular dystrophy. In this disease, patients can present with muscular weakness that is progressive over time, starting in the childhood or early adulthood, affecting both male and female. Duchenne and Becker muscular dystrophy is another differential diagnosis. We also have patients with a spinal muscular atrophy, especially the type 3 that presents with proximal muscle weakness affecting the limb. Inflammatory myositis is another one, especially for those with a quick onset of symptoms that progresses to muscle weakness. It typically affects the proximal muscles of the limbs. Amyotrophic lateral sclerosis can mimic many neuromuscular diseases and some patients can be diagnosed as ALS but have Pompe disease, especially when there is respiratory involvement. It's more or less the same for myasthenia gravis. We can sometimes have patient diagnosed of myasthenia gravis that that are actually having Pompe disease, especially if they are seronegative or they have symptoms of proximal weakness associated with fatigue.

What are the common findings among differential diagnoses

There are some common findings to take into account. For example, in the case of Duchenne and Becker muscular dystrophy, there is a progressive muscle weakness in the shoulder, pelvis, and lower limbs. In some of the scapulohumeral syndromes, we can see weakness of the shoulder with a scapular winging. In patients with myotonic dystrophy, it is often misdiagnosed as Pompe disease or the other way around because these patients develop proximal muscle weakness and they can also have some myotonic features. In the rigid spine syndrome, it is similar especially when patients have limited mobility of the spine and axial muscle weakness. I have already commented about myasthenia gravis and spinal muscular atrophy that should be taken into account. The same with polymyositis. It's also important to remember that there are other glycogen storage diseases that can also mimic Pompe disease and it can be sometimes difficult to differentiate.

What is the diagnostic algorithm for Pompe disease

The diagnostic algorithm has been modified considerably in the recent years. In the one that published in 2009 by the American Association of Neuromuscular and Electrodiagnostic Medicine, everything starts with a physical examination. In patients with mainly proximal muscle weakness affecting the pelvic muscle but also the scapular ones, we could do two different things. One is to do the quantified GAA enzyme activity test with a dry blood spot. If the activity is reduced, we can confirm this with a second test, using in most of the cases lymphocytes from the blood but could also be fibroblast. Or, we can do directly a PCR or gene sequencing of the GAA. If the result is positive, then the diagnosis is confirmed. If it is negative, then we always recommend reassess the diagnosis. If we have a patient that has the potential diagnosis of Pompe disease where muscle biopsy can be done and the biopsy reveals accumulation of glycogen, then we do the enzymatic activity test and continue with the genetic testing.

So as said, the diagnosis algorithm has been modified over the years. It is now more and more including genetic studies. We have come to a situation where we could do directly a genetic study if we suspect Pompe disease. The next generation sequencing has changed the reality of the diagnosis.

What is the muscle involvement that can be seen on MRI

MRI is a tool that can be helpful. This is a study that we published in 2016 where we studied 36 patients with late onset Pompe disease. We observed a clear pattern of fatty replacement in the MRI. We observed replacement of some muscles that were characteristic, for example, tongue muscle, subscapularis, paraspinal muscle, and abdominal muscles. These were very frequently affected. In the lower limbs we observed clear involvement of the gluteus muscle, especially the minimus and the medius, while the gluteus maximus were only affected in later stages of the disease. In the thighs, we observed that the involvement of gluteus muscle was continued with the involvement of the posterior muscles of the thighs, and in later stages also the quadriceps.

The gait of patients with Pompe disease typically shows Trendelenburg and pelvis anteversion, which is the consequence of fat replacement. So just to remind everyone that patients with Pompe can have an MRI that is very typical with involvement of the tongue, subscapularis, paraspinal, abdominal, gluteal, and posterior muscles of the thighs. I think that one good clue for the diagnosis is that the distal muscles are spared.

What is the role of newborn screening (NBS) in the diagnosis of Pompe disease

In the recent years, in some countries including the United States, newborn screening is a reality for patients with Pompe disease. They are, of course, advantages, drawbacks, and challenges. The main advantages are summarized here. Treatment, especially early in the course, is effective. So it's important that we diagnose patient as soon as possible because there is a treatment that can change their life. With NBS, we learned that the prevalence of Pompe is higher than estimated. Pre-symptomatic patients can be identified by NBS and be followed in the clinic. We can also know more about disease progression and how carriers can be affected.

There are, however, some challenges. For example, the late onset forms are much more common than the infantile forms. This means that patients can be diagnosed many years before they develop any symptom. There is not a clear agreement on how we monitor these patients, especially the ones that are late onset. There is also, of course, potential discrimination for life insurance and long term disability.

NBS data from the United States showed that we have a higher prevalence of the disease. In some cases, it can be as high as one case for every 17,000 people, which is much higher than what we knew from the epidemiological studies done before newborn screening. The other interesting thing is that the GAA activity level cannot differentiate between infantile onset and late onset Pompe disease. This can lead to mistakes. It's better to look at, for example, the symptom that patients may develop and to follow patients in clinics.

Will next generation sequencing (NGS) change the diagnostic paradigm

There are data coming from next generation sequencing outside of newborn screening. Here is one study that collected a large number of samples, 28 patients were identified with all of them having two mutations or two causative mutations of Pompe disease. This is from a cohort of patients with limb girdle muscle weakness.

How should we manage patients diagnosed at pre-symptomatic stage

Another reality is that we have sometimes patients that are diagnosed in a pre-symptomatic stage, for example, adult patients with high levels of creatine kinase. We identify the disease either because there are some changes in the muscle biopsy or because we do the dry blood test and see a reduction in the enzyme activity. In all these cases, the question is what we do with them. The new reality is patients are diagnosed many years before they start with symptoms.

I think one of the big issues right now, especially in the US, is that 75% of the patients that are picked up at birth on the newborn screening have the late onset genetic variant and they may not manifest for anywhere from 8 to 20 years. How do we follow these patients? What should be the paradigm? What should be the frequency of follow up? We really don't have clear guidelines. It's not clear especially in a system like the US where insurances will have to pay for these visits. How are we going to pay for these visits and stuff like that? I think there are questions that have been raised by the newborn screening. But it's also important because the infantile onset disease will be picked up early and we can manage them.

Discussion Question 1

What Are the Clues for Pompe Disease in Those with Limb-Girdle Muscle Weakness

Dr. Mozaffar: Now I am going to serve as the moderator and ask Dr. Diaz Manera to help out with three questions that I had thought of. One of them was when you see a patient with limb girdle pattern of muscle weakness, what are the diagnostic clues that will make you lean towards or direct the workup towards Pompe disease?

Dr. Diaz Manera: Gluteal muscle is always affected in Pompe, along with psoas muscle. Another important clue is the more severe involvement of the posterior muscles of the thighs than the quadriceps. Quadriceps tend to be fine until late in the disease course. Distal muscles in the lower limbs are spared in Pompe disease, in both early and late stage of the disease. So if we see, for example, an atrophy of the gastrocnemius of the calves, this is probably not Pompe disease. Axial involvement is very typical in Pompe disease. Patients can have difficulties to extend the trunk when lying flat in the bed. They also have respiratory involvement. So if we have a combination of respiratory insufficiency and gluteal muscle weakness, we always need to think Pompe disease.

I have mentioned the confirmatory tests and MRI findings. I would like to point out here that the EMG can also be helpful. If we have suspicion of Pompe disease and we do an EMG, especially when we explore the paraspinal muscle, and we see myotonic features, that is very suggestive of the disease. It's not a specific because it can also be seen in many other muscular diseases such as myotonic dystrophy. But I think it's something to add to the diagnosis of Pompe.

Dr. Mozaffar: I think there is another diagnostic clue that I have sometimes found useful. There is a 22% risk of developing cranial or other body vascular abnormalities in Pompe disease. So the presence of aneurysms or dilation of the aorta may be common in Pompe patients. If I have a patient that has a history of aneurysms or vascular dilatation and with all the typical features that Dr. Diaz Manera mentioned, I would think very highly of Pompe disease. So that's another clue there.

Discussion Question 2

What is the Best Way to Test for Pompe Disease (Dry Blood Spot or Genetic Sequencing)

Dr. Mozaffar: Dr. Diaz-Manera, I wanted to hear of your thoughts on the best way of testing for Pompe disease. At least as we talked about, the paradigm shifted in the US because of the availability of free genetic testing. Most of the cases of Pompe are being picked up on genetic testing. But how do you feel about the enzyme assay and is it still a valid way of testing versus whole genome sequencing? Nothing is perfect and let's say if you only find one mutation, what is your strategy to find the second mutation?

Dr. Diaz Manera: You're completely right. We need to decide if we go for a genetic test or for dried blood spot.

When I was in Spain, Dried Blood Spot test was the first choice. It was very useful because in most of the cases, not in all but in I would say more than 95% of the cases, you can detect the decrease in the activity. Sometimes it's borderline, it's not clearly pathogenic and it can happen in patients that are carrier who have just one mutation. This is when it becomes a bit tricky. But in many other occasions you can clearly see that the GAA enzyme activity is reduced. Then this leads to genetic testing that demonstrate the mutations, in our experience in around 90% of the cases. So this is the algorithm. I have a suspicion of Pompe and then this allowed me to diagnose the patient.

Here in UK, it is completely different because we do next generation sequencing (NGS) to all patients. So when a patient comes in and we suspect muscle dystrophy or a muscle disease, we do NGS. In most of the cases we can identify patients with Pompe disease. As you said, what can happen is that you have just one mutation.

If you have one mutation and you have not done the enzyme activity test, I would do it for sure., either this is the dry blood spot or analysis in lymphocytes. The guidelines recommend that the diagnosis can be made if you demonstrate the activity using two tissues. These two tissues mean blood, fibroblast, and/or muscle. I would advocate for muscle. So if you have doubts, do an MRI, for example, and identify a muscle that is not completely replaced by fat and take a muscle biopsy, because this will allow you to do the GAA enzyme activity test, to see if there is glycogen accumulation, and if are lysosomal vacuoles in the in the muscle fiber. So you will be able to find pathologic changes that are supportive of diagnosis.

Dr. Mozaffar: That's pretty much what we do as well. One point that I wanted to bring out, especially in the context of the enzymatic assay, is that in certain populations, especially the Japanese and the Southeast Asian population, there is a reasonably high incidence of what we call pseudo deficiency, where they have two genetic mutations in cis. They're not disease-causing mutation, but they interfere with the enzymatic assay and artificially lower the value. You just have to be mindful of that.

In our IPaNeMA study, 1% of the 900 patients had pseudo deficiency. The rate goes up when you're dealing with a population that has more Asian individuals. So just to be mindful that the diagnosis of Pompe disease should never be made on the basis of a low enzyme alone. It should always be confirmed with a second testing, be it muscle biopsy, be it mutation analysis, and that's going to be important.

Discussion Question 3

When to Initiate Enzyme Replacement Treatment in Pompe Disease

Dr. Mozaffar: Dr. Diaz Manera, I wanted to ask you the last question, which is somewhat controversial, especially now that in the US we are picking up cases at birth with most of these being late onset. What would be your threshold for starting enzyme replacement therapy in somebody who's pre-symptomatic or at risk genetically for Pompe disease? I have recognized that between Europe and the US there are already differences. I know, for instance, in France they would not start patients on enzyme replacement unless they have respiratory involvement. I wanted to hear your thoughts on what threshold would be for starting treatment.

Dr. Diaz Manera: In my opinion, when we think about this treatment, we sometimes are prompted to say that this is just an economic problem. I don't agree with that. I think that's of course one of the reasons why we discussed this is, the drug is expensive, but there are all the other things to take into account. When we are going to ask patients to start the treatment, that means that every two weeks they need to come to the hospital and spend almost half a day being infused with a treatment just because we think that they can develop symptoms. We think that this treatment can reduce the chances of the symptoms to present earlier. As of today, we don't really know if the treatment can delay the onset of symptoms. We think that's possible. But there is not any study that have demonstrated in late onset Pompe disease that starting the treatment in patients who are two years old can delay the onset of symptoms from 20 to 35.

Just to have an example, on the other hand, I think that what cannot happen (this is what is happening now) is that you have some patients that start very late. So for me, waiting until patients have respiratory involvement is not correct. What I would do is that we need to follow the patient very carefully. This means that we need to see the patients at least twice a year in the clinics with muscle

function test. I would include in the muscle function evaluation the time test, like for example, the 6-minute walking test, the time to walk 10 meters test, and functional analysis.

If we identify that there is a worsening of the muscle function or if we identify that there is fat replacement in, for example, the paraspinal muscle, gluteal adductor magnus, this is compatible with a disease that has started to destroy muscle. We are seeing that the muscle is suffering, the muscle is being replaced by fat. For me, that's the first moment when we should start treating patients. I don't think that we need to wait until patients come and say, I'm starting to have problems in my life. I think that we need to monitor these patients very closely. As soon as we see something either in muscle function test or MRI, we start the treatment.

Disclosures

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Transcript edited for clarity.

Part 1

Disease Overview

Tahseen Mozaffar, MD

Joannes Cassianus Pompe (1901-1945)

- Studied medication at Utrecht, Netherlands.
- On December 27, 1930, Dr. Pompe carried out a postmortem on a 7-month-old girl who died of pneumonia
- He found the enlarged heart, now known to be characteristic of infantile form of the disease and demonstrated glycogen deposition

Pompe. *Ned Tijdscr Geneeskd*. 1932;76:304

Disease Mechanism

Synonyms

- Glycogen storage disease type II (GSD II) and acid maltase deficiency (AMD)

A Lysosomal Storage Disease

- Deficiency of acid α-glucosidase (GAA), which leads to the accumulation of lysosomal glycogen

Autosomal Recessive

- GAA 17q25.3 gene mutations
- More than 300 mutations have been described in GAA

Forms and Epidemiology

Two Forms

- Infantile Form (IOPD)
  - Classic: within a few months of birth
  - Non-classic: age 1
  - Cardiomegaly, muscle weakness
- Late Onset Form (LOPD)
  - More common than IOPD
  - Any age (infancy, childhood, adult)
  - Progressive muscle weakness

Epidemiology

- Mean age of onset: ~ 29 years old.
- Incidence ~ 1/40,000. Infantile form: 1 in 35,000-138,000. Late onset form: 1 in 57,000
- In the US, frequency of all forms is as high as 1 in 40,000
- Certain populations are at higher risk: African Americans, Taiwanese, Dutch

Characteristic Findings

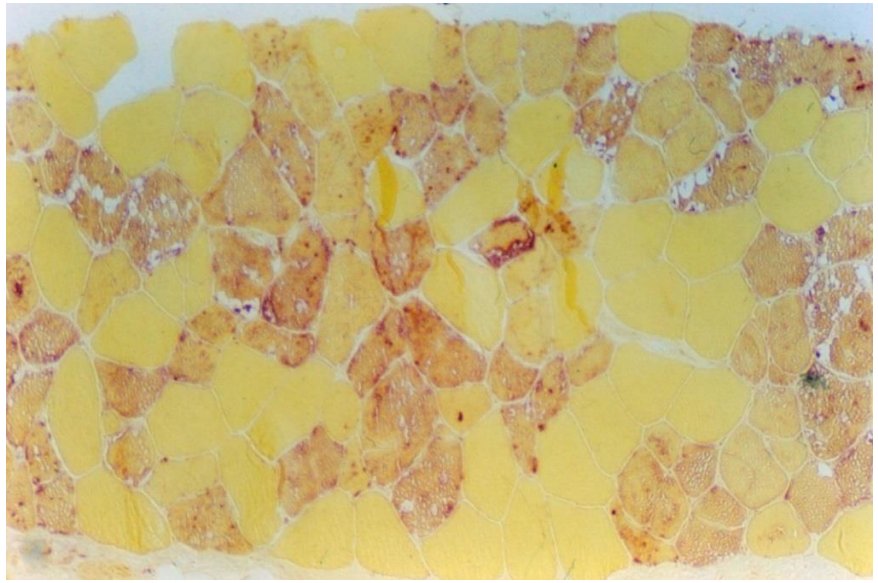
Table 2. Findings suggestive of Pompe disease

Assessment	Findings
Neurologic testing	
Manual (MRC) or quantitative muscle testing	Pattern of weakness: usually proximal greater than distal
Electromyography*	Markedly increased muscle membrane irritability
	Myotonic discharges (typical or atypical, may be observed only in the paraspinal muscles)
	Brief MUAPs (small amplitude and short duration)
Nerve conduction studies	Normal
Respiratory	
FVC seated and supine	≥10% drop in FVC from seated to supine testing†
Laboratory	
Creatine kinase	Ranges from normal to up to 15 times the upper limit of normal

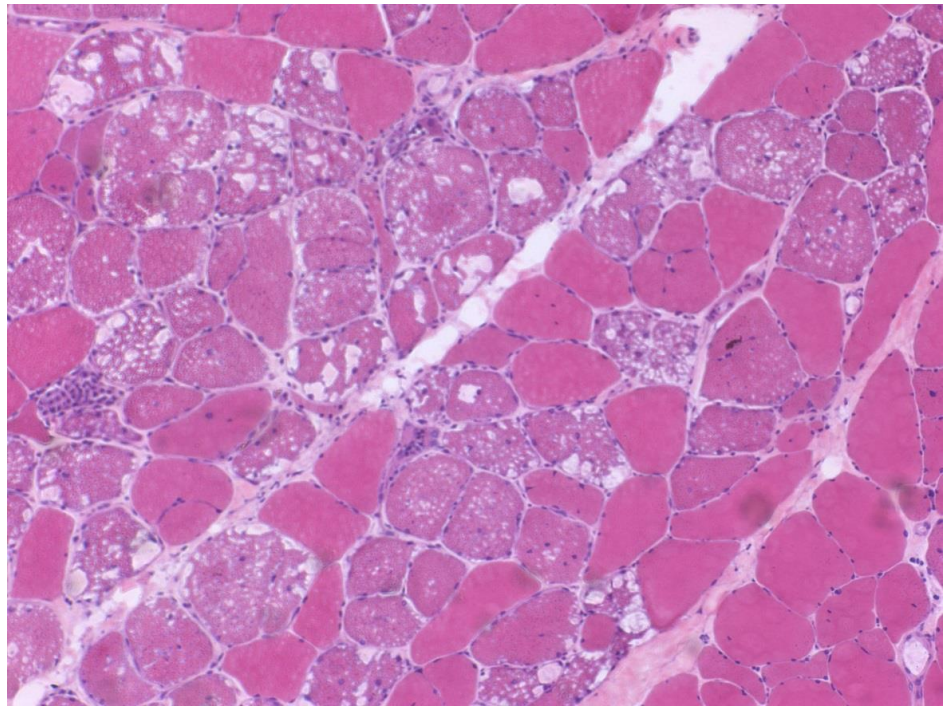
MRC, Medical Research Council; MUAP, motor unit action potential; FVC, forced vital capacity.
**Findings may vary, depending on clinical involvement and muscles sampled.*
†This finding is suggestive of diaphragm weakness.

American Association of Neuromuscular & Electrodiagnostic Medicine. *Muscle Nerve.* 2009;40:149-160.

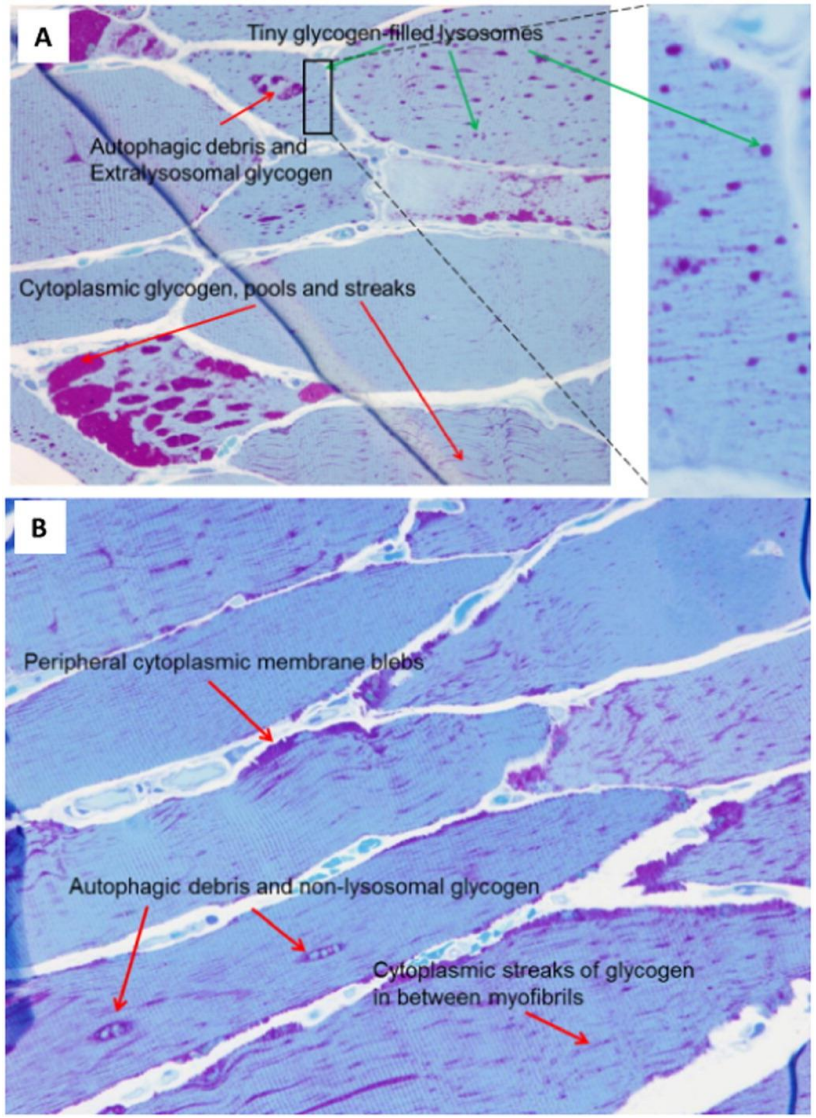
Histopathology

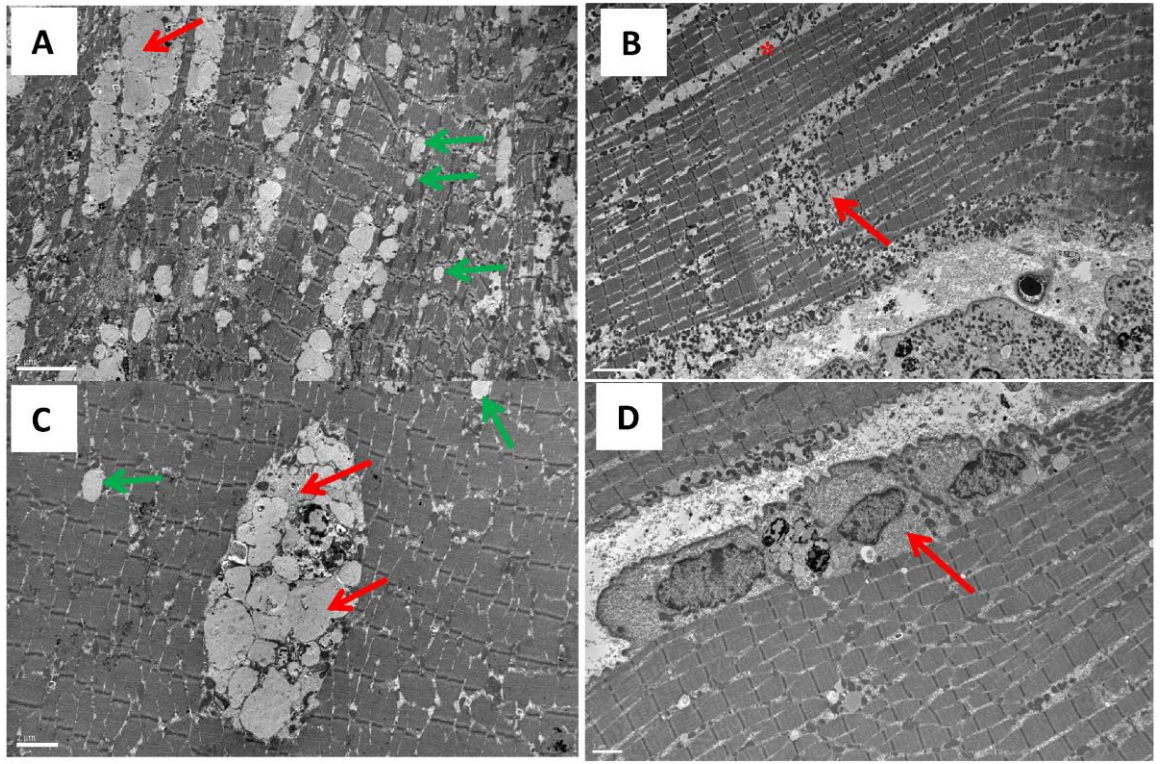


PAS: excess glycogen and acid phosphatase



H&E: multiple vacuoles of various sizes in single muscle fibers





Presence of Lysosomal-Bound and Free Cytoplasmic Glycogen and Autophagic Material in Skeletal Muscle

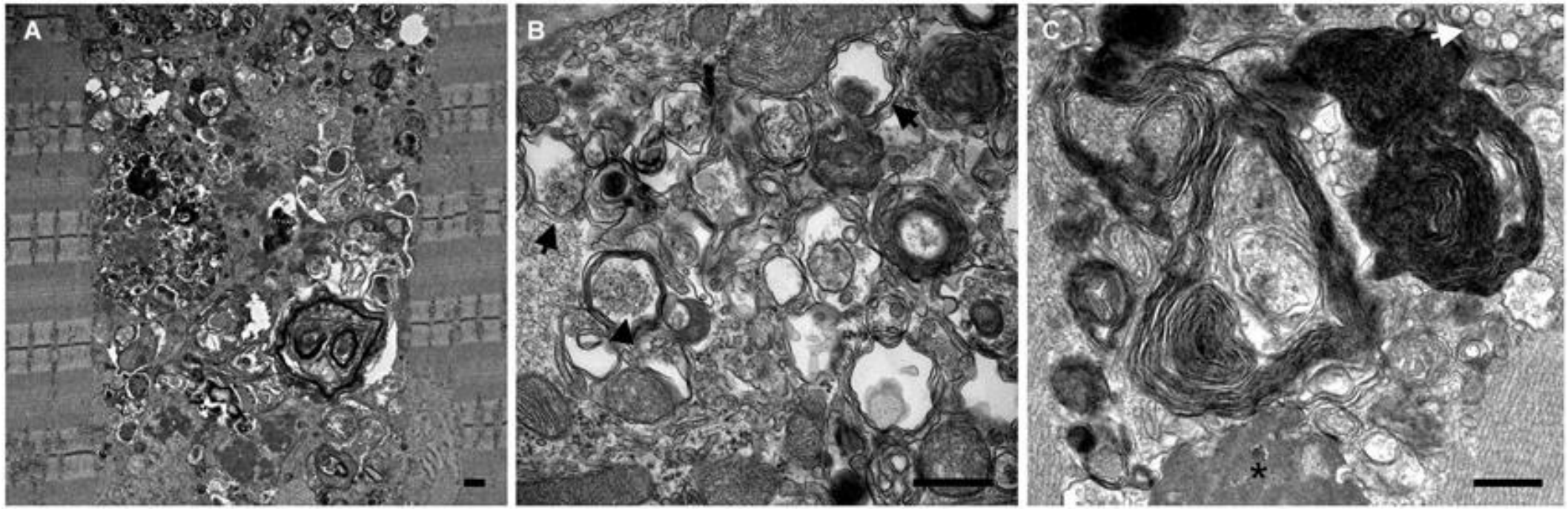
van der Ploeg. *Mol Genet Metab*. 2016;119:115-123.

EM Images in GAA-KO Mouse

Autophagic build-up

Double membrane autophagosomes with undigested cytosolic material

Multimembrane structures



van der Ploeg. *Mol Genet Metab*. 2016;119:115-123

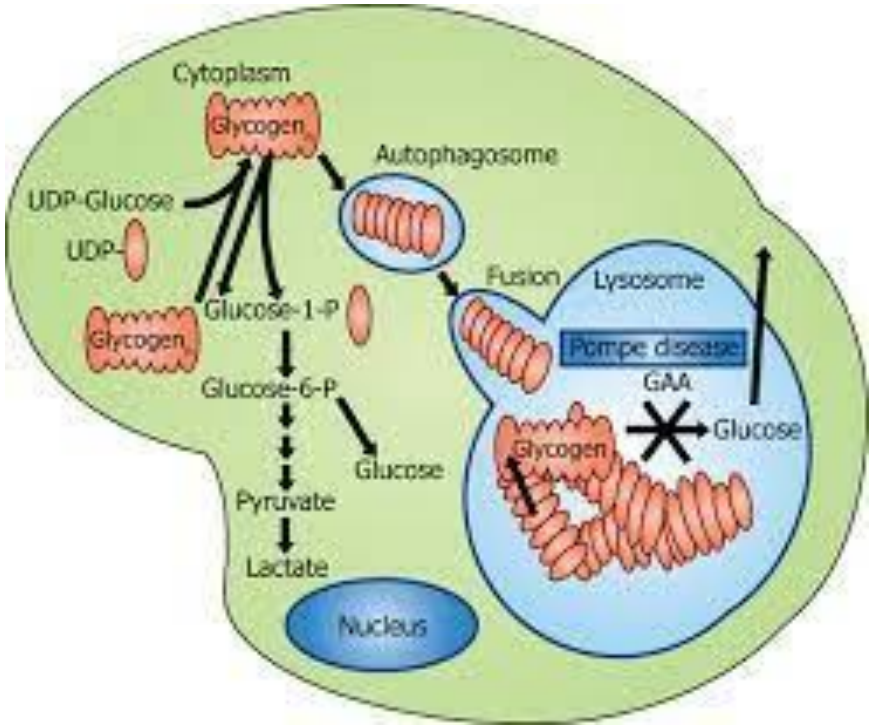
Pathophysiology

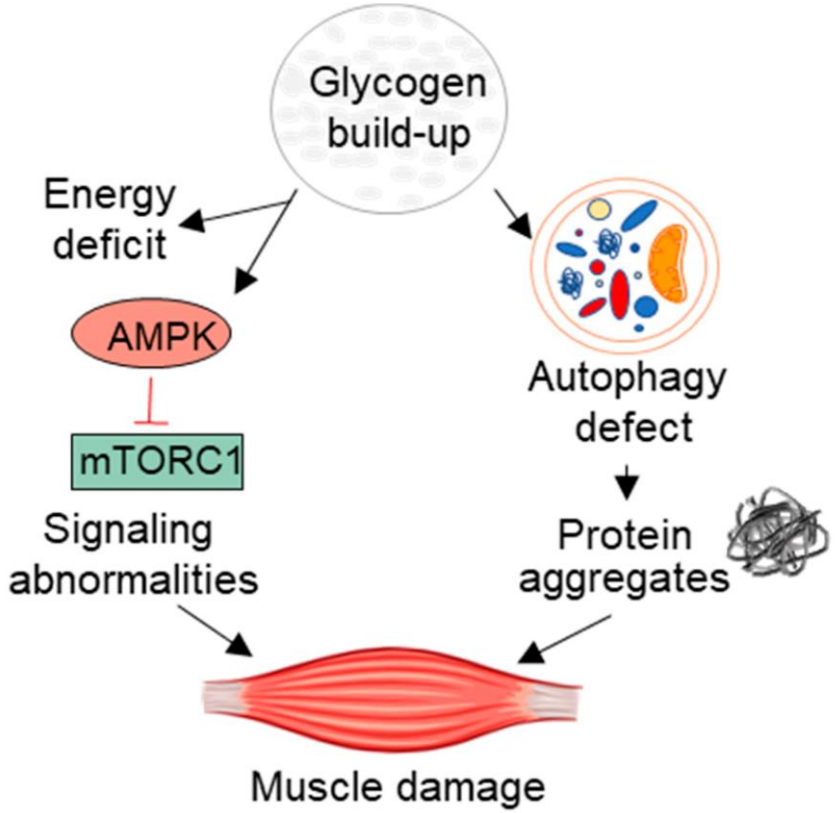
Progressive expansion of glycogen-filled lysosomes in multiple tissues. Skeletal and cardiac muscle most affected

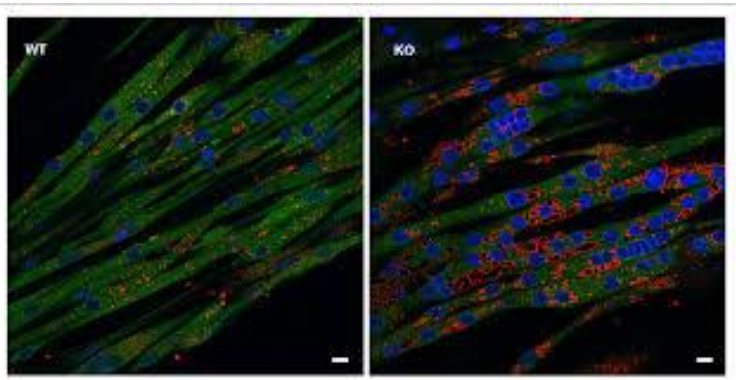
Abnormal autophagy (Engel 1970) with autophagic build-up:

- Causes loss of contractility and muscle mass

- Affects the trafficking and delivery of the recombinant enzyme

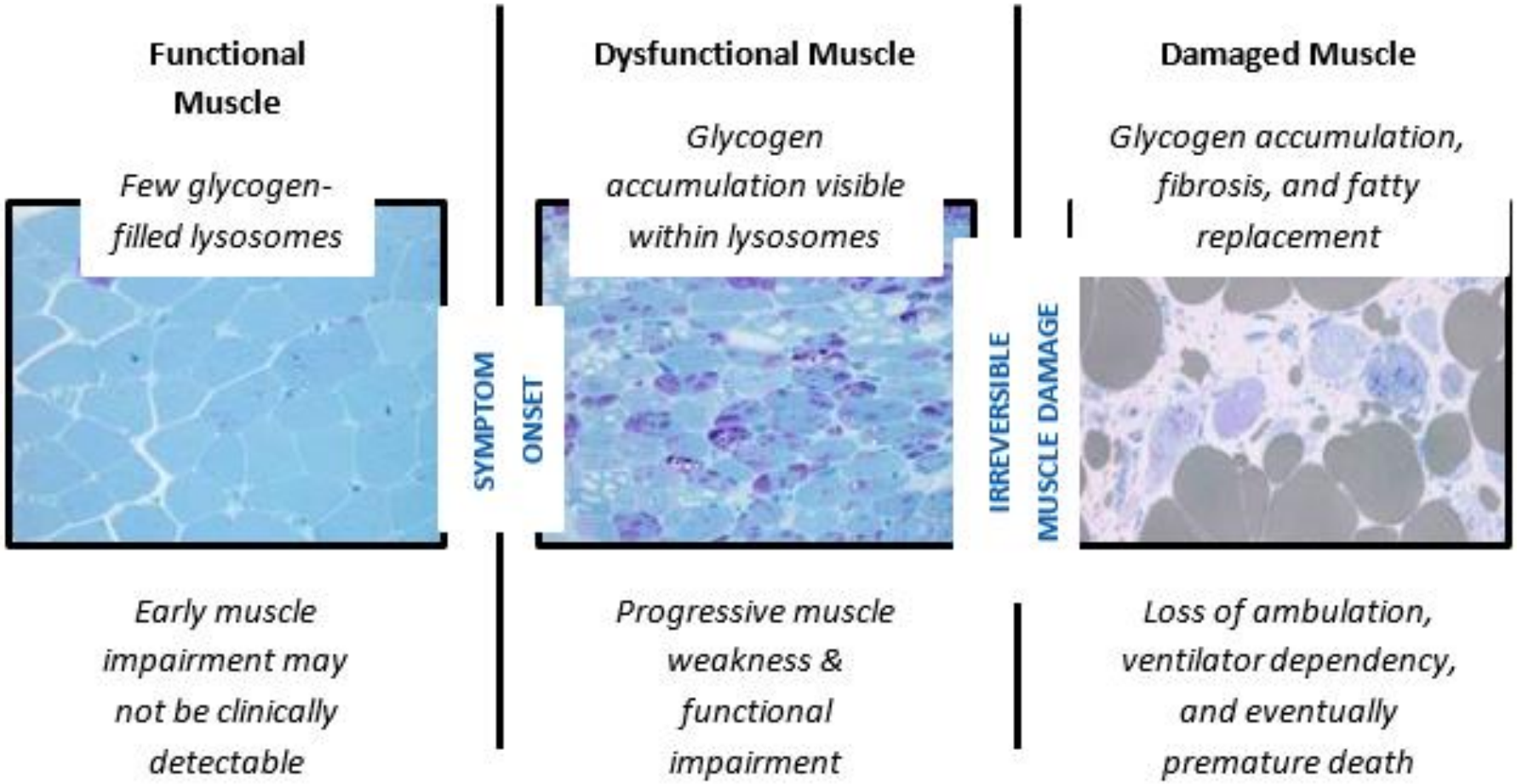






Cupler. *Muscle Nerve*. 2011;45:319-333, Meena. Biomolecules 2020;10:1339, Lim. Front Aging Neurosci 2014;23:177

Progression of Disease



Muscle biopsy images courtesy of Beth Thurberg, Genzyme Corporation. van der Ploeg et al. *Lancet* 2008; 372: 1342–53.

Late Onset Pompe Disease (LOPD)

Brain (1970) **93,** 599–616.

ACID MALTASE DEFICIENCY IN ADULTS: STUDIES IN FOUR CASES OF A SYNDROME WHICH MAY MIMIC MUSCULAR DYSTROPHY OR OTHER MYOPATHIES[1]

BY

ANDREW G. ENGEL

(From the Mayo Clinic and Mayo Foundation: Section of Neurology and Neuromuscular Research Laboratory, Rochester, Minnesota)

The spectrum and diagnosis of acid maltase deficiency

Andrew G. Engel, M.D., Manuel R. Gomez, M.D., Marjorie E. Seybold, M.D., and Edward H. Lambert, M.D., Ph.D.

Engel. *Neurology*. 1973:23:95-106.

LOPD
Prevalence in Neuromuscular Clinics

Investigating Late-Onset Pompe Prevalence in Neuromuscular Medicine Academic Practices

The IPaNeMA Study

- Prospective study of 921 patients presenting to tertiary neuromuscular neurology practices for proximal muscle weakness, isolated hyperCKemia, or neck flexor weakness
- **1%** of patients were found to have LOPD.

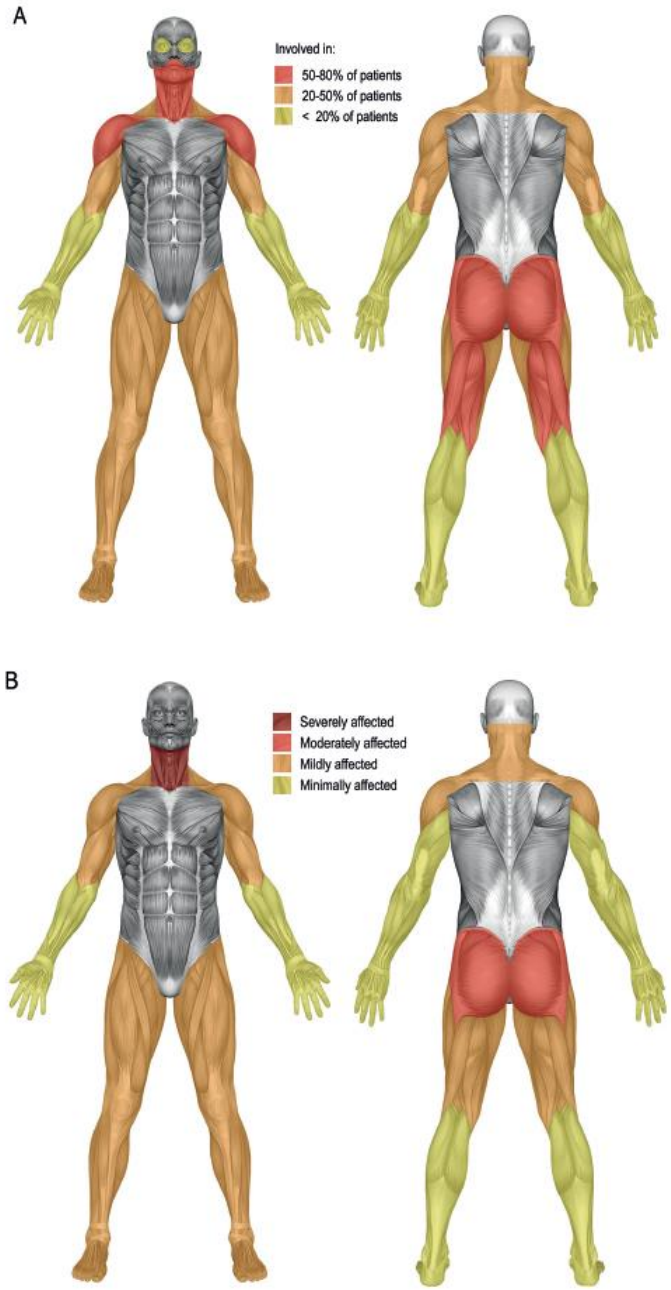
Table 4 Diagnosed Pompe Patient Characteristics (n = 9)

Age (y)	52.2	(20.5)
	N	**%**
Sex		
Female/Male	6/3	66.7/33.3
Ethnicity		
Hispanic/Not Hispanic	1/8	11.1/88.9
White/Caucasian	8	88.9
Black/African American	1	11.1
Inclusion criteria		
Proximal weakness	9	100
Neck weakness	5	55.6
High creatine kinase	7	77.8

Wencel. *Neurol Genet*. 2021;7:e623.

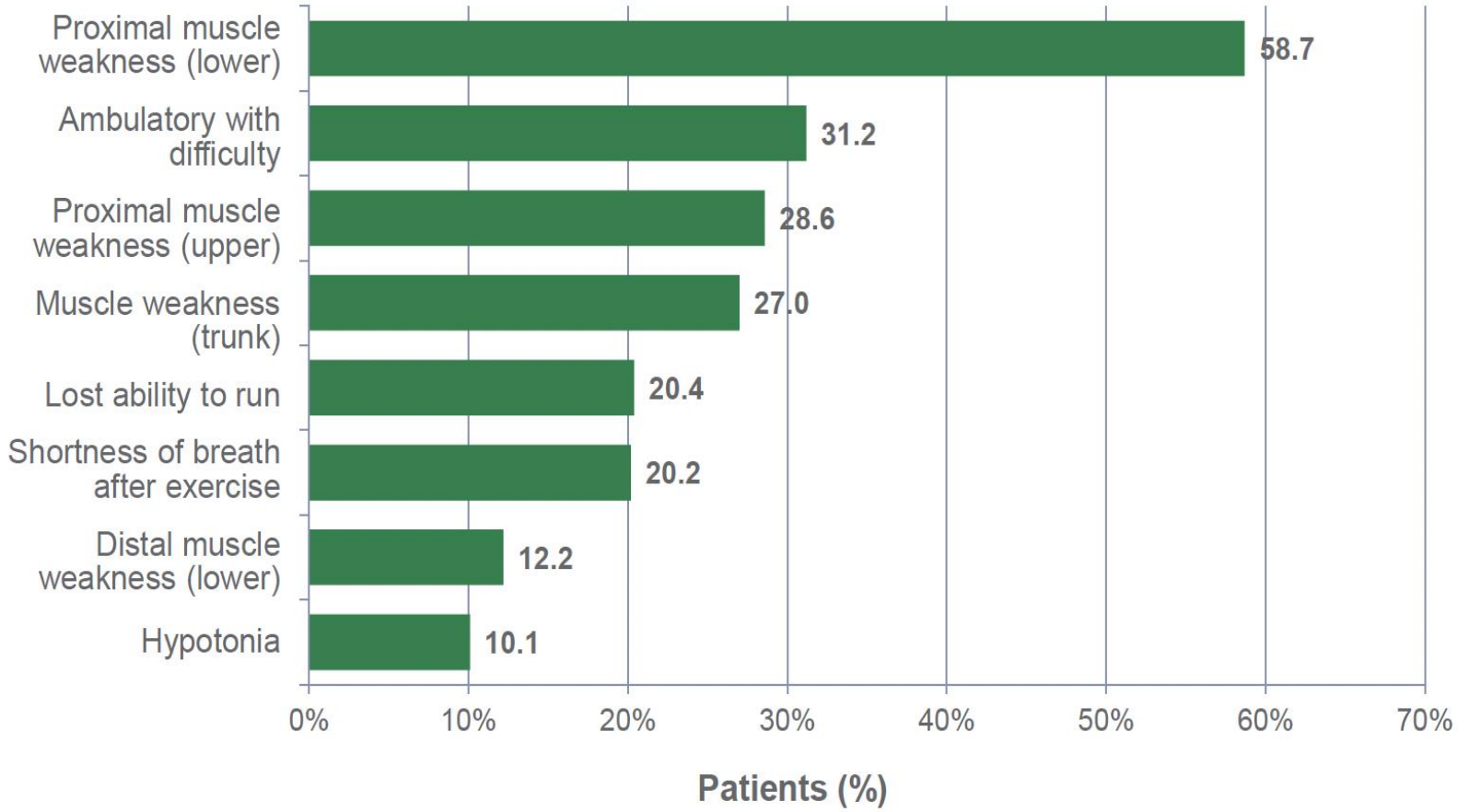
LOPD
Clinical Picture

- Clinical spectrum much broader than initially recognized
- Onset of symptoms at any age, ranging from infancy to late adulthood
- Limb-girdle muscle weakness is the cardinal feature. Respiratory insufficiency is in the majority of patients
- Less familiar features include ptosis, bulbar weakness, and scapular winging.
- Neck drop and camptocormia is quite common. Infraspinatus muscle weakness very common, even in the absence of scapular winging



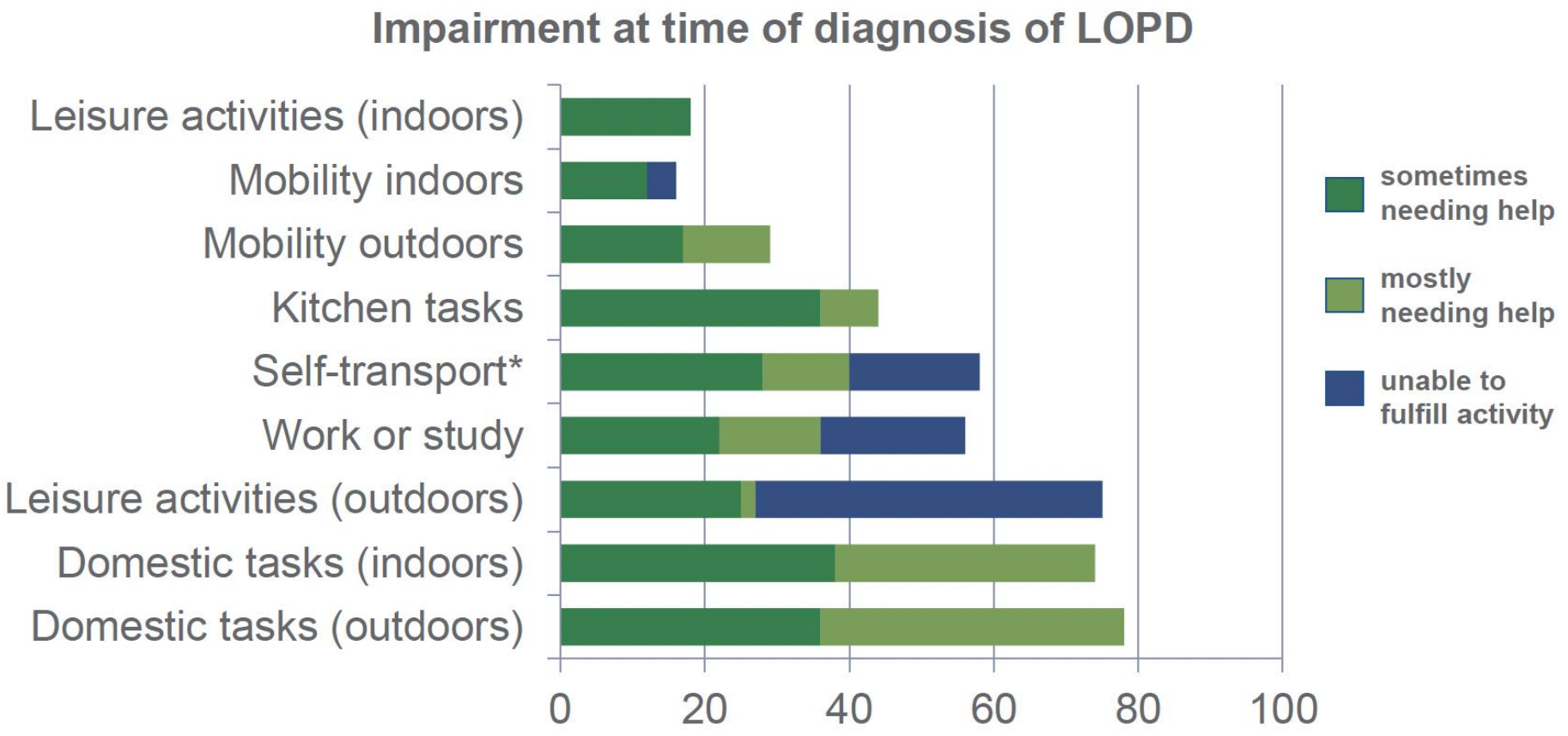
Thesis work CI van capelle (Erasmus)

LOPD
Proximal Muscle Weakness Is Most Common



Kishnani. *Am J Med Genet A*. 2013;161:2431-2443.

LOPD
Severely Impaired Health Status at Diagnosis



Rigter. *Mol Gen Metab*. 2012;107:448-455.

LOPD
Patterns of Weakness

A cohort of newly diagnosed Pompe disease patients

N = 74

Age = 48 (18-81)

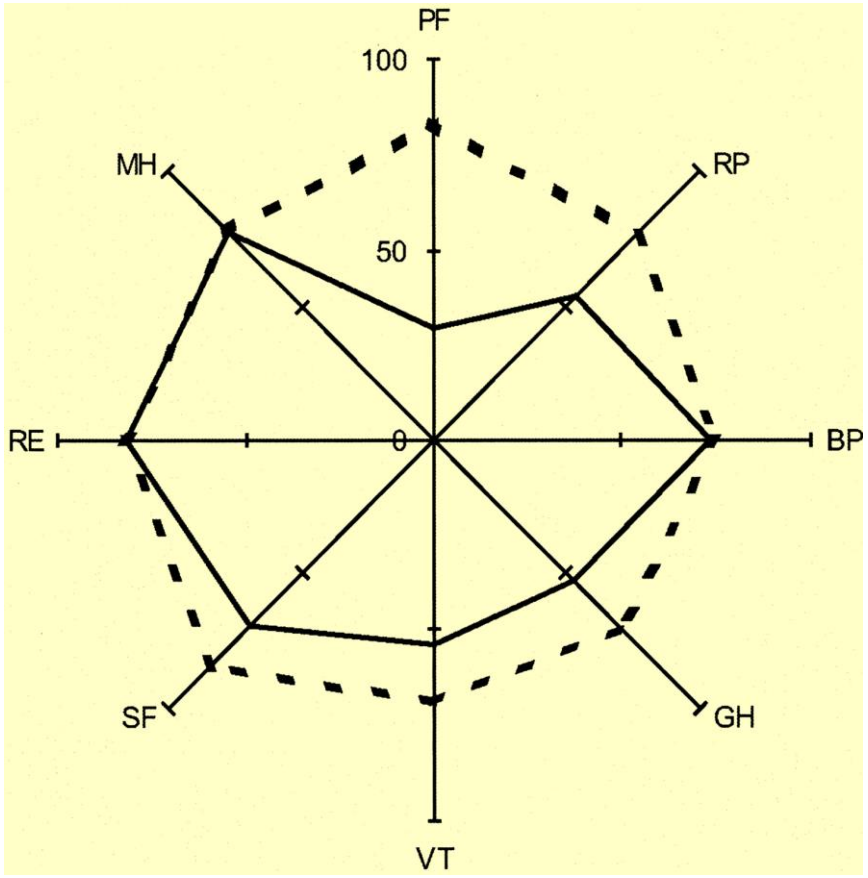
Female: 56%

Male: 44%

- Isolated hyperCKemia (12%)
- HyperCKemia + generalized LGMW + ventilation (61%)
- HyperCKemia + shoulder LGMW (9.5%)
- HyperCKemia + pelvic LGMW (14.8%)
- HyperCKemia + ventilation (2.7%)

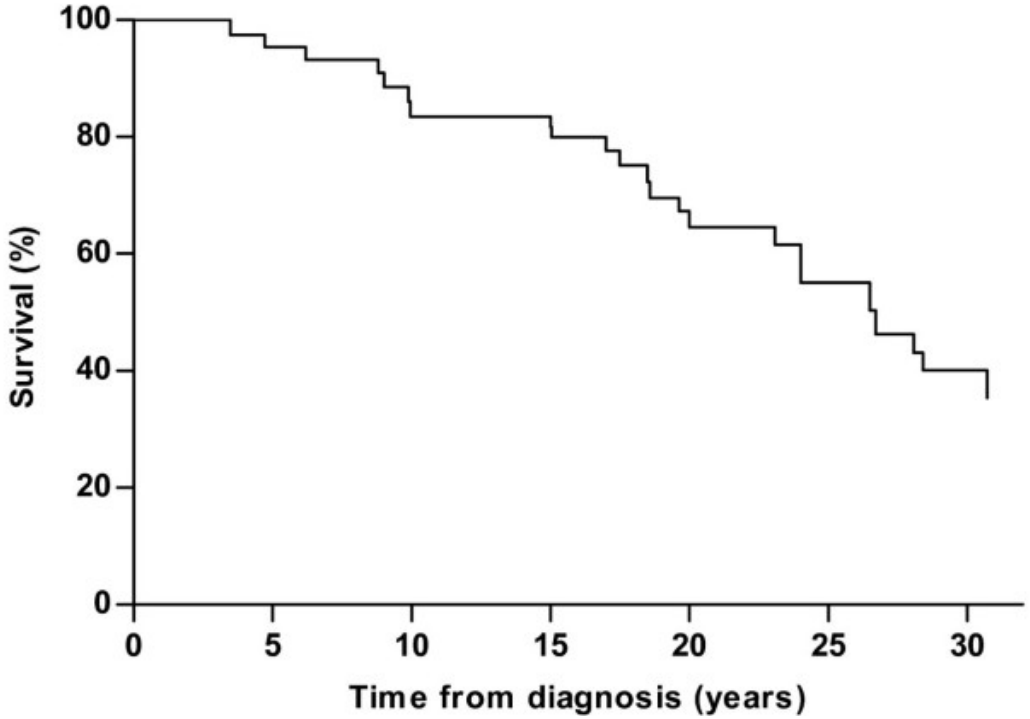
Lukacs. *Neurology*. 2016;87:295-298.

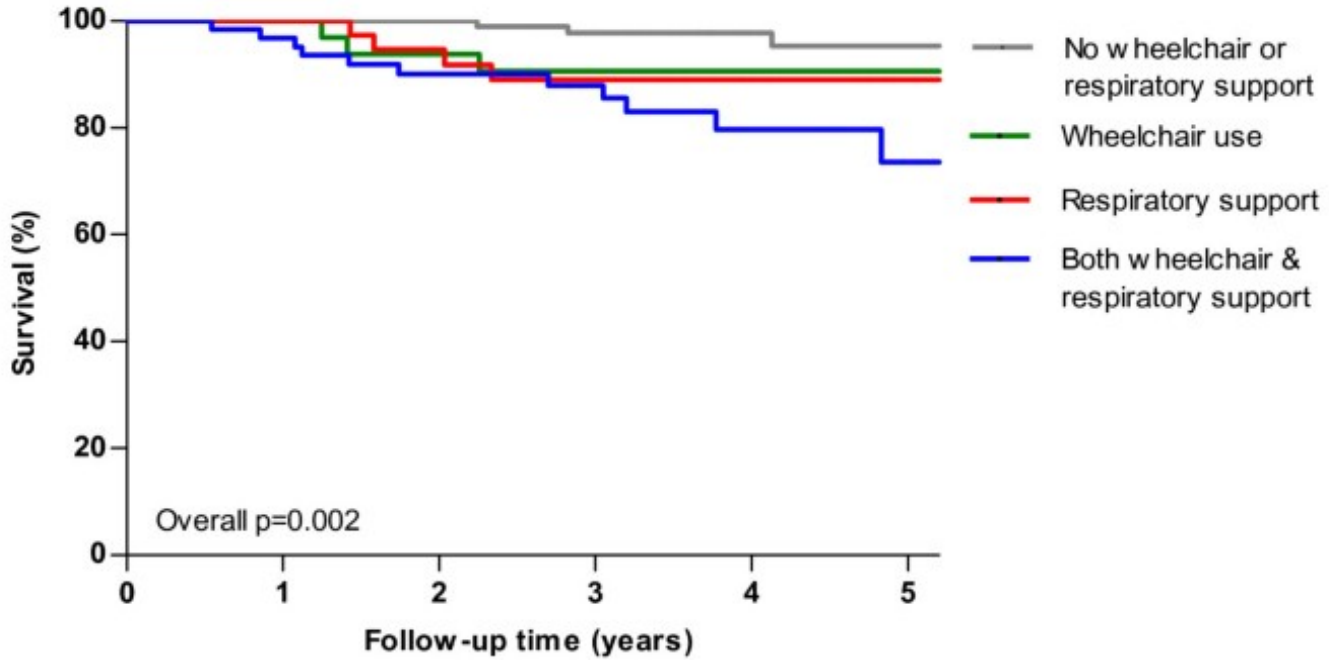
LOPD
Reduced Quality of Life, Affecting All Domains



Hagemans. *Neurology*. 2004;63:1688-1692.

LOPD
Increased Mortality

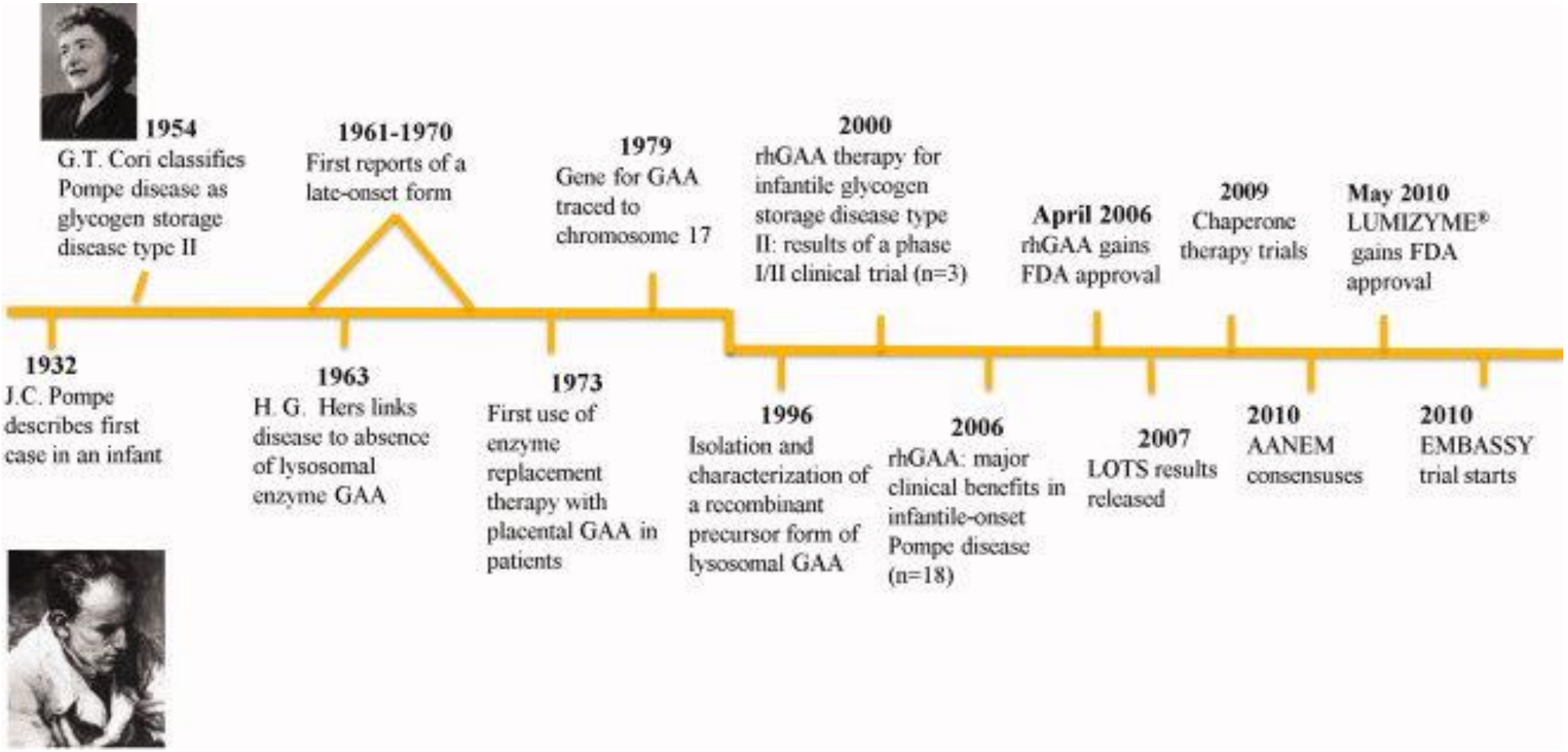




Analysis	Median follow-up time (range)	Observed no. deaths (O)	Expected no. deaths (E) *	Ratio (O/E)	P -value
1	2.3 (<1 month-7 years)	5	2.3	2.2	0.09
2	3.3 (<2 months-7 years)	9	2.8	3.2	0.002

Güngör. *Orphanet J Rare Dis*. 2011;6:34.

Disease-Modifying Agent



Cupler EJ. *Muscle Nerve*. 2012 Mar;45(3):319-33.

Recent Advances in Treatment

Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial

Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial

Recent advances in enzyme replacement therapy and the prospect of gene therapies.

An exciting period for patients with Pompe disease

Diaz-Manera. *Lancet Neurol*. 2021;20(12):1012-1026. Schoser. *Lancet Neurol*. 2021;20(12):1027-1037.

Investigational Gene Therapies – Examples

Gene Therapy Research: Enable a Single Administration that Leads to Sustained Enzyme Expression, as Secreted by the Liver or Muscle

Gene Therapy Vector	Transgene	Target Tissue
AAV2/8 (in vivo)	GAA	Liver
AAV SPK3006 (in vivo)	Secretable GAA	Liver
AAV8 (in vivo)	GAA	Muscle
LV (ex vivo)	GILT-GAA fusion	CD34+ HSCs
AAV (in vivo)	In development	In development
AAV (in vivo)	CD63-GAA fusion	Liver
AAV (in vivo)	GAA	CNS

Ronzitti. *Ann Transl Med.* 2019;7(13). www.askbio.com/gene-therapy-pipeline, accessed 3/2021. Clinicaltrials.gov, accessed 6/2021. www.audentestx.com/pompe-disease, accessed 3/2021. www.avrobio.com/our-pipeline, accessed 3/2021. investors.avrobio.com/news-releases/news-release-details/avrobio-presents-new-preclinical-data-lentiviral-gene-therapy, accessed 6/2021. www.amicusrx.com/programs-pipeline/pipeline, accessed 3/2021.

Part 2

Diagnostic Approach

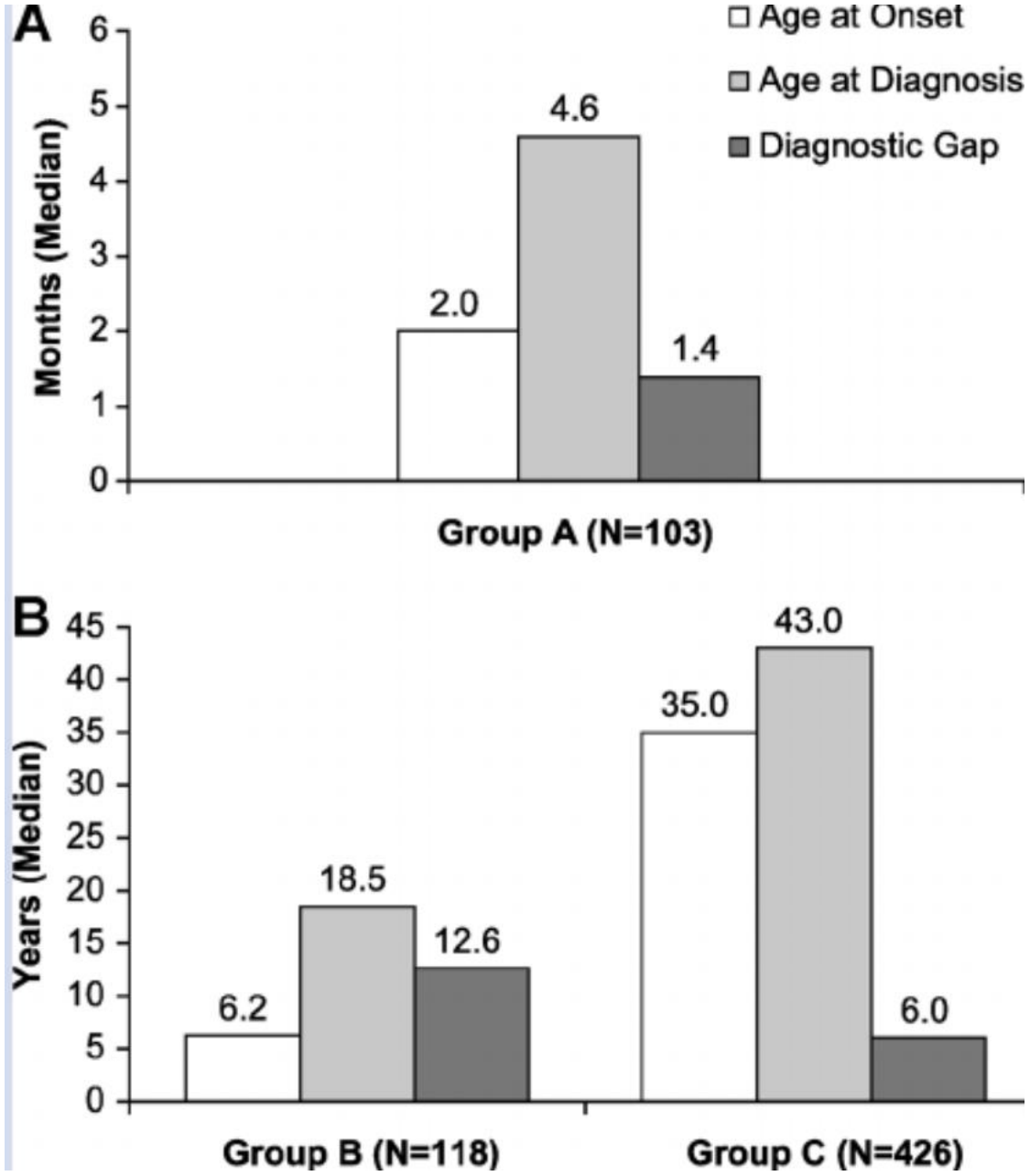
Jordi Diaz Manera
MD, PhD

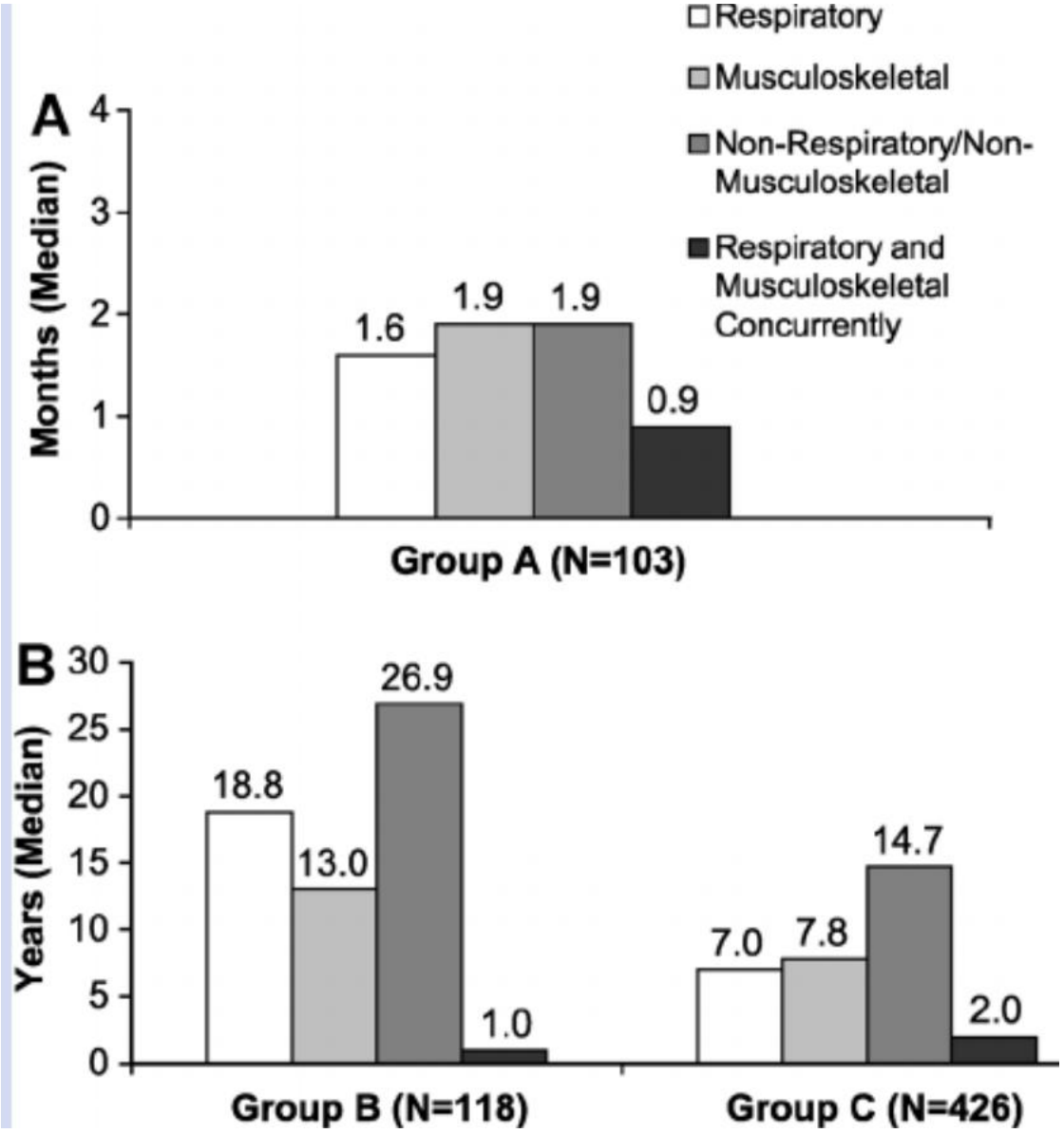
Diagnostic Delay in Pompe Disease

There is a significant delay in the diagnosis of Popme disease, fatal in IOPD and irreversible impairment in LOPD.

Significant morbidity develops before LOPD patients get diagnosed. Quality of life greatly impacted.

Disease is treatable with recent advances in therapy.





Kishnani. *Am J Med Genet A*. 2013;161:2431-2443

LOPD

Differential Diagnosis

Disorder type	Diagnoses
Dystrophies	• Limb-girdle muscular dystrophy • Dystrophinopathies (Duchenne and Becker muscular dystrophy) • Myofibrillar myopathy • Myotonic dystrophy type 2 • Scapuloperoneal syndromes • Danon disease • X-linked myopathy with excessive autophagy • Facioscapulohumeral muscular dystrophy
Inflammatory myopathies	• Polymyositis • Inclusion body myositis
Congenital myopathies	• Nemaline rod myopathy • Central core and multiminicore myopathy • Centronuclear myopathy • Hyaline body myopathy • Other congenital myopathies
Other metabolic myopathies	• Debranching enzyme deficiency • Branching enzyme deficiency • McArdle disease (late-onset) • Mitochondrial myopathy • Lipid disorder myopathies
Motor neuron disorders	• Spinal muscular atrophy types II and III • Kennedy disease • Amyotrophic lateral sclerosis
Neuromuscular junction disorders	• Myasthenia gravis • Congenital myasthenic syndromes • Lambert-Eaton syndrome

American Association of Neuromuscular & Electrodiagnostic Medicine. *Muscle Nerve.* 2009;40:149-160.

LOPD – Selected Differentials

Limb-Girdle Muscular Dystrophy

- Genetic disorder, 1:14,500 to 123,000
- Male and female.
- Age of onset: 8-15 year

Duchenne and Becker Muscular Dystrophy

- Genetic disorders, 1:20,000
- Duchenne: Male. Age of onset: 3-5 years
- Becker: Mostly male. Age of onset: 5-15 years

Spinal Muscular Atrophy

- Genetic disorder, 1:10,000.
- Male and female.
- Age of onset: 6-18 months

LOPD – Selected Differentials

Inflammatory Myositis

- Polymyositis
  - 1:10,000 to 100,000
  - Age 31-60 years mostly. More common in women
- Inclusion Body Myositis
  - 1:15,000 to 65,000
  - Age over 50 years. Primarily men

Amyotrophic Lateral Sclerosis

- 1:35,000 to 65,000
- Age 40-70 years. More males than females

Myasthenia Gravis

- An autoimmune disease
- 1:2,500 to 7,000
- Adult. Male and female.

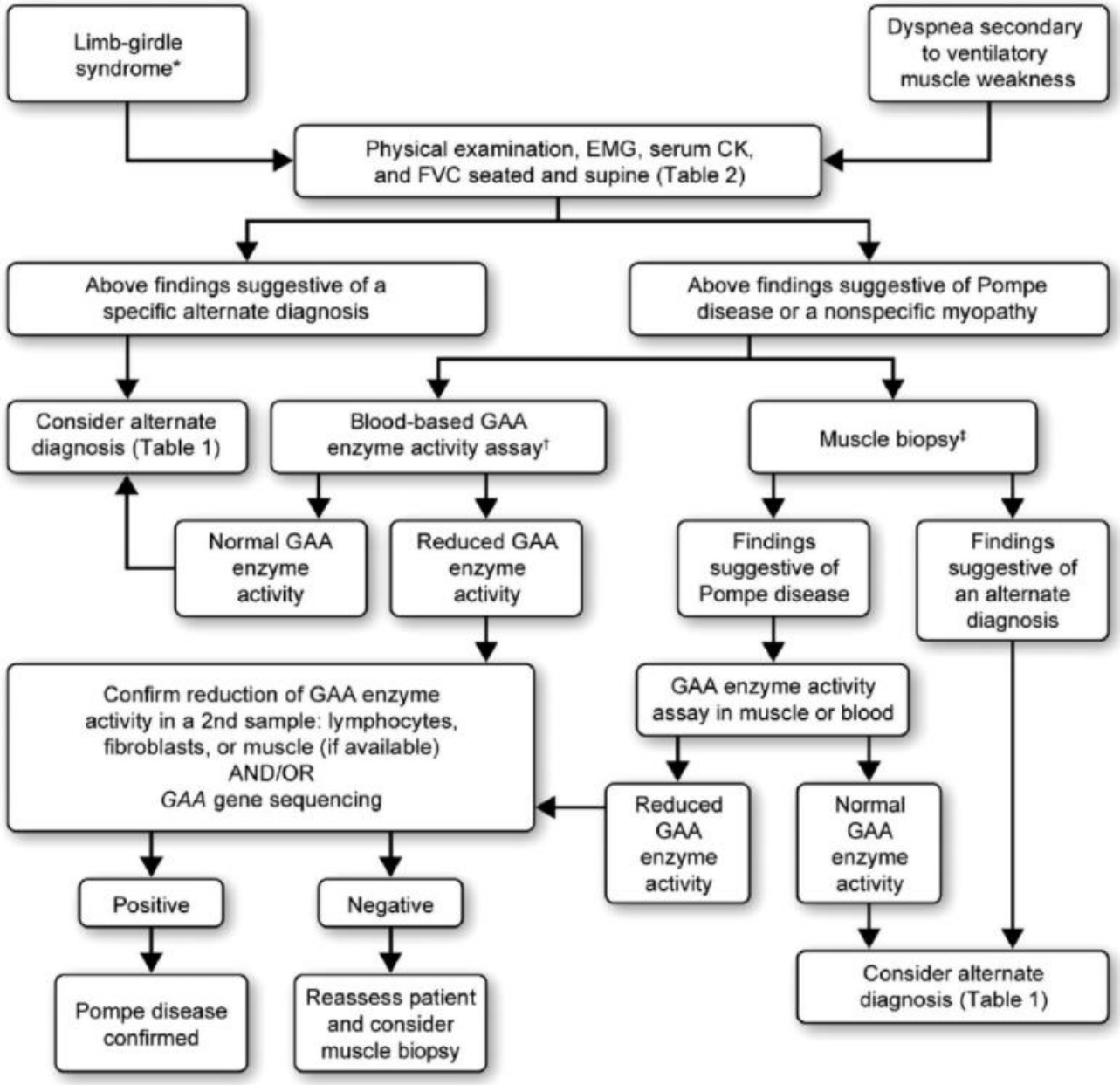
LOPD – Common Findings Among Differentials

Disease for Which It can be Mistaken	⇑CK	Findings in Common
Duchenne, Becker, Limb-Girdle Type	X	Progressive muscle weakness in shoulders, pelvis, and lower limbs
Scapulohumeral Syndromes		Weakness of shoulder girdle, wining of scapula
Myotonic Dystrophy-2	X	Proximal muscle weakness, fatigue, cramps, irritative EMG
Rigid Spine Syndrome		Limited mobility of the spine, low back pain, axial muscle weakness
Myasthenia Gravis		Fatigue and generalized muscle weakness, respiratory distress
Spinal Muscular Atrophy	X	Muscle weakness and atrophy
Polymyositis	X	Subacute proximal muscle weakness
Glycogen Storage Disease IIIa, IV, V, VII	X	Hypotonia and hepatomegaly in childhood, muscle weakness, exercise intolerance
Danon Disease	X	Hypertrophic cardiomyopathy, vacuolar myopathy with glycogen storage
Mitochondrial Myopathies	X	Muscle weakness, exercise intolerance, cardiomyopath

Miguel. *Rev Neurol* 2012; 54(8):497-507

LOPD

Diagnostic Algorithm



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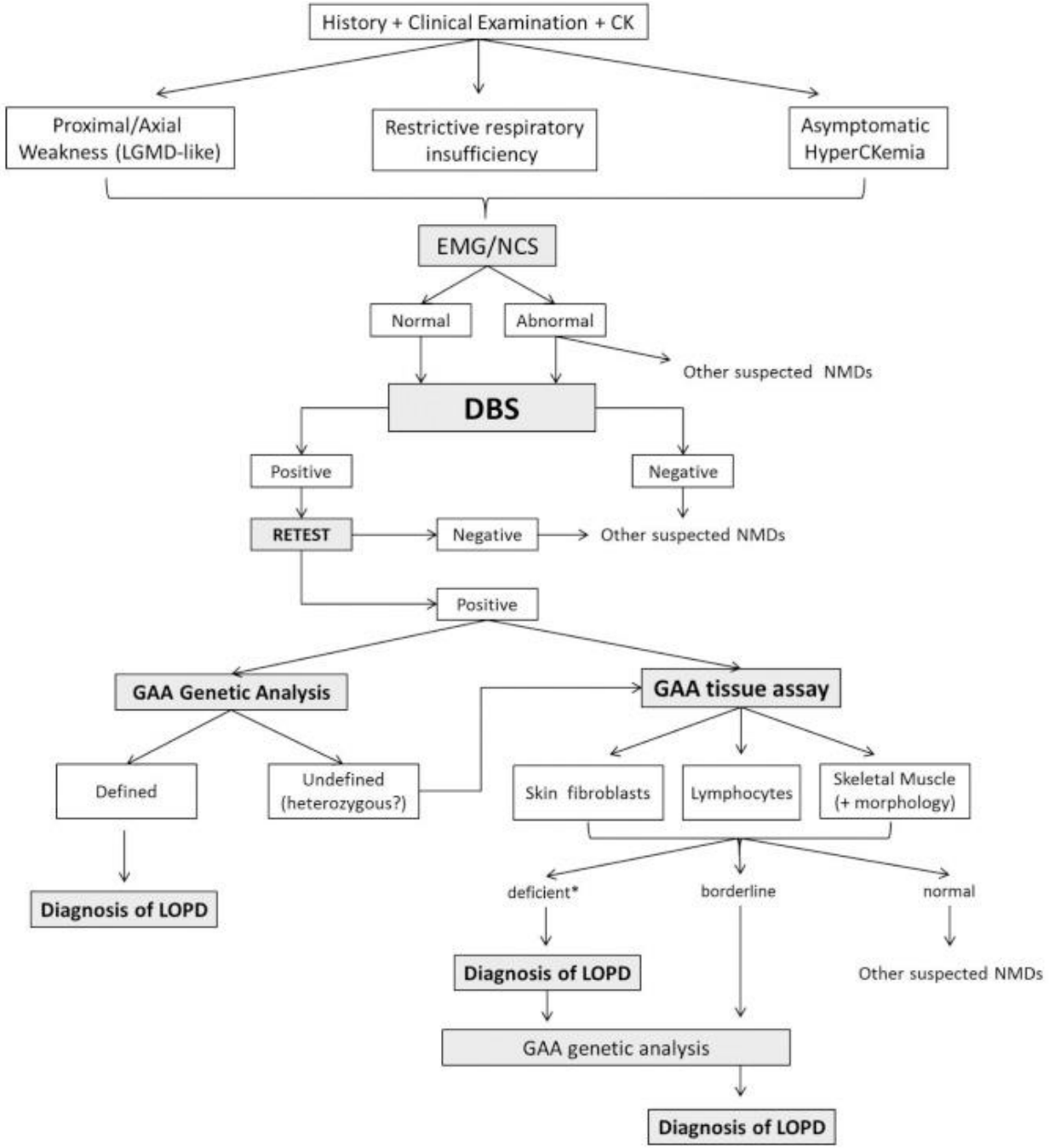
LOPD

Diagnostic Algorithm



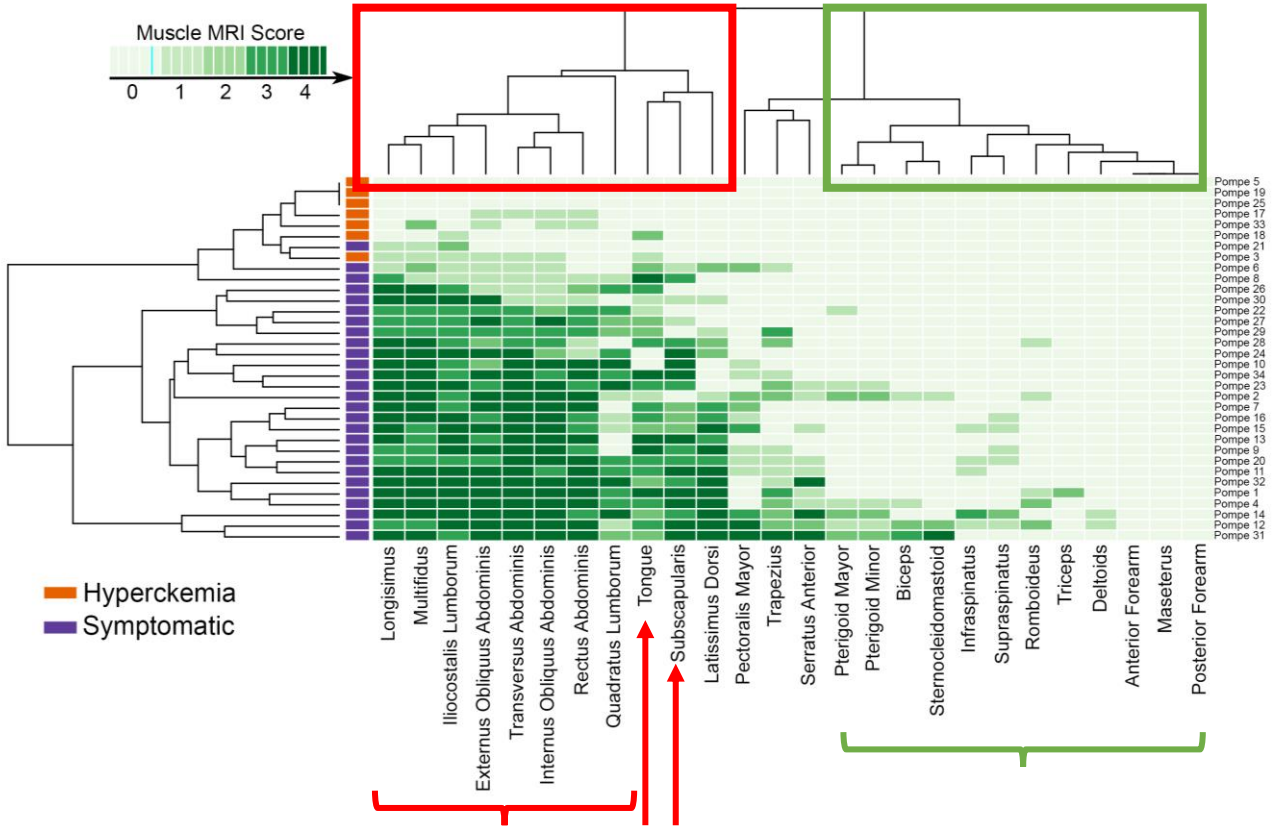
Toscano. Acta Myol. 2013;32(2):78-81

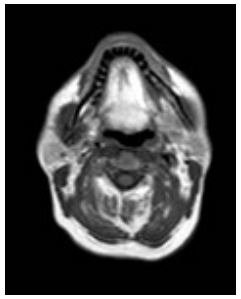
Muscle MRI Findings in Childhood/Adult Onset Pompe Disease Correlate with Muscle Function

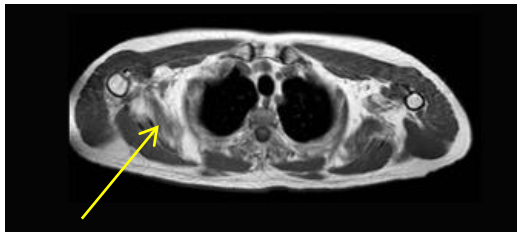
Sebastián Figueroa-Bonaparte[1,2], Sonia Segovia[1,2], Jaume Llauger[3], Izaskun Belmonte[4], Irene Pedrosa[4], Aída Alejaldre[1,2], Mercè Mayos[5], Guillermo Suárez-Cuartín[5], Eduard Gallardo[1,2], Isabel Illa[1,2], Jordi Díaz-Manera[1,2]*, Spanish Pompe Study Group[¶]

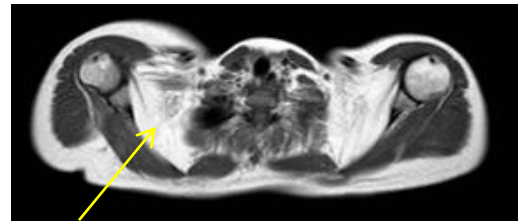
PLOS ONE
2016

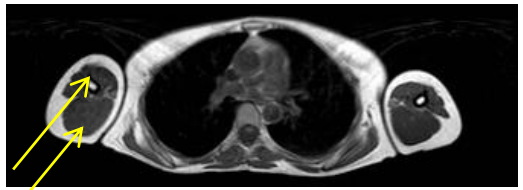
Natural history study Adult Pompe Barcelona
N=36
MUSCLE MRI AT BASELINE VISIT

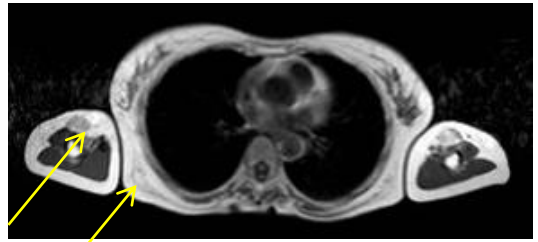


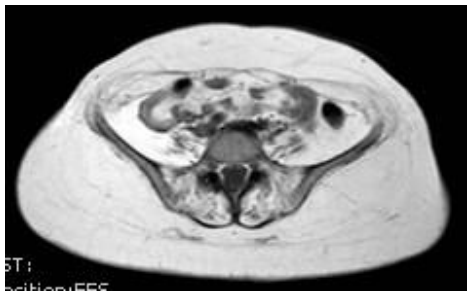


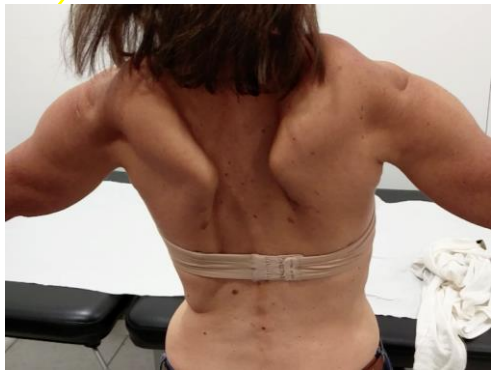












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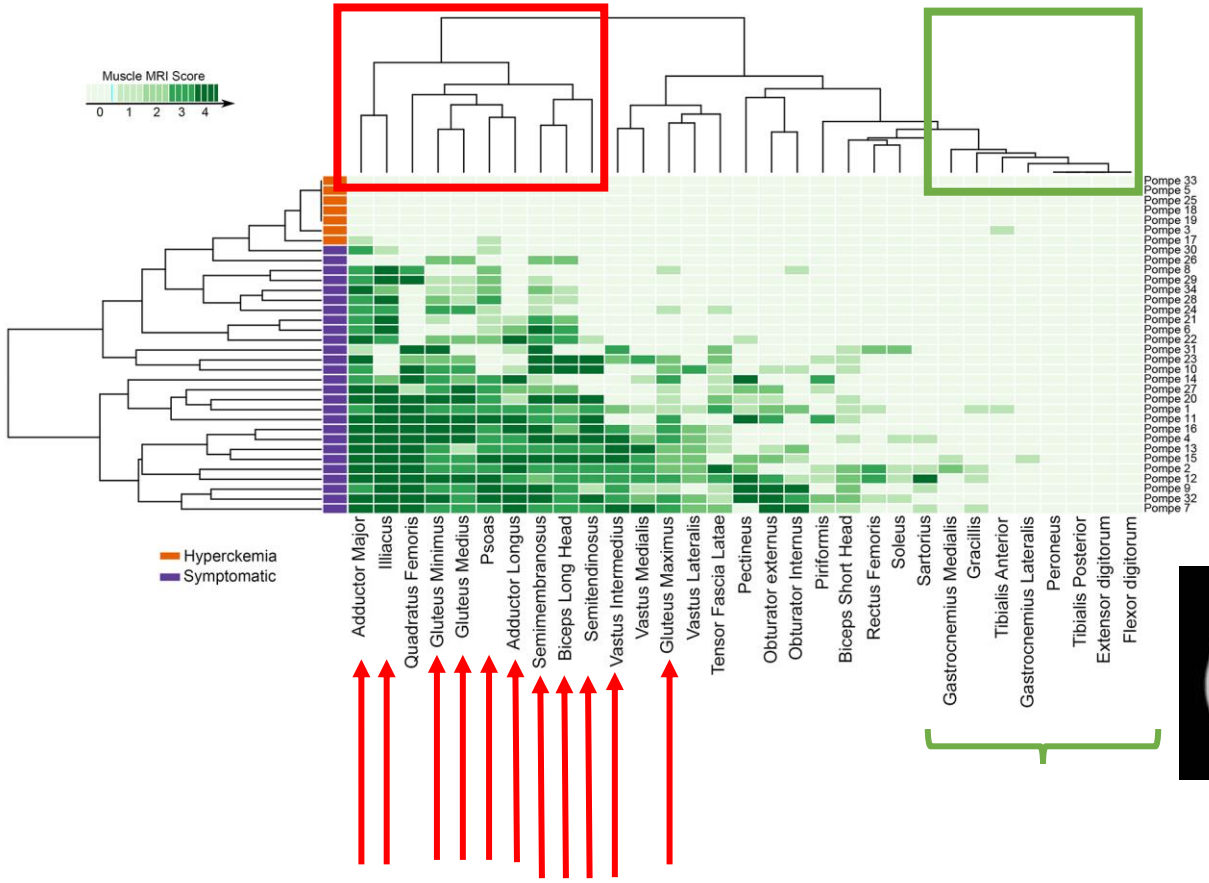
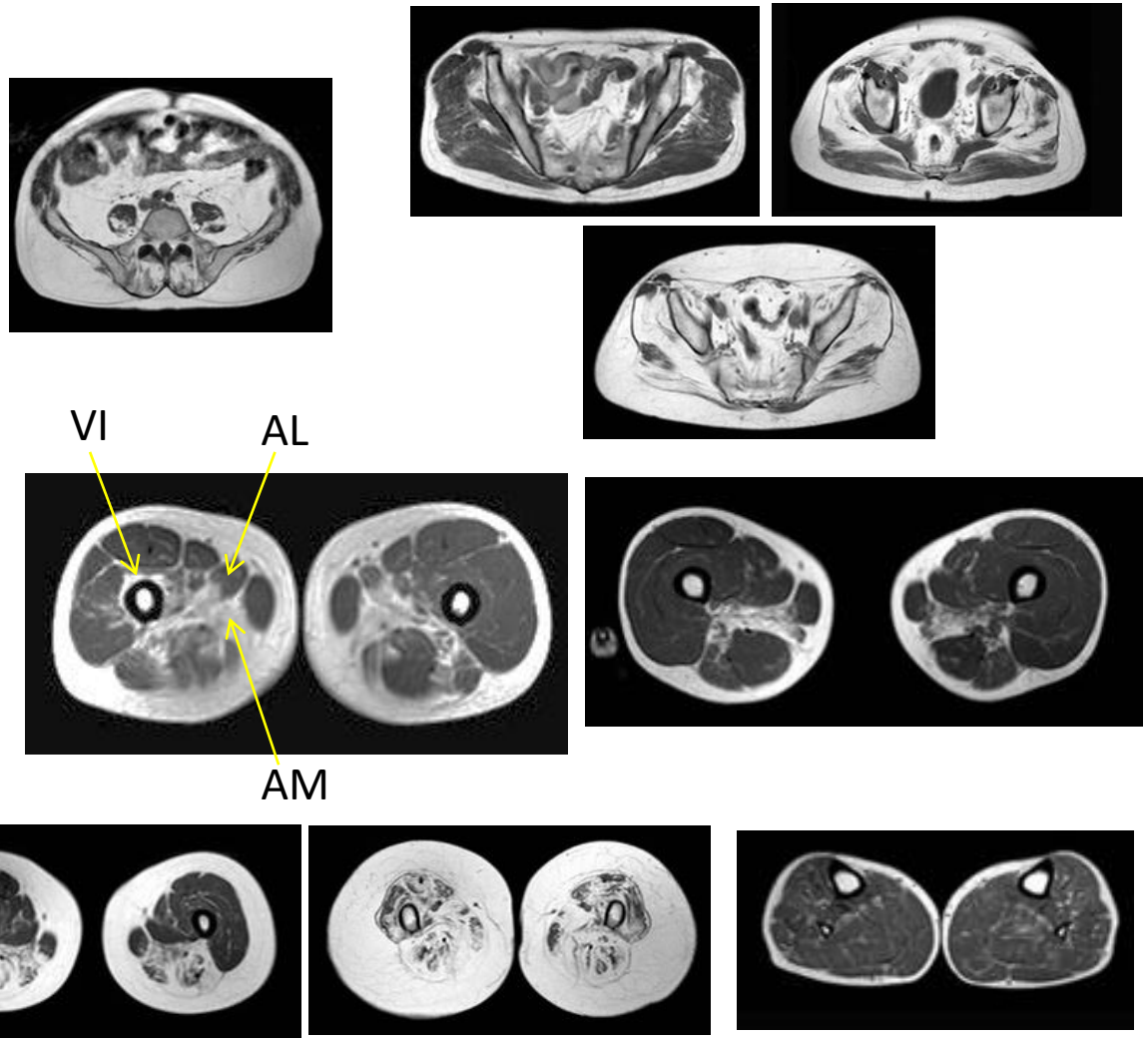
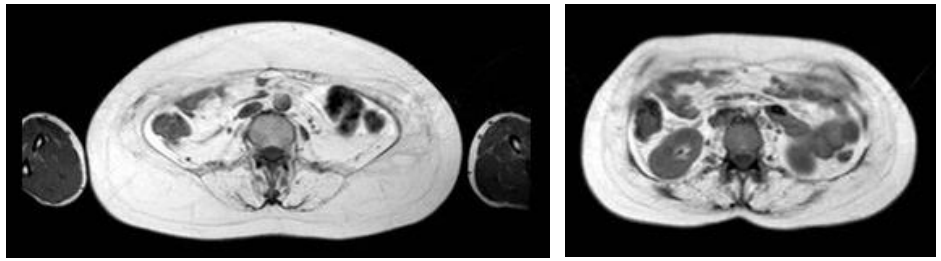




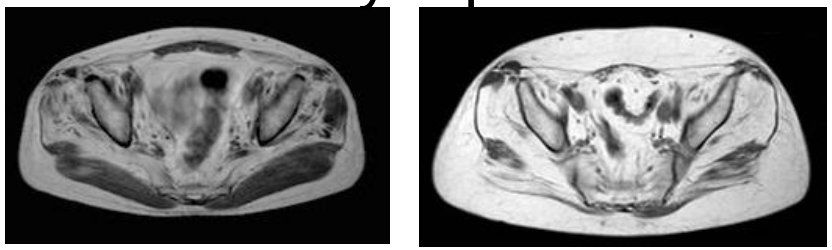
Pompe Patients Do Have a Typical Gait Pattern

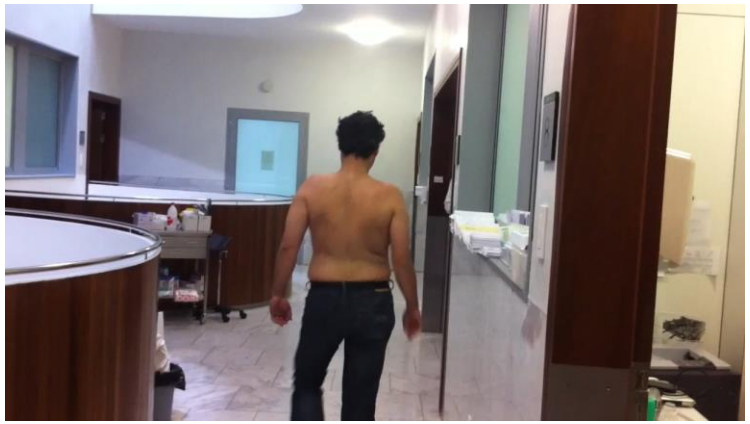
Abdominal and paraspinal fatty replacement



+

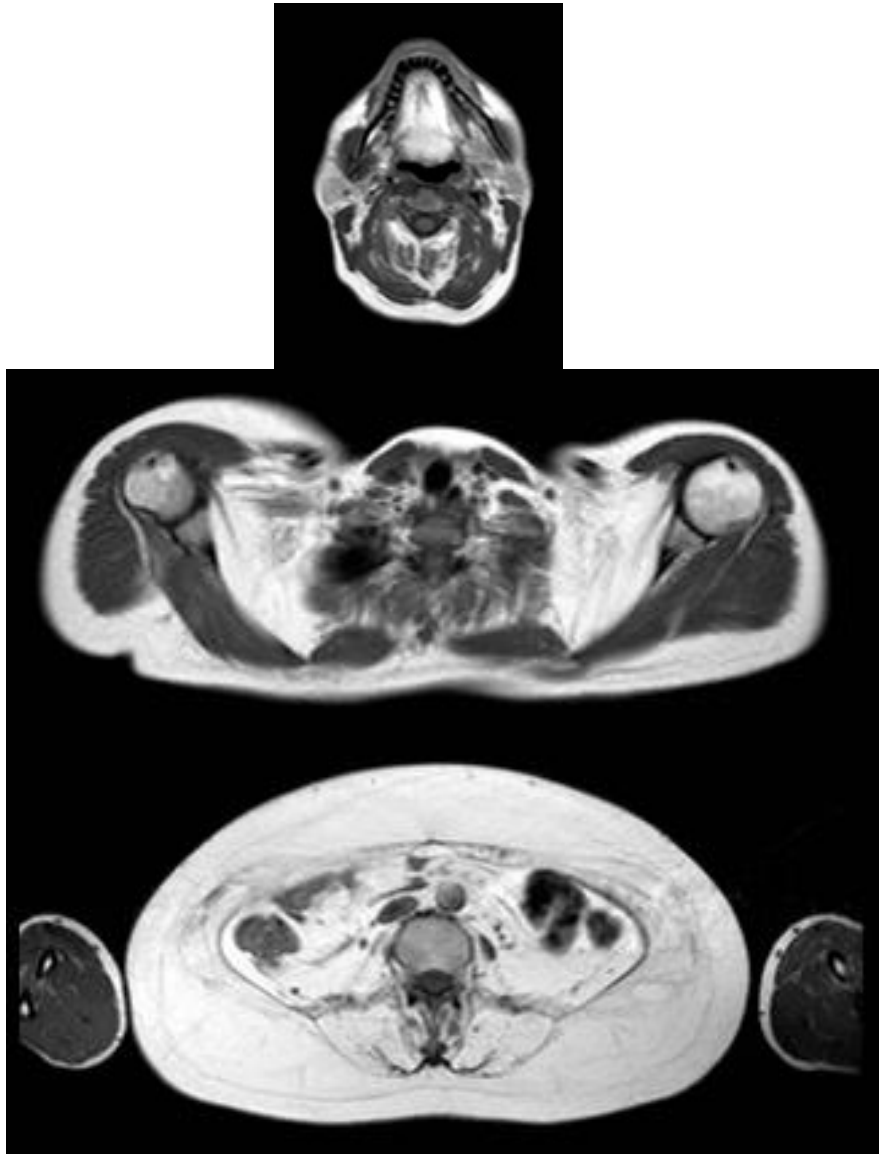
Pelvis fatty replacement

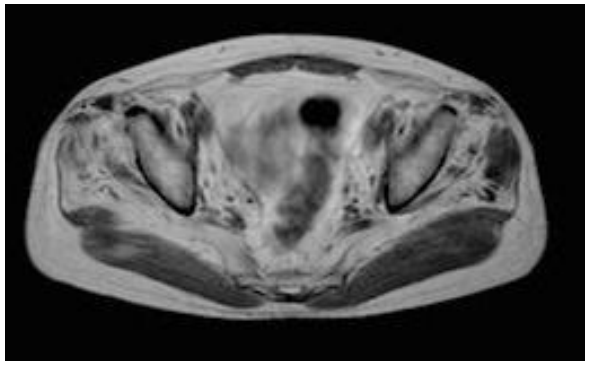


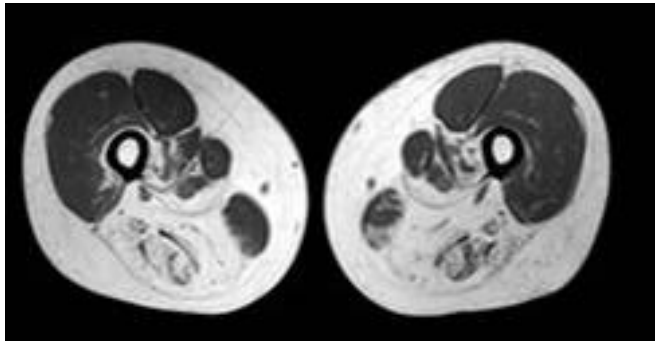


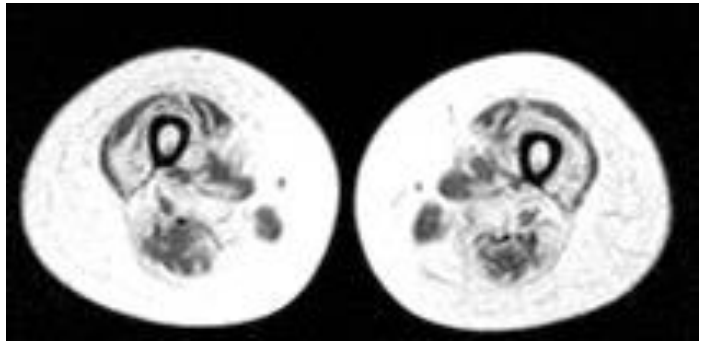
Trendelemburhg + pelvis anteversion

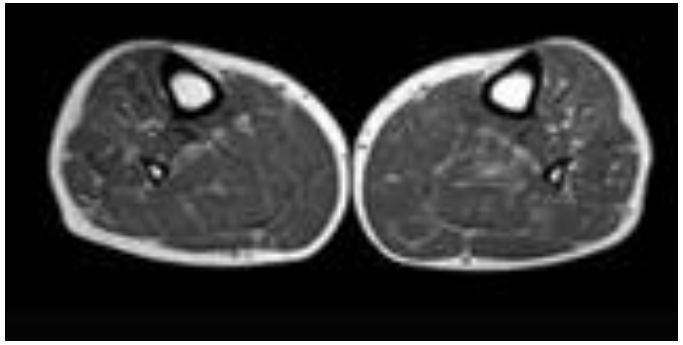
The Pompe Pattern of Fatty Replacement











Newborn Screening (NBS) in the Diagnosis of IOPD and LOPD

Advantage

- Treatment, especially early in the course, is effective for reversing or preventing cardiomyopathy, respiratory insufficiency, ventilator dependence
- Prevalence is higher than estimated. Presymptomatic patients can be identified and monitored
- Knowledge on how the disease progresses and whether carriers are affected

Drawbacks and Challenges

- Late onset forms are much more common than infantile forms (75%:25%). These late onset forms may not manifest until in their teens or much later.
- No clear agreement on how to monitor these individuals. May result in unnecessary anxiety/depression, modification of diet and lifestyle, and treatment and testing.
- Discrimination for life insurance and long-term disability

Missouri Data Jan 2013 – Dec 2018

Table 2. Results of Confirmatory Pompe Testing.

Total Screened	~467,000
Screen Positives	274
Confirmed Disorders	46
Infantile Onset Pompe Disease	10
Later-onset Pompe Disease	36
Genotypes of Unknown Significance	8
Pseudodeficiencies	53
Carriers	65
Normal	97
Lost to Follow-up	5
Positive Predictive Value (PPV)	17.1%
False Positive Rate (FPR)	0.05%

California Data after 1 year

Table 2. California Pompe disease screening results (among screen positives) by neonatal factors.

	Classic Infantile-Onset	Suspected Late-Onset	Carrier	Pseudo-Deficiency	No Disorder	Overall
Sex						
Female	1	5	14	11	6	37
Male	1	11	20	9	10	51
Nursery						
NICU	2	1	4	11	14	32
Non-NICU	0	15	30	9	2	56
Maturity						
Premature	1	2	4	8	2	17
Full term	1	14	30	12	14	71
Total	2	16	34	20	16	88
Birth prevalence	5/1,000,000 (1 in 226,600)	36/1,000,000 (1 in 28,300)	75/1,000,000 (1 in 13,300)	45/1,000,000 (1 in 22,700)		

Table 4. Allelic frequency by race/ethnicity.

	Pathogenic		Pseudodeficiency Allele		Uncertain Significance	
Race/Ethnicity	**Count**	**Allele Frequency**	**Count**	**Allele Frequency**	**Count**	**Allele Frequency**
African American (n = 37,340)	6	161/1,000,000 (1 in 6200)	4	107/1,000,000 (1 in 9300)	3	80/1,000,000 (1 in 12,500)
Asian/Pacific Islander (API, n = 69,510)	15	216/1,000,000 (1 in 4600)	30	432/1,000,000 (1 in 2300)	6	86/1,000,000 (1 in 11,600)
Hispanic (n = 214,049)	14	66/1,000,000 (1 in 15,300)	7	33/1,000,000 (1 in 30,600)	5	23/1,000,000 (1 in 42,800)
White (n = 115,281)	17	148/1,000,000 (1 in 6800)	11	95/1,000,000 (1 in 10,480)	2	17/1,000,000 (1 in 57,600)

NBS: Pompe is much more common than seen in neuromuscular clinic

Klug. *Int J Neonatal Screen* 2020;6:11, Tang. *Int J Neonatal Screen* 2020;6:9

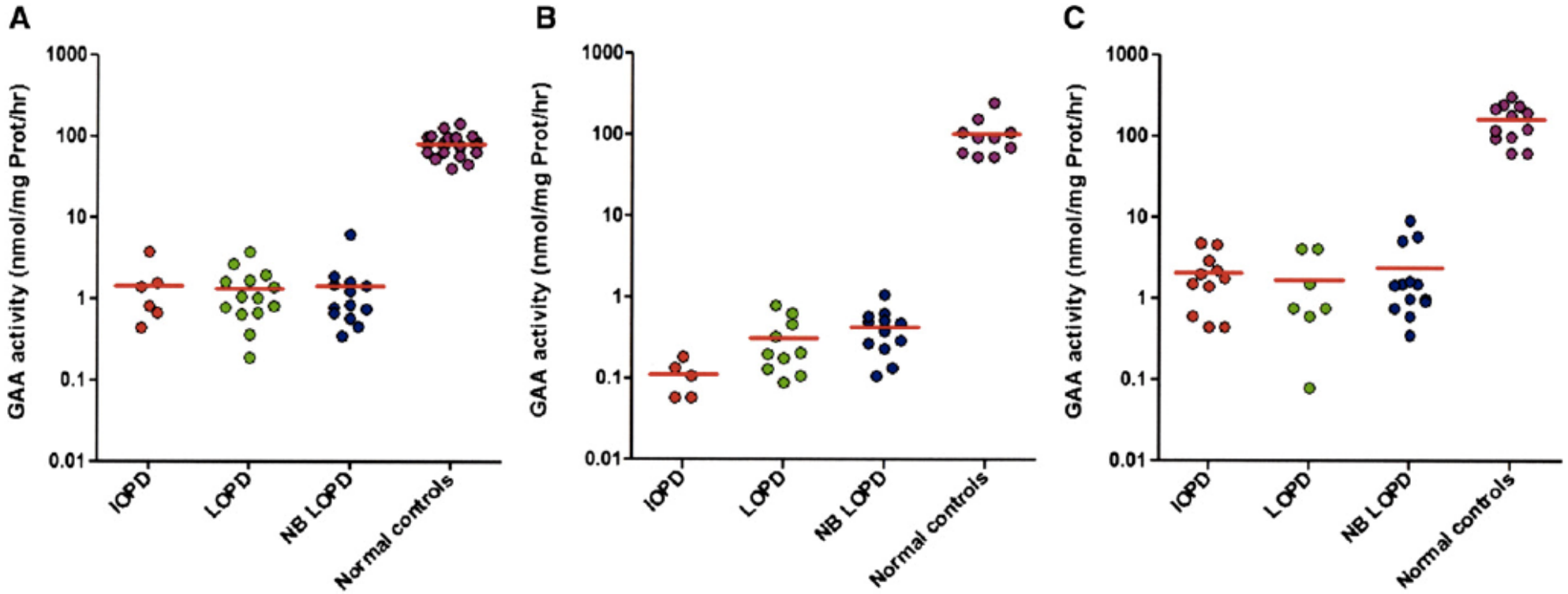
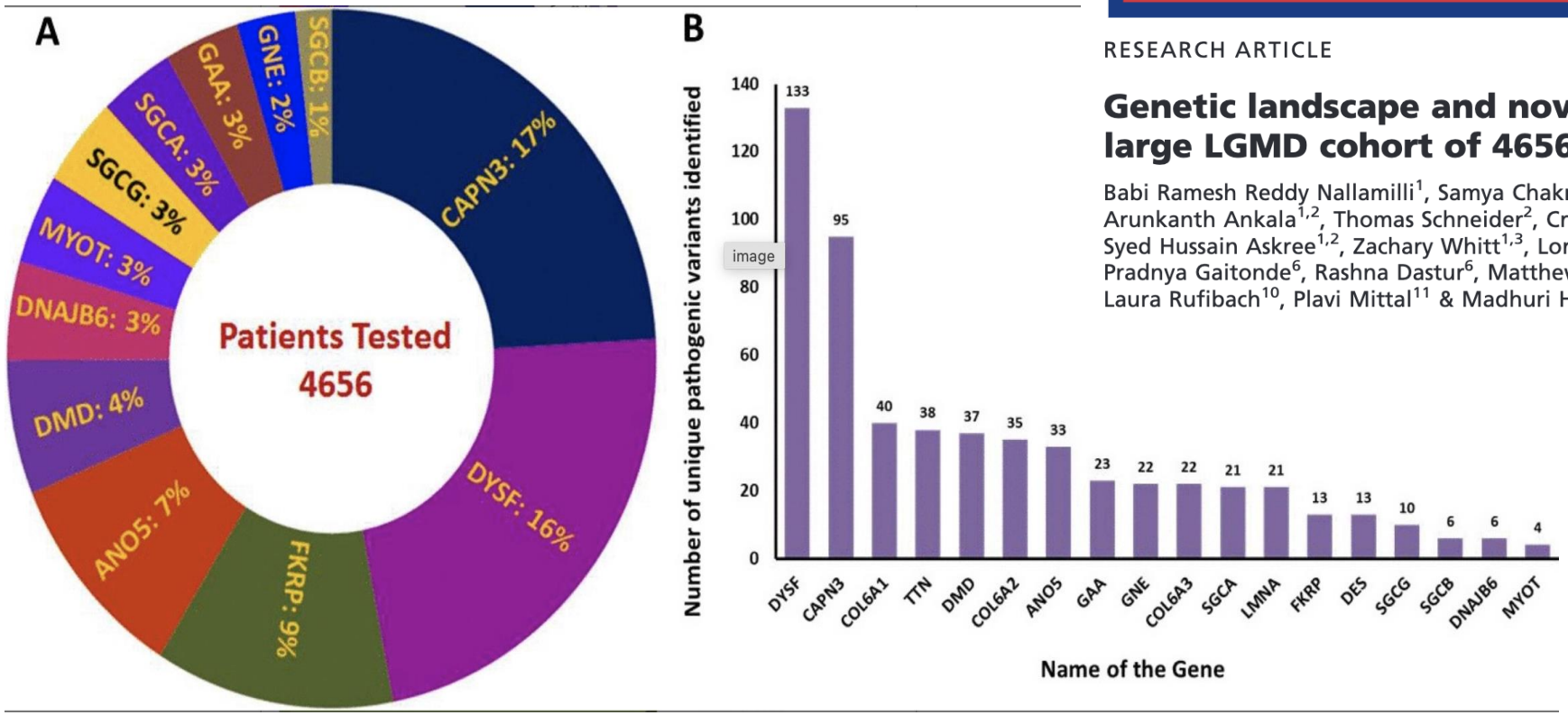


Figure 2. GAA activity of newborns with infantile-onset Pompe disease *(IOPD)*, patients with later-onset Pompe disease *(LOPD)*, newborns with later-onset Pompe disease *(NB LOPD)*, and control subjects. **A,** Lymphocyte GAA activity assayed with 4-methylumbelliferyl-α-D-glucopyranoside *(4MU)*; **B,** fibroblast GAA activity assayed with 4MU; **C,** fibroblast GAA activity assayed with glycogen.

NBS: GAA levels cannot differentiate between IOPD and LOPD

Chien. *J Pediatr* 2011;158:1023-7

Next Generation Sequencing (NGS) in the Diagnosis of LOPD



ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

Genetic landscape and novel disease mechanisms from a large LGMD cohort of 4656 patients

Babi Ramesh Reddy Nallamilli[1], Samya Chakravorty[1], Akanchha Kesari[1,2], Alice Tanner[1,2], Arunkanth Ankala[1,2], Thomas Schneider[2], Cristina da Silva[2], Randall Beadling[2], John J. Alexander[1,2], Syed Hussain Askree[1,2], Zachary Whitt[1,3], Lora Bean[1,2], Christin Collins[1], Satish Khadilkar[4,5], Pradnya Gaitonde[6], Rashna Dastur[6], Matthew Wicklund[7], Tahseen Mozaffar[8], Matthew Harms[9], Laura Rufibach[10], Plavi Mittal[11] & Madhuri Hegde[1]

The paradigm to diagnose LOPD may be changing: More cases picked up on NGS

Nallamilli. *Ann Clin Transl Neurol*. 2018;5:1574-1587

Summary of GAA variants identified in LOPD patients.

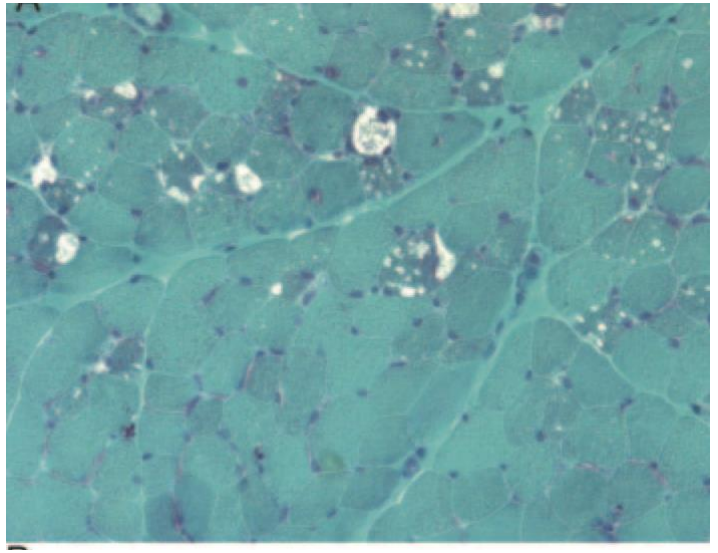
Identification of 28 patients with two GAA pathogenic variants indicates the increased prevalence of LOPD in this study

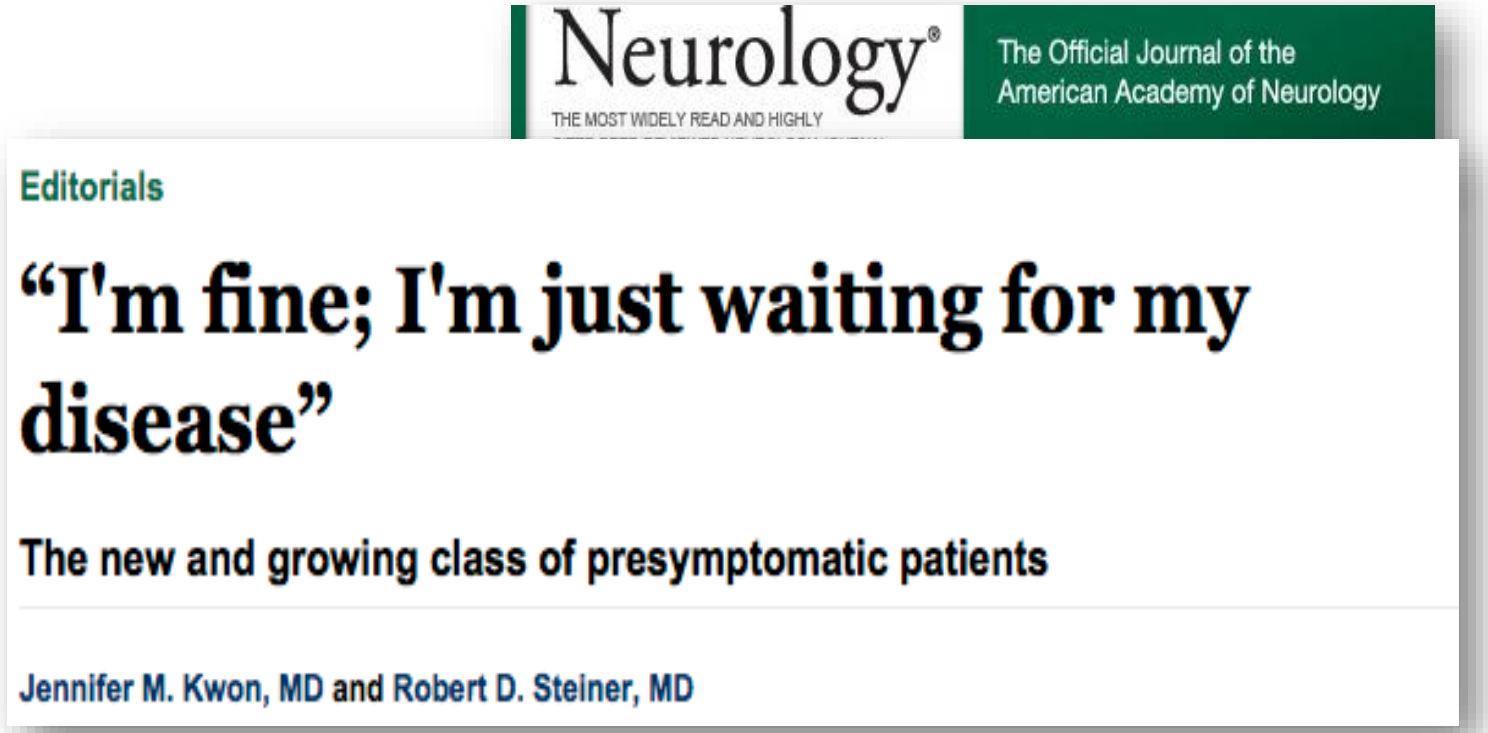
Patient ID	Gender	Age	Gene	Variant 1	Variant 2
AOP1	Female	61	*GAA*	c.-32-13T>G	c.1124G>T (p.R375L)
AOP2	Female	79	*GAA*	c.-32-13T>G	c.2140delC
AOP3	Female	33	*GAA*	c.-32-13T>G	c.525delT
AOP4	Male	71	*GAA*	c.-32-13T>G	c.1912G>T (p.G638W)
AOP5	Unknown	54	*GAA*	c.-32-13T>G	c.2512C>T(p.Q838X)
AOP6	Male	66	*GAA*	c.-32-13T>G	c.2481 + 102_2646 + 31del (Exon 18 deletion)
AOP7	Male	70	*GAA*	c.-32-13T>G	c.2481 + 102_2646 + 31del (Exon 18 deletion)
AOP8	Female	44	*GAA*	c.-32-13T>G	c.2481 + 102_2646 + 31del (Exon 18 deletion)
AOP9	Male	18	*GAA*	c.-32-13T>G	c.2481 + 102_2646 + 31del (Exon 18 deletion)
AOP10	Male	40	*GAA*	c.-32-13T>G	c.2238G>A(p.W746X)
AOP11	Male	59	*GAA*	c.-32-13T>G	c.1655T>C(p.L552P)
AOP12	Male	70	*GAA*	c.736delC	c.546G>A(p.T183T)
AOP13	Female	53	*GAA*	c.-32-13T>G	c.1841C>A(p.T614K)
AOP14	Male	68	*GAA*	c.-32-13T>G	c.1143delC
AOP15	Female	40	*GAA*	c.853C>T(p.P285S)	c.2560C>T(p.R854X)

Nallamilli. *Ann Clin Transl Neurol*. 2018;5:1574-1587.

Diagnosis Made at Pre-Symptomatic Stage

- 21 yo man, active, healthy
- 1.5 x CK for 13 months, dx with LOPD
  - GAA mutations c.-32–13T>G and c.655G A (p.Gly219Arg)
  - Normal echo
  - Muscle biopsy at 19 months
- Yearly exams (echo). At 16 years: more assessments (PFTs, MRI, in vivo NMR)





Kwon. *Neurology* 2011; 77(6):522-523