



# AWARENESS AND DEVELOPMENTS IN THE TREATMENT OF POMPE DISEASE

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**ABSTRACT:** Pompe disease is a hereditary, uncommon (one in every 40,000 births) and frequently deadly ailment that affects the heart and skeletal muscles. Mutations in a gene that produces an enzyme called acid alpha-glucosidase cause it (GAA). This article is meant to raise awareness among Pompe disease patients. We also talk about new future treatments on the market for the treatment of Pompe illness.

Keywords:

Pompe disease, Glycogen storage disease type II, Enzyme replacement therapy, Gene therapy, Pompe disease diagnosis, Early symptom recognition, Pulmonary function testing, Cardiac monitoring, New therapeutic options, Patient advocacy groups

**INTRODUCTION:** Glycogen storage disorder type II (or) Acid Maltase Deficiency or Pompe disease is a monogenic autosomal recessive illness characterised by a lack of lysosomal alpha glycosidase and mutations in the GAA gene on chromosome 17, which is primarily found in the cardiac and skeletal muscles [1,6]. The glycogen-degrading enzyme acid alpha Glycosidase, which is normally found in Lysosomes but is lacking in Pompe disease, was identified by Belgian biochemist Henn-Grey Hers in 1963[2]. The two kinds of Pompe disease are infantile onset Pompe disease (IOPD) and late onset Pompe disease (LOPD) [1]. Hypotonia, feeding problems, muscle weakness, limited weight gain, and respiratory problems are all signs of IOPD in the first month of life. After 12 months, symptoms such as increased muscle weakness (trunk and lower limbs) appear, and cardiac involvement includes rhythm problems such as Wolf Parkinson-white syndrome, ECG abnormalities, and ascending aorta dilatation. Respiratory issues are the leading cause of death in people with LOPD [3][7]. Pompe disease is a single disease continuum that can afflict anyone at any age and exhibits phenotypic heterogeneity, as well as varying rates of progression and organ involvement which can be

confirmed by a genetic profile diagnosis whereas measuring urine tetra saccharide G1C4 acts as Additional evidence. [5, 9]. Pompe disease is the first known lysosomal storage disease at this time. Enzyme replacement therapy [ERT] with recombinant human GAA is the only treatment for pompe disease [4]. It was first tested in 1973 and is now approved in Europe and the United States at a dose of 20mg/kg delivered biweekly through IV infusion. High resolution light microscopy [HRLM] and computer assisted Histomorphometry have been established to analyse patient samples [8].

**AWARENESS ON POMPE:** Pompe disease, like many other rare diseases, is severely underdiagnosed or misdiagnosed, and it is frequently misunderstood. The condition, which can mirror other disorders, is unfamiliar to most physicians and other healthcare workers. As a result, many patients may go for years without learning what is causing their symptoms. A patient's treatment might begin as soon as he or she receives a diagnosis. This can aid in the maintenance or enhancement of their quality of life. Greater public awareness tends to lead to more research funding, which could lead to new and better treatments, and possibly a cure [10].

#### LIFE EXPECTANCY:

The type of Pompe disease a patient has, the severity of symptoms, and how well they are managed all influence the patient's life expectancy.

Typical infantile onset the most severe type of the condition, Pompe disease, manifests symptoms within a few months of birth. Affected babies generally die of cardiac disease within their first year of life if they are not treated [23].

The disease is less severe in the non-classical infantile-onset variant. It manifests in the first year of life and progresses more slowly, but patients frequently develop heart disease and breathing issues, which can be fatal if not treated promptly [22].

Pompe disease with a late onset can happen at any age. The acid alpha-glucosidase enzyme is found in higher concentrations in patients with this type of disease than in people with more severe types of the disease [31]. Patients with late-onset illness may also experience muscle weakness and respiratory difficulties [21]. If the disease strikes in childhood, they can live to be 30 years old, and if it strikes in maturity, they can live to be 50 years old. In general, the later the onset of the disease, the slower the progression of the disease and the longer the life expectancy [11,25].

#### COMPLICATIONS:

- **INFANTILE ONSET:**

GAA activity is essentially complete or partial in infants with Pompe illness [17]. Eating disorders, low weight gain, delayed motor milestones, and respiratory issues with superimposed lung infections are all symptoms that appear in the first few months of life [14]. Hypertrophic cardiomyopathy, cardiorespiratory failure, and generalised severe muscle weakness with floppy new born syndrome characterise this classic type,

which appears shortly after birth [18,20]. If undetected and mistreated, newborns usually do not survive beyond their first year of life [15].

- LATE ONSET:

The non-classical or late-onset variant of Pompe disease is milder than the classical version. Its symptoms might appear at any time after the age of one year [16]. Involvement of the cardiac system is extremely uncommon, while signs of skeletal muscle involvement are common [24]. Myopathy and respiratory issues progress slowly, resulting in varied degrees of disability and a reduction in average life expectancy. Many of the patients require the use of a wheelchair or respiratory support [12,19].

### PROGNOSIS:

A thorough clinical evaluation, a complete patient and family history, and a number of tests are used to diagnose Pompe illness [27]. Blood can be drawn from people suspected of having Pompe disease, and the function and activity of the acid alpha glucosidase enzyme in white blood cells (leukocytes) can be determined [28]. When a leukocyte or blood spot assay is used to make a diagnosis of Pompe disease, it must be verified via molecular genetic testing (DNA analysis) or another enzyme assay [26]. Sleep studies, breathing tests to measure lung capacity, and electromyography, a test to measure muscle activity, are some of the other procedures that may be used to diagnose or assess symptoms linked with Pompe disease [29]. Chest x-rays, electrocardiograms, and echocardiograms are some of the techniques used to evaluate the heart. Pre-implantation genetic diagnostics (testing an embryo to see if it shares the parents' genetic problems) may also be a possibility [13,30].

### COMMORBITIDITIES:

- INFANTILE ONSET

Hepatomegaly, significant cardiomegaly, weakness, and hypotonia are all symptoms of the juvenile phase of Pompe disease. Comorbidities associated with musculoskeletal problems, such as inflexible spine syndrome, limb-girdle weakness, and exercise intolerance, might occur in the non-classic form [32]. They may also exhibit gastrointestinal symptoms such as difficulties swallowing and feeding, as well as a lack of weight gain [25].

- LATE ONSET

LOPD, or late-onset Pompe disease, is a multisystem condition. Patients have gradual muscle weakening and respiratory insufficiency, which results in early impairment, assisted ventilation, and death [33]. Exercise intolerance, myalgia, and postural weakness, such as difficulties walking, running, climbing stairs, or standing up from the floor, may also be observed in patient [34].

## SURVILLANCE WITH POMPE:

The international Pompe community has declared April 15 to be International Pompe Day every year! The purpose of International Pompe Disease Awareness Day is to raise international awareness of the disease [36].

- **PREVENTING/AVOIDING CONTAGIOUS ILLNESS:**

All immunizations should be kept up to date, according to the standards. Because of the increased risk of problems in Pompe patients due to decreased respiratory function, the flu and pneumonia vaccines are specifically mentioned. Coughs, colds, and fevers should also be treated aggressively because of the increased risk of complications. While people with Pompe disease are just as susceptible to colds, flus, and other illnesses as the general public, the more serious problems that might occur make it necessary for those with Pompe disease and their families to take extra care in order to keep as healthy as possible [36,37].

- **DIET PLAN**

In terms of diet, all of the published guidelines agree that "excellent nutrition" is critical. But what precisely does that imply? Some experts advocate for a high-protein, low-carbohydrate diet, while others advise patients to have a well-balanced diet [38]. All agree, however, that good nutrition is critical for those with Pompe disease to stay as healthy as possible. This holds true for the broader public, as it does for many other things. As with any diet, it's crucial to discuss any specific diets you want to try or that you want your child to try with your medical specialists and obtain their opinion [39].

- **PHYSICAL THERAPY/EXERCISE:**

All of the published guidelines also suggest that people with Pompe work with a physical therapist who is experienced with the disease to develop an activity plan that is right for them [40]. For some, this may entail walking for a prescribed length/distance, for others, strength/resistance training, and for still others, passive stretching and passive movement with the assistance of a physical therapist [41]. It's also important to remember that it's fine to be inventive! What works for one individual with Pompe may or may not work for another. As a result, it is critical for members of the Pompe community to avoid comparing themselves to others. Instead, everyone should work with a physical therapist to discover a solution that works for them [34].

## DEVELOPMENTS IN THE TREATMENT OF POMPE DISEASE:

The available treatment options for the pompe disease are:

- ENZYME REPLACEMENT THERAPY:

The only treatment currently available is "enzyme replacement therapy," which tries to refill the GAA deficit through an intravenous infusion of industrially produced "rhGAA" (recombinant human GAA) [42].

The first medication for Pompe disease was authorised by the FDA in 2006. It consists of regular IV infusions of alglucosidase alfa, a man-made enzyme. [43] When you have Pompe disease, the medicine replaces an enzyme in your body that isn't working properly. Enzyme replacement therapy (ERT) is presently the sole treatment for the illness that has been approved. More studies are needed to prove that enzyme replacement treatment is successful [44].

- GENE THERAPY:

Gene therapy is still a promising option, and research on it is progressing. In Pompe disease, gene therapy aims to enhance respiratory capacity by restoring acid alpha-glucosidase (GAA) synthesis and activity in key tissues such as the diaphragm. Other gene therapy attempts aim to restore the body's ability to make acid alpha-glucosidase (GAA) by inserting a 'normal' GAA gene copy into the patient's liver cells (through intravenous injection) or bone marrow stem cells (removed out of the body, modified outside the body, and reintroduced) (HSCGT; hematopoietic stem cell gene therapy) [45].

Modalities of gene therapy In vivo gene therapy involves injecting a gene delivery vector (viral or nonviral) directly into the receiver of the gene transfer. The majority of the experience in Pompe disease has come via AAV vector-mediated gene transfer. AAV vectors have been injected directly into the bloodstream to target muscle, the liver, or numerous tissues, or intracerebroventricularly to target the central nervous system [46].

- SUPPORTIVE THERAPY:

Symptomatic and supportive treatment for Pompe disease is also available. Because most patients have some degree of respiratory impairment and/or respiratory failure, breathing support may be required. Strengthening respiratory muscles with physical therapy may be beneficial. During the night and/or during sections of the day, especially during respiratory tract infections, some patients may require mechanical ventilation, which can be provided via non-invasive or invasive methods [47].

Because Pompe illness weakens the muscles that allow you to chew and swallow, you may need to take extra precautions to ensure proper nutrition and weight gain. To reduce the risk of aspiration, certain individuals may require specific, high-calorie diets and the learning of skills to adjust the size and texture of food [40]. A feeding tube inserted via the nose, down the oesophagus, and put directly into the stomach of some children through a small surgical hole in the abdominal wall [39].

*upcoming influx of new therapies into the pompe disease:*

- Gene therapies will be the future of the Pompe disease market because of long-term efficacy.
- This gene therapy has long-term efficacy and eliminates the need for a regular dosing schedule, which will have a significant influence on the lives of people with Pompe disease.
- The FDA approved Avalglucosidase alfa-ngpt (Nexviazyme) in 2021 to treat patients one year of age and older with late-onset Pompe disease.
- There is presently only one medication available in the Pompe disease market: Sanofi Genzyme's Myozyme (agalsidase beta), which is available in both Germany and Japan and is sold in the United States under the brand name Lumizyme.
- For patients who had stabilised on Myozyme, a combination of ERT with Clenbuterol or Albuterol (Salbutamol or Ventolin in the UK) has shown modest benefit (alglucosidase alpha).
- Stopping skeletal and respiratory muscle glycogen production and subsequent buildup by blocking the gene GYS1 through substrate reduction treatment, or SRT, is a novel strategy to treating Pompe disease.
- The Muscular Dystrophy Association is now arranging the Pompe Disease Patient-Focused Drug Development Meeting, which will allow patients and their families to share their personal experiences with stakeholders.
- Artificially stimulating lysosomal exocytosis is still in early, pre-clinical stages of development, meaning this potential treatment approach has not been tested in humans. But ongoing research into this new approach could lead to a new way of treating Pompe disease.
- Chaperone therapy for Pompe illness is now in clinical trials and tries to restore function to the faulty GAA enzyme [48].

## CONCLUSION:

The awareness and development elements of Pompe illness offer society the knowledge needed to live a healthy existence. The celebration of International Pome Day provides information on life expectancy, scope, and other factors. For pompe disease, ERT is a widely utilised treatment. However, scientists have devised a novel approach that may improve the efficacy of enzyme replacement therapy in the treatment of Pompe illness. Several gene treatments are now in Phase I/II testing and are likely to hit the market in the next decade in the United States.

## REFERENCES:

1. Kyung-Sun Park Two Approaches for a Genetic Analysis of Pompe Disease: A Literature Review of Patients with Pompe Disease and Analysis Based on Genomic Data from the General Population.

DOI: [10.3390/children8070601](https://doi.org/10.3390/children8070601)[PMC, GOOGLE SCHOLAR]

2. Lara Kohler, Rosa Puertollano, Nina Ruben pompe disease: From basic science therapy

DOI: [10.1007/s13311-018-0655-y](https://doi.org/10.1007/s13311-018-0655-y) [PMC, PUBMED]

3. Edward J Cupler<sup>1</sup>, Kenneth I Berger, Robert T Leshner, Gil I Wolfe, Jay J Han, Richard J Barohn, John T Kissel, Consensus treatment recommendations for late-onset Pompe disease.

DOI: [10.1002/mus.22329](https://doi.org/10.1002/mus.22329)[PMC, PUBMED]

4. Yin-Hsiu Chien, Wuh-Liang Hwu, Ni-Chung Lee Pompe disease: early diagnosis and early treatment make a difference.

DOI: [10.1016/j.pedneo.2013.03.009](https://doi.org/10.1016/j.pedneo.2013.03.009)[PMC, PUBMED]

5. Uwe Mellies, Frédéric Lofaso Pompe disease: a neuromuscular disease with respiratory muscle involvement.

DOI: [10.1016/j.rmed.2008.12.009](https://doi.org/10.1016/j.rmed.2008.12.009)[PMC, PUBMED]

6. FIORE MANGANELLI and LUCIA RUGGIERO Clinical features of Pompe disease  
PMCID: [PMC3866902](https://pubmed.ncbi.nlm.nih.gov/3866902/)[GOOGLE SCHOLAR]

7. Priya S. Kishnani<sup>a</sup>, Hernán, M. Amartino<sup>b</sup>, Christopher Lindberg<sup>c</sup>, Timothy M. Miller<sup>d</sup>, Amanda Wilson<sup>d</sup>, Joan Keutzer<sup>d</sup> :Methods of diagnosis of patients with Pompe disease: Data from the Pompe Registry[GOOGLE SCHOLAR]

8. Beth L Thurberg, Colleen Lynch Maloney, Charles Vaccaro, Kendra Afonso, Anne Chun-Hui Tsai, Edward Bossen, Priya S Kishnani & Michael O'Callaghan Characterization of pre- and post-treatment pathology after enzyme replacement therapy for pompe disease [GOOGLE SCHOLAR]

9. Monica Y. Niño, Mark Wijgerde, Douglas Oliveira Soares de Faria, Marianne Hoogeveen-Westerveld, Atze J. Bergsma, Mike Broeders, Nadine A. M. E. van der Beek, Hannerieke J. M. van den Hout, Ans T. van der Ploeg, Frans W. Verheijen & W. W. M. Pim Pineapple Enzymatic diagnosis of Pompe disease: lessons from 28 years of experience [GOOGLE SCHOLAR]

10. Raising Awareness About Pompe Disease - Pompe Disease News

<https://pompediseasenews.com/2020/09/08/raising-awareness-about-pompe..>

11.How Does Pompe Disease Affect Life Expectancy?

<https://pompediseasenews.com/2019/10/28/how-does-pompe-disease-affect...>

12.Pompe Disease Complications

<https://www.rarediseaseadvisor.com > disease-info-pages>

13.Pompe disease causes, symptoms, diagnosis, prognosis & treatm...

<healthjade.com/pompe-disease>

14.NORD (National Organization for Rare Disorders). 2021. Pompe disease – NORD Accessed July 14, 2021.

15.van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet*. 2008; 372(9646): 1342-1353. doi:10.1016/S0140-6736(08)61555-X

16.Manganelli F, Ruggiero L. Clinical features of pompe disease. *Acta Myol*. 2013;32(2):82-84.

17.Di Rocco M, Buzzi D, Tarò M. Glycogen storage disease type II: clinical overview. *Acta Myol*. 2007;26(1):42-44.

18.Kishnani PS, Howell RR. Pompe disease in infants and children. *J Pediatr*. 2004;144(5 Suppl):S35-S43. doi:10.1016/j.jpeds.2004.01.053

19.Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline [published correction appears in *Genet Med*. 2006 Jun;8(6):382. ACMG Work Group on Management of Pompe Disease [removed]; Case, Laura [corrected to Case, Laura E]]. *Genet Med*. 2006;8(5):267-288. doi:10.1097/01.gim.0000218152.87434.f3

20.Chien YH, Hwu WL. A review of treatment of Pompe disease in infants. *Biologics*. 2007;1(3):195-201.

21.Van den Hout JM, Kamphoven JH, Winkel LP, et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. *Pediatrics*. 2004;113(5): e448-e457. doi:10.1542/peds.113.5.e448

22.Gambetti P, DiMauro S, Baker L. Nervous system in Pompe's disease. *Ultrastructure and biochemistry. J Neuropathol Exp Neurol*. 1971;30(3):412-430. doi:10.1097/00005072-197107000-00008.

23.Sakurai I, Tosaka A, Mori Y, Imura S, Aoki K. Glycogenosis type II (Pompe). The fourth autopsy case in Japan. *Acta Pathol Jpn*. 1974;24(6):829-846. doi:10.1111/j.1440-1827.1974.tb00851.x

24.Alejaldre A, Díaz-Manera J, Ravaglia S, et al. Trunk muscle involvement in late-onset Pompe disease: study of thirty patients. *Neuromuscul Disord*. 2012;22 Suppl 2:S148-S154. doi:10.1016/j.nmd.2012.05.011

25.van der Beek NA, de Vries JM, Hagemans ML, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis*. 2012;7:88. Published 2012 Nov 12. doi:10.1186/1750-1172-7-88

26. Vissing J, Lukacs Z, Straub V. Diagnosis of Pompe Disease Muscle Biopsy vs Blood-Based Assays. *JAMA Neurol*. 2013;70(7):923–927.

doi: 10.1001/2013.jamaneurol.486

27. Pompe Disease Information Page. <https://www.ninds.nih.gov/Disorders/All-Disorders/Pompe-Disease-Information-Page>

28.The emerging phenotype of long-term survivors with infantile Pompe disease. *Genet. Med.*, 14 (2012), pp. 800-810.

29. Pompe disease in infants: improving the prognosis by newborn screening and early treatment. *Pediatrics*, 124 (2009), pp. 1116-112

30.A large-scale nationwide newborn screening program for Pompe disease in Taiwan: towards effective diagnosis and treatment. *Am. J. Med. Genet. A*, 164A (2014), pp. 54-61



31. Winkel, L.P., et al., The natural course of non-classic Pompe's disease; a review of 225 published cases. *J Neurol*, 2005. 252(8): p. 875-84.
32. H.A. van Kooten, C.H.A. Roelen, E. Brusse, et al. Cardiovascular disease in non-classic pompe disease: a systematic review., *Neuromuscular Disorders*. 2020, doi: <https://doi.org/10.1016/j.nmd.2020.10.009>
33. Toscano A, Rodolico C, Musumeci O. Multisystem late onset pompe disease (LOPD): an update on clinical aspects. *Annals of translational medicine*. 2019 Jul;7(13).
34. Barba-Romero MA, Barrot E, Bautista-Lorite J, Gutierrez-Rivas E, et al. Clinical guidelines for late-onset Pompe disease. *Rev Neurol*. 2012 Apr 16;54(8):497-507.
35. Living Healthy with Pompe  
<https://worldpompe.org/international-pompe-day/602-living-healthy-with-pompe>
36. Int'l Pompe Day  
[www.worldpompe.org/international-pompe-day](http://www.worldpompe.org/international-pompe-day)
37. International Pompe Association  
<https://www.worldpompe.org>
38. Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain* 2005; 128:671-7. 10.1093/brain/awh384 [PubMed] [CrossRef] [Google Scholar]
39. Foveae MM, van den Berg LE, Kruijshaar ME, et al. Exercise training in adults with Pompe disease: the effects on pain, fatigue, and functioning. *Arch Phys Med Rehabil* 2015; 96:817-22. 10.1016/j.apmr.2014.11.020 [PubMed] [CrossRef] [Google Scholar]
40. van den Berg LE, Favejee MM, Wens SC, et al. Safety and efficacy of exercise training in adults with Pompe disease: evaluation of endurance, muscle strength and core stability before and after a 12-week training program. *Orphanet J Rare Dis* 2015; 10:87. 10.1186/s13023-015-0303-0 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
41. Willems HME, van den Heuvel E, Schoemaker RJW, et al. Diet and Exercise: a Match Made in Bone. *Curr Osteoporosis Rep* 2017; 15:555-63. 10.1007/s11914-017-0406-8 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
42. Latest Updates in Pompe Disease Treatment - Patient Worthy  
<https://patientworthy.com/2020/05/27/latest-updates-in-pompe-disease...>
43. Research update - New Treatment Developments for Pompe ...  
<https://pompe.uk/pompe-news/new-treatment-developments-for-pompe-disease>
44. Pompe Disease - Latest News and Research Updates  
<https://www.medindia.net/healthnews/pompe-disease-news.asp>
45. Pompe Disease | ASGCT - American Society of Gene & Cell ...<https://patienteducation.asgct.org/disease-treatments>
46. Kishnani PS, Hwu WL, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 2006; 148:671-6. [Crossref] [PubMed]
47. Pompe Disease News Home - Pompe Disease News  
<https://pompediseasenews.com>
48. FDA Approves New Treatment for Pompe Disease | FDA  
<https://www.fda.gov/.../fda-approves-new-treatment-pompe-disease>