HHS Public Access

Author manuscript

J Inherit Metab Dis. Author manuscript; available in PMC 2025 January 01.

Published in final edited form as:

J Inherit Metab Dis. 2024 January ; 47(1): 93–118. doi:10.1002/jimd.12654.

Gene Therapy for Glycogen Storage Diseases

Dwight D. Koeberl[1,2,*], **Rebecca L. Koch**[1], **Jeong-A Lim**[1], **Elizabeth D. Brooks**[1], **Benjamin D. Arnson**[2], **Baodong Sun**[1], **Priya S. Kishnani**[1,2]

[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical School, Durham, NC, United States

[2]Department of Molecular Genetics & Microbiology, Duke University Medical Center, Durham, NC, United States

Abstract

Glycogen storage disorders (GSDs) are inherited disorders of metabolism resulting from the deficiency of individual enzymes involved in the synthesis, transport, and degradation of glycogen. This literature review summarizes the development of gene therapy for the GSDs. The abnormal accumulation of glycogen and deficiency of glucose production in GSDs lead to unique symptoms based upon the enzyme step and tissues involved, such as liver and kidney involvement associated with severe hypoglycemia during fasting and the risk of long-term complications including hepatic adenoma/carcinoma and end stage kidney disease in GSD Ia from glucose-6-phosphatase deficiency, and cardiac/skeletal/smooth muscle involvement associated with myopathy +/− cardiomyopathy and the risk for cardiorespiratory failure in Pompe disease. These symptoms are present to a variable degree in animal models for the GSDs, which have been utilized to evaluate new therapies including gene therapy and genome editing. Gene therapy for Pompe disease and GSD Ia has progressed to Phase I and Phase III clinical trials, respectively, and are evaluating the safety and bioactivity of adeno-associated virus vectors. Clinical research to understand the natural history and progression of the GSDs provides invaluable outcome measures that serve as endpoints to evaluate benefits in clinical trials. While promising, gene therapy and genome editing face challenges with regard to clinical implementation, including immune responses and toxicities that have been revealed during clinical trials of gene therapy that are underway.

Take home message: Gene therapy for the glycogen storage diseases is under development, addressing an unmet need for specific, stable therapy for these conditions.

Keywords

Gene therapy; glycogen storage disease; genome editing; animal models; clinical trials

[*]To whom correspondence should be addressed: Dwight D. Koeberl, Box 103856, Duke University Medical Center, Durham, NC 27710, Phone: (919) 681-9919, dwight.koeberl@duke.edu.

Author Contributions

Conceptualization: DDK, PSK; Manuscript writing and editing: DDK, RLK, JAL, EDB, BDA, BS, PSK; Review: DDK

Guarantor

Dwight D. Koeberl

Background

Glycogen metabolism involves a series of coordinated enzymatic reactions that includes the synthesis and breakdown of glycogen polymers (Supplementary Figure S1).[1] Deficiencies in any of the enzymes or transport proteins involved in the glycogen synthesis and degradation pathways can result in a GSD (Table 1; types 0a, 0b, Ia, Ib, II, III, IV, V, VI, IX).[2,3] In addition, deficiencies in enzymes whose actions are external to the canonical glycogen metabolism pathways can result in excessive glycogen accumulation and thus are classified as a GSD (types VII, X, XI-LDHA, XI-FBS, XII, XIII).[2,3] Furthermore, there are several disorders that are classified as both a GSD and another disorder, including Lafora disease and RBCK1 deficiency which are polyglucosan storage disorders, and Pompe and Danon disease which are lysosomal storage disorders. Therefore, the list of GSDs included in Table 1 is selective and not considered to be a comprehensive list of all known GSDs. PGM1 deficiency was historically referred to as GSD XIV but has been re-classified as a congenital disorder of glycosylation[4] and is not discussed further in this review.

The liver and skeletal muscle normally store large quantities of glycogen and therefore are the most commonly affected tissues. For this reason, GSDs are classified by the primary organs involved – liver, muscle, or both – though additional organs may be involved. Individuals with liver GSDs often present in infancy or early childhood with fasting hypoglycemia due to the inability to produce sufficient free glucose to maintain euglycemia as well as hepatomegaly due to the accumulation of glycogen in hepatocytes. Glycogen in the skeletal muscle provides substrates for muscle contraction, and therefore GSDs that principally affect the skeletal muscle are characterized by skeletal myopathy, muscle pain and weakness, cramps, and exercise intolerance. Cardiomyopathy and arrythmias are commonly observed in GSDs that involve the cardiac muscle. The overall incidence of all GSDs is approximately 1:10,000–25,000 live births.[5–7] The severity of symptoms along with the lack of standardized management strategies have driven the discovery and development of new therapies including enzyme replacement therapy (ERT) and gene therapy, which are still under development and have been shown to be efficacious in preventing disease progression and reversing disease involvement.

The purpose of this review is to summarize recent developments in a review of current literature relevant to the topic of gene therapy for GSDs, while acknowledging previous reviews of some aspects of the field.[8–10] Specialized considerations and the stage of development for gene therapy or related technologies will be described. Animal models being used for gene therapy or with potential to be used for gene therapy are included (Table 2); a comprehensive review of all GSD animal models can be found in Almodóvar-Payá et al.[10]

Natural history and animal models for the GSDs

Given the lack of specific, effective therapy in general for GSD, gene therapy has been developed for several of the individual GSDs.[8] However, the preclinical research done in advance of clinical trials requires the availability of authentic animal models to evaluate safety and efficacy. Furthermore, natural history studies are critical for characterizing

disease progression and providing endpoints and biomarkers for clinical trials. To date, natural history data has been published for GSD Ia, Ib, II, III, IV, VI, and IX, yet many are limited to retrospective chart reviews with small patient numbers from specific countries or populations, and thus additional comprehensive natural history studies with inclusion of larger patient cohorts and representation from across the world are warranted. Several retrospective and prospective natural history studies on GSDs have been conducted or are ongoing, providing the much-needed characterization of these disorders for current and future gene therapy investigations. Herein, we summarize the available natural history data and animal models briefly by GSD type, and compare the phenotypes of animal models to those of affected patients.

i. GSD 0a and 0b

GSD 0a is associated with deficiency in glycogen synthase 2 (GYS2), disrupting glycogen synthesis in the liver. Patients often present with fasting ketotic hypoglycemia, short stature, postprandial hyperglycemia, lactic acidosis, and hyperalaninemia with normal insulin levels. There are limited published reports on affected adolescent and adult individuals, and therefore long-term disease sequelae is not clear. Current management strategies include dietary intervention to prevent fasting hypoglycemia.[11] No animals models are available for GSD 0a.

GSD 0b is associated with deficiency in glycogen synthase 1 (GYS1) which disrupts glycogen synthesis in the muscle, causing cardiomyopathy, cardiac arrythmia, muscle weakness, and exercise intolerance.[12,13] Patients are managed symptomatically and there is a long-term risk of cardiac arrest. A *Gys1*$^{-/-}$ mouse model features impaired cardiac function, edema, pooling of blood, and hemorrhagic liver.[14] It has a poor survival rate, yet ~10% survive birth and live through late adulthood with no apparent functional differences despite exhibiting significant cardiac fibrosis.

ii. GSD Ia and Ib

GSD Ia and Ib result in a defect in glycogenolysis and gluconeogenesis as a result of deficient glucose-6-phosphatase α or glucose-6-phosphate translocase, respectively. Guidelines for the management of GSD I have been previously published.[15–17] The natural history of hepatocellular adenoma (HCA) formation in GSD I has been detailed in several retrospective chart reviews, including the ages when HCA develops and the relationship of HCA with metabolic control.[18–21] A cohort of affected individuals from the Netherlands (N=39), both with optimal and non-optimal metabolic control, were assessed for the natural course of renal disease.[22] A 2021 review details the current management options, burden, and unmet needs in GSD Ia,[23] providing support for clinical trials targeting GSD Ia. Findings from a retrospective, observational study on individuals with GSD Ib in England (N=35) was published in 2021,[24] and key findings include the impact of GSD Ib on growth, fasting tolerance, bone health, as well as renal, endocrine, and gastrointestinal manifestations. That study was limited in conclusions it could draw on the natural history in adulthood due to limited adult cases (N=7). The natural history of GSD Ib is continuously evolving with the utility of pharmaceuticals to treat neutropenia and neutrophil dysfunction, including granulocyte colony-stimulating factor and empagliflozin.[25,26] Additional natural

history data on GSD Ib is needed to better define future gene therapy clinical trials and should include data on affected individuals from around the world. Lastly, patient-reported outcomes and psychosocial impacts of disease are now being detailed in GSD I,[27–31] improving our understanding of disease natural history.

A naturally occurring GSD Ia dog model features a missense variant resulting in a methionine to isoleucine substitution in codon 121 of *G6PC*, which causes hepatomegaly, hypoglycemia, renomegaly, lactic acidemia hypercholesterolemia, hypertriglyceridemia, hepatocellular carcinoma and renal disease (Table 2).[32–35] A GSD Ia mouse model was developed by disruption of the *G6pc1* gene in exon 3 by a neomycin cassette. These mice demonstrated slow growth, hypoglycemia, hyperlipidemia, hepatomegaly, renomegaly and generalized dysplasia of cartilage.[36] Tamoxifen inducible $G6pc^{-/-}$ mice models specific to liver, kidney or intestines have been developed (Table 2).[37–40] A $G6pt^{-/-}$ mouse model featured the expected neutropenia in addition to other features of GSD I.[41] A tamoxifen-inducible $G6pt^{-/-}$ mouse model demonstrated the expected phenotype, albeit milder and with increased survival.[42]

iii. GSD II (Pompe disease)

GSD II, more often referred to as Pompe disease, is caused by deficiency in acid α-glucosidase within the lysosome and primarily affects the skeletal muscle, cardiac muscle, and diaphragm. Patients are classified as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) based on age of symptom onset.[43] A natural history study on disease progression in IOPD was conducted using clinical data from 20 affected Dutch infants and 133 cases reported in the literature.[44] A retrospective, multinational, multicenter natural history study on IOPD (N=168 cases) detailed the progression of disease, including the characterization and onset of cardiorespiratory involvement, muscle weakness, feeding difficulties, as well as survival curves and prognosis.[45] Additional natural history data on adults with LOPD has been published, with a prospective observational study (N=94) detailing the clinical features and pattern of muscle weakness as well as prognostic factors for disease progression.[46] An additional prospective international observational study on LOPD (N=268 from 15 countries) reported higher mortality than the general population in untreated adults with Pompe disease and identified levels of disability and impact on participation as factors associated with mortality.[47] ERT with alglucosidase alfa was approved for patients with Pompe disease in Europe and the United States in 2006, with the next generation ERT avalglucosidase alfa gaining approval for use in the United States in 2021 for individuals with LOPD one year of age or older, and in 2022 was approved for use in Europe for all patients with Pompe disease. Immunomodulation strategies have since been employed to induce immune tolerance to ERT in affected individuals who are cross-reactive immunologic material (CRIM)-negative and would otherwise develop an IgG antibody immune response to the ERT, leading to a deeper understanding of the natural history of CRIM-negative individuals that otherwise would have succumbed to the disease despite ERT.[48] ERT for Pompe disease has drastically improved the survival rates in affected individuals,[49–53] resulting in the emergence of new phenotypes, including variable central nervous system involvement in children with IOPD[54–61] and progression of disease in individuals with LOPD treated with ERT, including respiratory function and functional

outcomes.[49,62,63] Furthermore, the addition of Pompe disease to newborn screening (NBS) programs in Taiwan in 2005[64] and the United States Recommended Uniform Screening Panel in 2015 has permitted early diagnosis of patients with IOPD, as well as those with LOPD who otherwise appear healthy.[65] Natural history of patients who are detected on newborn screening is continuing to evolve; studies in Taiwan and the United States are shedding light on the early involvement and a characteristic phenotype in infants and children with LOPD diagnosed via NBS.[54,65]

There are numerous animal models for Pompe disease (Table 2). A GAA knockout mouse model has been used most commonly for gene therapy development which displays progressive muscle weakness from glycogen accumulation in heart and skeletal muscle.[66] Another potentially useful model for gene therapy development is a naturally occurring dog model found in Swedish Lapphunds which had clinical signs of vomiting, progressive muscular weakness, loss of condition and myocardial hypertrophy caused by generalized glycogen accumulation in skeletal, esophageal, cardiac and smooth muscles.[67]

iv. GSD III

GSD III is caused by deficient glycogen debranching enzyme (GDE) activity, resulting in disrupted glycogenolysis. Affected patients are classified as GSD IIIa if they experience liver and muscle involvement or GSD IIIb if they exhibit liver involvement only. Management guidelines for GSD III have been previously published[68] and the liver, skeletal muscle, and heart involvement in GSD III has been characterized in various reports. The International Study on GSD III (ISGSDIII) was conducted and included a multi-center retrospective review of growth and development and hepatic, neuromuscular, and cardiac complications in individuals with GSD III (175 cases with follow-up into adulthood in 91 cases).[69] Yet, the data was largely cross-sectional rather than longitudinal and thus may not fully represent the breadth of long-term complications in GSD III. The natural course of liver disease in affected pediatric and adult individuals (N=26) was described and revealed key findings on liver pathology, imaging, and biochemistry, including support for using Glc_4 as a biomarker of liver disease progression.[70] The extent of cardiomyopathy in GSD III (N=33) was described in a retrospective review which detailed the increase in wall thickness and left ventricular mass through adulthood in affected individuals with GSD IIIa compared to GSD IIIb.[71] A retrospective, longitudinal natural history study detailed the clinical, biochemical, radiological, functional, and histopathological aspects of the disease course in adults with GSD III (N=25) as well as confirmed the use of Glc_4 as a biomarker of GSD III.[72] Furthermore, the musculoskeletal manifestations in GSD IIIa from affected pediatric and adult individuals (N=22) were detailed, providing support for monitoring performance on functional assessments in future clinical trials.[73]

Four GSD III mouse models with different *Agl* gene variants have been described, all demonstrating glycogen accumulation in the muscle and liver (Table 2).[74–77] There is also a naturally occurring curly-coated retriever dog model that demonstrates initial elevations of liver enzymes, muscle enzymes, and urine Glc_4, as well as hepatomegaly with glycogen accumulation in liver and muscle. With disease progression, there was an increase in hepatic

fibrosis and eventual cirrhosis in some dogs with a contaminant decease in liver and muscle enzymes as well as urine Glc_4 (Table 2).[78,79]

v. GSD IV

GSD IV is caused by reduced or deficient glycogen branching enzyme (GBE) activity and results in abnormal glycogen synthesis and the formation of polyglucosan. The clinical spectrum of GSD IV is heterogenous and encompasses severe neurological and neuromuscular manifestations, myopathy, cardiomyopathy, and progressive liver fibrosis, and can present in the neonatal period, infancy, early childhood, adolescence, or adulthood (Adult Polyglucosan Body Disease, APBD). A summary of management for all GSD IV phenotypes, including APBD, was previously published.[80] Additionally, a recent review of all published cases with GSD IV that had symptom onset before the age of 25 years (N=179) evaluated the extent of multisystem tissue involvement and revealed the pitfalls of the traditional subtype classification system.[81] Rather than classifying patients into discrete hepatic or neuromuscular subtypes, Kiely et al[81] recognized that GBE deficiency can cause a spectrum of manifestations across multiple tissue systems and affected individuals may exhibit differing degrees of hepatic, neuromuscular, and/or cardiac involvement over time. An additional natural history study focused on APBD (N=50 cases) defined the cardinal signs of the disease and the typical stages of disease progression.[82] Long-term clinical surveillance and natural history data on GSD IV is needed for future gene therapy investigations to better catalog the phenotypic variation in a granular manner. As of May 2023, there is an active retrospective and prospective natural history study on GSD IV, including the adult-onset form APBD (NCT02683512).

There are two naturally occurring large animals displaying clinical features more similar to early onset GSD IV with early mortality; these are the Norwegian Forest Cat and American Quarter Horse (Table 2).[83–89] Three mouse models for GSD IV are described, with clinical signs consistent with early, juvenile and adult onset (Table 2).[90,91] The adult-onset model used homologous recombination to knock in the most common variant found in patients of Ashkenazi Jewish descent with APBD, c.986A>C (p.Y329S), and has been used in a previous gene therapy study.[91]

vi. GSD V

GSD V, commonly referred to as McArdle disease, is caused by deficient muscle glycogen phosphorylase (myophosphorylase) which disrupts glycogenolysis in the muscle. Patients typically present as adults with muscle cramping and rhabdomyolysis during exercise, and the ability to resume moderate, aerobic exercise after resting – the “second wind phenomenon”. No natural history study of McArdle disease has been published to date. Management strategies for GSD V have been reviewed.[92] There are naturally occurring Charolais cattle and Merino sheep models for McArdle disease, with the sheep being used for gene therapy to date (Table 2).[93–95] The affected sheep exhibited exercise intolerance and muscle biopsy samples showed a lack of myophosphorylase and the accumulation of excessive glycogen.[95] A knock-in mouse model for GSD V was generated by introducing the common p.R50X mutation in exon 1 of the *Pygm* gene.[96] The homozygous ($Pygm^{R50X/R50X}$) mice exhibit similar phenotypes as shown in human patients,

including lack of myophosphorylase expression and massive glycogen accumulation in skeletal muscles, elevated plasma creatine kinase activity, exercise-induced myoglobinuria, exercise intolerance, and progressive muscle degeneration, fibrosis and inflammation (Table 2).[96–98] A zebrafish model for GSD V is also described (Table 2).[99]

vii. GSD VI and IX

GSD IX is caused by deficient phosphorylase kinase (PhK) activity in the liver and/or the muscle, whereas GSD VI is caused by deficient liver glycogen phosphorylase activity. PhK in the liver phosphorylates and activates glycogen phosphorylase, and therefore patients with GSD VI and GSD IX experience disruption in glycogenolysis and can present very similarly with fasting hypoglycemia and hepatomegaly. The first natural history review of GSD VI and GSD IX was a retrospective chart review of affected individuals in Canada (N=4 GSD VI, N=17 GSD IX).[100] This report highlighted the long-term complications of GSD VI and GSD IX, including HCA and progressive fibrosis. A follow-up retrospective chart review of individuals with GSD VI and GSD IX in England (N=9 GSD VI, N=13 GSD IX) was conducted to determine the extent of liver involvement at presentation versus the most recent follow up, highlighting that although GSD VI and IX are often considered “mild” clinically, chronic histological changes could be seen in all liver biopsies.[101] However, published data from these retrospective natural history studies are limited to that of affected children and young adults, emphasizing the need for longitudinal data on affected adults. Additional systemic literature reviews have further detailed clinical data on cases with GSD VI (N=63), GSD IX α2 (N=183), GSD IX β (N=17), and GSD IX γ2 (N=30).[102,103] The reviews were conducted in a complementary manner so that findings can be compared to one another, including the age at initial presentation, frequency of clinical findings, and pathology findings on liver biopsy. Both reviews were not able to fully address the long-term outcomes and complications on GSD VI or GSD IX due to limited published follow-up reports, emphasizing the need for studies with longitudinal data to guide future clinical trials. Moreover, there has been no publication of natural history data for GSD IX α1. Therefore, the critical need for comprehensive, longitudinal natural history study data on GSD VI and all subtypes of GSD IX remains. As of May 2023, there is an active retrospective and prospective natural history study on GSD VI and GSD IX (NCT04454216).

There are no known naturally occurring large animal models for GSD VI, but there is promise for use in future gene therapy development with a GSD VI mouse model (C57BL/6N-*Pygl*$^{tm1a(KOMP)Wtsi}$ or *Pygl*$^{-/-}$) (Table 2).[104] *Pygl*$^{-/-}$ mice have enlarged hepatocytes from glycogen accumulation with progression to hepatic fibrosis accompanied by increased transaminase concentrations in older *Pygl*$^{-/-}$ mice.[104]

There are no known naturally occurring large animal models for GSD IX, but two murine models exist, γ2 and β (Table 2). A GSD IX γ2 mouse model (C57BL/6 N-*Phkg2*$^{tm1.1(KOMP)Vlcg}$/JMmucd or *Phkg2*$^{-/-}$) has massive glycogen accumulation in the liver leading to hepatomegaly, early liver fibrosis with elevations in serum liver transaminases, and hypoglycemia.[105] A rat model (gsd/gsd) has also been described.[106–108] A GSD IX β mouse model (C57BL/6NJ-*Phkb*$^{em1(IMPC)J}$/Mmjax or *Phkb*$^{-/-}$) developed mild fasting hypoglycemia with elevated blood ketones in the fed and fasting state and histology revealed

enlarged, glycogen-filled hepatocytes with minimal collagen deposition at 40 weeks of age.[109]

viii. GSD VII

GSD VII is caused by deficient muscle phosphofructokinase activity, resulting in a block in muscle glycolysis. GSD VII typically presents similarly to GSD V with exercise-induced muscle cramping; however, patients do not experience a second wind phenomenon. A high carbohydrate meal aggravates symptoms, which has been termed the “out of wind phenomenon”. The management strategies for GSD VII have been reviewed.[92]

A naturally occurring nonsense mutation in exon 21 of the *PFKM* gene has been described in English Springer Spaniels, Cocker Spaniels, and Whippet dogs (Table 2).[110–112] The affected dogs demonstrated mild exercise intolerance, rare muscle cramps, increased serum creatine kinase activity, but had no myoglobinuria.[110] A new missense point mutation (c.550 C>T) in the *PFKM* gene associated with muscle phosphofructokinase deficiency was later described in Wachtelhunds dogs presenting with exercise intolerance and hemolytic anemia.[113,114] The knockout mouse model of GSD VII ($Pfkm^{-/-}$) developed hemolysis, increased erythropoiesis, and exercise intolerance, as well as high glycogen accumulation and increased vascularization and fiber necrosis in the skeletal muscles. High lethality (about 60%) in the $Pfkm^{-/-}$ mice was observed at around weaning age and those surviving mostly died before 6 months of age (Table 2).[115]

ix. GSD XV

GSD XV is caused by deficient glycogenin-1 activity which results in abnormal glycogen synthesis and the formation of polyglucosan in the skeletal muscle and heart. To date, literature on GSD XV is limited to case reports describing the clinical presentation either with skeletal myopathy or cardiomyopathy.[116–129] Rodents carry a single Gyg gene compared to humans and other mammals that carry two glycogenin isoforms: *Gyg1* and *Gyg2*. A knock-out mouse model of GSD XV ($Gyg^{-/-}$) has been characterized with deficient GYG activity in the muscle, heart, liver, and brain.[130] This model recapitulates the patient phenotype with skeletal muscle weakness and glycogen accumulation in skeletal muscle and heart. However, an important distinction is affected patients accumulate polyglucosan (diastase-resistant glycogen) whereas the $Gyg^{-/-}$ mice accumulate diastase-sensitive glycogen in skeletal muscle and heart tissue.

Preclinical research in GSD gene therapy

Gene therapy has been defined as viral vector-mediated gene delivery, or gene replacement therapy, which has been adapted to deliver the components needed for genome editing.[131] This review will focus on viral vector-mediated gene therapy and genome editing that achieve stable benefits from transgene delivery. However, other clinically relevant therapeutic methods utilizing nucleotides, including encapsulated mRNA, are summarized briefly in Table 1.

i. GSD Ia and Ib

Preclinical development of gene therapy and genome editing for GSD Ia— While dietary therapy has succeeded in prolonging lifespan of people with this condition, it fails to reliably prevent long-term complications of GSD Ia including hepatocellular adenoma or carcinoma formation, as well as end-stage kidney disease. Preclinical studies have demonstrated the correction of G6Pase deficiency in the liver and hypoglycemia (Table 3), although only AAV1, AAV2 with adenovirus, and AAV9 vectors have corrected kidney abnormalities. AAV vector-mediated gene therapy has achieved long-term efficacy in GSD Ia in multiple studies;[9] however, the duration of efficacy in these studies was limited as hepatic AAV vector genome abundance declined rapidly followed by a more gradual loss of biochemical correction.[132–134] General approaches to this problem have included higher vector dosages[135,136] and re-administration of the vector, prior to the formation of anti-AAV antibodies.[137] These approaches have not comprehensively addressed the loss of efficacy due to the loss of AAV vector genomes in animal models for genetic disease. For example, a recent study in neonatal *G6pc* −/− mice revealed that despite the correction of G6Pase deficiency by AAV vector-mediated gene therapy, autophagy was only partially restored in liver.[138] Similarly, gradual loss of efficacy from gene therapy has been shown in canine models of GSD Ia.[139–141] Puppies treated with gene therapy vectors have increased G6pase expression and decreased glycogen in the liver. However, the effect is transient and the dogs required re-administration of vector and constant dietary monitoring. Gene therapy was able to improve the dogs blood glucose during fasting but ultimately failed to prevent kidney failure and liver adenoma and carcinoma, which developed over multiple years following initial treatment.[34] In contrast, treatment with AAV vector-mediated gene therapy combined with continuous nutrition prevented long-term complications of gene therapy in the canine model, confirming the value of good metabolic control in the successful treatment of GSD Ia that has also been reported in patients.[20,142]

Genome editing promises to address the limitations of gene therapy by stably integrating the therapeutic sequence in chromosomal DNA. Genome editing has been initiated to correct a mutation or integrate a transgene as a method to stably treat liver metabolic diseases and hemophilia, including GSD Ia, hemophilia B, ornithine transcarbamylase deficiency, and phenylketonuria.[143–146] The underlying strategy depends upon the stable transduction of hepatocytes through genome editing, which prevents the loss of episomal AAV genomes due to cell division that limits the efficacy of gene replacement therapy. Increasingly genome editing studies use CRISPR/Cas9 as a nuclease, due to its flexibility and high nuclease activity. An initial genome editing study used a zinc finger nuclease (ZFN) mediated genome editing method, which demonstrated an advantage for genome editing in comparison with gene replacement therapy.[143] Intriguingly, the addition of bezafibrate to induce autophagy during genome editing of *G6pc* −/− mice more effectively corrected the liver abnormalities of GSD Ia, achieving normal G6Pase activity in liver and widespread transduction of hepatocytes.[147] More recently, CRISPR/Cas9 based genome editing has been used to correct a mutation causing GSD Ia in mice.[148] Instead of inserting a full length transgene, they targeted the most common mutation in GSD Ia patients, *G6PC*-p.R83C, which represents 32% of all diseased alleles in humans. Two AAV vectors were used, one expressing Cas9 and a single guide RNA, and a second containing the repair template

sequence. GSD Ia mice treated with the CRISPR/Cas9 based editing vectors had 0.7% of alleles edited and G6pase expression was 4% of WT after 8 weeks of treatment. The edited mice had serum triglycerides, cholesterol, lactic acid, and uric acid levels comparable to wild type controls and showed improved blood glucose levels during fasting. All treated mice survived, while none of the untreated GSD Ia mice survived to 16 weeks. A recent study of CRISPR/Cas9-medatied genome editing in the canine model for GSD Ia revealed the integration of a *G6PC* transgene in up to 1% of alleles for over 16 months.[149] These preclinical studies with CRISPR/Cas9 or with ZFN-mediated genome editing demonstrated that correcting mutations causing GSD Ia or inserting a fully functional transgene hold promise for more stably treating GSD Ia, in comparison with gene replacement therapy.

Gene therapy for GSD Ib corrected liver, but not hematologic abnormalities— GSD Ib is caused by glucose-6-phosphate transporter deficiency, and features neutropenia in addition to the liver and kidney involvement seen in GSD Ia.[150] AAV vector-mediated gene therapy has corrected the liver involvement of mice with GSD Ib without impacting neutropenia and its consequences.[151] Notably, an AAV vector containing the *G6PC* promoter/enhancer driving *G6PT* expression corrected liver glycogen and prevented hypoglycemia. However, neutropenia was not corrected, indicating a lack of hematologic cell transduction. Similarly, mice with GSD Ib were treated with an adenoviral vector expression *G6PT* benefited from correction of liver involvement and hypoglycemia transiently, without impacting neutropenia.[152]

ii. Pompe disease

The availability of ERT has decreased mortality among patients with infantile-onset Pompe disease, facilitating a greater understanding of the natural history of these patients.[52] However, muscle weakness (neck flexor weakness, dorsiflexor weakness, myopathic facies, ptosis and strabismus) has persisted despite treatment with ERT.[53,153,154] There remains a high risk for patients with IOPD to develop anti-GAA antibodies that decrease benefits from ERT,[155] especially those that are CRIM-negative and a subset of CRIM-positive patients. The limitations of ERT have driven the development of gene therapy as an alternative (Table 4). Preclinical studies have generally confirmed both a lower dose requirement and higher degree of efficacy from liver-based expression of GAA, or liver depot gene therapy that can induce immune tolerance to GAA that prevents and/or suppresses anti-GAA antibody formation.[156] Studies with muscle-based GAA expression required higher vector dosages (Table 4).[157,158] A unique strategy of intracerebroventricular administration of an AAV vector decreased glycogen in the brain and spinal cord, but not in the muscles.[159] Overall, studies have demonstrated that liver depot gene therapy with an AAV vector corrected GAA deficiency in the heart and skeletal muscle, and improved muscle function testing in *GAA* −/− mice with Pompe disease.[160–163]

It is expected that gene therapy with AAV vectors will be less effective early in life due to the accelerated loss of episomal vector genomes from rapid growth accompanied by cell division, which especially affected liver-targeted gene therapy.[135,137,164,165] Although AAV vectors have advanced to successful clinical trials based upon liver transgene expression,[166] the loss of vector genomes during infancy has exceeded the rate expected solely from

cell division in the liver.[164,165] Approaches to this problem have included higher vector dosages,[135,136] and early re-administration of the vector, prior to the formation of anti-AAV antibodies.[137] These approaches have not comprehensively addressed the loss of efficacy in animal models for genetic disease following neonatal administration of AAV vectors. However, the long-term benefits of gene therapy in infant mice with Pompe disease confirmed the potential value of treatment early in life.[163,167,168]

Preclinical data have suggested the early treatment with gene therapy might be successful in Pompe disease; however, the dose requirements will be higher for treatment very early in life. One study directly compared the efficacy of a potentially clinically feasible dose of an rAAV8 vector in infant and adult GAA-KO mice.[163] Biochemical correction and muscle function were evaluated 50 weeks following intravenous administration of the same absolute vector dosages at 10 days or 2 months of age to assess the effects of gene therapy either early or later in life. Unsurprisingly the degree of biochemical correction was greater in the adult-treated mice, because AAV vector transduction is more stable in older animals that have completed the rapid growth phase of infancy. Furthermore, the weight-based vector dose for treatment of infants was approximately 3-fold higher than for adults.[163] Given these data, the dose requirement to achieve similar efficacy will be higher for the treatment of young patients and the benefits from gene replacement therapy early in life will be relatively less than those from later treatment.

Genome editing has been demonstrated in an *in vitro* experiment with human induced pluripotent stem cells from a patient with Pompe disease.[169] This study confirmed that integration of a GAA-expressing transgene in the *AAVS1* locus corrected GAA deficiency and decreased glycogen content of patient cells. Nuclease-free strategies have been developed for genome editing in hemophilia B,[170] which might decrease the risks from genome editing by eliminating the need for double-stranded DNA breaks; however, the transgene integration efficiency was less than 1% and potentially too low to treat liver metabolic diseases. Thus, nuclease-mediated genome editing to create a liver depot for the treatment of Pompe disease could enhance the treatment of very young patients with Pompe disease.

iii. GSD III

GSD III is categorized based upon tissue involvement, either liver and muscle (GSD IIIa) or only the liver (GSD IIIb). Currently no curative treatment is available for the disease. Symptomatic treatment does not prevent ongoing disease progression, including liver involvement and variable myopathy or cardiomyopathy (see “Natural history and animal models for the GSDs” section) and dietary interventions do little to alter the long-term course and morbidity of the disease.[171–173] In the absence of an effective therapy, patients with GSD III will continue to experience progressive liver failure and muscle damage accompanied by increased morbidity and mortality.

ERT is not a feasible treatment approach for GSD III due to the lack of a natural receptor-mediated uptake of the therapeutic enzyme from the blood into target tissues. Chronic daily administration of rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR), partially prevented glycogen accumulation in skeletal muscle and liver and reversed hepatic

fibrosis in a canine model of GSD IIIa,[174] but this treatment is not ideal given the toxicity of chronic rapamycin use. Liver-targeted gene silencing of glycogen synthase 2 (*GYS2*) by lipid nanoparticle mediated delivery siRNA prevented progression of glycogen accumulation and fibrosis in the liver, but this treatment had no effect on the muscle in a GSD IIIa mouse model.[175] Gene therapy with AAV vectors, AAV9 in particular, could provide a treatment strategy for GSD III as AAV9 vectors can reliably transduce both liver and muscle tissues. However, a major challenge of using this approach for GSD III is the inability to package the large (4.6 kb) human *GDE* cDNA into a single AAV vector due to the size limitation of AAV. To overcome this limitation, Vidal et al. reported that liver-restricted overexpression of secretable human GAA with an AAV vector in GSD IIIa mice reduced glycogen content in liver but not in muscle.[76] In the same study, the authors used a dual overlapping AAV vector system to split the human *GDE* cDNA into two halves and package them into two separate AAV vectors. Upon co-administration of the two AAV vectors, functional hGDE expression was achieved in liver and muscle tissues of GSD IIIa mice.[76] However, this dual vector approach requires administration of very high doses of the two AAV vectors, which may potentially lead to adverse hepatotoxicity or even liver failure in patients.[176,177] Recently, Lim et al. reported an innovative gene therapy approach with AAV vectors expressing a small bacterial GDE (Pullulanase derived from *Bacillus subtilis*) in a mouse model of GSD IIIa.[77] Intravenous injection of an AAV9 vector containing a 2.2-kb codon-optimized Pullulanase cDNA driven by the ubiquitous CMV enhancer/chicken β-actin (CB) promoter (AAV-CB-Pull) into infant GSD IIIa mice significantly decreased (by 75–80%) glycogen accumulation in the heart and skeletal muscles (not in the liver) and significantly improved muscle function after 10 weeks.[77] Subsequent treatment with an AAV8 vector (AAV-LSP-Pull) containing an immunotolerant liver-specific promoter (LSP) further reduced liver glycogen content by 75%, significantly decreased liver size, and completely reversed hepatic fibrosis.[77] In a follow-up study, Lim et al. demonstrated that intravenous injection of an AAV vector containing a tandem LSP-CB dual promoter (AAV-dual-Pull) into adult GSD IIIa mice effectively decreased Pullulanase-induced cytotoxic T lymphocyte (CTL) response and enabled persistent therapeutic Pullulanase expression in liver and muscle, accompanied by the reversal of liver fibrosis and improved muscle function.[178] In contrast, the AAV-CB-Pull vector elicited a strong transgene-related CTL response, resulting in only transient Pullulanase expression in adult GSD IIIa mice. This study emphasized the value of liver-restricted transgene expression using a LSP in preventing immune responses to gene therapy.

iv. GSD IV

To date, gene therapy has only been investigated in the *Gbe1*$^{ys/ys}$ mouse model. In 2019, Yi and colleagues reported on a gene therapy study where 14-day-old *Gbe1*$^{ys/ys}$ mice received a single intravenous injection of AAV9 vector containing a CB promoter and human GBE expression cassette (AAV9-CB-hGBE).[179] At 3 months of age (10 weeks post-treatment), treated mice exhibited increased GBE activity in the brain, heart, and skeletal muscles, but not the liver, yet this effect waned and only the heart retained increased GBE expression by 9 months. Consistent with the GBE activity levels, the AAV copy numbers (copies/nucleus) were reduced by 90% in the liver, heart, brain, and skeletal muscles. At 3 months of age, treated mice exhibited glycogen levels comparable to wild type levels in the quadricep

and gastrocnemius muscles, and reduced glycogen levels in the brain and liver. This trend was consistent in treated mice evaluated at 9 months, despite the lack of detectable GBE activity in those tissues. Plasma biochemistry at treated mice at 9 months of age revealed reduction of liver transaminase and creatine kinase, suggesting alleviation of tissue damage in the liver and skeletal muscle. Additional studies are warranted to determine the functional improvements as a result of gene therapy in the *Gbe1*$^{ys/ys}$ mouse.

v. GSD V

The ovine model for GSD V has recently been used to develop treatments in two ways: first, by using gene therapy to express muscle glycogen phosphorylase and second, by using pharmaceuticals to cause regeneration of muscles leading to re-expression of myophosphorylase in muscles. Intramuscular injection of an adenovirus 5 and/or an AAV2 vector expressing myophosphorylase caused expression of functional myophosphorylase in sheep affected with GSD V.[180] Interestingly, in the same study, it was noted that damage to muscle fibers caused by injection with positive control vectors expressing LacZ caused re-expression of non-muscle isoforms of glycogen phosphorylase. Other studies in the GSD V ovine model have shown similar re-expression of non-muscle isoforms of myophosphorylase using valproate and notexin.[181,182] Recently, an AAV-mediated gene therapy was tested in the *Pygm*$^{R50X/R50X}$ mice. Intraperitoneal injection of an AAV8 vector expressing mouse muscle glycogen phosphorylase driven by a synthetic muscle-specific promoter (AAV8-tMCK-Pygm) into early post-natal *Pygm*$^{R50X/R50X}$ mice led to therapeutic levels of gene expression in hind limb skeletal muscles at 8 weeks of age, accompanied by reduced muscle glycogen levels, improved skeletal muscle pathology, and enhanced functional performance in voluntary wheel running.[183]

Clinical trials investigating gene therapy for GSD

i. GSD Ia

A Phase I/II clinical trial investigating the safety and efficacy of a single intravenous injection of an AAV8-mediated *G6PC* replacement (DTX401) at various doses (2.0×10^{12} GC/kg or 6.0×10^{12} GC/kg with or without a prophylactic steroid regimen) in adults with GSD Ia was completed in 2021 (Table 1; NCT03517085) with an ongoing follow-up extension study monitoring the long-term safety and efficacy in individuals that received the DTX401 infusion (Table 1; NCT03970278). As of April 2023, there is an active Phase III randomized, double-blind, placebo-controlled clinical trial to determine the efficacy and safety of DTX401 in individuals 8 years and older with GSD Ia (Table 1; NCT05139316).

ii. Pompe disease

The minimum effective dose for a liver-expressing AAV8 vector, AAV2/8-LSPhGAA, was only 2×10^{11}/kg body weight in mice with Pompe disease,[162,184] supporting the potential benefits of a low dose appropriate for early phase clinical trials. A Phase I clinical trial with AAV2/8-LSPhGAA vector administered intravenously (Table 1; NCT03533673) has enrolled adults with late-onset Pompe disease.[185] The first cohort of that study demonstrated preliminary safety as well as bioactivity, based upon the absence of any related serious adverse events and upon the presence of significantly increased muscle GAA activity after

52 weeks.[186] As of January 2023, one additional study of AAV vector gene therapy is currently recruiting infants with Pompe disease (Table 1; NCT05567627). One previous clinical trial enrolled 5 participants (age 18–180 months old) in a study of an AAV1 vector injected in the diaphragm, and showed stable effects on tidal volume for 180 days.[187] Although promising, this approach has been considered too invasive and localized in its benefits to be developed as an effective therapy for all patients. Consequently, there is an unmet need for the development of genetic therapies to stably treat Pompe disease. Two additional studies have enrolled subjects, although no data have been published (Table 1; NCT04174105 and NCT04093349). In the absence of an effective gene therapy for infants with Pompe disease, this population will continue to experience progressive loss of muscle function accompanied by increased morbidity and mortality.

Current challenges for gene therapy in GSD

The challenges to the field that affect gene therapy are also an issue for the GSDs. These mainly involve the limitations of gene therapy with regard to efficacy and safety. These challenges include dose requirements and immune responses, which are linked, as well as other toxicities that are specific to the vector systems. For example, T cell mediated immunity against AAV capsid proteins has been associated with the generally asymptomatic elevation of liver transaminases; however, transgene expression has been eliminated when immune suppression was not effective against these immune responses.[188] Such hepatotoxicity could be more problematic in GSDs that have liver-directed gene therapies and/or GSDs that involve the liver, including GSD III.[189] Another risk is the potential for liver tumorigenesis, currently limited to rodent studies with AAV vectors;[190] however, GSD I has been associated with hepatocellular adenoma and carcinoma formation.[191] To date preclinical experiments demonstrated that tumorigenesis was disease-related and not related to gene therapy in GSD Ia.[192] Higher dosages will be required to treat muscle involvement in some GSDs, which has been associated with acute toxicity in clinical trials of AAV9 vector-mediated gene therapy for muscular dystrophy.[193] Pre-existing antibodies against the viral vector will prevent some patients from being treated with gene therapy, until methods to deplete antibodies and allow successful transduction of tissues in these individuals are available.[194] A recent study demonstrated the ability to re-administer an AAV vector efficaciously following an immune suppression consisting of bortezimib and an anti-CD20 monoclonal antibody in mice with Pompe disease.[195] Finally, other vector systems have unique risks, including bone marrow ablation for lentiviral gene therapy,[196] and hepatotoxicity for adenoviral vector gene therapy.[197] In summary, each of these potential risks must be considered and weighed versus anticipated benefits during the planning of clinical trials for GSDs, including disease-specific risks.

Conclusions regarding the state of the art

Progress toward comprehensive understanding of the genetic and biochemical bases of the GSDs has allowed the development of resources needed to develop gene therapy for these disorders, including animal models and vectors for gene therapy. An extension of gene replacement therapy to perform genome editing holds promise for the stable correction of enzyme deficiencies underlying GSDs, which will be critical to treatment

early in life. The limitations of these therapies have been recognized during preclinical development, including the loss of transgene expression due to cell division and the risks of cytotoxic immune responses. Any AAV vector might pose risks from integrating into an oncogene, which could be increased from genome editing. Furthermore, new risks have been recognized during clinical trials, including unexpected toxicities that could complicate clinical trials enrolling patients with GSDs. Despite these limitations, gene therapy and genome editing hold great promise for the treatment of GSDs and could address the unmet need for new therapies for these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to acknowledge the Y.T. and Alice Chen Pediatric Genetics and Genomics Research Center for its encouragement of this work.

Funding

DDK was funded by grant R01AR079223 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Conflict of Interest

Dr. Koeberl, Dr. Lim, Dr. Sun, and Dr. Kishnani have developed technology that is discussed in this review. If the technology is commercially successful in the future, the developers and Duke University may benefit financially. Dr. Koeberl has served as a consultant for Sangamo Therapeutics, Moderna, Genzyme Sanofi, Amicus, and Vertex; has received grant support from Viking Therapeutics, Genzyme Sanofi, Roivant Rare Diseases, and Amicus; and has held equity in Asklepios Biopharmaceutical (AskBio), which is developing gene therapy for Pompe disease. Dr. Sun has received grant support from Valerion Therapeutics, Selecta Biosciences, Roivant Sciences, Alnylam Pharmaceuticals, Actus Therapeutics, Asklepios BioPharmaceutical, Inc. (AskBio), Codexis, Inc., APBD Research Foundation, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01AR079572). Dr. Kishnani has received research/grant support from Genzyme Sanofi, Amicus Therapeutics, Takeda Pharmaceutical and Kriya Therapeutics; has received consulting fees from Kriya Therapeutics, Sanofi Genzyme, Amicus Therapeutics, Maze Therapeutics, Asklepios Biopharmaceutical (AskBio), Moderna, and Ultragenyx; is a member of the Pompe and Gaucher Disease Registry Advisory Board for Genzyme Sanofi, the Amicus scientific advisory board, the Baebies scientific advisory board, the Glycogen Storage Disease 1a Advisory Board for Moderna and Ultragenyx; has held equity in Asklepios BioPharmaceutical (AskBio); and has equity options from Kriya Therapeutics and Maze Therapeutics. Dr. Koch, Dr. Brooks, and Dr. Arnson report no disclosures.

Data Availability Statement

All original data sources are provided in the manuscript.

References

1. Adeva-Andany MM, et al. , Glycogen metabolism in humans. BBA Clin, 2016; 5: p. 85–100. [PubMed: 27051594]
2. Stone WL, Basit H, and Adil A, Glycogen Storage Disease, in StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
3. Kanungo S, et al. , Glycogen metabolism and glycogen storage disorders. Annals of Translational Medicine, 2018; 6(24).

4. Altassan R, et al. , International consensus guidelines for phosphoglucomutase 1 deficiency (PGM1-CDG): Diagnosis, follow-up, and management. J Inherit Metab Dis, 2021; 44(1): p. 148–163. [PubMed: 32681750]
5. Kishnani PS and Chen Y-T, Disorders of Glycogen Metabolism, in Rudolph's Pediatrics. 23 ed. New York, NY: McGraw-Hill Education; 2018.
6. Kishnani PS and Chen Y-T, Glycogen Storage Diseases and Other Inherited Disorders of Carbohydrate Metabolism, in Harrison's Principles of Internal Medicine. 19 ed. New York, NY: McGraw-Hill Education; 2014.
7. Chen Y-T, Kishnani PS, and Koeberl D, Glycogen Storage Diseases, in The Online Metabolic and Molecular Bases of Inherited Disease. New York, NY: McGraw-Hill Education; 2019.
8. Kishnani PS, Sun B, and Koeberl DD, Gene therapy for glycogen storage diseases. Hum Mol Genet, 2019; 28(R1): p. R31–r41. [PubMed: 31227835]
9. Chou JY and Mansfield BC, Gene therapy and genome editing for type I glycogen storage diseases. Frontiers in Molecular Medicine, 2023; 3.
10. Almodóvar-Payá A, et al. , Preclinical research in glycogen storage diseases: A comprehensive review of current animal models. International Journal of Molecular Sciences, 2020; 21(24): p. 1–50.
11. Iijima H, et al. , Novel GYS2 mutations in a Japanese patient with glycogen storage disease type 0a. Molecular Genetics and Metabolism Reports, 2021; 26.
12. Cameron JM, et al. , Identification of a novel mutation in GYS1 (muscle-specific glycogen synthase) resulting in sudden cardiac death, that is diagnosable from skin fibroblasts. Mol Genet Metab, 2009; 98(4): p. 378–382. [PubMed: 19699667]
13. Kollberg G, et al. , Cardiomyopathy and Exercise Intolerance in Muscle Glycogen Storage Disease 0. New England Journal of Medicine, 2007; 357(15): p. 1507–1514. [PubMed: 17928598]
14. Pederson BA, et al. , Abnormal cardiac development in the absence of heart glycogen. Mol Cell Biol, 2004; 24(16): p. 7179–7187. [PubMed: 15282316]
15. Kishnani PS, et al. , Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genetics in Medicine, 2014; 16(11): p. e1. [PubMed: 25356975]
16. Labrune P, et al. , Guidelines for management of glycogen storage disease type I - European Study on Glycogen Storage Disease Type I (ESGSD I). European Journal of Pediatrics, 2002; 161(0): p. S112–S119. [PubMed: 12373584]
17. Visser G, et al. , Consensus guidelines for management of glycogen storage disease type 1b - European Study on Glycogen Storage Disease Type 1. European Journal of Pediatrics, 2002; 161(0): p. S120–S123. [PubMed: 12373585]
18. Wang DQ, et al. , Natural history of hepatocellular adenoma formation in glycogen storage disease type I. J Pediatr, 2011; 159(3): p. 442–446. [PubMed: 21481415]
19. Haring MPD, et al. , High childhood serum triglyceride concentrations associate with hepatocellular adenoma development in patients with glycogen storage disease type Ia. JHEP Rep, 2022; 4(8): p. 100512. [PubMed: 35811762]
20. Dambska M, et al. , Prevention of complications in glycogen storage disease type Ia with optimization of metabolic control. Pediatr Diabetes, 2017; 18(5): p. 327–331. [PubMed: 28568353]
21. Rake JP, et al. , Glycogen storage disease type I: diagnosis, management, clinical course and outcome. Results of the European Study on Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr, 2002; 161 Suppl 1: p. S20–34. [PubMed: 12373567]
22. Martens DH, et al. , Renal function in glycogen storage disease type I, natural course, and renopreservative effects of ACE inhibition. Clin J Am Soc Nephrol, 2009; 4(11): p. 1741–1746. [PubMed: 19808227]
23. Derks TGJ, et al. Glycogen Storage Disease Type Ia: Current Management Options, Burden and Unmet Needs. Nutrients, 2021. 13, DOI: 10.3390/nu13113828.
24. Halligan R, et al. , The natural history of glycogen storage disease type Ib in England: A multisite survey. JIMD Rep, 2021; 59(1): p. 52–59. [PubMed: 33977030]

25. Grünert SC, et al. , Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. Genet Med, 2022; 24(8): p. 1781–1788. [PubMed: 35503103]
26. Dale DC, et al. , Neutropenia in glycogen storage disease Ib: outcomes for patients treated with granulocyte colony-stimulating factor. Curr Opin Hematol, 2019; 26(1): p. 16–21. [PubMed: 30451720]
27. Garbade SF, et al. , Impact of glycogen storage disease type I on adult daily life: a survey. Orphanet Journal of Rare Diseases, 2021; 16(1): p. 371. [PubMed: 34479584]
28. Kaiser N, et al. , Glycemic control and complications in glycogen storage disease type I: Results from the Swiss registry. Mol Genet Metab, 2019; 126(4): p. 355–361. [PubMed: 30846352]
29. Sechi A, et al. , Quality of life in adult patients with glycogen storage disease type I: results of a multicenter italian study. JIMD Rep, 2014; 14: p. 47–53. [PubMed: 24363035]
30. Storch E, et al. , Psychosocial functioning in youth with glycogen storage disease type I. J Pediatr Psychol, 2008; 33(7): p. 728–738. [PubMed: 18296725]
31. Grünert SC, et al. , Patient-reported outcomes on empagliflozin treatment in glycogen storage disease type Ib: An international questionnaire study. JIMD Rep, 2023; 64(3): p. 252–258. [PubMed: 37151361]
32. Brix AE, et al. , Glycogen storage disease type Ia in two littermate Maltese puppies. Vet Pathol, 1995; 32(5): p. 460–465. [PubMed: 8578635]
33. Kishnani PS, et al. , Isolation and nucleotide sequence of canine glucose-6-phosphatase mRNA: identification of mutation in puppies with glycogen storage disease type Ia. Biochem Mol Med, 1997; 61(2): p. 168–177. [PubMed: 9259982]
34. Brooks ED, et al. , Long-term complications of glycogen storage disease type Ia in the canine model treated with gene replacement therapy. J Inherit Metab Dis, 2018; 41(6): p. 965–976. [PubMed: 30043186]
35. Kishnani PS, et al. , Canine model and genomic structural organization of glycogen storage disease type Ia (GSD Ia). Vet Pathol, 2001; 38(1): p. 83–91. [PubMed: 11199168]
36. Lei KJ, et al. , Glucose-6-phosphatase dependent substrate transport in the glycogen storage disease type-1a mouse. Nat Genet, 1996; 13(2): p. 203–209. [PubMed: 8640227]
37. Mutel E, et al. , Targeted deletion of liver glucose-6 phosphatase mimics glycogen storage disease type 1a including development of multiple adenomas. J Hepatol, 2011; 54(3): p. 529–537. [PubMed: 21109326]
38. Mutel E, et al. , Control of blood glucose in the absence of hepatic glucose production during prolonged fasting in mice: induction of renal and intestinal gluconeogenesis by glucagon. Diabetes, 2011; 60(12): p. 3121–3131. [PubMed: 22013018]
39. Clar J, et al. , Targeted deletion of kidney glucose-6 phosphatase leads to nephropathy. Kidney Int, 2014; 86(4): p. 747–756. [PubMed: 24717294]
40. Penhoat A, et al. , Protein-induced satiety is abolished in the absence of intestinal gluconeogenesis. Physiol Behav, 2011; 105(1): p. 89–93. [PubMed: 21402089]
41. Chen LY, et al. , Impaired glucose homeostasis, neutrophil trafficking and function in mice lacking the glucose-6-phosphate transporter. Hum Mol Genet, 2003; 12(19): p. 2547–2558. [PubMed: 12925567]
42. Raggi F, et al. , Development and characterization of an inducible mouse model for glycogen storage disease type Ib. J Inherit Metab Dis, 2018; 41(6): p. 1015–1025. [PubMed: 29967951]
43. Kishnani PS, et al. , Pompe disease diagnosis and management guideline. Genet Med, 2006; 8(5): p. 267–288. [PubMed: 16702877]
44. van den Hout HM, et al. , The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics, 2003; 112(2): p. 332–340. [PubMed: 12897283]
45. Kishnani PS, et al. , A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr, 2006; 148(5): p. 671–676. [PubMed: 16737883]
46. van der Beek NAME, et al. , Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet Journal of Rare Diseases, 2012; 7(1): p. 88. [PubMed: 23147228]

47. Güngör D, et al. , Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. Orphanet Journal of Rare Diseases, 2011; 6(1): p. 34. [PubMed: 21631931]
48. Desai AK, et al. , Immunological challenges and approaches to immunomodulation in Pompe disease: a literature review. Ann Transl Med, 2019; 7(13): p. 285. [PubMed: 31392197]
49. Dornelles AD, et al. , A Systematic Review and Meta-Analysis of Enzyme Replacement Therapy in Late-Onset Pompe Disease. J Clin Med, 2021; 10(21).
50. Strothotte S, et al. , Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol, 2010; 257(1): p. 91–97. [PubMed: 19649685]
51. Toscano A. and Schoser B, Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol, 2013; 260(4): p. 951–959. [PubMed: 22926164]
52. Kishnani PS, et al. , Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology, 2007; 68(2): p. 99–109. [PubMed: 17151339]
53. Nicolino M, et al. , Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genet Med, 2009; 11(3): p. 210–219. [PubMed: 19287243]
54. Chien YH, et al. , Long-term prognosis of patients with infantile-onset Pompe disease diagnosed by newborn screening and treated since birth. J Pediatr, 2015; 166(4): p. 985–991.e981–982. [PubMed: 25466677]
55. Chien YH, et al. , Brain development in infantile-onset Pompe disease treated by enzyme replacement therapy. Pediatr Res, 2006; 60(3): p. 349–352. [PubMed: 16857770]
56. Hsu Y-K, et al. , Evaluating brain white matter hyperintensity, IQ scores, and plasma neurofilament light chain concentration in early-treated patients with infantile-onset Pompe disease. Genetics in Medicine, 2023; 25(1): p. 27–36. [PubMed: 36399131]
57. Korlimarla A, et al. , An emerging phenotype of central nervous system involvement in Pompe disease: from bench to bedside and beyond. Ann Transl Med, 2019; 7(13): p. 289. [PubMed: 31392201]
58. van Gelder CM, et al. , Facial-muscle weakness, speech disorders and dysphagia are common in patients with classic infantile Pompe disease treated with enzyme therapy. J Inherit Metab Dis, 2012; 35(3): p. 505–511. [PubMed: 22008944]
59. Prater SN, et al. , The emerging phenotype of long-term survivors with infantile Pompe disease. Genetics in Medicine, 2012; 14: p. 800–810. [PubMed: 22538254]
60. Hahn A, et al. , Outcome of patients with classical infantile pompe disease receiving enzyme replacement therapy in Germany. JIMD Rep, 2015; 20: p. 65–75. [PubMed: 25626711]
61. van den Dorpel JJA, et al. , Diffusion tensor imaging of the brain in Pompe disease. J Neurol, 2022.
62. Stockton DW, et al. , Respiratory function during enzyme replacement therapy in late-onset Pompe disease: longitudinal course, prognostic factors, and the impact of time from diagnosis to treatment start. J Neurol, 2020; 267(10): p. 3038–3053. [PubMed: 32524257]
63. Gutschmidt K, et al. , STIG study: real-world data of long-term outcomes of adults with Pompe disease under enzyme replacement therapy with alglucosidase alfa. Journal of Neurology, 2021; 268(7): p. 2482–2492. [PubMed: 33543425]
64. Chien YH, et al. , Early detection of Pompe disease by newborn screening is feasible: results from the Taiwan screening program. Pediatrics, 2008; 122(1): p. e39–45. [PubMed: 18519449]
65. Huggins E, et al. , Early clinical phenotype of late onset Pompe disease: Lessons learned from newborn screening. Mol Genet Metab, 2022; 135(3): p. 179–185. [PubMed: 35123877]
66. Raben N, et al. , Targeted disruption of the acid alpha-glucosidase gene in mice causes an illness with critical features of both infantile and adult human glycogen storage disease type II. J Biol Chem, 1998; 273(30): p. 19086–19092. [PubMed: 9668092]
67. Walvoort HC, Dormans JA, and van den Ingh TS, Comparative pathology of the canine model of glycogen storage disease type II (Pompe's disease). J Inherit Metab Dis, 1985; 8(1): p. 38–46. [PubMed: 3921759]
68. Kishnani PS, et al. , Glycogen Storage Disease Type III diagnosis and management guidelines. Genetics in Medicine, 2010; 12(7).

69. Sentner CP, et al. , Glycogen storage disease type III: diagnosis, genotype, management, clinical course and outcome. J Inherit Metab Dis, 2016; 39(5): p. 697–704. [PubMed: 27106217]
70. Halaby CA, et al. , Liver fibrosis during clinical ascertainment of glycogen storage disease type III: a need for improved and systematic monitoring. Genetics in Medicine, 2019; 21(12): p. 2686–2694. [PubMed: 31263214]
71. Vertilus SM, et al. , Echocardiographic manifestations of Glycogen Storage Disease III: increase in wall thickness and left ventricular mass over time. Genet Med, 2010; 12(7): p. 413–423. [PubMed: 20526204]
72. Hijazi G, et al. , A retrospective longitudinal study and comprehensive review of adult patients with glycogen storage disease type III. Molecular genetics and metabolism reports, 2021; 29: p. 100821–100821.
73. Paschall A, et al. , Physical therapy assessment and whole-body magnetic resonance imaging findings in children with glycogen storage disease type IIIa: A clinical study and review of the literature. Mol Genet Metab, 2021; 134(3): p. 223–234. [PubMed: 34649782]
74. Liu KM, Wu JY, and Chen YT, Mouse model of glycogen storage disease type III. Mol Genet Metab, 2014; 111(4): p. 467–476. [PubMed: 24613482]
75. Pagliarani S, et al. , Glycogen storage disease type III: A novel Agl knockout mouse model. Biochim Biophys Acta, 2014; 1842(11): p. 2318–2328. [PubMed: 25092169]
76. Vidal P, et al. , Rescue of GSDIII Phenotype with Gene Transfer Requires Liver- and Muscle-Targeted GDE Expression. Mol Ther, 2018; 26(3): p. 890–901. [PubMed: 29396266]
77. Lim JA, et al. , A Novel Gene Therapy Approach for GSD III Using an AAV Vector Encoding a Bacterial Glycogen Debranching Enzyme. Mol Ther Methods Clin Dev, 2020; 18: p. 240–249. [PubMed: 32637453]
78. Gregory BL, et al. , Glycogen storage disease type IIIa in curly-coated retrievers. J Vet Intern Med, 2007; 21(1): p. 40–46. [PubMed: 17338148]
79. Brooks ED, et al. , Natural Progression of Canine Glycogen Storage Disease Type IIIa. Comp Med, 2016; 66(1): p. 41–51. [PubMed: 26884409]
80. Koch RL, et al. , Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: A clinical practice resource. Molecular Genetics and Metabolism, 2023; 138(3): p. 107525. [PubMed: 36796138]
81. Kiely BT, et al. , A novel approach to characterize phenotypic variation in GSD IV: Reconceptualizing the clinical continuum. Frontiers in Genetics, 2022; 13.
82. Mochel F, et al. , Adult polyglucosan body disease: Natural History and Key Magnetic Resonance Imaging Findings. Annals of Neurology, 2012; 72(3): p. 433–441. [PubMed: 23034915]
83. Coates JR, et al. , A case presentation and discussion of type IV glycogen storage disease in a Norwegian Forest Cat. Progress in Veterinary Neurology, 1996; 7(1): p. 5–11.
84. Fyfe JC, et al. , A complex rearrangement in GBE1 causes both perinatal hypoglycemic collapse and late-juvenile-onset neuromuscular degeneration in glycogen storage disease type IV of Norwegian forest cats. Mol Genet Metab, 2007; 90(4): p. 383–392. [PubMed: 17257876]
85. Ward TL, et al. , Glycogen branching enzyme (GBE1) mutation causing equine glycogen storage disease IV. Mamm Genome, 2004; 15(7): p. 570–577. [PubMed: 15366377]
86. Ward TL, et al. , Genetic mapping of GBE1 and its association with glycogen storage disease IV in American Quarter horses. Cytogenetic and Genome Research, 2003; 102(1–4): p. 201–206.
87. Render JA, et al. , Amylopectinosis in fetal and neonatal Quarter Horses. Veterinary Pathology, 1999; 36(2): p. 157–160. [PubMed: 10098645]
88. Valberg SJ, et al. , Glycogen branching enzyme deficiency in quarter horse foals. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine, 2001; 15(6): p. 572–580.
89. Sponseller BT, et al. , Muscular weakness and recumbency in a Quarter Horse colt due to glycogen branching enzyme deficiency. Equine Veterinary Education, 2003; 15(4): p. 182–188.
90. Akman HO, et al. , Generation of a novel mouse model that recapitulates early and adult onset glycogenosis type IV. Hum Mol Genet, 2011; 20(22): p. 4430–4439. [PubMed: 21856731]

91. Akman HO, et al. , A novel mouse model that recapitulates adult-onset glycogenosis type 4. Human Molecular Genetics, 2015; 24(23): p. 6801–6810. [PubMed: 26385640]
92. Lucia A, et al. , Clinical practice guidelines for glycogen storage disease V & VII (McArdle disease and Tarui disease) from an international study group. Neuromuscular Disorders, 2021; 31(12): p. 1296–1310. [PubMed: 34848128]
93. Angelos S, et al. , Myophosphorylase deficiency associated with rhabdomyolysis and exercise intolerance in 6 related Charolais cattle. Muscle Nerve, 1995; 18(7): p. 736–740. [PubMed: 7783763]
94. Tsujino S, et al. , Cloning of bovine muscle glycogen phosphorylase cDNA and identification of a mutation in cattle with myophosphorylase deficiency, an animal model for McArdle's disease. Neuromuscul Disord, 1996; 6(1): p. 19–26. [PubMed: 8845714]
95. Tan P, et al. , A splice-site mutation causing ovine McArdle's disease. Neuromuscul Disord, 1997; 7(5): p. 336–342. [PubMed: 9267848]
96. Nogales-Gadea G, et al. , Knock-in mice for the R50X mutation in the PYGM gene present with McArdle disease. Brain, 2012; 135(Pt 7): p. 2048–2057. [PubMed: 22730558]
97. Brull A, et al. , Phenotype consequences of myophosphorylase dysfunction: insights from the McArdle mouse model. J Physiol, 2015; 593(12): p. 2693–2706. [PubMed: 25873271]
98. Real-Martinez A, et al. , Low survival rate and muscle fiber-dependent aging effects in the McArdle disease mouse model. Sci Rep, 2019; 9(1): p. 5116. [PubMed: 30914683]
99. Migocka-Patrzałek M, et al. , The effect of muscle glycogen phosphorylase (Pygm) knockdown on zebrafish morphology. The International Journal of Biochemistry & Cell Biology, 2020; 118: p. 105658. [PubMed: 31747538]
100. Roscher A, et al. , The natural history of glycogen storage disease types VI and IX: Long-term outcome from the largest metabolic center in Canada. Mol Genet Metab, 2014; 113(3): p. 171–176. [PubMed: 25266922]
101. Degrassi I, et al. , Liver histology in children with glycogen storage disorders type VI and IX. Digestive and Liver Disease, 2021; 53(1): p. 86–93. [PubMed: 32505569]
102. Grünert SC, Hannibal L, and Spiekerkoetter U, The Phenotypic and Genetic Spectrum of Glycogen Storage Disease Type VI. Genes, 2021; 12.
103. Fernandes SA, et al. , Benign or not benign? Deep phenotyping of liver Glycogen Storage Disease IX. Molecular Genetics and Metabolism, 2020; 131(3): p. 299–305. [PubMed: 33317799]
104. Wilson LH, et al. , Liver Glycogen Phosphorylase Deficiency Leads to Profibrogenic Phenotype in a Murine Model of Glycogen Storage Disease Type VI. Hepatol Commun, 2019; 3(11): p. 1544–1555. [PubMed: 31701076]
105. Gibson RA, et al. , Characterization of liver GSD IX gamma2 pathophysiology in a novel Phkg2(−/−) mouse model. Mol Genet Metab, 2021; 133(3): p. 269–276. [PubMed: 34083142]
106. Malthus R, et al. , Glycogen-storage disease in rats, a genetically determined deficiency of liver phosphorylase kinase. Biochem J, 1980; 188(1): p. 99–106. [PubMed: 6931596]
107. Clark DG, et al. , A glycogen storage disease (gsd/gsd) rat: studies on lipid metabolism, lipogenesis, plasma metabolites, and bile acid secretion. Metabolism, 1980; 29(5): p. 415–420. [PubMed: 6929400]
108. Maichele AJ, et al. , Mutations in the testis/liver isoform of the phosphorylase kinase gamma subunit (PHKG2) cause autosomal liver glycogenosis in the gsd rat and in humans. Nat Genet, 1996; 14(3): p. 337–340. [PubMed: 8896567]
109. Arends CJ, et al. , A Mouse Model of Glycogen Storage Disease Type IX-Beta: A Role for Phkb in Glycogenolysis. Int J Mol Sci, 2022; 23(17).
110. Giger U, et al. , Metabolic myopathy in canine muscle-type phosphofructokinase deficiency. Muscle Nerve, 1988; 11(12): p. 1260–1265. [PubMed: 2976895]
111. Smith BF, et al. , Molecular basis of canine muscle type phosphofructokinase deficiency. J.Biol.Chem, 1996; 271(33): p. 20070–20074. [PubMed: 8702726]
112. Gerber K, et al. , Hemolysis, myopathy, and cardiac disease associated with hereditary phosphofructokinase deficiency in two Whippets. Vet Clin Pathol, 2009; 38(1): p. 46–51. [PubMed: 19228357]

113. Inal Gultekin G, et al. , Missense mutation in PFKM associated with muscle-type phosphofructokinase deficiency in the Wachtelhund dog. Mol Cell Probes, 2012; 26(6): p. 243–247. [PubMed: 22446493]
114. Hillstrom A, et al. , Hereditary phosphofructokinase deficiency in wachtelhunds. J Am Anim Hosp Assoc, 2011; 47(2): p. 145–150. [PubMed: 21311071]
115. Garcia M, et al. , Phosphofructo-1-kinase deficiency leads to a severe cardiac and hematological disorder in addition to skeletal muscle glycogenosis. PLoS Genet, 2009; 5(8): p. e1000615. [PubMed: 19696889]
116. Akman HO, et al. , Late-onset polyglucosan body myopathy in five patients with a homozygous mutation in GYG1. Neuromuscular Disorders, 2016; 26(1): p. 16–20. [PubMed: 26652229]
117. Barbosa-Gouveia S, et al. , Rapid Molecular Diagnosis of Genetically Inherited Neuromuscular Disorders Using Next-Generation Sequencing Technologies. J Clin Med, 2022; 11(10).
118. Ben Yaou R, et al. , Clinical heterogeneity and phenotype/genotype findings in 5 families with GYG1 deficiency. Neurol Genet, 2017; 3(6): p. e208. [PubMed: 29264399]
119. Colombo I, et al. , Longitudinal follow-up and muscle MRI pattern of two siblings with polyglucosan body myopathy due to glycogenin-1 mutation. J Neurol Neurosurg Psychiatry, 2016; 87(7): p. 797–800. [PubMed: 26203156]
120. Fanin M, et al. , GYG1 gene mutations in a family with polyglucosan body myopathy. Neurol Genet, 2015; 1(3): p. e21. [PubMed: 27066558]
121. Hedberg-Oldfors C, et al. , Functional characterization of GYG1 variants in two patients with myopathy and glycogenin-1 deficiency. Neuromuscul Disord, 2019; 29(12): p. 951–960. [PubMed: 31791869]
122. Hedberg-Oldfors C, et al. , Cardiomyopathy as presenting sign of glycogenin-1 deficiency-report of three cases and review of the literature. J Inherit Metab Dis, 2017; 40(1): p. 139–149. [PubMed: 27718144]
123. Luo S, et al. , Muscle pathology and whole-body MRI in a polyglucosan myopathy associated with a novel glycogenin-1 mutation. Neuromuscular Disorders, 2015; 25(10): p. 780–785. [PubMed: 26255073]
124. Malfatti E, et al. , A new muscle glycogen storage disease associated with glycogenin-1 deficiency. Neurology, 2015; 84.
125. Moslemi A-R, et al. , Glycogenin-1 Deficiency and Inactivated Priming of Glycogen Synthesis. New England Journal of Medicine, 2010; 362(13): p. 1203–1210. [PubMed: 20357282]
126. Nicolau S, et al. , GYG1: A distal myopathy with polyglucosan bodies. JIMD Reports, 2020; 55: p. 88–90. [PubMed: 32905144]
127. Tasca G, et al. , Start codon mutation of GYG1 causing late-onset polyglucosan body myopathy with nemaline rods. J Neurol, 2016; 263(10): p. 2133–2135. [PubMed: 27544502]
128. Hedberg-Oldfors C, et al. , Polyglucosan myopathy and functional characterization of a novel GYG1 mutation. Acta Neurologica Scandinavica, 2018; 137(3): p. 308–315. [PubMed: 29143313]
129. Lefeuvre C, et al. , Glycogenin-1 deficiency mimicking limb-girdle muscular dystrophy. Molecular Genetics and Metabolism Reports, 2020; 24.
130. Testoni G, et al. , Lack of Glycogenin Causes Glycogen Accumulation and Muscle Function Impairment. Cell Metabolism, 2017; 26(1): p. 256–266.e254. [PubMed: 28683291]
131. Chandler RJ and Venditti CP, Gene Therapy for Metabolic Diseases. Transl Sci Rare Dis, 2016; 1(1): p. 73–89. [PubMed: 27853673]
132. Koeberl DD, et al. , Early, sustained efficacy of adeno-associated virus vector-mediated gene therapy in glycogen storage disease type Ia. Gene Therapy, 2006; 13(17): p. 1281–1289. [PubMed: 16672983]
133. Lee YM, et al. , Prevention of hepatocellular adenoma and correction of metabolic abnormalities in murine glycogen storage disease type Ia by gene therapy. Hepatology, 2012; 56(5): p. 1719–1729. [PubMed: 22422504]
134. Luo X, et al. , Hepatorenal correction in murine glycogen storage disease type I with a double-stranded adeno-associated virus vector. Mol Ther, 2011; 19(11): p. 1961–1970. [PubMed: 21730973]

135. Cunningham SC, et al. , AAV2/8-mediated correction of OTC deficiency is robust in adult but not neonatal Spf(ash) mice. Mol Ther, 2009; 17(8): p. 1340–1346. [PubMed: 19384294]
136. Cotugno G, et al. , Long-term amelioration of feline Mucopolysaccharidosis VI after AAV-mediated liver gene transfer. Mol Ther, 2011; 19(3): p. 461–469. [PubMed: 21119624]
137. Lee EK, et al. , Long-term survival of the juvenile lethal arginase-deficient mouse with AAV gene therapy. Mol Ther, 2012; 20(10): p. 1844–1851. [PubMed: 22760543]
138. Gautam S, et al. , The signaling pathways implicated in impairment of hepatic autophagy in glycogen storage disease type Ia. Hum Mol Genet, 2020.
139. Weinstein DA, et al. , Adeno-Associated Virus-Mediated Correction of a Canine Model of Glycogen Storage Disease Type Ia. Human Gene Therapy, 2010; 21(7): p. 903–910. [PubMed: 20163245]
140. Brooks ED, et al. , Pathogenesis of growth failure and partial reversal with gene therapy in murine and canine Glycogen Storage Disease type Ia. Molecular Genetics and Metabolism, 2013; 109(2): p. 161–170. [PubMed: 23623482]
141. Brooks ED, et al. , Long-term complications of glycogen storage disease type Ia in the canine model treated with gene replacement therapy. Journal of Inherited Metabolic Disease, 2018; 41(6): p. 965–976. [PubMed: 30043186]
142. Lee YM, et al. , Long-term safety and efficacy of AAV gene therapy in the canine model of glycogen storage disease type Ia. J Inherit Metab Dis, 2018.
143. Landau DJ, et al. , In Vivo Zinc Finger Nuclease-mediated Targeted Integration of a Glucose-6-phosphatase Transgene Promotes Survival in Mice With Glycogen Storage Disease Type IA. Mol Ther, 2016; 24(4): p. 697–706. [PubMed: 26865405]
144. Yang Y, et al. , A dual AAV system enables the Cas9-mediated correction of a metabolic liver disease in newborn mice. Nat Biotechnol, 2016; 34(3): p. 334–338. [PubMed: 26829317]
145. Ohmori T, et al. , CRISPR/Cas9-mediated genome editing via postnatal administration of AAV vector cures haemophilia B mice. Sci Rep, 2017; 7(1): p. 4159. [PubMed: 28646206]
146. Richards DY, et al. , AAV-Mediated CRISPR/Cas9 Gene Editing in Murine Phenylketonuria. Mol Ther Methods Clin Dev, 2020; 17: p. 234–245. [PubMed: 31970201]
147. Kang HR, et al. , Bezafibrate Enhances AAV Vector-Mediated Genome Editing in Glycogen Storage Disease Type Ia. Mol Ther Methods Clin Dev, 2019; 13: p. 265–273. [PubMed: 30859111]
148. Arnaoutova I, et al. , Correction of metabolic abnormalities in a mouse model of glycogen storage disease type Ia by CRISPR/Cas9-based gene editing. Molecular Therapy, 2021; 29(4): p. 1602–1610. [PubMed: 33359667]
149. Arnson B, et al. , Genome editing using Staphylococcus aureus Cas9 in a canine model of glycogen storage disease Ia. Mol Ther Methods Clin Dev; In press.
150. Wendel U, et al. , Glycogen storage disease type Ib: infectious complications and measures for prevention. Eur.J.Pediatr, 1993; 152 Suppl 1: p. S49–S51. [PubMed: 7686491]
151. Kwon JH, et al. , Liver-directed gene therapy for murine glycogen storage disease type Ib. Hum Mol Genet, 2017; 26(22): p. 4395–4405. [PubMed: 28973635]
152. Yiu WH, et al. , Glucose-6-phosphate transporter gene therapy corrects metabolic and myeloid abnormalities in glycogen storage disease type Ib mice. Gene Ther., 2007; 14(3): p. 219–226. [PubMed: 17006547]
153. Jones HN, et al. , Oropharyngeal dysphagia in infants and children with infantile Pompe disease. Dysphagia, 2010; 25(4): p. 277–283. [PubMed: 19763689]
154. Yanovitch TL, et al. , Clinical and histologic ocular findings in pompe disease. J Pediatr Ophthalmol Strabismus, 2010; 47(1): p. 34–40. [PubMed: 20128552]
155. Banugaria SG, et al. , The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. Genet Med, 2011; 13(8): p. 729–736. [PubMed: 21637107]
156. Bond JE, Kishnani PS, and Koeberl DD, Immunomodulatory, liver depot gene therapy for Pompe disease. Cell Immunol, 2019; 342: p. 103737. [PubMed: 29295737]

157. Sun B, et al. , Correction of glycogen storage disease type II by an adeno-associated virus vector containing a muscle-specific promoter. Mol Ther, 2005; 11(6): p. 889–898. [PubMed: 15922959]
158. Keeler AM, et al. , Systemic Delivery of AAVB1-GAA Clears Glycogen and Prolongs Survival in a Mouse Model of Pompe Disease. Hum Gene Ther, 2019; 30(1): p. 57–68. [PubMed: 29901418]
159. Lee NC, et al. , A Neuron-Specific Gene Therapy Relieves Motor Deficits in Pompe Disease Mice. Mol Neurobiol, 2018; 55(6): p. 5299–5309. [PubMed: 28895054]
160. Franco LM, et al. , Evasion of immune responses to introduced human acid alpha-glucosidase by liver-restricted expression in glycogen storage disease type II. Mol.Ther, 2005; 12(5): p. 876–884. [PubMed: 16005263]
161. Ziegler RJ, et al. , Ability of adeno-associated virus serotype 8-mediated hepatic expression of acid alpha-glucosidase to correct the biochemical and motor function deficits of presymptomatic and symptomatic Pompe mice. Hum.Gene Ther, 2008; 19(6): p. 609–621. [PubMed: 18500944]
162. Han SO, et al. , Low-Dose Liver-Targeted Gene Therapy for Pompe Disease Enhances Therapeutic Efficacy of ERT via Immune Tolerance Induction. Mol Ther Methods Clin Dev, 2017; 4: p. 126–136. [PubMed: 28344998]
163. Han SO, et al. , Comparisons of Infant and Adult Mice Reveal Age Effects for Liver Depot Gene Therapy in Pompe Disease. Mol Ther Methods Clin Dev, 2020; 17: p. 133–142. [PubMed: 31909086]
164. Cunningham SC, et al. , Gene delivery to the juvenile mouse liver using AAV2/8 vectors. Mol.Ther, 2008; 16(6): p. 1081–1088.
165. Wang L, et al. , AAV8-mediated Hepatic Gene Transfer in Infant Rhesus Monkeys (Macaca mulatta). Mol Ther, 2011; 19(11): p. 2012–2020. [PubMed: 21811248]
166. Nathwani AC, et al. , Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med, 2014; 371(21): p. 1994–2004. [PubMed: 25409372]
167. Mah C, et al. , Sustained correction of glycogen storage disease type II using adeno-associated virus serotype 1 vectors. Gene Ther., 2005; 12(18): p. 1405–1409. [PubMed: 15920463]
168. Mah C, et al. , Physiological Correction of Pompe Disease by Systemic Delivery of Adeno-associated Virus Serotype 1 Vectors. Mol.Ther, 2007; 15(3): p. 501–507. [PubMed: 17245350]
169. van der Wal E, et al. , Large-Scale Expansion of Human iPSC-Derived Skeletal Muscle Cells for Disease Modeling and Cell-Based Therapeutic Strategies. Stem Cell Reports, 2018; 10(6): p. 1975–1990. [PubMed: 29731431]
170. Barzel A, et al. , Promoterless gene targeting without nucleases ameliorates haemophilia B in mice. Nature, 2015; 517(7534): p. 360–364. [PubMed: 25363772]
171. Kishnani PS, et al. , Glycogen storage disease type III diagnosis and management guidelines. Genet Med, 2010; 12(7): p. 446–463. [PubMed: 20631546]
172. Dagli A, Sentner CP, and Weinstein DA, Glycogen Storage Disease Type III, in GeneReviews((R)). Seattle (WA): University of Washington, Seattle; 2010.
173. Sentner CP, et al. , Heart Failure Due to Severe Hypertrophic Cardiomyopathy Reversed by Low Calorie, High Protein Dietary Adjustments in a Glycogen Storage Disease Type IIIa Patient. JIMD Rep, 2012; 5: p. 13–16. [PubMed: 23430911]
174. Yi H, et al. , Correction of glycogen storage disease type III with rapamycin in a canine model. J Mol Med (Berl), 2014; 92(6): p. 641–650. [PubMed: 24509886]
175. Pursell N, et al. , Inhibition of Glycogen Synthase II with RNAi Prevents Liver Injury in Mouse Models of Glycogen Storage Diseases. Mol Ther, 2018; 26(7): p. 1771–1782. [PubMed: 29784585]
176. Hinderer C, et al. , Severe Toxicity in Nonhuman Primates and Piglets Following High-Dose Intravenous Administration of an Adeno-Associated Virus Vector Expressing Human SMN. Human Gene Therapy, 2018; 29(3): p. 285–298. [PubMed: 29378426]
177. Feldman AG, et al. , Subacute Liver Failure Following Gene Replacement Therapy for Spinal Muscular Atrophy Type 1. J Pediatr, 2020.
178. Lim JA, Kishnani PS, and Sun B, Suppression of pullulanase-induced cytotoxic T cell response with a dual promoter in GSD IIIa mice. JCI Insight, 2022; 7(23).

179. Yi H, et al. , Systemic Correction of Murine Glycogen Storage Disease Type IV by an AAV-Mediated Gene Therapy. Human Gene Therapy, 2017; 28(3): p. 286–294. [PubMed: 27832700]
180. Howell JM, et al. , Adenovirus and adeno-associated virus-mediated delivery of human myophosphorylase cDNA and LacZ cDNA to muscle in the ovine model of McArdle's disease: expression and re-expression of glycogen phosphorylase. Neuromuscul Disord, 2008; 18(3): p. 248–258. [PubMed: 18343113]
181. Howell JM, Quinlivan R, and Sewry C, Investigation of possible treatment regimes for McArdle's disease using the sheep model of the disease. Neuromuscular Disorders, 2008; 18(9–10): p. 828-828.
182. Howell JM, et al. , Phosphorylase re-expression, increase in the force of contraction and decreased fatigue following notexin-induced muscle damage and regeneration in the ovine model of McArdle disease. Neuromuscul Disord, 2014; 24(2): p. 167–177. [PubMed: 24309536]
183. McNamara EL, et al. , Systemic AAV8-mediated delivery of a functional copy of muscle glycogen phosphorylase (Pygm) ameliorates disease in a murine model of McArdle disease. Hum Mol Genet, 2020; 29(1): p. 20–30. [PubMed: 31511858]
184. Han S, et al. , Minimum Effective Dose to Achieve Biochemical Correction With AAV Vector-Mediated Gene Therapy in Mice With Pompe Disease. Hum Gene Ther, 2022.
185. Kishnani PS, Sun B, and Koeberl DD, Gene therapy for glycogen storage diseases. Hum Mol Genet, 2019.
186. Smith EC, et al. , Phase I study of liver depot gene therapy in late-onset Pompe disease. Mol Ther, 2023.
187. Smith BK, et al. , Phase I/II trial of adeno-associated virus-mediated alpha-glucosidase gene therapy to the diaphragm for chronic respiratory failure in Pompe disease: initial safety and ventilatory outcomes. Hum Gene Ther, 2013; 24(6): p. 630–640. [PubMed: 23570273]
188. Nienhuis AW, Nathwani AC, and Davidoff AM, Gene Therapy for Hemophilia. Mol Ther, 2017; 25(5): p. 1163–1167. [PubMed: 28411016]
189. Okuda S, et al. , Fatal liver cirrhosis and esophageal variceal hemorrhage in a patient with type IIIa glycogen storage disease. Intern.Med, 1998; 37(12): p. 1055–1057. [PubMed: 9932641]
190. Chandler RJ, Sands MS, and Venditti CP, Recombinant Adeno-Associated Viral Integration and Genotoxicity: Insights from Animal Models. Hum Gene Ther, 2017; 28(4): p. 314–322. [PubMed: 28293963]
191. Reddy SK, et al. , Resection of hepatocellular adenoma in patients with glycogen storage disease type Ia. J.Hepatol, 2007; 47. p. 658–663. [PubMed: 17637480]
192. Kang HR, et al. , Pathogenesis of Hepatic Tumors following Gene Therapy in Murine and Canine Models of Glycogen Storage Disease. Mol Ther Methods Clin Dev, 2019; 15: p. 383–391. [PubMed: 31890731]
193. Buscara L, Gross DA, and Daniele N, Of rAAV and Men: From Genetic Neuromuscular Disorder Efficacy and Toxicity Preclinical Studies to Clinical Trials and Back. J Pers Med, 2020; 10(4).
194. Boutin S, et al. , Prevalence of serum IgG and neutralizing factors against adeno-associated virus types 1, 2, 5, 6, 8 and 9 in the healthy population: implications for gene therapy using AAV vectors. Hum.Gene Ther, 2010.
195. Choi SJ, et al. , Successful AAV8 readministration: Suppression of capsid-specific neutralizing antibodies by a combination treatment of bortezomib and CD20 mAb in a mouse model of Pompe disease. J Gene Med, 2023: p. e3509. [PubMed: 36994804]
196. Stok M, et al. , Lentiviral Hematopoietic Stem Cell Gene Therapy Corrects Murine Pompe Disease. Mol Ther Methods Clin Dev, 2020; 17: p. 1014–1025. [PubMed: 32462050]
197. Brunetti-Pierri N, et al. , Acute toxicity after high-dose systemic injection of helper-dependent adenoviral vectors into nonhuman primates. Hum.Gene Ther, 2004; 15(1): p. 35–46. [PubMed: 14965376]
198. Brooks ED, et al. , Pathogenesis of growth failure and partial reversal with gene therapy in murine and canine Glycogen Storage Disease type Ia. Mol Genet Metab, 2013; 109(2): p. 161–170. [PubMed: 23623482]
199. Matsui T, et al. , Generalized glycogen storage disease in Japanese quail (Coturnix coturnix japonica). Vet Pathol, 1983; 20(3): p. 312–321. [PubMed: 6576505]

200. Manktelow BW and Hartley WJ, Generalized glycogen storage disease in sheep. J Comp Pathol, 1975; 85(1): p. 139–145. [PubMed: 1055118]

201. Lyons RE, et al. , E7 (1057DeltaTA) mutation of the acidic alpha-glucosidase gene causes Pompe's disease in Droughtmaster cattle. Aust Vet J, 2017; 95(5): p. 138–142. [PubMed: 28444756]

202. Dennis JA, Healy PJ, and Reichmann KG, Genotyping Brahman cattle for generalised glycogenosis. Aust Vet J, 2002; 80(5): p. 286–291. [PubMed: 12074310]

203. Dennis JA and Healy PJ, Genotyping shorthorn cattle for generalised glycogenosis. Aust Vet J, 2001; 79(11): p. 773–775. [PubMed: 11789914]

204. Migocka-Patrzalek M, et al. , The effect of muscle glycogen phosphorylase (Pygm) knockdown on zebrafish morphology. Int J Biochem Cell Biol, 2020; 118: p. 105658. [PubMed: 31747538]

205. Skarnes WC, et al. , A conditional knockout resource for the genome-wide study of mouse gene function. Nature, 2011; 474(7351): p. 337–342. [PubMed: 21677750]

206. Smith BF, et al. , Molecular basis of canine muscle type phosphofructokinase deficiency. J Biol Chem, 1996; 271(33): p. 20070–20074. [PubMed: 8702726]

207. Giger U, et al. , Metabolic myopathy in canine muscle-type phosphofructokinase deficiency. Muscle Nerve, 1988; 11(12): p. 1260–1265. [PubMed: 2976895]

208. Testoni G, et al. , Lack of Glycogenin Causes Glycogen Accumulation and Muscle Function Impairment. Cell Metab, 2017; 26(1): p. 256–266 e254. [PubMed: 28683291]

209. Sun MS, et al. , Sustained hepatic and renal glucose-6-phosphatase expression corrects glycogen storage disease type Ia in mice. Hum.Mol.Genet, 2002; 11(18): p. 2155–2164. [PubMed: 12189168]

210. Ghosh A, et al. , Long-term correction of murine glycogen storage disease type Ia by recombinant adeno-associated virus-1-mediated gene transfer. Gene Ther., 2006; 13(4): p. 321–329. [PubMed: 16195703]

211. Koeberl DD, et al. , Efficacy of helper-dependent adenovirus vector-mediated gene therapy in murine glycogen storage disease type Ia. Mol.Ther, 2007; 15(7): p. 1253–1258. [PubMed: 17505475]

212. Koeberl DD, et al. , AAV vector-mediated reversal of hypoglycemia in canine and murine glycogen storage disease type Ia. Mol.Ther, 2008; 16(4): p. 665–672. [PubMed: 18362924]

213. Yiu WH, et al. , Complete normalization of hepatic G6PC deficiency in murine glycogen storage disease type Ia using gene therapy. Mol Ther, 2010; 18(6): p. 1076–1084. [PubMed: 20389290]

214. Grinshpun A, et al. , Neonatal gene therapy of glycogen storage disease type Ia using a feline immunodeficiency virus-based vector. Mol Ther, 2010; 18(9): p. 1592–1598. [PubMed: 20571544]

215. Puzzo F, et al. , Rescue of Pompe disease in mice by AAV-mediated liver delivery of secretable acid alpha-glucosidase. Sci Transl Med, 2017; 9(418).

216. Sun B, et al. , Correction of glycogen storage disease type II by an adeno-associated virus vector containing a muscle-specific promoter. Mol.Ther, 2005; 11(6): p. 889–898. [PubMed: 15922959]

217. Colella P, et al. , AAV Gene Transfer with Tandem Promoter Design Prevents Anti-transgene Immunity and Provides Persistent Efficacy in Neonate Pompe Mice. Mol Ther Methods Clin Dev, 2019; 12: p. 85–101. [PubMed: 30581888]

218. Zhang P, et al. , Immunodominant liver-specific expression suppresses transgene-directed immune responses in murine pompe disease. Hum Gene Ther, 2012; 23(5): p. 460–472. [PubMed: 22260439]

219. Doerfler PA, et al. , Copackaged AAV9 Vectors Promote Simultaneous Immune Tolerance and Phenotypic Correction of Pompe Disease. Hum Gene Ther, 2016; 27(1): p. 43–59. [PubMed: 26603344]

220. Rastall DP, et al. , Long-term, high-level hepatic secretion of acid alpha-glucosidase for Pompe disease achieved in non-human primates using helper-dependent adenovirus. Gene Ther, 2016; 23(10): p. 743–752. [PubMed: 27367841]

J Inherit Metab Dis. Author manuscript; available in PMC 2025 January 01.

Table 1.

Selected GSDs and Gene Therapy Considerations.

Type	Eponym	Affected Gene (Inheritance)	Deficient Enzyme	OMIM	Affected Tissues/ Cells	Challenges for Gene Therapy	Current Stage of Clinical Development
0a	---	*GYS2* (AR)	Glycogen synthase 2	240600	Liver	Lack of animal model	---
0b	---	*GYS1* (AR)	Glycogen synthase 1	611556	Skeletal muscle, heart	Available mouse model has a poor survival rate	---
Ia	von Gierke disease	*G6PC* (AR)	Glucose-6-phosphatase α	232200	Liver, kidneys	Increased apoptosis, decreased autophagy; resistance of kidney to transduction	Phase III clinical trial of gene replacement therapy (NCT05139316); Phase I encapsulated mRNA therapy (NCT05095727)
Ib		*SLC37A4* (AR)	Glucose-6-phosphate translocase	232220	Liver, kidneys, neutrophils	Similar to GSD Ia; plus need to transduce neutrophil precursor cells	---
II [a]	Pompe disease	*GAA* (AR)	Acid α-glucosidase	232300	Skeletal muscle, diaphragm, heart	Resistance to correction in advanced stages; need to treat early in infantile-onset	Phase I gene replacement therapy (NCT03533673; NCT05567627; NCT04174105; NCT04093349)
IIIa and IIIb	Cori disease	*AGL* (AR)	Glycogen debranching enzyme	232400	IIIa: liver, skeletal muscle, heart IIIb: liver	Very large cDNA prevents delivery with a single AAV vector; transduction of fibrotic liver	Phase I encapsulated mRNA therapy (NCT04990388), study terminated
IV	Andersen disease[b]	*GBE1* (AR)	Glycogen branching enzyme	232500	Liver, skeletal muscle, central and peripheral nervous systems, heart	Variable multisystem involvement, transduction of fibrotic liver	---
	Adult Polyglucosan Body Disease[c]			263570	Skeletal muscle, central and peripheral nervous systems, heart		---
V	McArdle disease	*PYGM* (AR)	Muscle glycogen phosphorylase (myophosphorylase)	232600	Skeletal muscle	Transduction of skeletal muscle	---
VI	Hers disease	*PYGL* (AR)	Liver glycogen phosphorylase	232700	Liver	Transduction of fibrotic liver	---
VII	Tarui disease	*PFKM* (AR)	Muscle phosphofructokinase	232800	Skeletal muscle, red blood cells	Transduction of skeletal muscle and red blood cells	---
IX α1 [d]	---	*PHKA1* (XL)	Phosphorylase kinase α1 subunit	300559	Skeletal muscle	Transduction of skeletal muscle	---

Type	Eponym	Affected Gene (Inheritance)	Deficient Enzyme	OMIM	Affected Tissues/ Cells	Challenges for Gene Therapy	Current Stage of Clinical Development
IX α2 [e]	---	*PHKA2* (XL)	Phosphorylase kinase α2 subunit	306000	Liver	Transduction of fibrotic liver, lack of animal model	---
IX β [f]	---	*PHKB* (AR)	Phosphorylase kinase β subunit	261750	Liver, skeletal muscle	Transduction of skeletal muscle and fibrotic liver	---
IX γ2 [g]	---	*PHKG2* (AR)	Phosphorylase kinase γ2 subunit	613027	Liver	Transduction of fibrotic liver	---
X	---	*PGAM2* (AR)	Phosphoglycerate mutase 2	261670	Skeletal muscle	Transduction of skeletal muscle, lack of animal model	---
XI-FBS [h]	Fanconi-Bickel syndrome	*SLC2A2* (AR)	Glucose transporter 2	227810	Liver, kidneys, pancreas, intestine	Transduction of multiple tissues, lack of animal model	---
XI-LDHA [h]	---	*LDHA* (AR)	Lactate dehydrogenase A	612933	Skeletal muscle, skin	Transduction of multiple tissues, lack of animal model	---
XII	---	*ALDOA* (AR)	Aldolase-a	611881	Skeletal muscle, red blood cells, brain	Transduction of multiple tissues, lack of animal model	---
XIII	---	*ENO3* (AR)	β-enolase	612932	Skeletal muscle	Transduction of skeletal muscle, lack of animal model	---
XV	---	*GYG1* (AR)	Glycogenin-1	613507	Skeletal muscle, heart	Available mouse model does not accumulate polyglucosan	---

Types of GSDs are categorized using roman numerals in chronological accordance with their discovery. Inheritance pattern includes autosomal recessive (AR) or X-linked (XL). The corresponding Online Mendelian Inheritance in Man (OMIM) for each GSD type is listed. Unless otherwise stated, metabolic defects affecting glycogenolysis are occurring in the cytoplasm. The National Clinical Trial (NCT) number is indicated where appropriate. "---" indicates none/not applicable. Current stage of clinical development in genetic material therapies, including gene replacement therapy and mRNA therapy, as of April 2023.

[a] GSD II (Pompe disease) is also classified as a lysosomal storage disease. Deficiency in lysosome-associated membrane protein 2 (Danon disease, OMIM 300257) is an X-linked disorder that results in a block in autophagy and accumulation of lysosomal glycogen in the heart and was previously classified as GSD IIb or pseudo-Pompe disease.

[b] The pediatric-onset form of GSD IV was previously referred to as Andersen disease.[80]

[c] The adult-onset form of GSD IV is often referred to as Adult Polyglucosan Body Disease (APBD).[80]

[d] GSD IXα1 is also referred to as GSD IXd.

[e] GSD IX α2 is also referred to as GSD IXa and was initially categorized as GSD VIII before being reclassified to GSD IX α2.

[f] GSD IX β is also referred to as GSD IXb.

[g] GSD IX γ2 is also referred to as GSD IXc.

[h] Both GLUT2 and lactate dehydrogenase A (also known as muscle lactate dehydrogenase or lactate dehydrogenase-M) deficiencies are classified as GSD XI.

[j] GSD XV is also known as Polyglucosan Body Myopathy 2.

Table 2.

GSD animal models and similarities with affected patients.

Type	Model	OMIA	Gene Variant	Laboratory Abnormalities	Similarities to Patients
0b	*Gys1*$^{-/-}$ mice[14]		Disruption of the *Gys1* gene upstream of exon 12	Laboratory abnormalities: Hypolactatemia Presentation: Early mortality, defects in cardiac development, reduced ventricular size, enlarged atria, edema, pooling of blood, hemorrhagic liver	Clinical presentation: Cardiomyopathy, cardiac arrythmia, muscle weakness, exercise intolerance
Ia	Maltese and Maltese crossbred dogs[32–35,198]	000418–9615	Naturally occurring M121I variant in *G6pc*	Laboratory abnormalities: Hypoglycemia, lactic acidosis, hyperlipidemia, elevated liver enzymes (AST, ALT, ALP, GGT) Presentation: Early mortality, hepatomegaly, growth failure, hepatocellular adenomas and carcinomas, renomegaly, chronic kidney disease with focal segmental glomerular sclerosis	Laboratory abnormalities: Fasting hypoglycemia, lactic acidosis, hyperlipidemia Clinical presentation: Hepatomegaly, short stature, hepatocellular adenomas, renomegaly, renal calcification, chronic kidney disease
	G6pc$^{-/-}$ mice[36]		Disruption of the *G6pc1* gene in exon 3 by a neomycin cassette	Laboratory abnormalities: Hypoglycemia, hyperlipidemia Presentation: Slow growth, hepatomegaly, renomegaly and generalized dysplasia of cartilage	
	Liver-specific *G6pc*$^{-/-}$ mice[37]		Excision of *G6pc* in exon 3 in liver induced by tamoxifen	Normoglycemia in fed state, hyperlipidemia, lactic acidosis and uricemia Presentation: Hepatomegaly, hepatocellular adenomas	
	Kidney-specific *G6pc*$^{-/-}$ mice[39]		Excision of *G6pc* in exon 3 in kidney induced by tamoxifen	Laboratory abnormalities: Normoglycemia during fasting, mild uricemia, elevations in urine uric acid, magnesium and phosphate, microalbuminuria and proteinuria Presentation: Renomegaly	
	Intestine-specific *G6pc*−/− mice[40]		Excision of *G6pc* in exon 3 in intestines induced by tamoxifen	Presentation: Lack of satiety effect when fed a protein enriched diet	
Ib	*G6pt*$^{-/-}$ mice[41]		Disruption of the *G6pt* gene in exon 1 and intron 1 by a neomycin cassette	Laboratory abnormalities: Hypoglycemia, hyperlipidemia, elevated uric acid and lactic acid, immune deficiency with neutropenia and lymphopenia Presentation: Slow growth, hepatomegaly, renomegaly	Laboratory abnormalities: Similar to GSD Ia plus neutropenia, impaired neutrophil function Clinical presentation: Similar to GSD Ia plus inflammatory bowel disease
	TM *G6pt*$^{-/-}$ mice[42]		Disruption of the *G6pt* gene induced by tamoxifen	Laboratory abnormalities: Elevations in creatininuria and albuminuria, some mice with elevations of AST and ALT, hyperlipidemia, fasting normoglycemia, uricemia, spotty glycogen accumulation in liver, reduced splenic white pulp, hypocellularility of bone marrow, amyloidosis in large and small intestines	

J Inherit Metab Dis. Author manuscript; available in PMC 2025 January 01.

Type	Model	OMIA	Gene Variant	Laboratory Abnormalities	Similarities to Patients
				Presentation: Not growth retarded, hepatomegaly, renomegaly, hepatocellular adenoma	
II [a]	Japanese Quail[199]	000419–93934	Naturally occurring	Laboratory abnormalities: Severe accumulation of glycogen deposits in skeletal, cardiac and smooth muscle and nerve cells of the brain and spinal cord Presentation: Progressive inability to move their wings or to right themselves	Clinical presentation: *IOPD:* Muscle weakness, hypotonia, cardiomyopathy, cardiorespiratory failure *LOPD:* Skeletal muscle involvement with early Involvement of diaphragm
	Swedish Lapphund dog[67]	000419–9615	Naturally occurring c.2237G>A change in the *GAA* gene	Laboratory abnormalities: Myocardial hypertrophy caused by generalized glycogen accumulation in skeletal, esophageal, cardiac and smooth muscles Presentation: Vomiting, progressive muscular weakness, loss of condition	
	Sheep[200]	000419–9940	Unknown	Presentation: Incoordination, lethargy, loss in condition, enlarged, dilated heart	
	Cattle[201–203]	000419–9913	Naturally occurring deletion in exon 7 in Brahman and Droughtmaster Cattle, in exon 13 in Brahman cattle, in exon 13 in Shorthorn cattle	Laboratory abnormalities: Early cytoplasmic vacuolation in neurons in spinal cord, skeletal muscle and cardiomyocytes Presentation: Ill-thrift and muscle weakness	
	Gaa$^{-/-}$ mice[66]		*Neo* insertion in exon 6 of *GAA*	Laboratory abnormalities: No GAA protein detected, glycogen accumulation of lysosomes in heart and skeletal muscle, sarcomere degradation and loss of myofibrils Presentation: Reduced physical activity, decreased muscle function, older mice exhibit weak, waddling gait, splayed legs, muscle wasting in lower limbs and back	
	Gaa$^{-/-}$ Mice expressing hGAA		Transgenic *Gaa*$^{-/-}$ strain with tetracycline inducing production of hGAA in skeletal muscle or liver	Laboratory abnormalities: GAA activity present and decreased glycogen in skeletal muscle and heart, but not other organs, for transgenic mice with muscle promoter and GAA activity and decreases glycogen in the liver, but not other organs for transgenic mice with liver promoter, except during doxycycline administration	
III	Curly-coated Retriever dog[79]	001577–9615	Naturally occurring deletion in exon 32 leading to truncated protein	Laboratory abnormalities: Anecdotal hypoglycemia after prolonged fasting and exercise, elevated AST, ALP, ALT, and urine Glc_4 that decrease over time, variable elevations in CK, glycogen accumulation in liver, muscles and nerves Presentation: Hepatomegaly, liver fibrosis, cirrhosis	Laboratory abnormalities: *GSD IIIa and GSD IIIb:* fasting ketotic hypoglycemia, hyperlipidemia Clinical presentation: *GSD IIIa:* hepatomegaly, short stature, liver fibrosis, skeletal muscle weakness, cardiac arrhythmias, cardiomyopathy *GSD IIIb:* hepatomegaly, short stature, liver fibrosis
	Agl$^{-/-}$ mice[74–77]		Disruption between exons 5 and 6	Laboratory abnormalities: Hypoglycemia at early timepoints, glycogen accumulation in liver, heart, skeletal muscle, elevations of AST, ALT, and ALP	

J Inherit Metab Dis. Author manuscript; available in PMC 2025 January 01.

Type	Model	OMIA	Gene Variant	Laboratory Abnormalities	Similarities to Patients
				Presentation: 50% mortality before 40 weeks of age, hepatomegaly, progressive hepatic fibrosis, decreased muscle performance	
			Deletion of exons 32–34	Laboratory abnormalities: Hypoglycemia and glycogen accumulation in liver, heart, skeletal muscle and brain, elevations of AST, ALT, ALP and CK Presentation: Higher mortality in adult mice, hepatomegaly, no hepatic fibrosis, inflammation or adenomas detected, decreased muscle performance	
			Disruption of exons 6–10	Laboratory abnormalities: Hypoglycemia and glycogen accumulation in liver, heart, skeletal muscle and brain Presentation: Hepatomegaly, muscle weakness	
			Deletion of exons 6–10	Laboratory abnormalities: Elevation of plasma ALT, urinary Glc_4 Presentation: Hepatomegaly, hepatic fibrosis, impaired muscle function	
IV	Norwegian Forest Cat[83]	000420–9685	Naturally occurring deletion from intron 11 to 12	Presentation: Early mortality, progressive neurologic and musculoskeletal disease	Clinical presentation: *Pediatric-onset:* Hepatomegaly, liver fibrosis or cirrhosis, cardiomyopathy, cardiac arrhythmias and conduction abnormalities, decreased fetal movement, hypotonia, arthrogryposis *APBD:* Neurogenic bladder, muscle weakness, spastic paraparesis, peripheral neuropathy
	American Quarter Horse[85–89]	000420–9796	Naturally occurring nonsense mutation in *GBE*	Laboratory abnormalities: Undetectable GBE activity in the heart, skeletal muscle, liver, and peripheral blood cells, and resemble the severe perinatal/congenital phenotype, with significant accumulation of polyglucosan *in utero* Presentation: Early demise prenatal or perinatal	
	Gbe1$^{neo/neo}$ mice[90]		Interruption of intron 7 in *Gbe1*	Laboratory abnormalities: Reduced synthesis of GBE, accumulation of glycogen in muscle and liver, reduced glucose during glucose tolerance test Presentation: Phenotype more similar to juvenile-onset GSD IV, widespread polyglucosan accumulation	
	Gbe1$^{-/-}$ mice[90]		Deletion of exon 7 in *Gbe1*	Laboratory abnormalities: No synthesis of GBE, reduced glycogen Presentation: Phenotype more similar to perinatal lethal GSD IV, in utero accumulation of polyglucosan with demise prenatal or perinatal	
	Gbe1$^{ys/ys}$ mice[91]		Knock-in of p.Y329S mutation into exon 7 in *Gbe1*	Laboratory abnormalities: Reduced synthesis of GBE, accumulation of glycogen in brain, heart, muscle and liver, fasting hypoglycemia, elevated serum CK Presentation: Phenotype more similar to adult onset GSD IV, muscle weakness, liver fibrosis	

Type	Model	OMIA	Gene Variant	Laboratory Abnormalities	Similarities to Patients
V	Charolais cattle[93,94]	001139–9913	Point mutation of C to T in codon 489 that led to an arginine to trytophan substitution in the myophosphorylase protein	Presentation: Exercise intolerance and rhabdomyolysis caused by a phosphorylase deficiency in skeletal muscle	Laboratory abnormalities: Myoglobinuria Clinical presentation: Exercise intolerance, muscle pain and cramps, “second-wind” phenomenon
	Merino sheep[95]	001139–9940	Splice site mutation at the 3’ end of intron 19 of the *PYGM* gene, resulting in an 8-base frameshift deletion at the 5’ end of exon 20, thereby disrupting the open reading frame and causing premature truncation of the protein	Laboratory abnormalities: Lack of myophosphorylase and the accumulation of excessive glycogen in muscle Presentation: Exercise intolerance	
	Pygm$^{R50X/R50X}$ mice[96–98]		p.R50X mutation in exon 1 of the *Pygm* gene	Laboratory abnormalities: Elevated plasma CK, exercise-induced myoglobinuria; lack of myophosphorylase expression and massive glycogen accumulation in skeletal muscles Presentation: Exercise intolerance, and progressive muscle degeneration, fibrosis and inflammation	
	Zebrafish[204]		*pygma* and *pygmb* morpholino knockdown	Laboratory abnormalities: Reduced Pygm, glycogen accumulation in subsarcolemmal region Presentation: Altered and disintegrated muscle structure	
VI	C57BL/6N-*Pygl*$^{tm1a(KOMP)Wtsi}$ or *Pygl*$^{-/-}$[104,205]		Disruption of exons 2 and 3	Laboratory abnormalities: Ketotic hypoglycemia, serum triglycerides, cholesterol, and lactic acid were significantly lower in *Pygl*$^{-/-}$ mice than in WT mice Presentation: Progressive elevations of hepatic glycogen	Laboratory abnormalities: fasting ketotic hypoglycemia, hyperlipidemia Clinical presentation: Hepatomegaly, liver fibrosis
VII	English Springer Spaniels, American Cocker Spaniels, and Whippet dogs[112,206,207]	000421–9615	Nonsense mutation (c.2228 A>G) that caused premature termination of protein translation and rapid degradation of a truncated muscle phosphofructokinase protein	Laboratory abnormalities: Increased serum creatine kinase activity without myoglobinuria, Phosphofructokinase deficiency caused rhabdomyolysis during exercise Presentation: Mild exercise intolerance, rare muscle cramp	Laboratory abnormalities: myoglobinuria, hyperuricemia, reticulocytosis, elevated serum bilirubin Clinical presentation: Exercise intolerance, muscle pain, cramps, “out-of-wind” phenomenon
	Wachtelhunds[113,114]	000421–9615	Missense point mutation (c.550C>T) in the *PFKM* gene	Laboratory abnormalities: Hemolytic anemia Presentation: Exercise intolerance	
	Pfkm$^{-/-}$ mice[115]		Deletion of the 5’ end promoter region and exon 3	Laboratory abnormalities: Hemolysis, increased erythropoiesis, high glycogen accumulation, increased vascularization and fiber necrosis in the skeletal muscles Presentation: Exercise intolerance and high mortality (about 60%)	
IX β	*Phkb*$^{-/-}$ mice[109]		Deletion of exon4 using CRISPR technology	Laboratory abnormalities: Mild hypoglycemia after 6–8 hours of fasting, and blood ketones were elevated in the fed and fasting state, mildly elevated in ALT and AST, reduced glycogen phosphorylase activity in liver	Laboratory abnormalities: Fasting hypoglycemia, hyperlipidemia Clinical presentation: Hepatomegaly, liver

J Inherit Metab Dis. Author manuscript; available in PMC 2025 January 01.

Type	Model	OMIA	Gene Variant	Laboratory Abnormalities	Similarities to Patients
				and muscles Presentation: Hepatomegaly	fibrosis, short stature, hypotonia, muscle weakness
IX γ2	*Phkg2*$^{-/-}$ mice[105]		Deletion of exon 2 to exon 10	Laboratory abnormalities: Glycogen accumulation in the liver, elevated serum AST and ALT and urine Glc_4, fasting and non-fasting hypoglycemia Presentation: Hepatomegaly with enlarged hepatocytes with pale cytoplasm, distinct cell membranes, and concentrated pyknotic nuclei. Early perisinusoidal liver fibrosis and decreased body weight at 1 month of age	Laboratory abnormalities: Fasting hypoglycemia, hyperlipidemia Clinical presentation: Hepatomegaly, liver fibrosis, short stature
XV	*Gyg*$^{-/-}$ mice[208]		Knockout-first on chromosome 3 upstream of exon	Laboratory abnormalities: Accumulation of glycogen in cardiac and skeletal muscles, enlarged glycogen granules Presentation: Early death in most pups due to cardiorespiratory failure, decreased performance in endurance testing	Clinical presentation: Muscle weakness, cardiomyopathy, cardiac arrhythmia, heart failure

The corresponding Online Mendelian Inheritance in Man (OMIM) for each GSD type is listed.

[a]Other mouse models for GSD II (Pompe disease) have been described, but only those use for gene therapy experiments are described here.

Table 3:

First decade of gene therapy for GSD Ia.[a]

Serotype	Effective dose (vg/kg), IV administration to either neonatal or infantile (12 days old) *G6pc*$^{-/-}$ mice	Duration of elevated blood glucose during fasting (>100 mg/dL)	Biochemical correction
AAV2 + adenovirus vector co-administration [209]	Alternate protocol: ~3×10^{12} infectious units AAV2/kg and ~1×10^{10} plaque forming units adenovirus vector/kg at birth, and an additional 5×10^{11} infectious units/kg of AAV2 at 2 weeks old	0 hours (not fasted)	Liver and kidney
AAV8 [132]	~2×10^{14} vg/kg	2 hours	Liver
AAV1 [210]	~2×10^{14} vg/kg	0 hours (not fasted)	Liver and kidney
Helper-dependent adenovirus [211]	~2×10^{12} vg/kg	2 hours	Liver
Double-stranded AAV8 [212]	~1×10^{13} vg/kg[b]	2 hours	Liver
Double-stranded AAV1 [212]	~3×10^{13} vg/kg	0 hours (not fasted)	Liver
AAV8 [213]	~1×10^{13} vg/kg	6 hours	Liver
Feline immunodeficiency virus [214]	Alternate protocol: ~1×10^{10} viral particles/kg at 1 day old, and an additional ~2×10^{9} viral particles/kg at 7 days of age	0 hours (not fasted)	Liver
Double-stranded AAV9 [134]	~2×10^{13} vg/kg	8 hours	Liver and kidney
AAV8 [133]	~3×10^{13} vg/kg	24 hours	Liver

[a] Studies published between 2002 and 2011, summarizing progress of gene replacement therapy.

[b] Also treated puppies with GSD Ia.

Table 4:

Characteristics of vectors and promoters in preclinical studies for Pompe disease.

Vector/serotype	Promoter type	Age administered	Dose/route of administration (vg per kg)	Evidence of efficacy	Duration of follow-up	Anti-GAA antibodies
AAV2/8-LSPhGAA [162]	Liver-specific	Adult GAA-KO mice	8×10^{10} to 2×10^{12} IV	Biochemical/muscle function correction	36 weeks	Absent
AAV2/8-LSPhGAA [163]	Liver-specific	Neonatal GAA-KO mice	4×10^{12} IV	Biochemical/respiratory function correction	50 weeks	Absent
AAV8-sp7-D8-coGAA [215]	Liver-specific	Adult GAA-KO mice, cynomolgus monkeys	5×10^{11} to 2×10^{12} IV	Biochemical/muscle function correction	12 weeks	Absent
AAV2/6-MCKhGAA [216]	Muscle-specific	Adult GAA-KO mice	4×10^{12} IM	Biochemical correction	24 weeks	Present
AAV2/8-CBhGAA [160]	Constitutive	Adult GAA-KO mice	4×10^{12} IV	Lack of biochemical efficacy	12 weeks	Present
AAV9-hGAA [217]	Tandem liver/ muscle-specific	Neonatal GAA-KO mice	6×10^{12} IV	Biochemical/muscle function correction	16 weeks	Absent
AAVB1-DES-hGAA [158]	Muscle/neuron-specific	Adult GAA-KO mice	4×10^{13} IV	Biochemical/respiratory function correction	24 weeks	Not reported
AAV2/8-LSPhGAA + AAV2/9-CBhGAA [218]	Liver-specific + constitutive	Adult GAA-KO mice	8×10^{11} (LSP) and 4×10^{12} (CB), both IV	Biochemical/muscle function correction	18 weeks	Absent
AAV9-LSP-coGAA + AAV9-DES-coGAA [219]	Liver-specific + Muscle/neuron-specific	Adult GAA-KO mice	5×10^{13} IV	Biochemical/muscle function correction	8 weeks	Present
HD-Ad/hGAA (helper-dependent adenovirus) [220]	Liver-specific	Adult baboons	1×10^{12} intrahepatic	Elevated GAA activity	24 weeks	Detected, low titer (1:20)
RRL.PPT.SFFV.GAA.bPRE4*.SIN (lentiviral) [196]	Constitutive	Adult GAA-KO mice	Not applicable	Biochemical/muscle function correction	52 weeks	Absent