nature reviews disease primers

https://doi.org/10.1038/s41572-023-00456-z

Primer

Check for updates

Glycogen storage diseases

William B. Hannah[1], Terry G. J. Derks[2], Mitchell L. Drumm[1], Sarah C. Grünert[3], Priya S. Kishnani[4] & John Vissing[5]

Abstract

Glycogen storage diseases (GSDs) are a group of rare, monogenic disorders that share a defect in the synthesis or breakdown of glycogen. This Primer describes the multi-organ clinical features of hepatic GSDs and muscle GSDs, in addition to their epidemiology, biochemistry and mechanisms of disease, diagnosis, management, quality of life and future research directions. Some GSDs have available guidelines for diagnosis and management. Diagnostic considerations include phenotypic characterization, biomarkers, imaging, genetic testing, enzyme activity analysis and histology. Management includes surveillance for development of characteristic disease sequelae, avoidance of fasting in several hepatic GSDs, medically prescribed diets, appropriate exercise regimens and emergency letters. Specific therapeutic interventions are available for some diseases, such as enzyme replacement therapy to correct enzyme deficiency in Pompe disease and SGLT2 inhibitors for neutropenia and neutrophil dysfunction in GSD Ib. Progress in diagnosis, management and definitive therapies affects the natural course and hence morbidity and mortality. The natural history of GSDs is still being described. The quality of life of patients with these conditions varies, and standard sets of patient-centred outcomes have not yet been developed. The landscape of novel therapeutics and GSD clinical trials is vast, and emerging research is discussed herein.

Sections

[1]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, OH, USA. [2]Division of Metabolic Diseases, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [3]Department of General Paediatrics, Adolescent Medicine and Neonatology, Medical Centre-University of Freiburg, Faculty of Medicine, Freiburg, Germany. [4]Division of Medical Genetics, Department of Paediatrics, Duke University Medical Center, Durham, NC, USA. [5]Copenhagen Neuromuscular Center, Copenhagen University Hospital, Copenhagen, Denmark. e-mail: wbh16@case.edu

Introduction

Glycogen storage diseases (GSDs) are a group of disorders characterized by a biochemical deficit in glycogenesis (glycogen synthesis), glycogenolysis (breakdown of glycogen to glucose, via glucose-6-phosphate (G6P)) or glycolysis (conversion of glucose into pyruvate). These complicated, heterogeneous multi-organ conditions vary substantially in terms of presentation, clinical and biochemical phenotype, and treatment. GSDs can be broadly classified as hepatic GSDs or muscle GSDs depending on the primary system affected (Fig. 1).

Glycogen content in affected tissue is markedly increased in many GSDs, although glycogen storage is decreased in GSD 0 (glycogen synthase deficiency). The structure of glycogen is normal or abnormal. The dysfunction in some GSDs overlaps with other metabolic pathways; for example, glucose-6-phosphatase (G6Pase), which is defective in GSD I, is functionally located at the intersection of glycogenolysis and gluconeogenesis (glucose production from some non-carbohydrate precursors; in humans mainly lactate, glycerol, alanine and glutamine). Most genes implicated in GSDs encode cytosolic proteins. However, acid α-glucosidase (which is affected in Pompe disease; also known as GSD II) is localized to lysosomes and, accordingly, this disorder is also considered a lysosomal storage disease. Moreover, G6Pase and glucose-6-phosphate transporter protein (G6PT) (proteins encoded by the genes involved in GSD I) localize to either the endoplasmic reticulum (ER) or the ER membrane.

Some conditions that were historically considered GSDs are now classified as different disorders owing to improvements in understanding of pathophysiology and disease mechanisms. The International Classification of Inherited Metabolic Disorders (ICIMD) includes 1,450 disorders of which 66 are disorders of carbohydrate metabolism[1] (for an updated list of diseases, see the Inborn Errors of Metabolism Knowledgebase). The focus of this Primer is diseases caused by genetic defects that are associated predominantly with abnormalities of glycogen metabolism and that are recognized in the literature as GSDs, namely, GSD 0a, GSD 0b, GSD I, Pompe disease, GSD III, GSD IV, GSD V, GSD VI, GSD VII, GSD IX, GSD X, GSD XI (lactate dehydrogenase subunit A deficiency), GSD XII, GSD XIII, phosphoglucomutase 1 deficiency–congenital disorder of glycosylation (PGM1-CDG; previously called GSD XIV), GSD XV, Fanconi–Bickel syndrome (FBS) and phosphoglycerate kinase (PGK) deficiency. Of note, both lactate dehydrogenase subunit A deficiency and FBS are sometimes referred to as GSD XI in the literature. In this Review, GSD XI refers to lactate dehydrogenase subunit A deficiency, and FBS is referred to by eponym.

GSDs seem to represent a phenotypic disease continuum. Compelling examples of this continuum include infantile-onset and late-onset Pompe disease and prenatal-onset GSD IV and adult-onset GSD IV, which is also known as adult polyglucosan body disease (APBD). For example, infantile-onset and late-onset Pompe disease have the same mechanism, which is accumulation of glycogen in lysosomes owing to variants in *GAA* that cause poor function of the GAA enzyme. The severity of disease and clinical manifestations differ between infantile-onset and late-onset disease owing to genotype–phenotype correlation. Owing to the similar disease mechanisms, the differences in severity and presentation reflect a continuum of one disease process. Understanding of the variable expressivity of these rare conditions improved with the identification of more patients with time, increased awareness and improved genetic testing (which allowed the diagnosis and subsequent characterization of individuals with atypical phenotypes). Table 1 and Supplementary Table 1 provide an overview of the clinical sequelae and inheritance patterns of various GSDs.

Phenotypic characterization of individuals with a suspected GSD usually involves thorough medical history taking, physical examination, laboratory tests and imaging. Diagnosis of individuals with

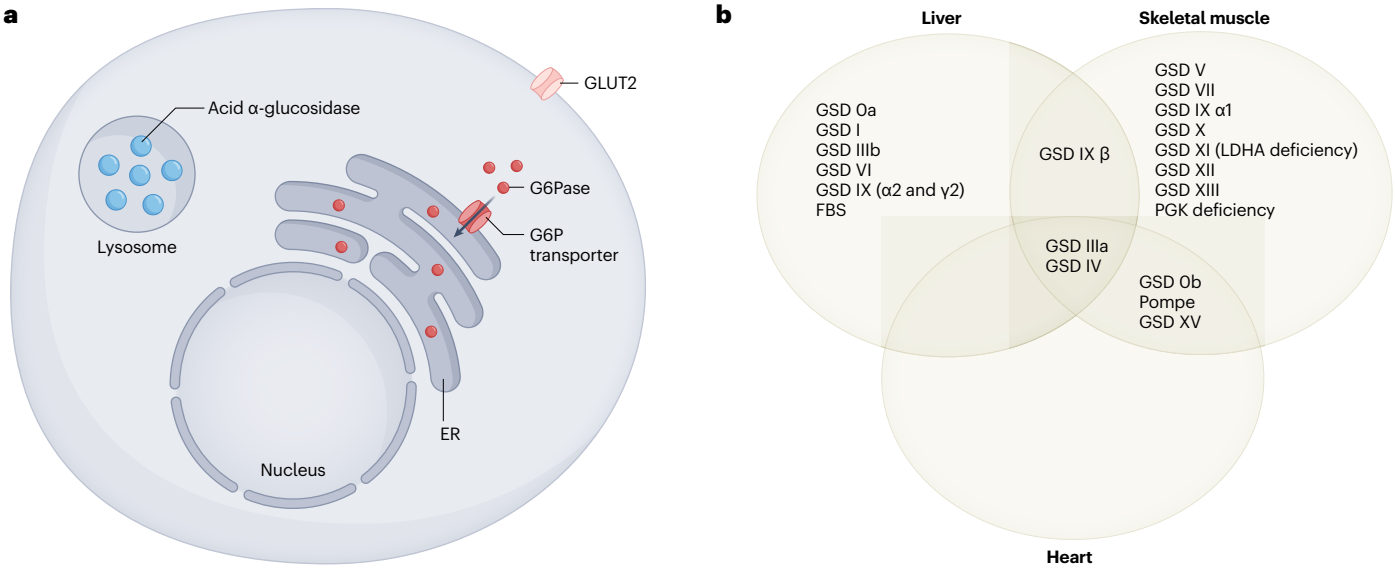

Fig. 1 | Cell biology and organs affected in GSDs. a, Fanconi–Bickel syndrome (FBS) is caused by pathogenetic variants in *SLC2A2*, which encodes the GLUT2 transporter. This transporter is localized to cell membranes. Pathogenetic variants in *GAA* (encodes acid α-glucosidase) cause glycogen storage disease (GSD) II, also known as Pompe disease. Acid α-glucosidase is localized to lysosomes. Pathogenetic variants in *G6PC1* (encodes glucose-6-phosphatase, G6Pase) and *SLC37A4* (encodes glucose-6-phosphate (G6P) transporter) cause GSD I. Both of these proteins are localized to the endoplasmic reticulum (ER). **b**, Some GSDs predominantly affect the liver, heart and skeletal muscle. Other systems and organs are affected in some GSDs (not shown), including the kidneys and nervous system. LDHA, lactate dehydrogenase A; PGK, phosphoglycerate kinase.

Table 1 | Clinical features of GSDs

Condition (alternative name)	Genes	Enzyme or transporter	Inheritance	Clinical features	Other considerations
GSD 0a	*GYS2*	Hepatic glycogen synthase	AR	Fasting ketotic hypoglycaemia. Postprandial hyperglycaemia and elevated lactate[168–170], short stature and low bone density[168]	Distinguished from other hepatic GSDs by normal liver size[169]
GSD 0b	*GYS1*	Muscle glycogen synthase	AR	Exercise intolerance, hypertrophic cardiomyopathy[171], sudden death with exercise with no prior exercise intolerance or heart structural abnormalities[172], and adult-onset myopathy without cardiomyopathy[173]	Very rare
GSD I (von Gierke disease)	*G6PC1* (GSD Ia) and *SLC37A4* (GSD Ib)	G6Pase (GSD Ia) and G6PT (GSD Ib)	AR	Metabolic anomalies such as hypoglycaemia, lactic acidosis and elevated triglycerides and uric acid. Hepatomegaly, hepatocellular adenomas with malignant potential, nephromegaly, renal tubular and glomerular disease and multi-organ involvement. In GSD Ib, neutropenia, neutrophil dysfunction and inflammatory bowel disease[174]	Blood lactate rises quickly with hypoglycaemia. Presence of hypoketotic hypoglycaemia
GSD II (Pompe disease)	*GAA*	Acid α-glucosidase	AR	Infantile-onset Pompe disease is lethal without treatment[35]. Manifestations affect multiple organs and include hypertrophic cardiomyopathy[175], hypotonia[175] and motor delay[175]. Late-onset Pompe disease affects multiple organs, weakness, can present at any age without cardiomyopathy in the first year of life[61,176]	None
GSD III (Cori disease or Forbes disease)	*AGL*	Glycogen debranching enzyme	AR	Variable hepatic phenotype. Fasting hypoglycaemia with elevated ketones in some, hyperlipidaemia, hepatomegaly, elevated AST and ALT[12]. Mild periportal fibrosis to cirrhosis may occur. GSD IIIa: myopathy, variable muscle and cardiac phenotype	None
GSD IV (Andersen disease)	*GBE1*	Glycogen branching enzyme	AR	Phenotypic variability. GSD IV may be best considered as a clinical continuum in which patients have varying involvement of hepatic, cardiac and neurologic features. Historically, subtypes described include classic (progressive) hepatic subtype with hepatosplenomegaly, liver dysfunction, progressive cirrhosis, cardiomyopathy, hypotonia, failure to thrive, and death often by 3 to 5 years of age without liver transplantation. Another subtype, APBD, is an adult-onset neurodegenerative disorder and can present with gait difficulty, progressive neurogenic bladder, autonomic dysfunction, sensory loss and variable cognitive difficulty among less common phenotypes described in refs.[45,126,177]	Other phenotypes historically described include fatal perinatal neuromuscular subtype, congenital/neonatal neuromuscular subtype, non-progressive hepatic subtype, and childhood/juvenile neuromuscular subtype that are described in cited literature
GSD V (McArdle disease)	*PYGM*[a]	Myophosphorylase	AR	With exercise, quick development of myalgia, fatigue, cramps, tachypnoea and tachycardia[7]. Other manifestations include elevated CK (usually), propensity for rhabdomyolysis[7,25], contractures, risk of compartment syndrome[7,25] and variable symptoms of weakness	Second-wind phenomenon[178] almost unique to GSD V (also seen in PGM1-CDG), pre-exercise ingestion of sucrose improves exercise intolerance[76]
GSD VI (Hers disease)	*PYGL*	Liver glycogen phosphorylase	AR	Variable hepatic and metabolic phenotype[9]. Commonly presents with hepatomegaly and poor growth, with broad range of presenting age[179]. Other manifestations include hypoglycaemia with ketosis, elevated liver transaminases, hyperlipidaemia, osteoporosis, liver fibrosis[180] and cirrhosis[179]	None
GSD VII (Tarui disease)	*PFKM*	Muscle PFK	AR	Typical form is associated with exercise intolerance with contractures and myoglobinuria[38] and, at times, with haemolytic anaemia and hyperuricaemia or gout[38]. Atypical phenotypes include myopathy in infancy with respiratory failure and death by age 2 years, haemolytic anaemia without myopathy and late-onset fixed weakness[38]	No second-wind phenomenon[77]. Sucrose ingestion before exercise leads to an 'out-of-wind phenomenon' with less exercise capacity[38,40]

Table 1 (continued) | Clinical features of GSDs

Condition (alternative name)	Genes	Enzyme or transporter	Inheritance	Clinical features	Other considerations
Hepatic GSD IX	*PHKA2* (GSD IX α2), *PHKB* (GSD IX β), *PHKG2* (GSD IX γ2)	Liver phosphorylase kinase α2 (GSD IX α2), liver and muscle phosphorylase kinase β2 (GSD IX β) and phosphorylase kinase γ2 (hepatic and testis isoform) (GSD IX γ2)	X-linked (GSD IX α2; female individuals can be affected depending on X-inactivation), AR (GSD IX β and GSD IX γ2)	GSD IX α2: boys usually present in first few years of life with failure to thrive with or without hepatomegaly[181]. Ketotic hypoglycaemia occurs in some patients; the number of ketotic hypoglycaemic events varies between individuals[9]. Variable elevations of transaminases and hyperlipidaemia[9,181], liver fibrosis[180], cirrhosis[181], variable hepatic and extra-hepatic features. Adults described as asymptomatic[9,182]. GSD IX β: rare with varying range of hepatic features[9]. Usually, identified owing to hepatomegaly[9,181]. Other manifestations include ketotic hypoglycaemia, elevated triglycerides[181], mild or absent muscle features[9]. GSD IX γ2: clinical features are typically more severe than other subtypes of GSD IX[8,9]. Manifestations include hypoglycaemia, risk of liver fibrosis and cirrhosis[8,9,181] (cirrhosis can occur in first years of life)[9] and liver adenomas[9]	GSD IX α2: heterozygous women may be unaffected or have variable severity of symptoms[8,9]. Liver fibrosis occurred in 1 of 3 individuals with GSD IX β[181]
Muscle GSD IX	*PHKA1* (GSD IX α1)	α-Subunit of muscle phosphorylase kinase	X-linked	Variable clinical presentation and age of onset[16]. CK may be elevated. Manifestations include muscle weakness, pain and stiffness with exercise, and atrophy[16]	Rare
GSD X	*PGAM2*	Muscle phosphoglycerate mutase	AR	Exercise intolerance with cramps and myalgia or pain[16,38] and rhabdomyolysis[16]. Around half of patients have recurrent myoglobinuria and elevated serum CK between episodes[38]	Rare
GSD XI (note that GSD XI is sometimes also used for Fanconi–Bickel syndrome)	*LDHA*	Lactate dehydrogenase A (skeletal muscle isoform)	AR	Exercise intolerance with cramps and painful stiffness[16], rhabdomyolysis, myoglobinuria[16], variable skin lesions[38,183–187]. Elevated serum CK can occur during myoglobinuria, with low serum lactate dehydrogenase concentration[38]	Rare. One woman described with uterine stiffness during pregnancy and delivery requiring Caesarean section[188]. One child with suspected GSD XI had intellectual disability[189]. One individual with apparently isolated skin findings[186]
GSD XII	*ALDOA*	Red blood cell fructose-1,6-bisphosphate aldolase A (erythrocyte and muscle isoform)	AR	Haemolytic anaemia, myopathy, rhabdomyolysis[16]. Variable features described include intellectual disability, short stature and dysmorphic facial features[16,190–195]	Rare. Enzyme might be thermolabile, as fever induces rhabdomyolysis and/or myoglobinuria[196,197]
GSD XIII	*ENO3*	β-Enolase	AR	Exercise intolerance, myalgia, rhabdomyolysis, muscle MRI with fatty infiltration	Rare. Very few individuals reported[198–201]. Non-ischaemic forearm testing with normal lactate; no benefit of glucose infusion on exercise[201]. Normal baseline CK reported in 2 individuals
GSD XV	*GYG1*	Glycogenin 1 (muscle isoform)	AR	Weakness, arrhythmias[16,202]. Phenotype may be predominantly skeletal myopathy or predominantly cardiomyopathy. Variable phenotype of characterized individuals detailed in Supplementary Table 1	Rare
PGM1-CDG (formerly GSD XIV)	*PGM1*	Phosphoglucomutase 1	AR	Two main phenotypes: primary myopathic and multisystem. The multisystem phenotype includes variable features of congenital malformations, muscle and heart involvement, hepatic features, haematological anomalies[31], hypoglycaemia, growth retardation and dilated cardiomyopathy[203]	Two patients with malignant hyperthermia and rhabdomyolysis after general anaesthesia and two patients with hypogonadotropic hypogonadism[203]; second-wind phenomenon reported (thought to be pathognomonic for GSD V)[204]

Table 1 (continued) | Clinical features of GSDs

Condition (alternative name)	Genes	Enzyme or transporter	Inheritance	Clinical features	Other considerations
Fanconi–Bickel syndrome (also called GSD XI)	*SLC2A2*	GLUT2	AR	Intolerance and postprandial elevations of glucose and galactose, fasting hypoglycaemia, hepatomegaly, proximal tubular nephropathy, glucosuria, short stature, accumulation of glycogen in liver and kidneys[205]	Rarely, cataracts[205]
PGK deficiency	*PGK1*	PGK	X-linked	Nonspherocytic haemolytic anaemia, myopathy with rhabdomyolysis and neurological features, including intellectual disability (anaemia, myopathy and neurological features appear to present in various combinations)[206,207]. Lower enzyme activity may lead to involvement of multiple systems and susceptibility to rhabdomyolysis[208]	Parkinsonism, with response to levodopa has been reported in some patients[207,209–212]. Retinitis pigmentosa[207,213] PGK deficiency may have peripheral nervous system disease and a phenotype resembling Charcot–Marie–Tooth disease[207]

This table describes some clinical features that have been described in GSDs but is not comprehensive. In a given disease, some manifestations are more common than others, and individuals present differently. More detailed descriptions of clinical features are discussed in Supplementary Table 1. ALT, alanine transaminase; APBD, adult polyglucosan body disease; AR, autosomal recessive; AST, aspartate transferase; CK, creatine kinase; G6Pase, glucose-6-phosphatase; G6PT, glucose-6-phosphate transporter protein; GSD, glycogen storage disease; PFK, phosphofructokinase; PGK, phosphoglycerate kinase; PGM1-CDG, phosphoglucomutase 1 deficiency–congenital disorder of glycosylation. [a]An autosomal dominant GSD has been described in individuals with a monoallelic *PYGM* missense variant[26]. Individuals with this GSD were described with adult-onset muscle weakness in the absence of exercise intolerance; notable differences between this novel GSD and GSD V were also described with histological and functional characterization[26].

a consistent phenotype of GSD is typically carried out with genetic testing and/or enzymatic testing. Outpatient management includes monitoring for new disease sequelae or progression and avoidance of metabolic decompensation. In hepatic GSDs, metabolic decompensation can be avoided by providing adequate nutrition (frequency, amount and type of food) and, in some disorders, with use of corn starch and high protein. Physical therapy and dietary management are often important aspects of care. Enzyme replacement therapy (ERT) for Pompe disease is an example of a therapeutic that is specific for a GSD. Some GSDs may require liver transplantation and other organ transplantation such as kidney transplantation in some patients with GSD I or heart transplantation in some patients with GSD III or GSD IV.

This Primer provides a summary of the pathophysiology, epidemiology, diagnosis and treatment of GSDs and is relevant for multidisciplinary health-care providers and researchers.

Epidemiology

Prevalence and incidence

The prevalence and incidence of individual GSDs varies substantially (Supplementary Table 2). Data on the epidemiology of GSDs are limited as reliable prevalence and incidence data have not been reported for some disorders, such as GSD 0a, GSD 0b, GSD VII, GSD X, GSD XI, GSD XII, GSD XIII, GSD XV, PGM1-CDG, FBS and PGK deficiency. Moreover, the basis of historical prevalence estimates can be unclear or relied on the best data available to make an estimate of prevalence. In addition, understanding of the natural history of GSDs is incomplete, these disorders are underdiagnosed[2] and some patients have attenuated disease phenotypes[3]. Well-designed and sustainably maintained registries are lacking for GSDs, as is generally the case for other rare diseases.

To our knowledge, no studies have suggested a difference in the prevalence or incidence between sexes for most autosomal recessive GSDs. However, one study reported 17 male and 3 female individuals among 20 patients with GSD IV after liver transplantation[4]. Furthermore, some studies have reported a higher frequency of male individuals than female individuals in GSD V cohorts[5,6], although this finding could reflect reporting bias[7]. Some GSDs, namely, GSD IX α1, GSD IX α2 and PGK deficiency, are inherited in an X-linked manner, therefore, prevalence of these disorders is higher in boys and men (Table 1). Of note, it is increasingly recognized that female patients with a heterozygous variant may have features of GSD IX α2 (refs. 8–10). The development of symptoms in females with a heterozygous variant is likely influenced by X-inactivation (also known as lyonization)[9]. Clinical ascertainment of GSDs may increase with increased availability of genetic testing[2], and this could affect our understanding of the epidemiology of these diseases.

Most GSDs have significant allelic heterogeneity, but founder variants have been described for some disorders (Supplementary Table 2). The presence of founder variants can partly explain the sometimes considerable difference in prevalence and/or incidence and also clinical manifestations between individuals of different ethnicities.

Phenotypic variation of some GSDs is broad, for example, paediatric-onset and adult-onset GSD IV and infantile-onset and late-onset Pompe disease. Accordingly, it is important to know whether prevalence estimates of GSDs encompass the broad phenotype or a specific presentation. For example, GSD IIIa (involving both liver and muscle) accounts for 85% of GSD III cases[11,12]. For Pompe disease, approximately 25% of patients have infantile-onset Pompe disease[13] although this proportion may differ by country, and our understanding is improving with follow-up of newborn screening (NBS).

Mechanisms/pathophysiology

Glycogen metabolism and GSDs

The compact structure of glycogen (Fig. 2) is essential for normal physiology and carbohydrate homeostasis. The liver is the major organ that releases free glucose to stabilize blood glucose levels to ensure an adequate supply of energy to dependent tissues. The liver is essential for glucose homeostasis, maintaining postprandial and fasting euglycaemia (normal blood glucose levels)[14]. By contrast, muscle catabolizes glycogen for energy. *G6PC1* (encoding G6Pase, which converts G6P into glucose) is expressed in liver and kidney but not in muscle[15]. G6Pase functions at the interface of glycogenolysis and gluconeogenesis and is uniquely necessary to produce glucose from both glycogen and alternative substrates. As systemic euglycaemia is maintained predominantly by the liver, hypoglycaemia is a predominant phenotypic feature in most hepatic GSDs but not in muscle GSDs.

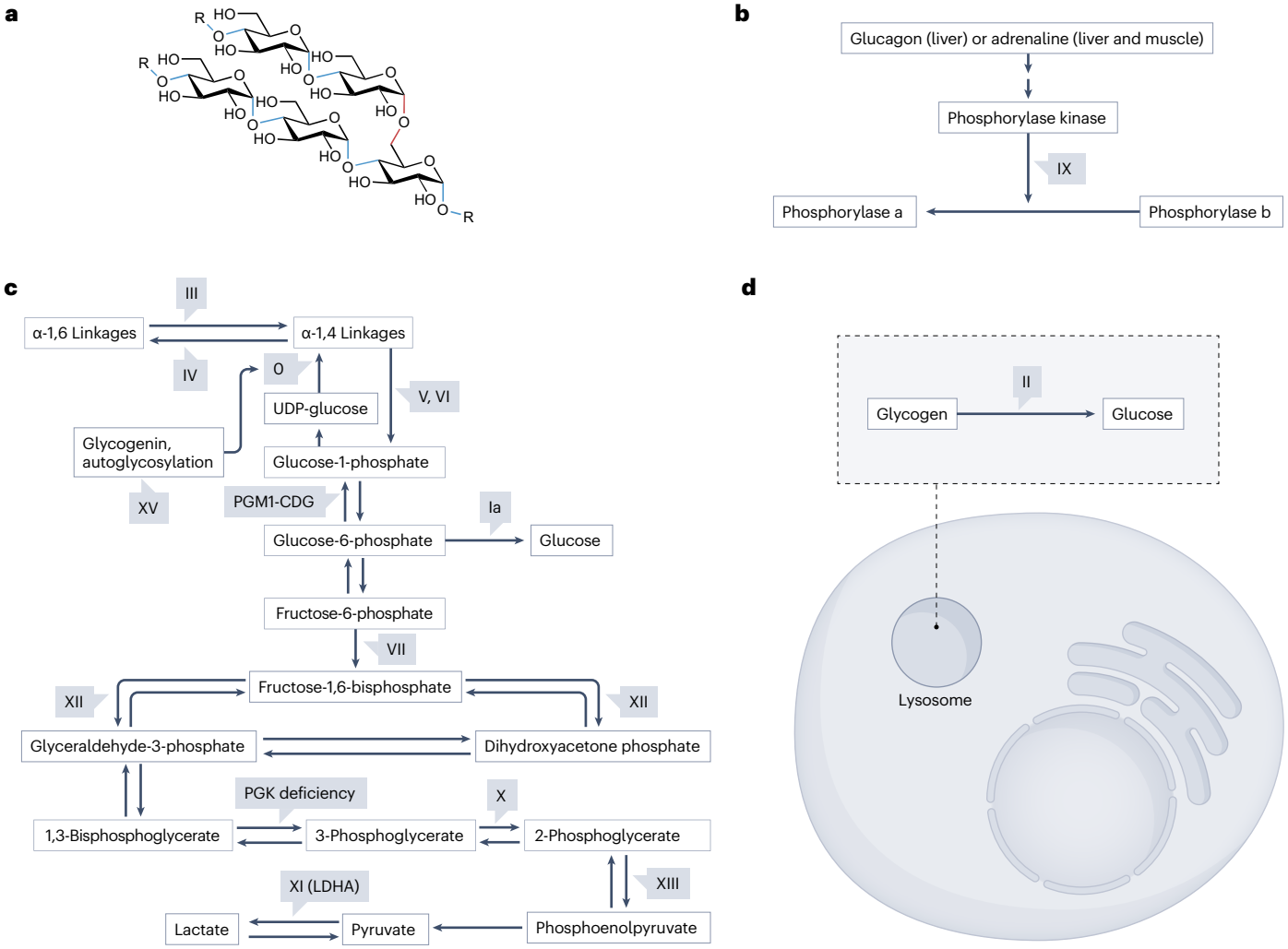

Fig. 2 | Biochemical defects in GSDs. a, Glycogen is a compact, spherical polymer. The structure of glycogen ensures efficient storage. Glycogen synthesis involves the formation of both straight chains (linked by α-1,4 glycosidic bonds) and branched chains (which occur every four to ten monomers and are linked by α-1,6 glycosidic bonds) of glycosyl units. During glycogenolysis, glucose monomers can be released from the α-1,4 glycosidic bonds or α-1,6 glycosidic bonds of glycogen. The branching of the glycogen polymer provides multiple loci for addition and removal of glucose monomers. **b**,**c**, The biochemical pathway of glycogen metabolism. Steps in the glycogen metabolism pathway that are associated with a glycogen storage disease (GSD) are indicated by the Roman numeral corresponding to the specific GSD. GSDs involve defects in glycogenesis (GSD 0, GSD IV, GSD XV), glycogenolysis (GSD I, GSD III, GSD V, GSD VI and GSD IX), glycolysis (GSD VII, GSD X, GSD XI and GSD XII) and gluconeogenesis (GSD I). Glycogenin 1 is self-glucosylating and provides a primer on which glycogen synthase acts (glycogenin 1 deficiency is associated with GSD XV). Two arrows following glucagon and adrenaline indicate that these hormones begin a signalling cascade. Reactions are shown to highlight GSDs. Some reactions involving the metabolites in the figure are omitted (such as the reactions catalysed by glucokinase/hexokinase and fructose-1,6-bisphosphatase). **d**, Pompe disease (GSD II) is characterized by inability to hydrolyse lysosomal glycogen. LDHA, lactate dehydrogenase A; PGK, phosphoglycerate kinase; PGM1-CDG, phosphoglucomutase 1 deficiency–congenital disorder of glycosylation; UDP, uridine diphosphate.

Physiological regulation of glycogen metabolism involves activation of phosphorylase kinase (PhK) via phosphorylation by protein kinase A[16]; activated PhK subsequently activates glycogen phosphorylase, which initiates glycogen catabolism[16]. Protein kinase A is activated in a cAMP-dependent manner via glucagon signalling in the liver or adrenaline signalling in liver and muscle; therefore, glucagon and adrenaline can stimulate glycogenolysis[17]. Additionally, enzymes (including protein kinase A) phosphorylate glycogen synthase, leading to inactivation of this enzyme and downregulation of glycogenesis[18]. By contrast, insulin can promote glycogenesis and inhibit glycogenolysis by activating protein phosphatase 1, which dephosphorylates glycogen phosphorylase and glycogen synthase[17].

Glucose is not the sole source of energy, and euglycaemia is tightly regulated in different nutritional states. The altruistic role of the liver is adaptive in different phases after a meal. In general, in the fed state, the liver is mainly a glucose-consuming organ, and all tissues use glucose, which is exogenously available[19]. Postabsorptive plasma glucose concentrations are maintained within a narrow range by the interplay of glucose-lowering insulin actions and glucose-raising glucagon actions. As time passes since the last meal, insulin levels will decrease and a

collaboration between multiple hormones (mainly glucagon, together with adrenaline, cortisol and growth hormone) acts to promote use of alternative energy sources in the primary defence against hypoglycaemia. Postprandially, the liver is the major contributor of endogenous glucose production, and glycogenolysis provides a greater portion than gluconeogenesis. In the hours that follow, this is gradually reversed and hepatic gluconeogenesis will provide a greater portion than glycogenolysis. Lactate, glycerol, proprionate and glucogenic amino acids serve as substrates when hepatic glycogen stores deplete. During prolonged fasting, gluconeogenesis is the predominant source of glucose, and both kidney and liver contribute to gluconeogenesis. With fasting, fatty acids will be oxidized in the liver to provide substrates for ketogenesis. The ketone bodies can account for approximately two-thirds of the brain's energy supply[20] and can provide an important energy source for the heart and other organs. Amino acids will also be catabolized[21].

Glycogenesis. GSD 0, GSD IV and GSD XV are caused by dysfunction of enzymes involved in glycogenesis (Fig. 2).

The process of glycogenesis requires the formation of a glucose 'primer' of at least four monomers. Glycogenin autocatalyses the formation of this primer, on which glycogen synthase then acts. The muscle isoform of glycogenin, glycogenin 1, is encoded by *GYG1*, and the hepatic isoform, glycogenin 2, is encoded by *GYG2*. The physical interaction between glycogenin and glycogen synthase is essential for formation of α-1,4 glycosidic bonds. Biallelic disease-causing variants in *GYG1* are associated with GSD XV (Table 1 and Supplementary Table 1). To date, no genetic diseases associated with variants in *GYG2* have been identified.

Glycogen synthase facilitates the addition of uridine diphosphate (UDP)-glucose onto the growing straight chain via α-1,4 glycosidic bonds. This enzyme is essential for glycogen synthesis, and dysfunctional enzyme is associated with GSD 0. Similar to glycogenin, glycogen synthase is encoded by genes with tissue-specific expression: *GYS2* encodes liver glycogen synthase (biallelic variants of *GYS2* cause hepatic GSD 0a), and *GYS1* encodes muscle glycogen synthase (biallelic variants of *GYS1* cause GSD 0b)[16]. Of note, a gain-of-function *GYS1* variant can cause a GSD in horses that is associated with accumulation of glycogen and glycogen-like polysaccharides in skeletal muscle[22–24]. However, there are no published cases of an autosomal dominant GSD related to a gain-of-function *GYS1* variant in humans.

Branched chains via α-1,6 glycosidic bonds are also crucial for the compact and efficient structure of glycogen. These branches are formed by the addition of glucose molecules via glycogen branching enzyme (GBE, encoded by *GBE1*). Defects in GBE are associated with GSD IV[16]. Biallelic *GBE1* variants are associated with a broad phenotypic spectrum that affects various organs, and GBE deficiency leads to accumulation of polyglucosan (a poorly branched glycogen).

Glycogenolysis. Glycogenolysis relies on specific enzymes for the catabolism of α-1,4 and α-1,6 glycosidic bonds. Terminal α-1,4 glycosidic bonds are broken by phosphorylation of glycogen by glycogen phosphorylase, to release glucose-1-phosphate (G1P). Glycogen phosphorylase comprises three isomers that are encoded by separate genes with expression in liver (*PYGL*), muscle (*PYGM*) and brain (*PYGB*). Owing to the tissue-specific expression of these genes, different organ systems are affected depending on which isoform of glycogen phosphorylase is dysfunctional.

Biallelic variants of *PYGM* are associated with the metabolic myopathy GSD V (also known as McArdle disease)[25]. Moreover, a monoallelic *PYGM* missense variant has been reported in individuals with an autosomal dominant GSD characterized by age-dependent muscle weakness and wasting but no energy deficiency and thus no exercise intolerance; functional and histological differences between this new GSD and GSD V have been described[26]. Biallelic variants of *PYGL* are associated with GSD VI[9]. To date, no genetic diseases associated with variants in *PYGB* have been identified.

The activation of glycogen phosphorylase is an important concept that involves complex hormonal regulation. Glycogen phosphorylase is activated by PhK, which is a hexadecamer comprising four copies of α-, β-, γ- and δ-subunits. The activity of the catalytic γ-subunit is affected by the three regulatory subunits (α, β and δ)[27]. The α-subunit is encoded by two X-linked genes, *PHKA1*, which is expressed in muscle, and *PHKA2*, which is expressed in the liver. Hemizygous variants in *PHKA1* have been identified in individuals with myopathy, referred to as GSD IX α1 (also known as GSD IXd)[9,16]. Hemizygous variants in *PHKA2* cause GSD IX α2 (also known as GSD IXa) and are the most common cause of GSD IX[9,16]. The β-subunit is encoded by *PHKB*, although tissue-specific splicing results in the production of multiple variants. Biallelic *PHKB* variants are associated with GSD IX β (also known as GSD IXb)[9,16]. Although *PHKB* is also expressed in muscle, muscle symptoms are usually absent or mild. The γ-subunit is encoded by several genes with tissue-specific expression, such as *PHKG2* in the liver. Of note, biallelic variants in *PHKG2* cause GSD IX γ2, also known as GSD IXc[9,16]. The δ-subunit is encoded by three genes with ubiquitous expression. To date, *PHKA1*, *PHKA2*, *PHKB* and *PHKG2* are the only four genes encoding PhK subunits that are known to be associated with a GSD.

As previously mentioned, glycogen phosphorylase is key for the catabolism of straight chain glycogen to G1P. By contrast, glycogen debranching enzyme (GDE, encoded by *AGL*) facilitates glycogenolysis at both α-1,6 and α-1,4 glycosidic bonds. GDE has two catalytic processes: transferring glucose monomers from the branch chain to the straight chain (via 4-α-D-glycosyltransferase activity) and hydrolysing a final α-1,6 glycosidic bond (via amylo-1,6-glucosidase activity). Notably, the reaction catalysed by GDE releases a small amount of free glucose[15,28]. Biallelic variants in *AGL* are associated with GSD III[29]. Most individuals with GSD III (~85% of patients) have both liver and muscle involvement (GSD IIIa) whereas the remaining individuals show only liver involvement (GSD IIIb). GSD IIIa is characterized by significant allelic heterogeneity[12], and variants in exon 2 have been implicated in GSD IIIb[30].

Following phosphorylation of straight chain monomers by glycogen phosphorylase, phosphoglucomutase 1 (PGM1) catalyses the reversible interconversion of G6P and G1P. PGM1 has a role in both glycogenesis and glycogenolysis. In glycogenesis, G1P is activated to UDP-glucose, which can then be added to a growing glycogen polymer. Following glycogenolysis, PGM1 converts G1P into G6P. Deficiency of PGM1 is caused by biallelic variants in *PGM1* and was formerly known as GSD XIV[31]. However, this condition is also a congenital disorder of glycosylation (CDG) given its role in N-linked glycosylation; therefore, this disorder is now referred to as PGM1-CDG[31].

G6P is a substrate for G6Pase, leading to glucose production, which in the liver can then be secreted for maintenance of euglycaemia. This process does not occur in muscle tissue, which lacks G6Pase. The three isoforms of G6Pase are encoded by *G6PC1*, *G6PC2* and *G6PC3*. *G6PC1* is the only gene associated with a hepatic GSD; biallelic variants of this gene cause GSD Ia[32]. Of note, biallelic *G6PC3* variants cause congenital neutropenia[33]. Biallelic *SLC37A4* variants are associated with GSD Ib[32]. *SLC37A4* encodes a transporter protein that transports G6P across ER

membranes[34] (Fig. 1). Because G6Pase is also involved in the final step of gluconeogenesis, both glycogenolysis and gluconeogenesis are blocked in GSD Ia and GSD Ib.

Although GSD I is associated with defects in enzymes functioning at the ER, most enzymes implicated in GSDs are cytosolic. Variants in *GAA* (encodes the lysosomal enzyme acid α-glucosidase (GAA)) cause Pompe disease[35]. Therefore, Pompe disease is classified as both a GSD and a lysosomal storage disease (Fig. 1). Biallelic variants in *GAA* are associated with both infantile-onset and late-onset Pompe disease. Genotype–phenotype correlation is important in Pompe disease[36,37] as some patients are cross-reactive immunological material negative (owing to deleterious variants leading to no GAA protein) and may develop antibodies to ERT.

Glycolysis. Defects in glycolysis can also lead to GSDs with muscle deposition of glycogen[38]. Deficiency of phosphofructokinase (PFK) in muscle is among the best described of these disorders.

PFK has three isoforms encoded by genes with tissue- or cell-specific expression[38]: *PFKL* (liver), *PFKP* (platelets) and *PFKM* (muscle). Biallelic variants in *PFKM* are associated with GSD VII[7]. Both *PFKM* and *PFKL* are expressed in erythrocytes, therefore, GSD VII is associated with partial PFK deficiency in erythrocytes[39], and individuals with GSD VII can have haemolytic anaemia. As glycolysis is impaired in those with GSD VII, pre-exercise ingestion of sucrose worsens exercise tolerance because of inhibition of lipolysis[40]. No genotype–phenotype correlation has been observed in GSD VII, and numerous variants have been described. A variant that affects exon 5 splicing accounts for ~68% of alleles in individuals of Ashkenazi Jewish ancestry[41].

Other disorders of glycolysis result in abnormal glycogen storage but have been described in only a small number of patients. Glycolytic defects include PGK deficiency, GSD X (muscle phosphoglycerate mutase (PGAM) deficiency, caused by biallelic *PGAM2* variants), GSD XI (lactate dehydrogenase A deficiency, caused by biallelic *LDHA* variants), GSD XII (aldolase A deficiency caused by biallelic *ALDOA* variants) and GSD XIII (β-enolase deficiency caused by biallelic *ENO3* variants)[16]. The clinical features of these conditions include myopathy and, at times, extraneuromuscular symptoms (Table 1).

Glucose transportation defects. Glucose homeostasis in different tissues is governed by glucose transporters (GLUTs) on cell membranes. Although rare, some individuals have inherited metabolic disorders that are caused by GLUT deficiencies. For example, the multisystem disorder FBS is caused by GLUT2 deficiency owing to biallelic *SLC2A2* variants. GLUT2 is a glucose transporter on plasma membranes of hepatocytes and pancreatic β-cells and on the basal membrane of renal proximal tubules and intestinal mucosa cells[42].

Diagnosis, screening and prevention

Clinical practice guidelines based on expert opinions have been developed for GSD I, Pompe disease, GSD III, GSD IV, GSD V, GSD VI, GSD VII, hepatic GSD IX and PGM1-CDG[7,9,12,31,32,35,43–45]. These guidelines contain both diagnostic and therapeutic considerations and are recommended reading for health-care professionals caring for patients with known or suspected GSDs. Histological findings and diagnostic testing for GSDs are summarized in Table 2.

Symptoms and phenotypes

The first step in diagnosis of GSDs is characterization of the patient's phenotype and clinical features (Table 1). The pathophysiology of hepatic GSDs can involve fasting intolerance-associated hypoglycaemia (such as in GSD 0a, I, III, VI, IX and FBS). Hypoglycaemia can lead to seizures, cognitive impairment and in severe cases coma and/or death. Glycogen deposition can lead to organomegaly and organ impairment (such as hepatomegaly and renomegaly as well as glomerulopathy and tubular dysfunction in GSD I). Adenomas with potential for malignant transformation may occur with hepatic GSDs, and some hepatic GSDs can be associated with fibrosis and cirrhosis. In some disorders, excess metabolites can affect other metabolic pathways, leading to disease. For example, in GSD I, the inability to convert G6P into glucose can result in lactic acidosis, elevated uric acid and hyperlipidaemia, which may result in gout, pancreatitis, fatty deposition of liver and other systemic sequelae.

Myopathy is a prominent feature of muscle GSDs. Some individuals with GSD V or those with some glycolytic defects have exercise intolerance and rhabdomyolysis as well as glycogen accumulation and impaired glucose use. Moreover, severe cardiomyopathy and arrhythmia risk can result from glycogen accumulation in the heart. For example, infantile-onset Pompe disease manifests as severe cardiomyopathy and skeletal myopathy. GSD IV can manifest with severe cardiomyopathy, liver fibrosis and skeletal myopathy.

Most often, individuals with suspected GSD have a broad differential diagnosis. GSDs with predominantly hepatic involvement will most often be considered if an individual has any combination of hypoglycaemia, failure to thrive, hepatomegaly, increased liver enzymes, hyperlipidaemia and hepatic adenomas. Muscle GSDs also have variable clinical presentation. Limb and trunk weakness may be seen in Pompe disease, GSD IIIa and GSD IV (and can be seen in GSD V and GSD XV). In some muscle GSDs, there may be exercise intolerance, fatigue, pain, myoglobinuria and rhabdomyolysis.

Diagnostic testing

Diagnostic work-up should include a thorough characterization of the patient phenotype by history taking, physical examination, basic clinical chemistry laboratory assays and imaging. Laboratory testing can identify liver disease (such as liver function tests and prothrombin time/international normalized ratio (PT/INR)), skeletal muscle disease (such as serum CK and aspartate aminotransferase (AST)) and involvement of other organ systems (for instance, elevated serum creatinine or proteinuria for renal involvement). Imaging can also provide details of organ involvement. For example, abdominal ultrasonography, CT or MRI can identify organomegaly, hepatic adenomas or liver fibrosis or cirrhosis, and echocardiography can identify cardiomegaly or pulmonary hypertension.

Genetic testing offers a non-invasive option for confirmatory diagnostic testing and often shortens the diagnostic odyssey. If one GSD is highly suspected owing to family history or suggestive clinical features, single gene testing using Sanger sequencing can be considered. More commonly, owing to the phenotypic overlap of GSDs, gene panel testing is used. The precise gene panel to be evaluated depends on clinical judgement and may include genes associated with GSDs, hypoglycaemia, rhabdomyolysis or neuromuscular disease. Custom gene panels may also be considered. Next-generation sequencing analysis is the most common methodology for gene panel testing and, in some laboratories, allows detection of deletions and/or duplications. Exome sequencing and genome sequencing are increasingly used in individuals with a broad differential diagnosis. Variant interpretation typically follows guidelines of the American College of Medical Genetics and Genomics and the Association of Molecular Pathology[46].

Table 2 | Histological findings and diagnostic testing for GSDs

Condition	Histological findings	Diagnostic testing		Additional considerations[a]
		Enzyme	Genetic	
GSD 0a	Decreased hepatic glycogen content[170]	Not clinically available	Biallelic PLP *GYS2* variants	NA
GSD 0b	Decreased glycogen content in muscles[171,172]. Predominance of type 1 muscle fibres and mitochondrial proliferation in some patients[171,172]	Not clinically available	Biallelic PLP *GYS1* variants	NA
GSD I	Liver cells distended by glycogen and fat (observed as numerous large lipid vacuoles). Glycogen accumulation in liver is normal or modestly increased, and is much lower than in GSD III, GSD VI or hepatic GSD IX[32]. Fibrosis does not occur[32] and G1P to glucose ratio is normal. Accumulated glycogen is located in cytoplasm and is diastase sensitive and PAS positive[32]	For GSD Ia, G6Pase enzyme activity in liver tissue	Biallelic PLP *G6PC1* variants (GSD Ia) or biallelic PLP *SLC37A4* variants (GSD Ib)	NA
GSD II (Pompe disease)	Glycogen levels are markedly elevated in skeletal and cardiac muscle (infantile-onset Pompe disease) and can be mildly elevated in skeletal muscle (late-onset Pompe disease) and other tissues. Glycogen is usually observed in the lysosomes[12,214]. In advanced disease, lysosomal membranes rupture, and glycogen from lysosomes may spill into cytoplasm. Defective autophagy has been observed in skeletal muscle of animal models (increased formation of autophagosomes and poor fusion to lysosomes)[215]	GAA activity testing is available in blood, fibroblast or muscle specimens	Biallelic PLP variants in *GAA*	NA
GSD III	Markedly elevated glycogen in cytoplasm of hepatocytes (GSD IIIa and IIIb) with abnormal glycogen structure (G1P to glucose ratio) and in the skeletal muscle and rarely heart (GSD IIIa)[12]. Accumulation of limit dextrin. Some lipid accumulation (much fewer lipid vacuoles than in GSD I)[32,216]. Fibrosis ranges from early mild periportal fibrosis to cirrhosis[12]; periportal fibrosis is a very early finding[32]. Muscle biopsy and genetic testing can distinguish GSD IIIa from IIIb[12]	GDE activity assay for liver and muscle specimens. GDE activity can be measured in leukocytes, erythrocytes or cultured fibroblasts if regionally available[11,217]	Biallelic PLP *AGL* variants	Decreased G1P to glucose ratio can be a distinguishing feature
GSD IV	Accumulation of polyglucosan bodies and glycogen varies and accumulation may occur in liver, skeletal muscle, heart and peripheral nerves among other tissues[45]. G1P to glucose ratio normal to increased[12]. Amylopectin-like cytoplasmic glycogen is PAS positive and partially or fully diastase resistant[45]	Branching enzyme activity assay can be carried out on fibroblast, liver or muscle specimens	Biallelic PLP *GBE1* variants	In APBD, branching enzyme activity measured on muscle or skin fibroblasts may be reduced but not fully deficient. Muscle biopsy should have a part of the sural nerve. Histology and EM studies are informative for diagnosis of GSD IV
GSD V	Elevations of muscle or subsarcolemmal glycogen[7]. Normal G1P to glucose ratio[12]. Cytoplasmic glycogen is PAS positive and markedly elevated[12]	Muscle phosphorylase (myophosphorylase) activity assay is available for muscle specimens	Biallelic PLP *PYGM* variants	A 12-minute walk test may detect a second-wind phenomenon[7] but note limitations in young children[218]. Forearm non-ischaemic exercise test demonstrates flat lactate response with rise in ammonia[7]. Not specific but may inform defect in glycogen degradation[7]
GSD VI	Elevated glycogen in liver, with normal G1P to glucose ratio[12]. Cytoplasmic vacuoles with markedly elevated glycogen are PAS positive and diastase sensitive[9,216]. Rarely, fibrosis and steatosis can be seen	Phosphorylase activity can be measured in liver specimens	Biallelic PLP variants in *PYGL*	Fibrosis has been reported, as has cirrhosis[179,219,220]
GSD VII	Muscle glycogen content may be mildly elevated or in the upper limits of normal[7,12]. Normal G1P to glucose ratio[7,12]. Some PAS-positive amylopectin-like glycogen in the cytoplasm of muscle[12]	Phosphofructokinase activity can be measured in muscle specimens	Biallelic PLP *PFKM* variants	Forearm non-ischaemic exercise test is not specific but may inform a defect in glycogen degradation[7]
GSD IX	Hepatic: markedly elevated glycogen in hepatocytes. Normal G1P to glucose ratio[12]. Cytoplasmic vacuoles present, with PAS-positive and diastase-sensitive glycogen[9]. Portal fibrosis and steatosis may be present and can progress to liver cirrhosis in some individuals[8]. Muscle: muscle biopsy samples may have subsarcolemmal glycogen accumulation[38,8]	Phosphorylase b kinase activity can be measured in liver, blood and muscle (based on subtype). Enzyme activity in blood can be normal	Hemizygous PLP variant in *PHKA2* (GSD IX α2)/*PHKA1* (GSD IX α1). Heterozygous female patients with *PHKA2* variant may have symptoms. Biallelic PLP variants in *PHKB* (GSD IX β) or *PHKG2* (GSD IX γ2)	NA

Table 2 (continued) | Histological findings and diagnostic testing for GSDs

Condition	Histological findings	Diagnostic testing		Additional considerations[a]
		Enzyme	Genetic	
GSD X	Although muscle biopsy may have normal glycogen content[221–223,224], glycogen accumulation has been described[38,222,225,226]. Tubular aggregates in most patients[38,221,227]	Not clinically available	Biallelic PLP *PGAM2* variants	Tubular aggregates have not been described in other disorders of glycolysis[38]
GSD XI	Nonspecific myopathic changes described[38]. Muscle homogenate with deficit of LDH activity[38]	Not clinically available	Biallelic PLP *LDHA* variants	Blood LDH isoenzyme analysis by electrophoresis can be informative. Skin biopsy has suggested glycogen granules in epidermal cells[183]. Non-ischaemic forearm exercise test suggested flat lactate curve and high ammonium response[185]
GSD XII	Muscle biopsy usually has nonspecific findings[195]	Not clinically available	Biallelic PLP *ALDOA* variants	NA
GSD XIII	Increased subsarcolemmal glycogen particles reported in one individual[198]. Nonspecific, minimal changes and mild increase in glycogen in muscle described[200]. Minimal changes with no glycogen or lipid accumulation in muscle described[199]	Not clinically available	Biallelic PLP *ENO3* variants	NA
GSD XV	Variable features of glycogen and polyglucosan in skeletal muscle and endomyocardial biopsy samples[202,228–233]	Not clinically available	Biallelic PLP *GYG1* variants	As more individuals are described, histology should be better understood
PGM1-CDG	Five affected individuals had liver biopsy samples characterized by steatosis, cholestasis, mild fibrosis and/or bile duct atrophy[203]. Only two of these individuals had increased glycogen shown on PAS staining; one biopsy showed glycogen particles in hepatocytes on EM, but noted to be much less than other GSDs[203]. 10 of 12 muscle biopsy samples abnormal with myopathic changes (increased fibre size variation or internal nuclei) and/or fat or glycogen accumulation[31]	Not clinically available	Biallelic PLP *PGM1* variants	Transferrin analysis by isoelectric focusing has shown abnormal patterns. Mass spectrometry has shown variation in transferrin glycoforms[203]
FBS	Glycogen accumulation in the liver[205,234]. Renal biopsy has been noted to show normal glomeruli, interstitium and vessels; some proximal tubule cells have been reported to have megamitochondria[205,234]. Glycogen accumulation has been reported in some proximal tubule cells[205,234]	NA	Biallelic PLP *SLC2A2* variants	NA
PGK deficiency	Muscle biopsy can exhibit nonspecific changes[235]. PAS staining of muscle is usually normal with vacuolization sometimes seen with EM[207]. Histology not well described although five reports discussed the following: mild diffuse increase of PAS-positive material on muscle biopsy[38]; normal glycogen amount, atrophy of type II fibres, variability of fibre size, few internal nuclei and increased number of mitochondria[213]; normal light microscopy and minimal glycogen storage on EM[236]; no glycogen storage by PAS but muscle fibres type I and II showed same intensity of staining and diffuse and moderate peripheral and intermyofibrillary glycogen granule accumulation on EM (they noted very small light microscopy changes with few atrophic and angulous fibres)[237]; and mild increase in lipid droplets with normal glycogen concentration of muscle[238]	Red blood cell PGK1 activity. Measurement of enzyme activity is not clinically available in muscle tissue	Hemizygous PLP *PGK1* variant	NA

APBD, adult polyglucosan body disease; EM, electron microscopy; FBS, Fanconi–Bickel syndrome; G1P, glucose-1-phosphate; G6Pase, glucose-6-phosphatase; GAA, acid α-glucosidase; GDE, glycogen debranching enzyme; GSD, glycogen storage disease; LDH, lactate dehydrogenase; NA, not applicable; PAS, periodic acid–Schiff; PGK, phosphoglycerate kinase; PGM1-CDG, phosphoglucomutase 1 deficiency–congenital disorder of glycosylation; PLP, pathogenetic or likely pathogenetic. [a]When molecular testing is non-diagnostic, other testing may be considered, such as biopsy for GSDs (for which an invasive procedure is necessary for an informative specimen) or exercise testing in muscle GSDs. When evaluating a possible muscle GSD, clinicians should be mindful of precautions and risks of forearm exercise testing and consider non-ischaemic version of the test.

Some laboratories use refinements of those guidelines[47]. Limitations of genetic testing include the possibility of unidentified variants in tested genes and that the individual's symptoms have an aetiology that is not related to variants in the genes tested.

Unless testing for the presence or absence of known familial variants, results of genetic testing can include a positive result, a negative result and/or identification of variants of uncertain significance (VUS). Thorough genetic counselling is necessary to discuss the purpose, limitations and possible results of genetic testing. The identification of VUS is not diagnostic, and VUS are often reclassified as additional information about variants becomes available. Biallelic pathogenetic or likely pathogenetic variants in genes associated with autosomal

recessive inheritance reflect a positive result. Parental testing is necessary to determine whether two variants are present on the same allele (monoallelic; in cis) or on opposite alleles (biallelic; in trans). A pathogenetic or likely pathogenetic hemizygous variant in a gene associated with X-linked recessive inheritance reflects a positive result. Genetic counselling following diagnosis may include a discussion of inheritance, availability of genetic counselling for at-risk relatives and, if pertinent, the availability of carrier testing for a partner and counselling regarding family planning and prenatal diagnostics.

Negative or non-diagnostic results of genetic testing do not rule out GSD. Analysis of enzyme activity has an important role in diagnosing some GSDs owing to the limitations of molecular testing. Some enzymatic tests can be carried out on blood samples, such as for Pompe disease; however, other tests require tissue obtained via biopsy, with the tissue type depending on the condition. Functional tests can also be used for diagnosis of GSDs, such as the standardized non-ischaemic forearm exercise test, which is used to measure lactate and ammonia in venous blood from an exercised arm[48]. In complete enzymatic blocks, as in GSD V and GSD VII, the lactate response is flat and ammonia increases more than normal (because of activation of the myoadenylate deaminase reaction), whereas in other partial defects of glycolysis and glycogenolysis, lactate responses are blunted and ammonia responses are increased. More generally, individuals with GSD V, GSD VII or distal disorders of glycolysis have inadequate increase of lactate and substantial elevations of ammonia after exercise. In hepatic GSDs, liver biopsy for enzyme testing, histology for glycogen/polyglucosan body deposition and fat deposition, measurement of glycogen content and description of liver architecture (Table 2 and Fig. 3) can provide helpful information.

Distinguishing between GSDs

Some key features (and constellations of symptoms) can narrow differential diagnosis or increase the likelihood of a particular condition being diagnosed. An understanding of distinguishing clinical features can focus the clinician's history taking and physical examination and inform the GSD differential diagnosis. The family history may suggest X-linked inheritance. However, it needs to be recognized that there is a phenotypic spectrum and the index of suspicion needs to be high.

Some metabolites inform the differential diagnosis of GSDs and can be useful for disease surveillance in patients. For example, lactate, triglycerides and uric acid can be elevated in GSD I. Both GSD 0a and FBS present with postprandial hyperglycaemia, but FBS may be differentiated on the basis of additional clinical characteristics (failure to thrive, short stature, rickets, hepatomegaly and tubulopathy) and the absence of postprandial hyperlactataemia. In GSDs that affect muscle, creatine kinase (CK) and AST can be increased (such as in Pompe disease, GSD IIIa, GSD V and GSD VII). However, normal levels of these enzymes do not exclude diagnosis. Urine glucose tetrasaccharide (Glc4), a breakdown product of glycogen, can be increased in Pompe disease[49,50]. Moreover, there is a growing understanding that Glc4 levels can be elevated in some individuals with hepatic GSDs[49,51] and could be a useful biomarker for some GSDs and other conditions[51]. In addition, elevated or altered biotinidase activity could serve as a diagnostic and/or monitoring marker for hepatic GSDs[52].

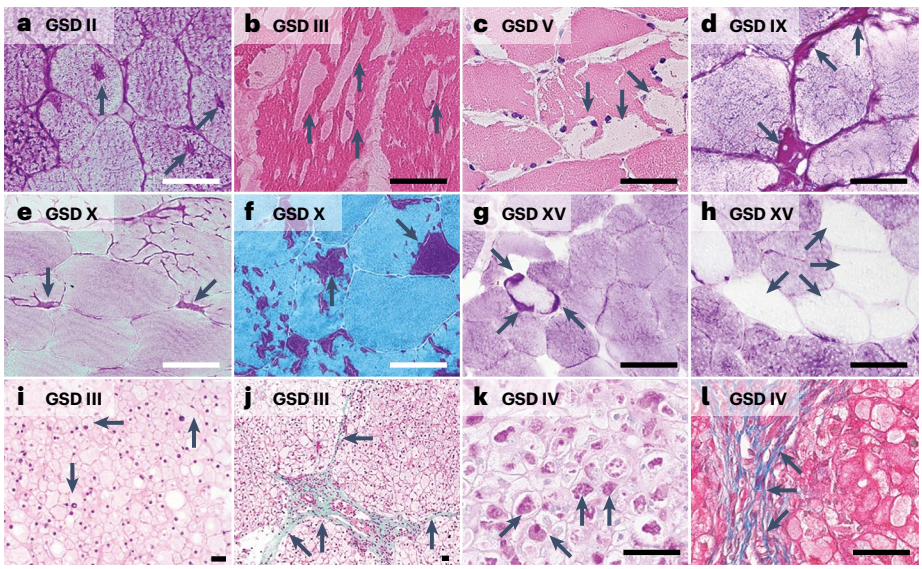

Fig. 3 | Histological features of muscle and liver GSDs. a–h, Muscle glycogen storage diseases (GSDs). Glycogen levels are increased in Pompe disease, GSD IX, GSD X and GSD XV but show a different pattern in GSD II, whereby glycogen-filled lysosomes are often more centrally located in the cell (part **a**; arrows), whereas glycogen deposits typically are more subsarcolemmal in GSD V (voids in part **c**; arrows) and GSD IX (part **d**; arrows) and GSD X (part **e**; arrows). In GSD XV, glycogen accumulates as periodic acid–Schiff (PAS) stain-positive, diastase-resistant inclusions known as polyglucosan bodies (part **g**; arrows), leaving other areas of muscle fibres devoid of glycogen content (pale fibres in part **h**; arrows). Glycogen accumulation is often very extensive in GSD III, disrupting the structure of the muscle cell and leaving a ragged (moth-eaten) appearance of the myocytes (part **b**; arrows). A characteristic feature of GSD X, besides subsarcolemmal glycogen accumulation, is the presence of tubular aggregates (part **f**; arrows), which is not seen in other GSDs. **i–l**, Liver GSDs. GSD III liver histology demonstrates cytoplasmic glycogen accumulation (part **i**; arrows), similar to patterns seen in both GSD VI and GSD IX. Liver fibrosis in GSD III can range from no significant fibrosis to advanced bridging fibrosis (green bands in part **j**; arrows). GSD IV is characterized by enlarged hepatocytes with polyglucosan that is PAS-positive and diastase resistant (part **k**; arrows), often with distorted hepatic architecture and fibrosis (blue bands in part **l**). Scale bars, 50 µm. Haematoxylin and eosin (H&E) staining in parts **b**,**c** and **i**. PAS staining in parts **a**,**d**,**e**,**g**,**h** and **k**. Trichome staining in parts **f**,**j** and **l**. Part **j** adapted with permission from ref. 241, Elsevier.

Differential diagnosis

Misdiagnosis or delayed diagnosis. Some data suggest mis- or delayed diagnosis of GSDs. For instance, initial misdiagnosis has been described in 90% of individuals with GSD V[53] and has been suggested to affect quality of life (QoL)[7]. Dried blood spot analysis of GAA activity of 3,076 adults with elevated CK and/or limb-girdle muscular weakness demonstrated that 2.4% had late-onset Pompe disease[54]. Similarly, exome sequencing of 1,001 individuals with unexplained limb-girdle weakness identified ten patients (~1%) with biallelic *GAA* variants[55]. Given the actionability and the possibility of either misdiagnosis or delayed diagnosis, it is important to recognize the common presentations and distinguishing characteristics of GSDs.

Hypoglycaemia. Hypoglycaemia has several causes (including metabolic and non-metabolic causes), therefore, it is important to consider overlapping and discriminating features of hepatic GSDs and other considerations on the differential diagnosis. These disorders include fatty acid oxidation disorders, ketogenesis defects, conditions that cause hyperinsulinism (such as Mendelian disorders or insulinoma), organic acidurias, gluconeogenic disorders and liver disease.

Hepatomegaly. The differential diagnosis of hepatomegaly is broad; however, most diseases are not associated with hypoglycaemia, which is a hallmark of several hepatic GSDs.

Myopathy. Numerous conditions can cause exercise intolerance, elevated CK and rhabdomyolysis. Of note, CK levels can be normal in some muscle GSDs, such as late-onset Pompe disease, GSD IIIa and GSD IV. Differential diagnoses include muscular dystrophies and multiple inherited disorders of intermediary metabolism (such as disorders of mitochondrial fatty acid oxidation, disorders of the carnitine cycle and mitochondrial disorders), among other genetic and non-genetic conditions. As always, the differential diagnosis guides history taking, examination and choice of laboratory investigations to evaluate distinguishing features of diseases.

Newborn screening

Historically, NBS for patients with rare diseases (including GSDs) had several limitations. Considerations for including disorders in NBS programmes include the benefit to newborns and feasibility[56]. NBS for metabolic conditions often requires metabolite detection, enzyme activity measurements or genetic tests using dried blood specimens. A limitation of NBS for GSDs is that the functional assays for many GSDs require muscle or liver tissue and are not possible with dried blood spots. Although numerous blood metabolites are often elevated in GSDs, there is no pathognomonic pattern that is both sensitive in the newborn and highly specific for a particular GSD. Also, available treatment must be weighed among other important factors when considering NBS panels.

An enzyme assay for Pompe disease that can be performed on blood specimens has been used for NBS[57]. In 2005, a NBS pilot programme for Pompe disease began in Taiwan[58] and, since then, other NBS programmes have incorporated screening for this disorder[57]. The next steps in patients who screen positive vary between programmes and may be two-tiered including genetic testing. Thorough clinical evaluation in patients who screen positive includes history and physical examination, diagnostic GAA activity assay, measurement of pertinent metabolites (such as CK, AST and urine Glc4) and *GAA* genetic testing. An in vitro functional assay has been developed to inform *GAA* variant interpretation following abnormal NBS[59].

Several lessons have been learned from the implementation of NBS for Pompe disease. For example, pseudodeficiency alleles (variants that affect the in vitro measurement of enzyme activity but are not disease causing) can lead to false positive results. In addition, NBS by enzymology does not distinguish infantile-onset and late-onset Pompe disease[60]; these disorders can be distinguished by the presence or absence of cardiomyopathy in the first year of life, and sometimes by genotype–phenotype correlation of the genetic variants reported. Moreover, NBS for Pompe disease has helped to characterize an emerging early phenotype of late-onset Pompe disease[61]. Of note, FBS may be identified by neonatal metabolic screening for galactosaemia owing to the presence of hypergalactosaemia[62–64].

NBS for inherited metabolic diseases is complicated and must be revisited as new screening modalities and treatments become available. In the future, NBS may be considered for other GSDs. Possible new screening approaches include genetic screening, which is being evaluated for use in NBS for treatable conditions with childhood onset. Both technical and ethical considerations have been raised for genetic screening in newborns including overdiagnosis, informed consent, data protection and legal regulation[65]. The possible role of genetic testing in NBS could have implications for the GSDs in the future given the lack of sensitive or specific biochemical markers that could be detected by tandem mass spectroscopy and the poor suitability of dried blood spot for enzyme assays of most GSDs.

Management

The GSDs with diagnostic and management guidelines are among the best-characterized GSDs, and the principles of management can guide the care of individuals with other GSDs. To date, such guidelines exist for GSD I[32,43,44], Pompe disease[35], GSD III[12], GSD IV[45], GSD V[7], GSD VI[9], GSD VII[7], hepatic GSD IX[9] and PGM1-CDG[31]. Regional or country-specific guidelines are also available for some GSDs, such as for GSD I, for which there are practice guidelines from the American College of Medical Genetics and Genomics and the European Study on Glycogen Storage Disease Type I[32,43,44]. This Primer focuses on surveillance of disease sequelae, diet, exercise and regular therapies given the importance to current care. Important aspects of management are summarized in Table 3 and Supplementary Table 3, focusing on the GSDs for which there are practice guidelines. In general, treatment options for genetic disorders are increasing[66], and the management of GSDs is progressing.

Surveillance of disease sequelae

Patients with GSDs should undergo monitoring for disease progression and identification of new manifestations. Guidelines for individual GSDs include recommendations for surveillance. GSD practice guidelines provide a structured plan for evaluating broad phenotypic features, which is important in such complex, multi-organ conditions. Metabolic expert centres are also an important resource for treatment of these disorders.

Clinical monitoring. Many GSDs are associated with impaired growth, failure to thrive, impaired physical activity, obesity and/or delayed puberty. Thus, assessment of growth and pubertal status should be part of every clinical examination in patients with GSDs.

Laboratory monitoring. Monitoring serum glucose concentrations over time is important in those with hepatic GSDs. Continuous glucose monitoring (CGM) is a powerful tool for the in-hospital and at-home

Table 3 | Summary of clinical practice guidelines and outpatient management of GSDs

Condition	Surveillance	Diet	Exercise	Regular outpatient treatment
GSD I[32,43,44]	Laboratory tests to monitor kidney and liver function. Levels of lipids and uric acid, a complete blood count and iron studies. In GSD Ib, differential to evaluate neutrophils. Imaging: liver and kidney imaging, echocardiography. Consider CGM	Avoid fasting. Feeding schedule per diet, corn starch dosing and foods to avoid (sucrose and lactose often limited)	Age-appropriate sports encouraged. Avoid contact or competitive sports owing to risk of liver injury	Consider angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for persistent microalbuminuria, frank proteinuria or evidence of hyperfiltration; consider low-purine diet and allopurinol for gout; hyperlipidaemia management, citrate (for hypocitraturia), thiazide (for hypercalcuria), adenoma management. For patients with GSD Ib: consideration of G-CSF[44] and empagliflozin[107,109]. Long-term use of nephrotoxic medications should be avoided. Liver transplantation can be considered
GSD II (Pompe disease)[35]	CK, AST, ALT, urine Glc4, BNP and, when receiving ERT, IgG against recombinant protein levels. Also, physical therapy evaluations, 24 h ambulatory electrocardiogram, echocardiography, CXR, swallow assessment, DEXA, upright and supine spirometry, polysomnography and hearing evaluation	High protein (20–25% protein)	Encourage exercise with guidance from physical therapist	ERT (alglucosidase alfa and, in some countries, avalglucosidase alfa)[90,91,239] in Europe[93], and in the USA, for LOPD only[94]. Albuterol may be considered to augment ERT[105]. Consideration of immune tolerance induction in individuals who are CRIM negative. Respiratory muscle training, maximize clearance of airway secretions
GSD III[12]	Liver function tests, coagulation studies, lipid levels, CK levels, monitoring of MELD score, abdominal imaging, echocardiography and consider CGM, and physical therapy evaluations	Avoid fasting; small and frequent feeds. Introduce corn starch at around 1 year of age in those with hypoglycaemia. High protein with low complex carbohydrates, and avoid simple sugars	Encourage exercise with guidance from physical therapist	Largely dietary management to avoid hypoglycaemia and support muscle health
GSD IV[45]	Paediatric onset: liver function tests, PT/INR, albumin, renal function panel, complete blood count, ammonia levels, 25-hydroxy vitamin D levels, AFP levels, liver and spleen imaging, physical therapy/occupational therapy. APBD: liver function tests, PT/INR, platelet count, brain and spinal cord imaging. All GSD IV (including APBD): periodic serum B-type natriuretic peptide or NT-proBNP, heart imaging, electrocardiography/ambulatory rhythm monitor, cystoscopy and imaging if indicated, bone density scan, vision examination, monitoring of height and weight	Individualized dietary recommendations directed by a metabolic dietician. Details in Supplementary Table 3	Exercise should be monitored including strengthening and/or optimizing movement and protection of fragile muscles	Routine immunizations. Hepatitis A and B vaccinations. See guidelines for details including timing of live vaccines that are contraindicated after liver transplantation. Guidelines describe considerations for liver and heart transplantation. Paediatric-onset GSD IV: prophylactic antibiotics for small bowel bacterial overgrowth and spontaneous bacterial peritonitis in those with compromised spleen function and neutropenia. Rule out spontaneous bacterial peritonitis when abrupt ascites. All GSD IV (including APBD): existing guidelines for lower urinary tract dysfunction may guide management. Referral to physical therapy and occupational therapy. Routinely screen for dysphagia (difficulty swallowing) in APBD
GSD V[7]	Serum CK levels, uric acid levels, haemoglobin A1c percentage, lipid profile. Evaluate weakness and muscle wasting. Routine imaging is not part of practice guidelines. Assess ADLs and QoL	Dietician involvement. Avoid excess weight. Sucrose supplementation (before exercise with careful planning)	Aerobic exercise to improve cardiorespiratory function. Exercise low–moderate intensity, at least 20 min 2–4 times/week preferably. Benefit and considerations for strength training and risk of contractures discussed in guidelines	Largely dietary and exercise. A carbohydrate-rich diet has been suggested as beneficial compared with a protein-rich diet. Pre-exercise sucrose improves exercise tolerance. For contractures, the inciting activity should be stopped and stretching avoided. Exercise should help for chronic pain, and opioids should be avoided
GSD VI[9]	AST, ALT, serum albumin and γ-glutamyl transferase levels, coagulation studies, abdominal imaging and, when indicated, DEXA and heart imaging. Monitor blood glucose and serum β-hydroxybutyrate	High protein; corn starch may be required before bedtime. Carbohydrate and fat restrictions as per guidelines	Avoid contact sports if there is hepatomegaly	Dietary treatment and symptomatic management

Table 3 (continued) | Summary of clinical practice guidelines and outpatient management of GSDs

Condition	Surveillance	Diet	Exercise	Regular outpatient treatment
GSD VII[7]	Routine imaging is not part of practice guidelines	Detailed studies to inform dietary management in GSD VII are needed	Aerobic exercise to improve cardiorespiratory function. Exercise low–moderate intensity, at least 20 min 2–4 times/week preferably	Largely dietary and exercise. Low-carbohydrate ketogenic diet demonstrated a benefit in one patient but larger cohort studies are needed. For contractures, the inciting activity should be stopped and stretching avoided. Exercise should help for chronic pain, and opioids should be avoided
Hepatic GSD IX[9]	AST, ALT, serum albumin and γ-glutamyl transferase levels, coagulation studies, abdominal imaging and, as indicated, DEXA and heart imaging. Also, monitor blood glucose and serum β-hydroxybutyrate levels	High protein; corn starch may be required before bed. Carbohydrate and fat restrictions as per guidelines	Avoid contact sports if hepatomegaly is present	Dietary treatment and symptomatic management
PGM1-CDG[31]	Serum IGF1, IGFBP3, TGB, TSH, free T4, ACTH, cortisol and glucose levels, liver function, liquid chromatography–mass spectrometry platforms for monitoring therapeutic response to galactose, liver imaging, transaminases, coagulation assessment, growth monitoring, liver monitoring and cardiac screening per guidelines, neurology and ophthalmology evaluations per guidelines	Nutritionist and speech therapist in those with cleft palate	No specific exercise recommendation to our knowledge	Oral D-galactose restores glycosylation and improves multiple symptoms[240]. Other treatments are used as needed, including thyroxine, cortisol, growth hormone, psychometric testing, nutritionist or speech therapy in those with cleft palate, ENT in those with Pierre–Robin sequence, early surgical intervention for midline malformations and supportive treatment for strabismus. Guidelines provide recommendations for referral and evaluation when bifid uvula, cleft palate or Pierre–Robin sequence are present

Table 3 attempts to summarize some important considerations for outpatient management of GSDs. Some of the referenced clinical practice guidelines were published years ago (GSD I in 2014 (The American College of Medical Genetics and Genomics) and 2002 (The European Study on Glycogen Storage Disease Type I), Pompe disease in 2006, GSD III in 2010, GSD IV in 2023, GSD V and VII in 2021, GSD VI and IX in 2019, and PGM1-CDG in 2021). Therefore, information is added to the table regarding additional common outpatient management practices along with some pertinent references. Please see individual guidelines for full details. More detailed descriptions of outpatient management and clinical practice guidelines can be found in Supplementary Table 3. ACTH, adrenocorticotropic hormone; ADL, activities of daily living; AFP, α-fetoprotein; ALT, alanine aminotransferase; APBD, adult polyglucosan body disease; AST, aspartate aminotransferase; CGM, continuous glucose monitoring; CK, creatine kinase; CRIM, cross-reactive immunological material; CXR, chest X-ray; DEXA, dual X-ray absorptiometry; ENT, ear, nose and throat; ERT, enzyme replacement therapy; G-CSF, granulocyte colony-stimulating factor; Glc4, glucose tetrasaccharide; GSD, glycogen storage disease; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; LOPD, late-onset Pompe disease; MELD, model for end-stage liver disease; NT-proBNP, aminoterminal pro B-type natriuretic peptide; PGM1-CDG, phosphoglucomutase 1 deficiency–congenital disorder of glycosylation; PT/INR, prothrombin time/international normalized ratio; QoL, quality of life; T4, thyroxine; TSH, thyroid-stimulating hormone.

care of individuals with hepatic GSDs[67–69] as it informs dosing of corn starch (a slow-release source of carbohydrate to extend fasting; see Lifestyle modifications, below), and in GSD I higher frequency and area under the curve (AUC) of blood glucose levels of <4 mmol/l is associated with higher frequencies of long-term sequelae including liver adenomas and microalbuminuria[70].

Useful laboratory tests for patients with hepatic GSDs include measurements of liver function (including alanine aminotransferase (ALT) and AST levels, and coagulation studies). Some hepatic GSDs have biomarkers of disease progression and metabolic control (such as liver function, muscle sequelae in GSD IIIa and other disorders, and kidney function in GSD I) (Table 3). It is important to acknowledge the limitations of traditional tumour markers (such as α-fetoprotein (AFP) and chorionic embryonic antigen (CEA)) and the lack of systematic studies on other tumour markers (such as PIVKA-II and glypican 3) in predicting malignant transformation of hepatocellular adenomas in patients with hepatic GSDs[32,71–73].

Routine laboratory testing is also important for GSDs that involve skeletal muscle. Obtaining baseline serum CK, AST and ALT levels is helpful to assess disease progression and response to treatment for muscle GSDs (such as response to ERT in Pompe disease). Other routine laboratory testing may be indicated, such as uric acid, haemoglobin A1c and lipid profiles for GSD V given the propensity for gout, diabetes mellitus and coronary artery disease. Urine Glc4 can be helpful to monitor response to therapy in Pompe disease and can be informative in hepatic GSDs.

Imaging. Periodic liver imaging is crucial for monitoring of individuals with hepatic GSDs. The specific features being evaluated depend on the type of GSD but can include adenoma burden, malignant transformation, fibrosis and cirrhosis. The age of first imaging, modality of imaging and mode of imaging differ between GSDs, and frequency of imaging is also affected by the patient's previous results. In general, liver ultrasonography can be used in younger children with transition to CT or MRI with and without contrast in older individuals or following abnormal findings. Liver elastography can be used in those with hepatic GSDs associated with a risk of progressive liver fibrosis. However, of note, imaging surveillance has several limitations, such as missed identification of liver adenomas with ultrasonography, or subtle changes in fibrosis with elastography.

Echocardiography is important for individuals at risk of cardiomyopathy and arrhythmias (such as those with Pompe disease, GSD III or GSD IV), and echocardiography is also indicated in GSD I given the risk of pulmonary hypertension in these patients. Other imaging is important for the surveillance of some GSDs, such as dual X-ray absorptiometry (DEXA) in individuals at risk of low bone mass and renal imaging in those with GSD I.

Specific examinations. Other types of routine surveillance vary between GSDs. For example, electrocardiography (ECG) and Holter monitoring are important examinations in individuals at risk of arrhythmia. In addition, polysomnography, video fluoroscopic swallowing

assessment and hearing evaluations are important in those with Pompe disease, given the well-documented features of sleep disorder, dysfunction of swallowing and sensorineural hearing loss, respectively, in this condition.

Assessment of muscular symptoms. Assessments of muscle function and status are essential for monitoring disease and functional status in patients with muscle GSDs. Useful assessments depend on patient age and their precise condition but typically include measurements of strength, function and kinematic posture. Some evaluations that can be performed based on patient age include Alberta Infant Motor Scales, Gross Motor Functional Measure and the 6-minute walk test. Muscle strength testing to evaluate for muscle weakness and signs of muscle wasting should be documented in the clinical physical examination. Ability to conduct activities of daily living and QoL should also be assessed. Imaging of the muscle can be informative in some GSDs[74,75]. Diaphragmatic weakness is seen in patients with Pompe disease, and when tolerated, upright and supine spirometry are valuable parts of the pulmonary function tests to monitor disease progression. Cycle ergometer testing can demonstrate the second-wind phenomenon in GSD V and can identify severely reduced oxidative capacity in disorders with complete enzymatic blocks, such as GSD V and GSD VII. The second-wind phenomenon is characterized by a steep increase in heart rate and perceived exertion during exercise, followed by a sudden relief of symptoms and decrease of heart rate after approximately 7–10 min of exercise. The phenomenon is a direct consequence of increased availability of alternative fuels (free fatty acids (FFAs) from the catabolism of adipose tissue and glucose from the liver glycogen stores)[76,77].

Outpatient treatment

Lifestyle modifications. Diet and exercise are cornerstones of management of GSDs. The involvement of a specialized metabolic dietician is crucial.

A serum glucose diary or CGM can be used in patients with hepatic GSDs to guide diet and corn starch regimens to maintain euglycaemia and to avoid overtreatment with carbohydrates, which can result in overweight and hepatomegaly[11]. Finding the correct treatment balance is essential. Fasting should be avoided. Fasting tolerance depends on patient age and the type of hepatic GSD. Infants with GSD I may require continuous overnight feeding until the pancreas produces adequate amylase. Owing to low pancreatic amylase, corn starch is not often tolerated before 6 months of age[78]. It can be introduced between 6 and 12 months of age, but diarrhoea may be a limiting factor[78]. In practice, clinical assessment of how corn starch is tolerated is important. However, corn starch should not be overdosed, to minimize excess calories, glycogen storage, gastrointestinal adverse effects and insulin resistance.

Corn starch may be needed in patients with other hepatic GSDs who have fasting intolerance. Severe hypoglycaemia can occur in multiple hepatic GSDs, and requires small and frequent feeds that are rich in carbohydrates. In patients with GSD I, simple sugars and sucrose or lactose should be limited, as both fructose and galactose are metabolized via G6P, which has defective metabolism in this condition. In some hepatic GSDs that have an intact gluconeogenic pathway, a high-protein diet can be helpful in providing an alternative source of glucose via glucogenic amino acids, minimizing glycogen storage and supporting synthesis of muscle protein[9,12]. In patients with GSD V, sucrose supplementation before exercise is often recommended with careful planning. Note that carbohydrate intake can worsen exercise tolerance in some glycolytic defects, such as GSD VII[38,40]. Individualized diet plans are important in individuals with GSD.

Exercise is an important aspect of management of muscle GSDs. In patients with GSD V and GSD VII, aerobic exercise can improve cardiorespiratory function, and low to moderate intensity exercise is preferable for at least 20 min two to four times per week. Guidance on exercise in individuals with Pompe disease is discussed in the practice guideline[35].

Medications that induce hypoglycaemia should be avoided in individuals with hepatic GSDs when possible. For example, β-blockers must be used with caution in those with hepatic GSDs and cardiomyopathy (such as in GSD IIIa) as they can promote hypoglycaemia and mask hypoglycaemic symptoms. Additionally, high-dose oestrogen should be avoided as an oral contraceptive in individuals with hepatic GSDs with hepatocellular adenoma owing to the potential contribution of oestrogen to the development of hepatocellular tumours; when considering contraception, the propensity for osteopenia must also be weighed. In caring for individuals with GSDs, the clinician should be mindful of the need for routine immunization to avoid illness.

Careful planning for surgical interventions and pregnancy is essential to decrease the risk of metabolic decompensation. Surgical planning requires involvement of an interdisciplinary team comprising the surgeon, anaesthesiologist, biochemical geneticist or metabolic specialist and metabolic dietician. The risks and benefits of surgery should be considered carefully. Medications that are used during surgery and that can induce rhabdomyolysis, such as succinylcholine, should be avoided in individuals with muscle GSDs. Moreover, appropriate laboratory tests to assess metabolic control should be undertaken pre-operatively and intra-operatively. In particular, glucose should be monitored closely in individuals with hepatic GSDs to maintain euglycaemia (lactate should also be monitored in GSD I and blood ketones in the ketotic GSDs). For surgery, two independent intravenous lines should be placed, one of which is solely for glucose. Labour and delivery planning must involve the obstetrician, biochemical geneticist or metabolic specialist and metabolic dietician. Appropriate fluids and nutrition are necessary to prevent catabolism with both surgery and labour, and practice guidelines provide insight.

Pharmacological management. Pharmacological management is often needed to treat elevated metabolites and other sequelae in individuals with hepatic GSDs. GSD I is a good example. Allopurinol may be needed in individuals with gout, and those with hyperlipidaemia may be prescribed lipid-lowering medications, as severe hypertriglyceridaemia can induce acute pancreatitis[32]. Moreover, individuals with GSD I often require low-dose angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) owing to progression of renal disease. Neutropenia and neutrophil dysfunction in individuals with GSD Ib can be treated with granulocyte colony-stimulating factor (G-CSF) or empagliflozin.

In 2006, the advent of ERT with alglucosidase alfa for Pompe disease introduced management targeted at the underlying metabolic defect. Multiple clinical trials showed improvements such as in cardiomyopathy and skeletal myopathy in individuals with infantile-onset Pompe disease with alglucosidase alfa compared with baseline[79–85]. ERT also showed efficacy in clinical trials for individuals with late-onset Pompe disease such as greater walking distance, stabilization of lung function, improved modified Gowers' manoeuvre (a timed muscle function test), lower serum CK concentrations and improvements in QoL[86–89]. This treatment has affected the natural history of both

infantile-onset and late-onset Pompe disease and set a precedent for therapeutics that mitigate directly the biochemical deficit. In the past 2 years, a second-generation ERT, avalglucosidase alfa, has been approved for infantile-onset Pompe disease and late-onset Pompe disease in Europe and for late-onset Pompe disease in the United States[90–94]. Therapy with cipaglucosidase alfa (a newer ERT) plus the enzyme stabilizer miglustat has been investigated[95] and has been approved in the European Union for adults who have late-onset Pompe disease[96].

Some infants lack cross-reactive immunological material (CRIM) and are more likely to develop high sustained antibody titres to the exogenous protein, which can reduce effectiveness of treatment[97–99]. A CRIM-negative status can be identified by western blot and can often be predicted by *GAA* genotype alone[100,101]. Standard of care in infants with CRIM-negative status is a short course of immunomodulation at the time of ERT initiation[102,103]. There is also benefit from immunomodulation in children already receiving ERT who develop high sustained antibody titres[104].

Additionally, β2 agonists such as extended release albuterol have been studied as a possible augmentation therapy for ERT in Pompe disease by increase of mannose-6-phosphate (M6P) receptors, thus facilitating cellular uptake[105]. In a phase I/II clinical trial of albuterol in late-onset Pompe disease, patients receiving albuterol saw improvements in forced vital capacity, forced expiratory volume in 1 s, 6-minute walk test and Gross Motor Function Measure (there were no significant increases in the placebo group)[105]. Other studies are investigating novel therapeutics for other GSDs that address the fundamental metabolic defect.

Therapeutics in the GSD field are expanding. Since 2020, sodium–glucose cotransporter 2 (SGLT2) inhibitors (such as empagliflozin and dapagliflozin, which were originally registered for use in type 2 diabetes mellitus) have been repurposed to treat neutropenia and neutrophil dysfunction in individuals with GSD Ib[106]. Indeed, empagliflozin has positive effects on all neutropenia and neutrophil dysfunction-associated symptoms with a substantial proportion of individuals having reduced G-CSF dosing or cessation of G-CSF treatment[107,108]. Possible benefits of empagliflozin treatment include improvement of inflammatory bowel disease, mucosal lesions and wound healing[109]. In addition, D-galactose improves multiple symptoms in individuals with PGM1-CDG including fatigability, exercise intolerance, hypogonadism, delayed puberty, frequency of hypoglycaemic events and rhabdomyolysis[31].

Organ transplantation. The first case reports about orthotopic liver transplantation in GSDs were published in 1983 for GSD I[110], in 1985 for GSD IV, in 1991 for GSD Ib and in 1997 for GSD IIIb. The absence of dedicated metabolic treatment facilities and limited pool of cadaveric organ donors may have stimulated the establishment of living donor liver transplantation programmes in some centres[111] and areas[112–117]. In the subsequent decades, long-term survival after metabolic and paediatric liver transplantation has markedly improved[118].

Observational studies reported that liver transplantation is clinically indicated in some patients with hepatic GSDs[119–124] and, in some instances, transplantation of multiple organs may be needed, such as combined liver and kidney transplantation in GSD I and combined liver and heart transplantation in GSD III and GSD IV. End-stage liver disease, multiple adenomas and hepatocellular carcinoma (HCC) are the most common indication for liver transplantation in individuals with GSDs[125]. More than 100 individuals with GSD I in North America have received liver transplantation, and there are some reports of liver transplantation in individuals with GSD III[12,32]. Liver transplantation should be also considered in individuals with classic, progressive GSD IV, bearing in mind the variable expressivity of GSD IV and the possible progression of cardiomyopathy and skeletal myopathy after the procedure[121]. Of note, liver transplantation does not correct the enzyme deficiency in the heart or skeletal muscle in those with GSD III or GSD IV[12,120]. Heart transplantation may be considered in children with GSD IV with severe cardiomyopathy[126].

Clinical guidelines suggest reserving transplantation in patients with GSD I to those with poor medical management, history of recurrent adenomas following liver resection, rapid increase in the number and size of adenomas, and with high risk of HCC[32]. However, it is increasingly acknowledged that liver transplantation could significantly improve the QoL of patients and their families. The risks and benefits of liver transplantation and existing management for patients with GSD must be weighed individually and against the background of emerging new, innovative treatments. For individuals with GSD Ib, SGLT2 inhibitors may be taken into account in this risk–benefit assessment[127]. A multidisciplinary approach between specialists in transplantation, metabolism and organ specialists (hepatologists, cardiologists) before, during and after transplantation is an important aspect of care.

Emergency treatment

Personalized emergency letters for patients with hepatic GSD can be generated online[128]. All individuals with GSDs should have a medical alert bracelet or emergency card to inform medical providers of potential risks pertinent to their specific condition (such as hypoglycaemia or rhabdomyolysis). Moreover, patients should be instructed to carry an emergency letter describing their underlying condition, suggestions for management, and contact information of the metabolic specialist. Individuals with hepatic GSDs should have an emergency kit with glucometer and source of glucose. Both glucagon and Ringer's lactate are contraindicated in GSD I, as they can lead to severe acidosis[129]. When an individual with hepatic GSD is ill, adequate glucose-containing fluids must be administered with careful dietary planning. Similarly, fluids are a mainstay of management of rhabdomyolysis in those with muscle GSDs. The clinician must also be mindful of the risk of compartment syndrome in applicable muscle GSDs.

The international consensus guidelines outline some emergency precautions and laboratory evaluation in individuals with PGM1-CDG. These include pertinent laboratory assessments to be obtained and treatment in those with hypoglycaemia, laboratory assessments to collect during acute infections given propensity for myoglobinuria, caution with anaesthetic agents given possible risk of malignant hyperthermia, and pertinent evaluation before surgery.

Quality of life

Several manifestations of GSDs can affect functional capacity and activities of daily living, and thereby QoL[89,130–133]. These manifestations include muscle weakness, cardiomyopathy, arrhythmia, abdominal distension, short stature and gastrointestinal disturbances. In hepatic GSDs, hypoglycaemia can lead to cognitive defects, and living with the fear of metabolic decompensation can be a huge burden for both patients and parents[132]. Sleep quality may be affected by short fasting intervals in those with hepatic GSDs, and sleep-disordered breathing has been described in Pompe disease[134–137].

In addition, some individuals with GSDs may have delayed diagnosis or misdiagnosis[7,53–55]. QoL can be evaluated using several methods,

including patient-reported outcomes (PROs). Most research of QoL in individuals with GSDs has focused on those with GSD I, Pompe disease or GSD V.

Patient quality of life

Validated GSD-specific QoL tools have not been developed, therefore the existing literature may not adequately reflect the psychosocial effect of GSD for patients and their families. However, some data on the precise effects of GSDs on QoL are available. Patients with hepatic GSDs may develop Avoidant/Restrictive Food Intake Disorder, which can affect QoL in various domains[138]. Moreover, children with GSD I are likely to have diminished QoL that persists into adulthood[132]. Adults with GSD I (age 16 years and older) had lower median short form 36 (SF-36) questionnaire scores for general health perception and social functioning compared with the Italian reference values and better scores for bodily pain and mental health[139]. Moreover, children with GSD I have been described as having more social problems, more internalizing symptoms and lower independent function based on the children's QoL ratings, compared with healthy controls[140]. In those with GSD I, QoL may be worse in those with GSD Ib, patients with kidney disease and women[139]. The need for nocturnal feeding in patients with GSD I can affect sleep, and administration of corn starch can interrupt school and affect social and professional life[132]. A study of Glycosade (modified corn starch to prolong periods without feeding) suggested that sleep disturbances that are present with standard corn starch may be improved with a transition to Glycosade[141]. One questionnaire of 34 adults with GSD I reported that this disorder conveys a burden on daily life (>85% of patients considered physical fitness either moderately or highly impaired); however, the questionnaire suggests that most patients live independent adult lives and maintain a positive attitude and ability to cope with their disease[142]. Numerous comorbidities in GSD I may affect QoL over time[132]. In addition, a prospective case–control study of 52 patients age 1–18 years with hepatic and unknown GSD types in Egypt and age- and sex-matched controls suggested altered mental and physical abilities in these patients[143]. Earlier diagnosis has been suggested to result in better QoL in those with hepatic GSDs[144]. Moreover, management can also affect QoL. For instance, empagliflozin has been suggested to improve QoL of both patients with GSD Ib and their caregivers[108].

Individuals with late-onset Pompe disease have been described to be considerably affected on physical health domains of the SF-36 survey but have slightly lower mental health domain scores compared with the general population[145]. Adults with Pompe disease receiving only supportive care have an estimated 17% lower health-related QoL measured by the EQ-5D instrument than the general Dutch population[146]. Moreover, a survey in China reported worse QoL and physical health in adults with late-onset Pompe disease compared with individuals with other rare diseases and emphasized the value of employment and social engagement for QoL[133]. In a meta-analysis of late-onset Pompe disease, use of ERT was suggested to positively affect physical QoL[147]. Additionally, a literature review of ERT in late-onset Pompe disease summarizes several studies that included QoL assessments[148]. Recent data from a phase III double-blind, randomized clinical trial in the extension period suggest that individuals taking avalglucosidase alfa maintained improvements in health-related QoL[149]. Consistent with the notion that effective ERT treatment may support improved QoL in individuals with late-onset Pompe disease, high, sustained antibody titres (which hinder ERT efficacy) were reported to be associated with a decline clinically that corresponded with changes in lung function, motor function and QoL[99]. The use of PROs can inform our management of individuals with GSDs, as shown in studies of late-onset Pompe disease[150–152].

Caregiver quality of life

Caregiver burden has been reported in caregivers of patients with Pompe disease; however, caregivers also value the ability to care for loved ones[153]. Caregivers of individuals with late-onset Pompe disease have been reported to have problems with mental health (50%), physical health (40%), and relationships and finances (<20%)[154]. In a questionnaire study in Egypt, the parents of children with GSDs (hepatic and unknown types) had altered mental and physical abilities compared with sex-matched parents of healthy children[143]. Parents of children with GSD I have also reported greater parenting stress and distress compared with parents of healthy children[140]. Caregiver QoL is likely affected in other GSDs, although this requires further investigation.

Outlook

Diagnosis and monitoring

Despite improvements in diagnosis and treatment of GSDs, subtle aspects of phenotypes and long-term sequelae are still being characterized, and treatments for some disorders are not yet available. Our understanding of the natural history of GSDs is improving, and advances in disease monitoring are important. As previously mentioned, CGM can be used in some hepatic GSDs. More recently, continuous ketone monitoring is being considered as a potential tool for patients at risk of ketoacidosis[155], and such monitoring may be promising for some patients with liver GSDs. Moreover, measuring biotinidase activity in those with hepatic GSDs has been evaluated as it is higher than normal in individuals with hepatic GSDs for reasons that are not well understood[156]. Biotinidase activity is higher in individuals with elevated triglycerides and is below normal in individuals with liver fibrosis and cirrhosis[156]. Because of these associations, changes in biotinidase activity over time could signal a metabolic process (such as fatty acid synthesis or anomalies of gluconeogenesis) or worsening liver disease[156]. Further studies are needed to determine the role of biotinidase activity measurements in monitoring patients with hepatic GSD[156].

New therapies and approaches

For many decades, management of GSDs was largely focused on disease surveillance and avoiding metabolic decompensation. Although some standard therapies, such as ERT in Pompe disease and empagliflozin in GSD Ib, are available, the efficacy of these treatments is reduced in some patients, such as ERT in those with CRIM-negative status. Further, data have indicated that despite being CRIM positive, up to a third or more of CRIM-positive patients with infantile-onset Pompe disease treated with ERT have high sustained antibody titres or sustained intermediate titres[97,157,158]. A retrospective analysis has indicated that regardless of CRIM status, individuals with infantile-onset Pompe disease with high sustained antibodies have a poorer ERT response[97]. Various approaches to immune tolerance have been studied in ERT-naive, CRIM-positive patients with infantile-onset Pompe disease including transient low-dose methotrexate[158] and a short course of rituximab, methotrexate and/or intravenous immunoglobulin (IVIG)[159]. Given the potential for immune tolerance induction to improve efficacy of ERT in CRIM-positive patients with infantile-onset Pompe disease, others have acknowledged a need to determine how to predict which CRIM-positive patients with infantile-onset Pompe disease are at risk

of developing high sustained antibody titres[97,157] and acknowledged a need for large longitudinal studies of immune tolerance induction in these infants.

Several other treatments for GSDs are in development (Fig. 4). Clinical trials are evaluating the use of adeno-associated virus (AAV)-mediated gene therapy in GSD Ia (NCT05139316) and Pompe disease

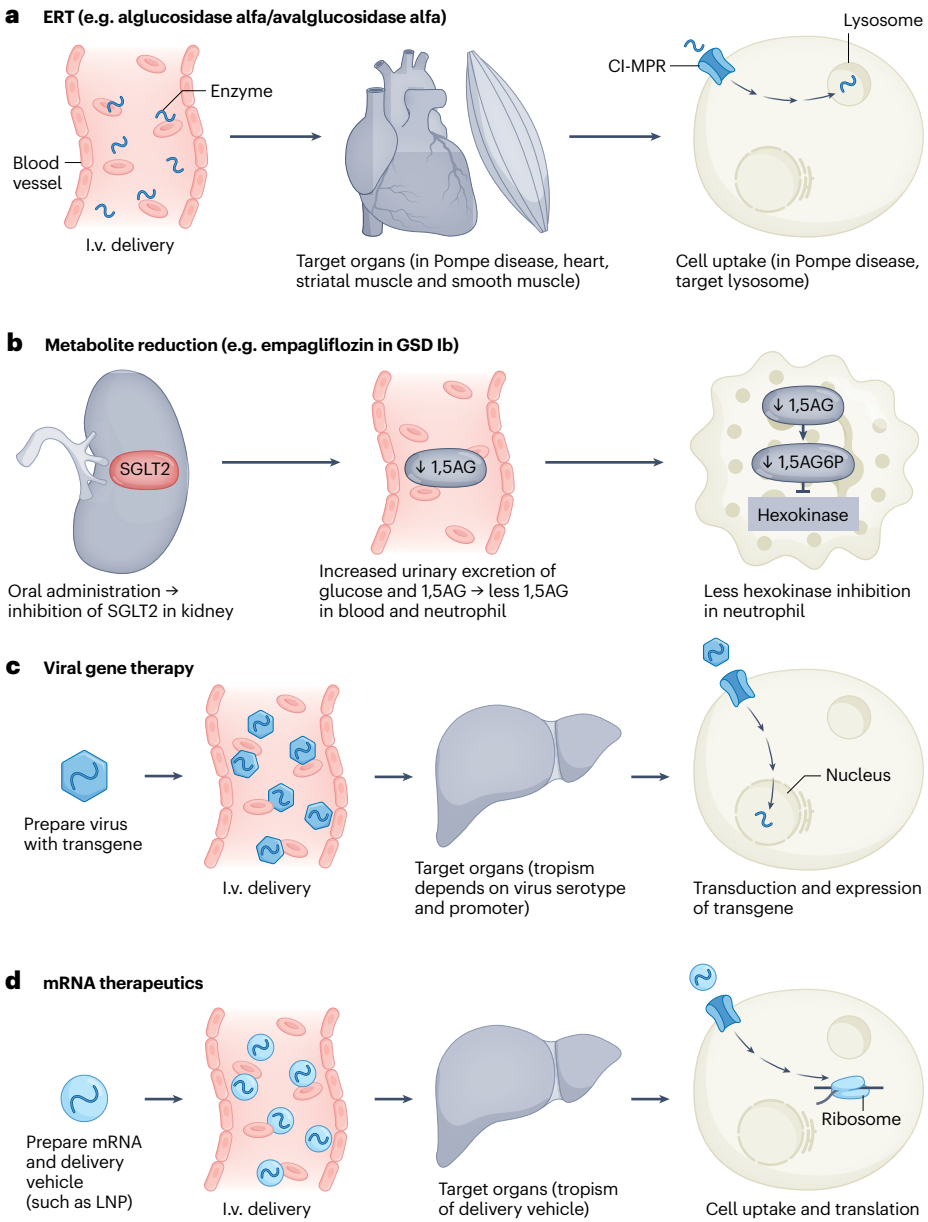

Fig. 4 | Standard treatments and investigational therapeutics for GSDs. For therapeutics illustrated in the figure, mechanisms of action and cellular trafficking are very simplified. Mechanisms, trafficking and other pertinent topics are described in the literature for enzyme replacement therapy (ERT)[242,243], viral gene therapy[244,245] and mRNA therapeutics[246,247]. **a**, ERT is standard of care for individuals with Pompe disease. Exogenous enzyme is administered (intravenously (i.v.) in this example of Pompe disease), following which, cells in the target organs (such as heart and striatal muscle) take up the enzyme via the cation-independent mannose-6-phosphate receptor (CI-MPR). The enzyme is then transported to the lysosome. **b**, Empagliflozin has been repurposed for the treatment of neutropenia and neutrophil dysfunction in glycogen storage disease (GSD) Ib. This drug inhibits sodium–glucose cotransporter 2 (SGLT2) in the kidney, thereby increasing urinary excretion of glucose and 1,5-anhydroglucitol (1,5AG). This increased excretion leads to less accumulation of the toxic metabolite 1,5-anhydroglucitol-6-phosphate (1,5AG6P). **c**, Viral gene transfer therapy is an investigational therapy for GSDs. Several organs and tissues can be targeted by viral vectors, and the tropism depends on the type of virus and the specific promoter used. In this example, i.v. administration is illustrated. For examples, the liver has been targeted in GSD Ia viral gene therapy trials, and either muscle or the liver have been targeted in trials in Pompe disease. **d**, mRNA therapies involve use of a delivery vehicle that has tissue specificity, resulting in uptake of the mRNA by cells, followed by translation to produce a protein of interest, such as an enzyme that is deficient. In this example, i.v. administration is illustrated. LNP, lipid nanoparticle.

(NCT03533673, NCT05567627, NCT04174105, NCT04093349)[160]. Viral serotypes and promoters with tissue-specific expression are leveraged for organ specificity, and diverse approaches are being studied[161,162]. For example, in late-onset Pompe disease, gene therapy can target muscle tissue. Other studies focus on transduction of hepatocytes to produce enzyme that is secreted and available to muscle tissue at constant levels. Liver-directed AAV therapy could also mitigate high antibody titres to the exogenous enzyme[161,163]. Pre-existing neutralizing antibodies to AAV may exclude individuals from gene therapy trials. There has been diverse research to investigate ways to decrease the effects of pre-existing anti-AAV antibodies. Such strategies have been reviewed[164] and include direct delivery of virus to the target organ, increasing dose, empty capsid delivery, modifying the capsid, immunosuppression, enzymes that cleave antibodies and other mechanisms[164]. Clinical trials of mRNA therapeutics for GSDs have been carried out, including GSD Ia (NCT05095727) and GSD III (NCT04990388). Anaplerotic approaches are being studied in the hepatic GSDs, providing Krebs intermediates as a glucose-sparing energy source. Building on recent precedent for innovative, effective treatments that address the fundamental molecular defects, such as ERT, studies are taking myriad mechanistic approaches. For example, in December 2022 the first in utero administration of ERT for a fetus with CRIM-negative infantile-onset Pompe disease was reported[165].

Of note, progress in the care of individuals with GSDs provides broadly relevant insight into multiple aspects of health care for people with other rare diseases. Research of GSD therapeutics models effective orphan drug development. In addition, the care of individuals with GSDs will continue to evolve and improve with organization of centres of excellence to foster a multidisciplinary approach to management. In recent years, individuals with GSDs have harnessed the growing capacity of telemedicine, a framework that has broad implications for other genetic conditions[166]. The ability of self-monitoring technologies, such as glucometers and CGM, makes this care model a good fit for certain patients with hepatic GSDs. Improvement in CGM devices may also help monitoring during clinical trials. The involvement of patients with GSDs and their families in the health-care process is fundamentally important to positive outcomes.

Unmet needs and future directions

Some individuals with GSDs have unmet care needs. Some GSDs have only recently been described, and further research is needed to identify the phenotypic features and natural histories of these complex diseases. Evidence-based national and international guidelines are needed for patient care in all GSDs. Such guidelines will need to be updated as our understanding of the conditions and progress in management improve. Moreover, some very well-described GSDs still lack effective treatments that target the biochemical defect, and patients with these disorders have poor prognosis.

Nonetheless, the future of care for individuals affected with GSDs is hopeful. An international collaboration surveyed patients, caregivers and health-care professionals to establish 11 research priorities for hepatic GSDs[167]. This work addresses unmet needs and can inform upcoming studies. Internationally, translational work and randomized controlled trials of investigational therapies are improving outcomes. At the interface of robust clinical trial research and patient engagement with cutting-edge care models, meaningful advances are being made to the longevity and QoL of patients with GSDs.

Published online: 07 September 2023

References

1. Ferreira, C. R., Rahman, S., Keller, M., Zschocke, J. & Group, I. A. An international classification of inherited metabolic disorders (ICIMD). *J. Inherit. Metab. Dis.* **44**, 164–177 (2021).
2. Brown, L. M. et al. Evaluation of glycogen storage disease as a cause of ketotic hypoglycemia in children. *J. Inherit. Metab. Dis.* **38**, 489–493 (2015).
3. Haring, M. P. D. et al. High childhood serum triglyceride concentrations associate with hepatocellular adenoma development in patients with glycogen storage disease type Ia. *JHEP Rep.* **4**, 100512 (2022).
4. Derks, T. G. J. et al. The potential of dietary treatment in patients with glycogen storage disease type IV. *J. Inherit. Metab. Dis.* **44**, 693–704 (2021).
5. Santalla, A. et al. Genotypic and phenotypic features of all Spanish patients with McArdle disease: a 2016 update. *BMC Genomics* **18**, 819 (2017).
6. Bruno, C. et al. McArdle disease: the mutation spectrum of *PYGM* in a large Italian cohort. *Hum. Mutat.* **27**, 718 (2006).
7. Lucia, A. et al. Clinical practice guidelines for glycogen storage disease V & VII (McArdle disease and Tarui disease) from an international study group. *Neuromusc. Disord.* **31**, 1296–1310 (2021).
Clinical practice guidelines based on expert opinions for GSD V and GSD VII.
8. Herbert, M. et al. Phosphorylase Kinase Deficiency. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK55061/ (updated 1 Nov 2018).
9. Kishnani, P. S. et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **21**, 772–789 (2019).
Clinical practice guidelines based on expert opinions for GSD VI and GSD IX diagnosis and management.
10. Cho, S. Y., Lam, C. W., Tong, S. F. & Siu, W. K. X-linked glycogen storage disease IXa manifested in a female carrier due to skewed X chromosome inactivation. *Clin. Chim. Acta* **426**, 75–78 (2013).
11. Schreuder, A. B. et al. Glycogen Storage Disease Type III. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK26372/ (updated 6 Jan 2022).
12. Kishnani, P. S. et al. Glycogen storage disease type III diagnosis and management guidelines. *Genet. Med.* **12**, 446–463 (2010).
Clinical practice guidelines based on expert opinion for GSD III diagnosis and management.
13. Martinez, M. et al. Infantile-onset Pompe disease with neonatal debut: a case report and literature review. *Medicine* **96**, e9186 (2017).
14. Dashty, M. A quick look at biochemistry: carbohydrate metabolism. *Clin. Biochem.* **46**, 1339–1352 (2013).
15. Adeva-Andany, M. M., Gonzalez-Lucan, M., Donapetry-Garcia, C., Fernandez-Fernandez, C. & Ameneiros-Rodriguez, E. Glycogen metabolism in humans. *BBA Clin.* **5**, 85–100 (2016).
16. Kanungo, S., Wells, K., Tribett, T. & El-Gharbawy, A. Glycogen metabolism and glycogen storage disorders. *Ann. Transl Med.* **6**, 474 (2018).
17. Han, H. S., Kang, G., Kim, J. S., Choi, B. H. & Koo, S. H. Regulation of glucose metabolism from a liver-centric perspective. *Exp. Mol. Med.* **48**, e218 (2016).
Provides a useful description of hormonal regulation of hepatic glucose metabolism.
18. Jiang, G. & Zhang, B. B. Glucagon and regulation of glucose metabolism. *Am. J. Physiol. Endocrinol. Metab.* **284**, E671–E678 (2003).
19. Ruderman, N. B., Aoki, T. T. & Cahill, G. F. in *Gluconeogenesis: Its Regulation in Mammalian Species* (eds Hanson, R. W. & Mehlman, M. A.) 515–530 (Wiley, 1976).
20. Sass, J. O. & Grünert, S. C. in *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases* (eds Blau, N., Duran, M., Gibson, K. M. & Dionisi-Vici, C.) 361–371 (Springer, 2014).
21. Ferrier, D. R. in *Lippincott Illustrated Reviews: Biochemistry* 7th edn Ch. 24 321–336 (Wolters Kluwer, 2017).
This book chapter, entitled 'The feed–fast cycle', provides a useful overview of different energy source contributions as individuals transition from postprandial to fasting states.
22. Herszberg, B. et al. A *GYS1* gene mutation is highly associated with polysaccharide storage myopathy in Cob Normand draught horses. *Anim. Genet.* **40**, 94–96 (2009).
23. Firshman, A. M., Valberg, S. J., Bender, J. B., Annandale, E. J. & Hayden, D. W. Comparison of histopathologic criteria and skeletal muscle fixation techniques for the diagnosis of polysaccharide storage myopathy in horses. *Vet. Pathol.* **43**, 257–269 (2006).
24. Hedberg-Oldfors, C. & Oldfors, A. Polyglucosan storage myopathies. *Mol. Asp. Med.* **46**, 85–100 (2015).
25. Martín, M. A. et al. Glycogen Storage Disease Type V. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK1344/ (updated 20 Jun 2019).
26. Echaniz-Laguna, A. et al. A new glycogen storage disease caused by a dominant *PYGM* mutation. *Ann. Neurol.* **88**, 274–282 (2020).
27. Brushia, R. J. & Walsh, D. A. Phosphorylase kinase: the complexity of its regulation is reflected in the complexity of its structure. *Front. Biosci.* **4**, D618–D641 (1999).
28. Zhai, L., Feng, L., Xia, L., Yin, H. & Xiang, S. Crystal structure of glycogen debranching enzyme and insights into its catalysis and disease-causing mutations. *Nat. Commun.* **7**, 11229 (2016).
29. Van Hoof, F. & Hers, H. G. The subgroups of type 3 glycogenosis. *Eur. J. Biochem.* **2**, 265–270 (1967).
30. Shen, J. et al. Mutations in exon 3 of the glycogen debranching enzyme gene are associated with glycogen storage disease type III that is differentially expressed in liver and muscle. *J. Clin. Invest.* **98**, 352–357 (1996).

31. Altassan, R. et al. International consensus guidelines for phosphoglucomutase 1 deficiency (PGM1-CDG): diagnosis, follow-up, and management. *J. Inherit. Metab. Dis.* **44**, 148–163 (2021).
Guidelines based on expert opinions for diagnosis, follow-up and management of PGM1-CDG.
32. Kishnani, P. S. et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American college of medical genetics and genomics. *Genet. Med.* **16**, e1 (2014).
Clinical practice guidelines based on expert opinions for GSD I diagnosis and management.
33. Boztug, K. et al. A syndrome with congenital neutropenia and mutations in G6PC3. *N. Engl. J. Med.* **360**, 32–43 (2009).
34. Burchell, A., Allan, B. B. & Hume, R. Glucose-6-phosphatase proteins of the endoplasmic reticulum. *Mol. Membr. Biol.* **11**, 217–227 (1994).
35. Kishnani, P. S. et al. Pompe disease diagnosis and management guideline. *Genet. Med.* **8**, 267–288 (2006).
Clinical practice guidelines based on expert opinions for diagnosis and management of Pompe disease.
36. Zampieri, S. et al. Splicing mutations in glycogen-storage disease type II: evaluation of the full spectrum of mutations and their relation to patients' phenotypes. *Eur. J. Hum. Genet.* **19**, 422–431 (2011).
37. Kroos, M., Hoogeveen-Westerveld, M., van der Ploeg, A. & Reuser, A. J. The genotype–phenotype correlation in Pompe disease. *Am. J. Med. Genet. C. Semin. Med. Genet.* **160C**, 59–68 (2012).
38. Akman, H. O., Oldfors, A. & DiMauro, S. in *Neuromuscular Disorders of Infancy, Childhood, and Adolescence* (eds Darras, B. T., Jones, H. R., Jr, Ryan, M. M. & DeVivo, D. C.) 735–760 (Elsevier, 2015).
39. Tarui, S. et al. Phosphofructokinase deficiency in skeletal muscle. a new type of glycogenosis. *Biochem. Biophys. Res. Commun.* **19**, 517–523 (1965).
40. Haller, R. G. & Lewis, S. F. Glucose-induced exertional fatigue in muscle phosphofructokinase deficiency. *N. Engl. J. Med.* **324**, 364–369 (1991).
41. Raben, N. & Sherman, J. B. Mutations in muscle phosphofructokinase gene. *Hum. Mutat.* **6**, 1–6 (1995).
42. Brown, G. K. Glucose transporters: structure, function and consequences of deficiency. *J. Inherit. Metab. Dis.* **23**, 237–246 (2000).
43. Rake, J. P. et al. Guidelines for management of glycogen storage disease type I – European Study on Glycogen Storage Disease type I (ESGSD I). *Eur. J. Pediatr.* **161**, S112–S119 (2002).
Guidelines based on expert opinions for GSD I from the European Study on Glycogen Storage Disease Type I.
44. Visser, G. et al. Consensus guidelines for management of glycogen storage disease type 1b – European Study on Glycogen Storage Disease Type 1. *Eur. J. Pediatr.* **161**, S120–S123 (2002).
Consensus guidelines based on expert opinions for management of GSD Ib, from the European Study on Glycogen Storage Disease Type 1.
45. Koch, R. L. et al. Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: a clinical practice resource. *Mol. Genet. Metab.* **138**, 107525 (2023).
Clinical practice guidelines based on expert opinions for GSD IV diagnosis and managment.
46. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **17**, 405–424 (2015).
47. Nykamp, K. et al. Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. *Genet. Med.* **19**, 1105–1117 (2017).
48. Kazemi-Esfarjani, P., Skomorowska, E., Jensen, T. D., Haller, R. G. & Vissing, J. A nonischemic forearm exercise test for McArdle disease. *Ann. Neurol.* **52**, 153–159 (2002).
49. Sluiter, W. et al. Rapid ultraperformance liquid chromatography-tandem mass spectrometry assay for a characteristic glycogen-derived tetrasaccharide in Pompe disease and other glycogen storage diseases. *Clin. Chem.* **58**, 1139–1147 (2012).
50. Young, S. P. et al. Assessing disease severity in Pompe disease: the roles of a urinary glucose tetrasaccharide biomarker and imaging techniques. *Am. J. Med. Genet. C. Semin. Med. Genet.* **160C**, 50–58 (2012).
51. Heiner-Fokkema, M. R. et al. The multiple faces of urinary glucose tetrasaccharide as biomarker for patients with hepatic glycogen storage diseases. *Genet. Med.* **22**, 1915–1916 (2020).
52. Paesold-Burda, P., Baumgartner, M. R., Santer, R., Bosshard, N. U. & Steinmann, B. Elevated serum biotinidase activity in hepatic glycogen storage disorders — a convenient biomarker. *J. Inherit. Metab. Dis.* **30**, 896–902 (2007).
53. Scalco, R. S. et al. Misdiagnosis is an important factor for diagnostic delay in McArdle disease. *Neuromuscul. Disord.* **27**, 852–855 (2017).
54. Lukacs, Z. et al. Prevalence of Pompe disease in 3,076 patients with hyperCKemia and limb-girdle muscular weakness. *Neurology* **87**, 295–298 (2016).
55. Topf, A. et al. Sequential targeted exome sequencing of 1001 patients affected by unexplained limb-girdle weakness. *Genet. Med.* **22**, 1478–1488 (2020).
56. Kemper, A. R. et al. Decision-making process for conditions nominated to the recommended uniform screening panel: statement of the US department of health and human services secretary's advisory committee on heritable disorders in newborns and children. *Genet. Med.* **16**, 183–187 (2014).
57. Keutzer, J. M. Establishing pompe disease newborn screening: the role of industry. *Int. J. Neonatal Screen.* **6**, 55 (2020).
58. Chien, Y. H. et al. Early detection of Pompe disease by newborn screening is feasible: results from the Taiwan screening program. *Pediatrics* **122**, e39–e45 (2008).
59. Goomber, S. et al. Development of a clinically validated in vitro functional assay to assess pathogenicity of novel GAA variants in patients with Pompe disease identified via newborn screening. *Front. Genet.* **13**, 1001154 (2022).
60. Prakash, S., Penn, J. D., Jackson, K. E. & Dean, L. W. Newborn screening for Pompe disease: parental experiences and follow-up care for a late-onset diagnosis. *J. Genet. Couns.* **31**, 1404–1420 (2022).
61. Huggins, E. et al. Early clinical phenotype of late onset Pompe disease: lessons learned from newborn screening. *Mol. Genet. Metab.* **135**, 179–185 (2022).
62. Yoo, H. W., Shin, Y. L., Seo, E. J. & Kim, G. H. Identification of a novel mutation in the *GLUT2* gene in a patient with Fanconi–Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia. *Eur. J. Pediatr.* **161**, 351–353 (2002).
63. Muller, D., Santer, R., Krawinkel, M., Christiansen, B. & Schaub, J. Fanconi–Bickel syndrome presenting in neonatal screening for galactosaemia. *J. Inherit. Metab. Dis.* **20**, 607–608 (1997).
64. Peduto, A. et al. A novel mutation in the *GLUT2* gene in a patient with Fanconi–Bickel syndrome detected by neonatal screening for galactosaemia. *J. Inherit. Metab. Dis.* **27**, 279–280 (2004).
65. Esquerda, M. et al. Ethical questions concerning newborn genetic screening. *Clin. Genet.* **99**, 93–98 (2021).
66. Bick, D. et al. An online compendium of treatable genetic disorders. *Am. J. Med. Genet. C. Semin. Med. Genet.* **187**, 48–54 (2021).
67. Herbert, M. et al. Role of continuous glucose monitoring in the management of glycogen storage disorders. *J. Inherit. Metab. Dis.* **41**, 917–927 (2018).
68. Peeks, F. et al. A retrospective in-depth analysis of continuous glucose monitoring datasets for patients with hepatic glycogen storage disease: recommended outcome parameters for glucose management. *J. Inherit. Metab. Dis.* **44**, 1136–1150 (2021).
69. Rossi, A. et al. A prospective study on continuous glucose monitoring in glycogen storage disease type Ia: toward glycemic targets. *J. Clin. Endocrinol. Metab.* **107**, e3612–e3623 (2022).
70. Kaiser, N. et al. Glycemic control and complications in glycogen storage disease type I: results from the Swiss registry. *Mol. Genet. Metab.* **126**, 355–361 (2019).
71. Lee, P. J. Glycogen storage disease type I: pathophysiology of liver adenomas. *Eur. J. Pediatr.* **161**, S46–S49 (2002).
72. Franco, L. M. et al. Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. *J. Inherit. Metab. Dis.* **28**, 153–162 (2005).
73. Okata, Y., Hatakeyama, T., Bitoh, Y., Aida, Y. & Yuichiro, T. Hepatocellular carcinoma with glycogen storage disease type 1a. *Pediatr. Int.* **62**, 744–745 (2020).
74. Verbeek, R. J. et al. Muscle ultrasound in patients with glycogen storage disease types I and III. *Ultrasound Med. Biol.* **42**, 133–142 (2016).
75. Diaz-Manera, J., Walter, G. & Straub, V. Skeletal muscle magnetic resonance imaging in Pompe disease. *Muscle Nerve* **63**, 640–650 (2021).
76. Vissing, J. & Haller, R. G. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N. Engl. J. Med.* **349**, 2503–2509 (2003).
A randomized, placebo-controlled crossover study of patients with GSD V that suggests that sucrose ingestion before exercise improves exercise tolerance.
77. Haller, R. G. & Vissing, J. No spontaneous second wind in muscle phosphofructokinase deficiency. *Neurology* **62**, 82–86 (2004).
A study of patients with GSD VII and GSD V reinforces the absence of spontaneous second-wind phenomenon in GSD VII.
78. Weinstein, D. A., Steuerwald, U., De Souza, C. F. M. & Derks, T. G. J. Inborn errors of metabolism with hypoglycemia: glycogen storage diseases and inherited disorders of gluconeogenesis. *Pediatr. Clin. North. Am.* **65**, 247–265 (2018).
79. Amalfitano, A. et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. *Genet. Med.* **3**, 132–138 (2001).
80. Winkel, L. P. et al. Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. *Muscle Nerve* **27**, 743–751 (2003).
81. Kishnani, P. S. et al. Recombinant human acid α-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* **68**, 99–109 (2007).
82. Klinge, L. et al. Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: results of a phase II clinical trial. *Neuromuscul. Disord.* **15**, 24–31 (2005).
83. Van den Hout, H. et al. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. *Lancet* **356**, 397–398 (2000).
84. Van den Hout, J. M. et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. *Pediatrics* **113**, e448–e457 (2004).
85. Van den Hout, J. M. et al. Enzyme therapy for pompe disease with recombinant human alpha-glucosidase from rabbit milk. *J. Inherit. Metab. Dis.* **24**, 266–274 (2001).
86. van der Ploeg, A. T. et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N. Engl. J. Med.* **362**, 1396–1406 (2010).
87. van der Ploeg, A. T. et al. Open-label extension study following the late-onset treatment study (LOTS) of alglucosidase alfa. *Mol. Genet. Metab.* **107**, 456–461 (2012).
88. 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.* **257**, 91–97 (2010).

89. Gungor, D. et al. Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. *J. Inherit. Metab. Dis.* **39**, 253–260 (2016).
90. Diaz-Manera, J. et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial. *Lancet Neurol.* **20**, 1012–1026 (2021).
91. Dimachkie, M. M. et al. Long-term safety and efficacy of avalglucosidase alfa in patients with late-onset Pompe disease. *Neurology* **99**, e536–e548 (2022).
92. Kishnani, P. S. et al. Safety and efficacy of avalglucosidase alfa in individuals with infantile-onset Pompe disease enrolled in the phase 2, open-label Mini-COMET study: the 6-month primary analysis report. *Genet. Med.* **25**, 100328 (2022).
93. Dhillon, S. Avalglucosidase alfa: first approval. *Drugs* **81**, 1803–1809 (2021).
94. Punnoose, A. R., Jeng, L. J. B., Maynard, J. W. & Review, T. Regulatory news: avalglucosidase alfa-ngpt (Nexviazyme) for late-onset Pompe disease-FDA approval summary. *J. Inherit. Metab. Dis.* **45**, 1015–1017 (2022).
95. Schoser, B. et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial. *Lancet Neurol.* **20**, 1027–1037 (2021).
96. Blair, H. A. Cipaglucosidase alfa: first approval. *Drugs* **83**, 739–745 (2023).
97. Banugaria, S. G. et al. The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. *Genet. Med.* **13**, 729–736 (2011).
98. Berrier, K. L. et al. CRIM-negative infantile Pompe disease: characterization of immune responses in patients treated with ERT monotherapy. *Genet. Med.* **17**, 912–918 (2015).
99. Patel, T. T. et al. The impact of antibodies in late-onset Pompe disease: a case series and literature review. *Mol. Genet. Metab.* **106**, 301–309 (2012).
100. Nino, M. Y. et al. Extension of the Pompe mutation database by linking disease-associated variants to clinical severity. *Hum. Mutat.* **40**, 1954–1967 (2019).
101. Bali, D. S. et al. Predicting cross-reactive immunological material (CRIM) status in Pompe disease using GAA mutations: lessons learned from 10 years of clinical laboratory testing experience. *Am. J. Med. Genet. C. Semin. Med. Genet.* **160C**, 40–49 (2012).
102. Poelman, E. et al. High sustained antibody titers in patients with classic infantile pompe disease following immunomodulation at start of enzyme replacement therapy. *J. Pediatr.* **195**, 236–243.e3 (2018).
103. Li, C. et al. Transforming the clinical outcome in CRIM-negative infantile Pompe disease identified via newborn screening: the benefits of early treatment with enzyme replacement therapy and immune tolerance induction. *Genet. Med.* **23**, 845–855 (2021).
104. Banugaria, S. G. et al. Bortezomib in the rapid reduction of high sustained antibody titers in disorders treated with therapeutic protein: lessons learned from Pompe disease. *Genet. Med.* **15**, 123–131 (2013).
105. Koeberl, D. D. et al. Improved muscle function in a phase I/II clinical trial of albuterol in Pompe disease. *Mol. Genet. Metab.* **129**, 67–72 (2020).
106. Veiga-da-Cunha, M., Wortmann, S. B., Grunert, S. C. & Van Schaftingen, E. Treatment of the neutropenia associated with GSD1b and G6PC3 deficiency with SGLT2 inhibitors. *Diagnostics* **13**, 1803 (2023).
107. Grünert, S. C. et al. Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. *Genet. Med.* **24**, 1781–1788 (2022). **Questionnaire study highlighting both safety and efficacy of empagliflozin in patients with GSD Ib**.
108. Grunert, S. C. et al. Patient-reported outcomes on empagliflozin treatment in glycogen storage disease type Ib: an international questionnaire study. *JIMD Rep* **64**, 252–258 (2023). **Questionnaire study describing patient-reported outcomes of empagliflozin use in GSD Ib**.
109. Grünert, S. C. et al. Improved inflammatory bowel disease, wound healing and normal oxidative burst under treatment with empagliflozin in glycogen storage disease type Ib. *Orphanet J. Rare Dis.* **15**, 218 (2020).
110. Malatack, J. J. et al. Liver transplantation for type I glycogen storage disease. *Lancet* **1**, 1073–1075 (1983).
111. Piper, J. B. et al. Living related liver transplantation in children: a report of the first 58 recipients at the university of Chicago. *Transpl. Int.* **7**, S111–S113 (1994).
112. Beyzaei, Z. et al. Liver transplantation in glycogen storage disease: a single-center experience. *Orphanet J. Rare Dis.* **17**, 127 (2022).
113. Chan, Y. C. et al. Modifiable factors affecting renal preservation in type I glycogen storage disease after liver transplantation: a single-center propensity-match cohort study. *Orphanet J. Rare Dis.* **16**, 423 (2021).
114. Yuen, W. Y., Quak, S. H., Aw, M. M. & Karthik, S. V. Long-term outcome after liver transplantation in children with type 1 glycogen storage disease. *Pediatr. Transpl.* **25**, e13872 (2021).
115. Irie, R. et al. Outcome for pediatric recipients of macrosteatotic liver grafts from living donors. *Liver Transpl.* **26**, 899–905 (2020).
116. Shimizu, S. et al. Longterm outcomes of living donor liver transplantation for glycogen storage disease type 1b. *Liver Transpl.* **26**, 57–67 (2020).
117. Troisi, R. I., Elsheikh, Y. M., Shagrani, M. A. & Broering, D. First fully laparoscopic donor hepatectomy for pediatric liver transplantation using the indocyanine green near-infrared fluorescence imaging in the Mmiddle East: a case report. *Ann. Saudi Med.* **34**, 354–357 (2014).
118. Moosburner, S. et al. Over 30 years of pediatric liver transplantation at the Charite-Universitatsmedizin Berlin. *J. Clin. Med.* **11**, 900 (2022).
119. Labrune, P. Glycogen storage disease type I: indications for liver and/or kidney transplantation. *Eur. J. Pediatr.* **161**, S53–S55 (2002).
120. Davis, M. K. & Weinstein, D. A. Liver transplantation in children with glycogen storage disease: controversies and evaluation of the risk/benefit of this procedure. *Pediatr. Transpl.* **12**, 137–145 (2008).
121. Matern, D. et al. Liver transplantation for glycogen storage disease types I, III, and IV. *Eur. J. Pediatr.* **158**, S43–S48 (1999).
122. Martin, A. P. et al. Successful staged kidney and liver transplantation for glycogen storage disease type Ib: a case report. *Transpl. Proc.* **38**, 3615–3619 (2006).
123. Lee, P. J., Muiesan, P. & Heaton, N. Successful pregnancy after combined renal-hepatic transplantation in glycogen storage disease type Ia. *J. Inherit. Metab. Dis.* **27**, 537–538 (2004).
124. Belingheri, M. et al. Combined liver–kidney transplantation in glycogen storage disease Ia: a case beyond the guidelines. *Liver Transpl.* **13**, 762–764 (2007).
125. Maheshwari, A., Rankin, R., Segev, D. L. & Thuluvath, P. J. Outcomes of liver transplantation for glycogen storage disease: a matched-control study and a review of literature. *Clin. Transpl.* **26**, 432–436 (2012).
126. Magoulas, P. L. & El-Hattab, A. W. Glycogen Storage Disease Type IV. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK115333/ (updated 1 Aug 2019).
127. Murko, S. et al. Liver transplantation in glycogen storage disease type Ib: the role of SGLT2 inhibitors. *Mol. Genet. Metab. Rep.* **35**, 100977 (2023).
128. Rossi, A. et al. A generic emergency protocol for patients with inborn errors of metabolism causing fasting intolerance: A retrospective, single-center study and the generation of https://www.emergencyprotocol.net. *J. Inherit. Metab. Dis.* **44**, 1124–1135 (2021). **Describing a generic emergency protocol for individuals with inborn metabolic disease; this publication has resources that are broadly relevent to metabolic disorders**.
129. Bali, D. S. et al. Glycogen Storage Disease Type I. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK1312/ (updated 14 Oct 2021).
130. Bordoli, C., Murphy, E., Varley, I., Sharpe, G. & Hennis, P. A systematic review investigating the effectiveness of exercise training in glycogen storage diseases. *Ther. Adv. Rare Dis.* **3**, 26330040221076497 (2022).
131. Hennis, P. J. et al. Aerobic capacity and skeletal muscle characteristics in glycogen storage disease IIIa: an observational study. *Orphanet J. Rare Dis.* **17**, 28 (2022).
132. Derks, T. G. J. et al. Glycogen storage disease type ia: current management options, burden and unmet needs. *Nutrients* **13**, 3828 (2021).
133. Chen, S., Wang, J., Zhu, J., Chung, R. Y. & Dong, D. Quality of life and its contributors among adults with late-onset Pompe disease in China. *Orphanet J. Rare Dis.* **16**, 199 (2021).
134. Kansagra, S., Austin, S., DeArmey, S., Kishnani, P. S. & Kravitz, R. M. Polysomnographic findings in infantile Pompe disease. *Am. J. Med. Genet. A* **161A**, 3196–3200 (2013).
135. Shah, N. M., Sharma, L., Ganeshamoorthy, S. & Kaltsakas, G. Respiratory failure and sleep-disordered breathing in late-onset Pompe disease: a narrative review. *J. Thorac. Dis.* **12**, S235–S247 (2020).
136. Kansagra, S. et al. Longitudinal polysomnographic findings in infantile Pompe disease. *Am. J. Med. Genet. A* **167A**, 858–861 (2015).
137. Boentert, M., Drager, B., Glatz, C. & Young, P. Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset Pompe disease. *J. Clin. Sleep Med.* **12**, 1623–1632 (2016).
138. Venema, A. et al. A retrospective study of eating and psychosocial problems in patients with hepatic glycogen storage diseases and idiopathic ketotic hypoglycemia: towards a standard set of patient-reported outcome measures. *JIMD Rep.* **63**, 29–40 (2022).
139. Sechi, A. et al. Quality of life in adult patients with glycogen storage disease type I: results of a multicenter italian study. *JIMD Rep.* **14**, 47–53 (2014).
140. Storch, E. et al. Psychosocial functioning in youth with glycogen storage disease type I. *J. Pediatr. Psychol.* **33**, 728–738 (2008).
141. Rousseau-Nepton, I. et al. Sleep and quality of life of patients with glycogen storage disease on standard and modified uncooked cornstarch. *Mol. Genet. Metab.* **123**, 326–330 (2018).
142. Garbade, S. F. et al. Impact of glycogen storage disease type I on adult daily life: a survey. *Orphanet. J. Rare Dis.* **16**, 371 (2021). **Excellent example of work to elucidate factors affecting QoL in a GSD**.
143. Sobhy, G. A., El-Shabrawi, M. & Safar, H. A new perspective on the quality of life of children with glycogen storage diseases. *Pediatr. Gastroenterol. Hepatol. Nutr.* **25**, 321–331 (2022).
144. Massese, M., Tagliaferri, F., Dionisi-Vici, C. & Maiorana, A. Glycogen storage diseases with liver involvement: a literature review of GSD type 0, IV, VI, IX and XI. *Orphanet J. Rare Dis.* **17**, 241 (2022).
145. Hagemans, M. L. et al. Late-onset Pompe disease primarily affects quality of life in physical health domains. *Neurology* **63**, 1688–1692 (2004).
146. Kanters, T. A. et al. Burden of illness of Pompe disease in patients only receiving supportive care. *J. Inherit. Metab. Dis.* **34**, 1045–1052 (2011).
147. Dornelles, A. D. et al. A systematic review and meta-analysis of enzyme replacement therapy in late-onset Pompe disease. *J. Clin. Med.* **10**, 4828 (2021).
148. Toscano, A. & Schoser, B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. *J. Neurol.* **260**, 951–959 (2013).
149. Kishnani, P. S. et al. Efficacy and safety of avalglucosidase alfa in patients with late-onset pompe disease after 97 weeks: a phase 3 randomized clinical trial. *JAMA Neurol.* **80**, 558–567 (2023).

150. Hamed, A. et al. Qualitative interviews to improve patient-reported outcome measures in late-onset Pompe disease: the patient perspective. *Orphanet J. Rare Dis.* **16**, 428 (2021).
151. Harfouche, M. et al. Use of the patient-reported outcomes measurement information system (PROMIS(R)) to assess late-onset Pompe disease severity. *J. Patient Rep. Outcomes* **4**, 83 (2020).
152. Yuan, M. et al. Positive association between physical outcomes and patient-reported outcomes in late-onset Pompe disease: a cross sectional study. *Orphanet J. Rare Dis.* **15**, 232 (2020).
153. Kanters, T. A., van der Ploeg, A. T., Brouwer, W. B. F. & Hakkaart, L. The impact of informal care for patients with Pompe disease: an application of the CarerQol instrument. *Mol. Genet. Metab.* **110**, 281–286 (2013).
154. Schoser, B. et al. The humanistic burden of Pompe disease: are there still unmet needs? A systematic review. *BMC Neurol.* **17**, 202 (2017).
155. Jaromy, M. & Miller, J. D. Potential clinical applications for continuous ketone monitoring in the hospitalized patient with diabetes. *Curr. Diab. Rep.* **22**, 501–510 (2022).
156. El-Gharbawy, A. et al. Beyond predicting diagnosis: is there a role for measuring biotinidase activity in liver glycogen storage diseases? *Mol. Genet. Metab. Rep.* **31**, 100856 (2022).
157. Desai, A. K., Kazi, Z. B., Bali, D. S. & Kishnani, P. S. Characterization of immune response in cross-reactive immunological material (CRIM)-positive infantile Pompe disease patients treated with enzyme replacement therapy. *Mol. Genet. Metab. Rep.* **20**, 100475 (2019).
158. Kazi, Z. B. et al. An immune tolerance approach using transient low-dose methotrexate in the ERT-naive setting of patients treated with a therapeutic protein: experience in infantile-onset Pompe disease. *Genet. Med.* **21**, 887–895 (2019).
159. Desai, A. K., Baloh, C. H., Sleasman, J. W., Rosenberg, A. S. & Kishnani, P. S. Benefits of prophylactic short-course immune tolerance induction in patients with infantile Pompe disease: demonstration of long-term safety and efficacy in an expanded cohort. *Front. Immunol.* **11**, 1727 (2020).
160. Koeberl, D. D. et al. Gene therapy for glycogen storage diseases. *J. Inherit. Metab. Dis.* https://doi.org/10.1002/jimd.12654 (2023).
161. Kishnani, P. S., Sun, B. & Koeberl, D. D. Gene therapy for glycogen storage diseases. *Hum. Mol. Genet.* **28**, R31–R41 (2019).
162. Salabarria, S. M. et al. Advancements in AAV-mediated gene therapy for pompe disease. *J. Neuromuscul. Dis.* **7**, 15–31 (2020).
163. Sun, B., Brooks, E. D. & Koeberl, D. D. Preclinical development of new therapy for glycogen storage diseases. *Curr. Gene Ther.* **15**, 338–347 (2015).
164. Schulz, M. et al. Binding and neutralizing anti-AAV antibodies: detection and implications for rAAV-mediated gene therapy. *Mol. Ther.* **31**, 616–630 (2023).
165. Cohen, J. L. et al. In utero enzyme-replacement therapy for infantile-onset pompe's disease. *N. Engl. J. Med.* **387**, 2150–2158 (2022).
166. Venema, A., Peeks, F., Rossi, A., Jager, E. A. & Derks, T. G. J. Towards values-based healthcare for inherited metabolic disorders: an overview of current practices for persons with liver glycogen storage disease and fatty acid oxidation disorders. *J. Inherit. Metab. Dis.* **45**, 1018–1027 (2022).
167. Peeks, F. et al. Research priorities for liver glycogen storage disease: an international priority setting partnership with the James Lind Alliance. *J. Inherit. Metab. Dis.* **43**, 279–289 (2020).
168. Kamenets, E. A. et al. Hepatic glycogen synthase (GYS2) deficiency: seven novel patients and seven novel variants. *JIMD Rep.* **53**, 39–44 (2020).
169. Kasapkara, C. S. et al. The variable clinical phenotype of three patients with hepatic glycogen synthase deficiency. *J. Pediatr. Endocrinol. Metab.* **30**, 459–462 (2017).
170. Orho, M. et al. Mutations in the liver glycogen synthase gene in children with hypoglycemia due to glycogen storage disease type 0. *J. Clin. Invest.* **102**, 507–515 (1998).
171. Kollberg, G. et al. Cardiomyopathy and exercise intolerance in muscle glycogen storage disease 0. *N. Engl. J. Med.* **357**, 1507–1514 (2007).
172. Cameron, J. M. 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.* **98**, 378–382 (2009).
173. Musumeci, O. et al. A new phenotype of muscle glycogen synthase deficiency (GSD0B) characterized by an adult onset myopathy without cardiomyopathy. *Neuromuscul. Disord.* **32**, 582–589 (2022).
174. Visser, G. et al. Neutropenia, neutrophil dysfunction, and inflammatory bowel disease in glycogen storage disease type Ib: results of the European Study on Glycogen Storage Disease type I. *J. Pediatr.* **137**, 187–191 (2000).
Excellent description of GSD Ib neutropenia, neutrophil dysfunction and inflammatory bowel disease including disease course and frequency.
175. van der Ploeg, A. T. & Reuser, A. J. Pompe's disease. *Lancet* **372**, 1342–1353 (2008).
176. Chan, J. et al. The emerging phenotype of late-onset Pompe disease: a systematic literature review. *Mol. Genet. Metab.* **120**, 163–172 (2017).
177. Kiely, B. T. et al. A novel approach to characterize phenotypic variation in GSD IV: reconceptualizing the clinical continuum. *Front. Genet.* **13**, 992406 (2022).
178. Lucia, A. et al. McArdle disease: what do neurologists need to know? *Nat. Clin. Pract. Neurol.* **4**, 568–577 (2008).
179. Grünert, S. C., Hannibal, L. & Spiekerkoetter, U. The phenotypic and genetic spectrum of glycogen storage disease type VI. *Genes* **12**, 1205 (2021).
180. Degrassi, I. et al. Liver histology in children with glycogen storage disorders type VI and IX. *Dig. Liver Dis.* **53**, 86–93 (2021).
181. Fernandes, S. A., Cooper, G. E., Gibson, R. A. & Kishnani, P. S. Benign or not benign? Deep phenotyping of liver glycogen storage disease IX. *Mol. Genet. Metab.* **131**, 299–305 (2020).
182. Willems, P. J., Gerver, W. J., Berger, R. & Fernandes, J. The natural history of liver glycogenosis due to phosphorylase kinase deficiency: a longitudinal study of 41 patients. *Eur. J. Pediatr.* **149**, 268–271 (1990).
183. Yoshikuni, K., Tagami, H., Yamada, M., Sudo, K. & Kanno, T. Erythematosquamous skin lesions in hereditary lactate dehydrogenase m-subunit deficiency. *Arch. Dermatol.* **122**, 1420–1424 (1986).
184. Takayasu, S., Fujiwara, S. & Waki, T. Hereditary lactate dehydrogenase M-subunit deficiency: lactate dehydrogenase activity in skin lesions and in hair follicles. *J. Am. Acad. Dermatol.* **24**, 339–342 (1991).
185. Serrano-Lorenzo, P. et al. Clinical, biochemical, and molecular characterization of two families with novel mutations in the *LDHA* gene (GSD XI). *Genes* **13**, 1835 (2022).
186. Nazzari, G. & Crovato, F. Annually recurring acroerythema and hereditary lactate dehydrogenase M-subunit deficiency. *J. Am. Acad. Dermatol.* **27**, 262–263 (1992).
187. Takeo, N. et al. Hereditary lactate dehydrogenase M-subunit deficiency with late-developing pustular psoriasis-like lesions. *J. Dermatol.* **43**, 1429–1432 (2016).
188. Maekawa, M., Sudo, K., Kanno, T. & Li, S. S. Molecular characterization of genetic mutation in human lactate dehydrogenase-A (M) deficiency. *Biochem. Biophys. Res. Commun.* **168**, 677–682 (1990).
189. Nagata, N. et al. Glycogen storage myopathy with abnormal lactate dehydrogenase. *Neuropediatrics* **13**, 103–107 (1982).
190. Beutler, E. et al. Red cell aldolase deficiency and hemolytic anemia: a new syndrome. *Trans. Assoc. Am. Physicians* **86**, 154–166 (1973).
191. Hurst, J. A., Baraitser, M. & Winter, R. M. A syndrome of mental retardation, short stature, hemolytic anemia, delayed puberty, and abnormal facial appearance: similarities to a report of aldolase a deficiency. *Am. J. Med. Genet.* **28**, 965–970 (1987).
192. Miwa, S. et al. Two cases of red cell aldolase deficiency associated with hereditary hemolytic anemia in a Japanese family. *Am. J. Hematol.* **11**, 425–437 (1981).
193. Santoro, L. et al. A new phenotype of aldolase a deficiency in a 14 year-old boy with epilepsy and rhabdomyolysis – case report. *Ital. J. Pediatr.* **48**, 39 (2022).
194. Yao, D. C. et al. Hemolytic anemia and severe rhabdomyolysis caused by compound heterozygous mutations of the gene for erythrocyte/muscle isozyme of aldolase, ALDOA(Arg303X/Cys338Tyr). *Blood* **103**, 2401–2403 (2004).
195. Papadopoulos, C. et al. Aldolase a deficiency: report of new cases and literature review. *Mol. Genet. Metab. Rep.* **27**, 100730 (2021).
196. Kreuder, J. et al. Brief report: inherited metabolic myopathy and hemolysis due to a mutation in aldolase A. *N. Engl. J. Med.* **334**, 1100–1104 (1996).
197. Mamoune, A. et al. A thermolabile aldolase a mutant causes fever-induced recurrent rhabdomyolysis without hemolytic anemia. *PLoS Genet.* **10**, e1004711 (2014).
198. Comi, G. P. et al. Beta-enolase deficiency, a new metabolic myopathy of distal glycolysis. *Ann. Neurol.* **50**, 202–207 (2001).
199. Musumeci, O. et al. Recurrent rhabdomyolysis due to muscle beta-enolase deficiency: very rare or underestimated? *J. Neurol.* **261**, 2424–2428 (2014).
200. Wigley, R. et al. The need for biochemical testing in beta-enolase deficiency in the genomic era. *JIMD Rep.* **50**, 40–43 (2019).
201. Buch, A. E. et al. Energy metabolism during exercise in patients with beta-enolase deficiency (GSDXIII). *JIMD Rep.* **61**, 60–66 (2021).
202. Moslemi, A. R. et al. Glycogenin-1 deficiency and inactivated priming of glycogen synthesis. *N. Engl. J. Med.* **362**, 1203–1210 (2010).
203. Tegtmeyer, L. C. et al. Multiple phenotypes in phosphoglucomutase 1 deficiency. *N. Engl. J. Med.* **370**, 533–542 (2014).
204. Preisler, N. et al. Impaired glycogen breakdown and synthesis in phosphoglucomutase 1 deficiency. *Mol. Genet. Metab.* **122**, 117–121 (2017).
205. Santer, R., Schneppenheim, R., Suter, D., Schaub, J. & Steinmann, B. Fanconi-Bickel syndrome-the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. *Eur. J. Pediatr.* **157**, 783–797 (1998).
206. Baba, K. et al. A mild clinical phenotype with myopathic and hemolytic forms of phosphoglycerate kinase deficiency (PGK Osaka): a case report and literature review. *Intern. Med.* **61**, 3589–3594 (2022).
207. Echaniz-Laguna, A. et al. Phosphoglycerate kinase deficiency: a nationwide multicenter retrospective study. *J. Inherit. Metab. Dis.* **42**, 803–808 (2019).
208. Vissing, J. et al. Level of residual enzyme activity modulates the phenotype in phosphoglycerate kinase deficiency. *Neurology* **91**, e1077–e1082 (2018).
209. Sotiriou, E., Greene, P., Krishna, S., Hirano, M. & DiMauro, S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. *Muscle Nerve* **41**, 707–710 (2010).
210. Sakaue, S. et al. Early-onset parkinsonism in a pedigree with phosphoglycerate kinase deficiency and a heterozygous carrier: do PGK-1 mutations contribute to vulnerability to parkinsonism. *NPJ Parkinsons Dis.* **3**, 13 (2017).
211. Virmani, T. et al. Levodopa responsive parkinsonism in two patients with phosphoglycerate kinase deficiency. *Mov. Disord. Clin. Pract.* **1**, 240–242 (2014).
212. Morales-Briceno, H. et al. Parkinsonism in PGK1 deficiency implicates the glycolytic pathway in nigrostriatal dysfunction. *Parkinsonism Relat. Disord.* **64**, 319–323 (2019).
213. Tonin, P. et al. Phosphoglycerate kinase deficiency: biochemical and molecular genetic studies in a new myopathic variant (PGK Alberta). *Neurology* **43**, 387–391 (1993).
214. Ausems, M. G. et al. A diagnostic protocol for adult-onset glycogen storage disease type II. *Neurology* **52**, 851–853 (1999).
215. Meena, N. K. & Raben, N. Pompe disease: new developments in an old lysosomal storage disorder. *Biomolecules* **10**, 1339 (2020).
216. McAdams, A. J., Hug, G. & Bove, K. E. Glycogen storage disease, types I to X: criteria for morphologic diagnosis. *Hum. Pathol.* **5**, 463–487 (1974).

217. Maire, I., Baussan, C., Moatti, N., Mathieu, M. & Lemonnier, A. Biochemical diagnosis of hepatic glycogen storage diseases: 20 years French experience. *Clin. Biochem.* **24**, 169–178 (1991).
218. Perez, M. et al. The second wind phenomenon in very young McArdle's patients. *Neuromuscul. Disord.* **19**, 403–405 (2009).
219. Lu, S. Q. et al. Glycogen storage disease type VI can progress to cirrhosis: ten Chinese patients with GSD VI and a literature review. *J. Pediatr. Endocrinol. Metab.* **33**, 1321–1333 (2020).
220. Labrador, E. & Weinstein, D. A. Glycogen Storage Disease Type VI. *GeneReviews* [online] https://www.ncbi.nlm.nih.gov/books/NBK5941/ (updated 27 Nov 2019).
221. Kissel, J. T. et al. Physiologic assessment of phosphoglycerate mutase deficiency: incremental exercise test. *Neurology* **35**, 828–833 (1985).
222. Tsujino, S., Shanske, S., Sakoda, S., Fenichel, G. & DiMauro, S. The molecular genetic basis of muscle phosphoglycerate mutase (PGAM) deficiency. *Am. J. Hum. Genet.* **52**, 472–477 (1993).
223. Tonin, P. et al. Unusual presentation of phosphoglycerate mutase deficiency due to two different mutations in PGAM-M gene. *Neuromuscul. Disord.* **19**, 776–778 (2009).
224. DiMauro, S., Miranda, A. F., Khan, S., Gitlin, K. & Friedman, R. Human muscle phosphoglycerate mutase deficiency: newly discovered metabolic myopathy. *Science* **212**, 1277–1279 (1981).
225. Bresolin, N., Ro, Y. I., Reyes, M., Miranda, A. F. & DiMauro, S. Muscle phosphoglycerate mutase (PGAM) deficiency: a second case. *Neurology* **33**, 1049–1053 (1983).
226. Vita, G. et al. Muscle phosphoglycerate mutase (PGAM) deficiency in the first Caucasian patient: biochemistry, muscle culture and 31P-MR spectroscopy. *J. Neurol.* **241**, 289–294 (1994).
227. Koo, B. & Oskarsson, B. Phosphoglycerate mutase deficiency (glycogen storage disease X) caused by a novel variant in PGAM-M. *Neuromuscul. Disord.* **26**, 688–690 (2016).
228. Malfatti, E. et al. A new muscle glycogen storage disease associated with glycogenin-1 deficiency. *Ann. Neurol.* **76**, 891–898 (2014).
229. Krag, T. O., Ruiz-Ruiz, C. & Vissing, J. Glycogen synthesis in glycogenin 1-deficient patients: a role for glycogenin 2 in muscle. *J. Clin. Endocrinol. Metab.* **102**, 2690–2700 (2017).
230. Ben Yaou, R. et al. Clinical heterogeneity and phenotype/genotype findings in 5 families with GYG1 deficiency. *Neurol. Genet.* **3**, e208 (2017).
231. Visuttijai, K. et al. Glycogenin is dispensable for glycogen synthesis in human muscle, and glycogenin deficiency causes polyglucosan storage. *J. Clin. Endocrinol. Metab.* **105**, 557–566 (2020).
232. Akman, H. O. et al. Late-onset polyglucosan body myopathy in five patients with a homozygous mutation in GYG1. *Neuromuscul. Disord.* **26**, 16–20 (2016).
233. 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.* **40**, 139–149 (2017).
234. Manz, F. et al. Fanconi–Bickel syndrome. *Pediatr. Nephrol.* **1**, 509–518 (1987).
235. Toscano, A. & Musumeci, O. Tarui disease and distal glycogenoses: clinical and genetic update. *Acta Myol.* **26**, 105–107 (2007).
236. Hamano, T., Mutoh, T., Sugie, H., Koga, H. & Kuriyama, M. Phosphoglycerate kinase deficiency: an adult myopathic form with a novel mutation. *Neurology* **54**, 1188–1190 (2000).
237. Rosa, R. et al. A new case of phosphoglycerate kinase deficiency: PGK Creteil associated with rhabdomyolysis and lacking hemolytic anemia. *Blood* **60**, 84–91 (1982).
238. DiMauro, S., Dalakas, M. & Miranda, A. F. Phosphoglycerate kinase deficiency: another cause of recurrent myoglobinuria. *Ann. Neurol.* **13**, 11–19 (1983).
239. Pena, L. D. M. et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naive and alglucosidase alfa-treated patients with late-onset Pompe disease: a phase 1, open-label, multicenter, multinational, ascending dose study. *Neuromuscul. Disord.* **29**, 167–186 (2019).
240. Radenkovic, S. et al. The metabolic map into the pathomechanism and treatment of PGM1-CDG. *Am. J. Hum. Genet.* **104**, 835–846 (2019).
241. Halaby, C. A. et al. Liver fibrosis during clinical ascertainment of glycogen storage disease type III: a need for improved and systematic monitoring. *Genet. Med.* **21**, 2686–2694 (2019).
242. Concolino, D., Deodato, F. & Parini, R. Enzyme replacement therapy: efficacy and limitations. *Ital. J. Pediatr.* **44**, 120 (2018).
243. Fukuda, T. et al. Autophagy and mistargeting of therapeutic enzyme in skeletal muscle in Pompe disease. *Mol. Ther.* **14**, 831–839 (2006).
244. Li, C. & Samulski, R. J. Engineering adeno-associated virus vectors for gene therapy. *Nat. Rev. Genet.* **21**, 255–272 (2020).
245. Kaufmann, K. B., Buning, H., Galy, A., Schambach, A. & Grez, M. Gene therapy on the move. *EMBO Mol. Med.* **5**, 1642–1661 (2013).
246. Swingle, K. L., Hamilton, A. G. & Mitchell, M. J. Lipid nanoparticle-mediated delivery of mrna therapeutics and vaccines. *Trends Mol. Med.* **27**, 616–617 (2021).
247. Kowalski, P. S., Rudra, A., Miao, L. & Anderson, D. G. Delivering the messenger: advances in technologies for therapeutic mRNA delivery. *Mol. Ther.* **27**, 710–728 (2019).

Acknowledgements
The authors thank T. Krag and M. Sheikh for their work preparing histological images for publication (Fig. 3), R. Koch for her review of the manuscript and for her contributions to preparing histological images and D. Bali for her thoughtful edits of Table 2.

Author contributions
Introduction (W.B.H.); Epidemiology (T.G.J.D.); Mechanisms/pathophysiology (M.L.D.); Diagnosis, screening and prevention (S.C.G.); Management (P.S.K.); Quality of life (J.V.); Outlook (W.B.H.); Overview of Primer (all authors). Authors contributed equally to this work and are listed alphabetically.

Competing interests
W.B.H. has received consulting fees from PTC Therapeutics and ReCode Therapeutics. T.G.J.D. declares that he experiences no competing interests concerning the content of this manuscript. However, there are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical, Inc., ModernaTX, Inc. and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316 and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum and Danone) and participation in a Data Safety Monitoring Board (NCT05095727) and advisory boards (Ultragenyx Pharmaceutical, Inc., ModernaTX, Inc. and Beam Therapeutics). For all private–public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG. S.C.G.: the Centre for Paediatrics and Adolescent Medicine Freiburg received funding for the following sponsor-initiated study, for which S.C.G. is a local subinvestigator: NCT05139316 – 'a study of adeno-associated virus serotype 8-mediated gene transfer of glucose-6-phosphatase in patients with glycogen storage disease type Ia (GSDIa)', sponsored by Ultragenyx Pharmaceutical, Inc. S.C.G. has received honoraria for educational lectures from Vitaflo GmbH and Ultragenyx Pharmaceutical Inc. and support for attending metabolic expert meetings from Nutricia Metabolics GmbH. S.C.G. participated in an advisory board for Ultragenyx Pharmaceutical, Inc. P.S.K. has received research/grant support from Sanofi Genzyme, Amicus Therapeutics and Kriya Therapeutics. P.S.K. has received consulting fees and honoraria from Sanofi Genzyme, Amicus Therapeutics, Maze Therapeutics, JCR Pharmaceutical, Asklepios Biopharmaceutical, Inc. (AskBio), Ultragenyx Pharmaceutical, Moderna, Inc. and Kriya Therapeutics. P.S.K. is a member of the Pompe and Gaucher Disease Registry Advisory Board for Sanofi Genzyme, Amicus Therapeutics and Baebies. P.S.K. has equity in Asklepios Biopharmaceutical, Inc. (AskBio), Maze Therapeutics, and equity options with Kriya Therapeutics. J.V. has received honoraria for acting as speaker or consulting for Sanofi Genzyme and Amicus Therapeutics and has participated in a clinical trial sponsored by Sanofi Genzyme without getting honorarium. M.L.D. has no competing interests to declare relevant to this article.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41572-023-00456-z.

Peer review information *Nature Reviews Disease Primers* thanks P. Labrune, T. Mozaffar, G. Ronzitti and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.