nature reviews disease primers

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

Primer

Glycogen storage diseases

In the format provided by the authors and unedited

Supplemental Table 1: Clinical Features of GSDs					
Condition	**Gene(s)**	**Enzyme(s) or transporter**	**Inheritance**	**Clinical features**	**Other considerations**
GSD 0a	*GYS2*	Hepatic glycogen synthase	AR	Fasting ketotic hypoglycemia. Postprandial hyperglycemia and elevated lactate.[1-3] Short stature and low bone density.[1]	GSD 0a distinguished from other hepatic GSDs by normal liver size.[2]
GSD 0b	*GYS1*	Muscle glycogen synthase	AR	Features include exercise intolerance and hypertrophic cardiomyopathy,[4] sudden death with exercise with no prior exercise intolerance or heart structural abnormalities,[5] and adult-onset myopathy without cardiomyopathy.[6]	Very small number of cases.
GSD I, von Gierke disease	*G6PC1* (GSDIa) and *SLC37A4* (GSD Ib)	G6Pase (GSD Ia) and G6PT (GSD Ib)	AR	Fasting hypoglycaemia, lactic acidosis, high triglycerides, elevated uric acid (tendency for gout), hepatomegaly, HCAs (with chromosome anomalies[7] and may be associated with poor metabolic control[8]) with malignant potential, nephromegaly, renal tubular and glomerular disease, osteoporosis, pulmonary hypertension[9,10], anemia[11], bleeding disorder[12-14]. In GSD Ib, neutropenia, neutrophil dysfunction, and IBD[15].	Blood lactate rises quickly with hypoglycemia. Hypoketotic hypoglycemia.
GSD II, Pompe disease	*GAA*	Acid alpha-glucosidase	AR	Infantile-onset Pompe disease: Lethal without treatment.[16] Hypertrophic cardiomyopathy,[17] hypotonia,[17] motor delay[17], conduction anomalies,[18] cardiorespiratory failure,[16] feeding difficulty,[17] neurological symptoms (such as sensorineural hearing loss, small fiber neuropathy, bulbar weakness, and learning difficulties).[19] Late-onset Pompe disease: presentation at any age without cardiomyopathy in the first year of life.[20,21] Proximal limb girdle weakness and involvement of the diaphragm.[20] Lingual weakness with swallowing difficulty,[22] ptosis, small fiber neuropathy,[23] osteoporosis,[24] and GI dysmotility.[25,26] In some, cardiac hypertrophy later in life and increased risk for arrhythmias.	Variable expressivity of LOPD is being better characterized with addition of GAA activity to some NBS programs.[21]

GSD III (Cori disease; Forbes disease)	*AGL*	Glycogen debranching enzyme	AR	Fasting hypoglycemia with elevated ketones may be seen, hyperlipidemia, hepatomegaly, elevated AST and ALT.[27] HCA in a minority of patients.[27,28] Risk of HCC.[29,30] Hepatic fibrosis and progression to cirrhosis may occur.[29-31] In GSD IIIa: increased CK (normal in some individuals), myopathy. Muscle weakness can be proximal and distal and spares respiratory muscles.[27] Left ventricular hypertrophy, risk of cardiomyopathy, increased risk for arrhythmias.	Hypoglycemia can occur with or without elevated ketones. Cirrhosis causes HCC in GSD III (as opposed to GSD I where HCC develops from adenomas).[32]
GSD IV (Andersen disease)	*GBE1*	Glycogen branching enzyme	AR	Phenotypic variability. GSD IV may be best considered as a clinical continuum in which different patients have varying involvement of hepatic, cardiac, and neurologic features. Historically, subtypes described include classic (progressive) hepatic subtype with hepatosplenomegaly, liver dysfunction and 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 features described in references. [33-35]	Other phenotypes historically described include fatal perinatal neuromuscular subtype, congenital/neonatal neuromuscular subtype, non-progressive hepatic subtype, and childhood/juvenile neuromuscular subtype which are described in cited literature.[33-35]
GSD V (McArdle disease)	*PYGM**	Myophosphorylase	AR	With exercise, quick development of myalgia, fatigue, cramps, tachypnea, and tachycardia.[36] Elevated CK (usually) and propensity to rhabdomyolysis.[36,37] Contractures. Risk of compartment syndrome.[36,37] Often, presentation in first decade but with variability.[37] Fixed muscle weakness in some patients (more common in proximal muscles and more likely with age).[37] Some individuals with episodes of myoglobinuria that can lead to acute kidney failure.[37] Compared to the general population, diabetes, gout, and coronary infarction are more common.[36]	Second-wind phenomenon[38] almost unique to GSD V (also seen in PGM1-CDG), Pre-exercise ingestion of sucrose improves exercise intolerance.[39]

GSD VI (Hers disease)	*PYGL*	Liver glycogen phosphorylase	AR	Variable.[40] Commonly presents with hepatomegaly and poor growth with broad range of presenting age.[41] Hypoglycemia with ketosis. Elevated liver transaminases, hyperlipidemia, osteoporosis. Liver fibrosis.[42] Cirrhosis described. Recently, large review elucidated that liver biopsy shows increased glycogen in most with liver fibrosis in ~32% and cirrhosis in ~11%.[41]	Hypoglycemia can occur with or without elevated ketones. Although sometimes considered a milder hepatic GSD, severe hypoglycemia and hepatomegaly reported.[40,43]
GSD VII (Tarui disease)	*PFKM*	Muscle phosphofructokinase	AR	Typical form associated with exercise intolerance with contractures and myoglobinuria[44] and at times with hemolytic anemia and hyperuricemia with gout.[44] Atypical phenotypes include a myopathy in infancy with respiratory failure and death by age 2, hemolytic anemia without myopathy, and late-onset fixed weakness.[44]	No second wind phenomenon.[45] Sucrose ingestion before exercise leads to an "out-of-wind phenomenon" with less exercise capacity.[44,46] Akman et al.[44] acknowledged that in the few children with the infantile/early childhood presentation, there was no molecular explanation despite PFK deficiency in setting of severe myopathy. They considered the possibility that there could be different molecular etiologies when considering the rare and severe, infantile presentation.[44]

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; females 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 ± hepatomegaly.[47] Ketotic hypoglycemia, when seen, varies in frequency.[40] Variable elevations of transaminases and HLD.[40,47] Liver fibrosis.[42] Variability in presence and severity of fibrosis; cirrhosis described.[47] Mild hypotonia and developmental delay have been described.[40,48] At times, delayed puberty.[40,48] Limited long-term natural history. Adults described as asymptomatic.[40,48] GSD IX β: Rare with varying range of hepatic features.[40] Usually identified due to hepatomegaly.[40,47] Ketotic hypoglycemia and elevated tryglycerides.[47] Muscle features either absent or mild.[40] GSD IX γ2: 25% of GSD IX but typically more severe clinical features.[40,49] Hypoglycemia usually more pronounced. Increased risk for liver fibrosis and cirrhosis[40,47,49] (cirrhosis can develop in first years of life).[40] Liver adenomas have been described.[40]	In hepatic GSD IX, hypoglycemia can occur with or without elevated ketones. GSD IX α2: heterozygous women may be unaffected or have variable severity of symptoms[40,49]; GSD IX β: liver fibrosis occurred in 1 of 3 affected individuals.[47]
Muscle GSD IX	*PHKA1* (GSD IX α1)	Alpha subunit of muscle phosphorylase kinase (GSD IX α1)	X-linked	Variable clinical presentation and age of onset. CK may be elevated. Manifestations include muscle weakness, pain and stiffness with exercise, and atrophy.[50]	Rare and variable.
GSD X	*PGAM2*	Muscle phosphoglycerate mutase	AR	Exercise intolerance with cramps and myalgia/pain[44,50]. Rhabdomyolysis.[50] About half of patients with recurrent myoglobinuria; elevated serum CK between episodes.[44]	Rare.
GSD XI (note that GSD XI is sometimes used for Fanconi-Bickel Syndrome also)	*LDHA*	Lactate dehydrogenase A (skeletal muscle isoform)	AR	Exercise intolerance with cramps and painful stiffness.[50] Rhabdomyolysis and myoglobinuria.[50] Skin lesions described as desquamating erythematosquamous, annular psoriasis-like, annular erythematous plaques, pustular psoriasis-like, and annually recurring acroerythema.[44,51-55] Elevated serum CK during myoglobinuria events may be seen with low serum lactate dehydrogenase concentrations.[44] One individual with apparently isolated skin findings.[54]	Rare. One woman described with uterine stiffness during pregnancy and delivery requiring Cesarean section.[56] There may be apparently isolated skin findings.[54] One child with suspected GSD XI was described as having intellectual disability.[57]

GSD XII	*ALDOA*	Red blood cell fructose-1,6-bisphosphate aldolase A (erythrocyte and muscle isoform)	AR	Rare. Hemolytic anemia, myopathy, rhabdomyolysis.[50] Variable features described include intellectual disability, short stature, dysmorphic facial features.[50,58-63]	Enzyme might be thermolabile, as fever induces rhabdomyolysis/myoglobinuria.[64,65] Hepatosplenomegaly has been reported in affected individual as has seizure or epilepsy.
GSD XIII	*ENO3*	Beta-enolase	AR	Rare. Very few individuals reported.[66-69] Reported features include exercise intolerance, myalgia, rhabdomyolysis, muscle MRI with fatty infiltration.	Nonischemic forearm testing with normal lactate; no benefit of glucose infusion on exercise.[69] Normal baseline CK reported in 2 individuals.
GSD XV	*GYG1*	Glycogenin 1 (muscle isoform)	AR	Rare. Weakness, arrhythmias.[50,70] Phenotype may be predominantly skeletal myopathy or predominantly cardiomyopathy. Severe cardiomyopathy may be present with no skeletal muscle weakness, potentially requiring heart transplantation.[71] Conversely, late-onset skeletal myopathy may present without an apparent cardiomyopathy.[72] A report of 7 individuals described 4 with symmetric proximal and distal weakness and variable symptoms of hip and shoulder girdle, lower legs, and hands; 2 with isolated proximal muscle weakness; and 1 with only hand and finger sequelae.[73] A series of 5 affected individuals (4 families) with limb girdle weakness revealed concomitant ischemic cardiomyopathy and bradycardia in one and only mild changes in cardiac evaluation in the other patients felt to be compatible with age.[74] Another series of 9 patients from 5 families showed myopathy with no apparent heart disease (except for 2 patients at age 58 and 76 who had cardiac anomalies in the setting of coronary artery disease).[75] Individuals with predominantly skeletal myopathy have been described as progressive early-onset limb-girdle weakness,[75] mildly progressive late-onset limb-girdle weakness,[74] and late-onset distal or scapuloperoneal involvement.[75]	

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, endocrine anomalies, and hematologic anomalies,[76] hypoglycemia, growth retardation, and dilated cardiomyopathy.[77]	Two cases of malignant hyperthermia and rhabdomyolysis after general anesthesia and two patients with hypogonadotropic hypogonadism[77]; second wind phenomenon (thought to be pathognomonic for GSD V) reported in PGM-CDG[78].
FBS (also called GSD XI), Fanconi-Bickel Syndrome	*SLC2A2*	GLUT2	AR	Intolerance and postprandial elevations of glucose and galactose, fasting hypoglycemia, hepatomegaly, proximal tubular nephropathy, glucosuria, short stature, accumulation of glycogen in liver and kidneys.[79]	Rarely, cataracts.[79]
PGK deficiency	*PGK1*	Phosphoglycerate kinase	X-linked	May manifest with nonspherocytic hemolytic anemia, myopathy with rhabdomyolysis, and neurologic features, including intellectual disability (anemia, myopathy, and neurologic features appear to present in different combinations).[80,81] Lower enzyme activity may lead to involvement of multiple systems and susceptibility to rhabdomyolysis.[82]	Parkinsonism, with response to levodopa reported.[81,83-86] Retinitis pigmentosa[81,87] PGK deficiency may have peripheral nervous system disease and a phenotype resembling Charcot-Marie-Tooth disease.[81]

Supplemental Table 1. 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. *An autosomal dominant GSD has been described in individuals with a monoallelic *PYGM* missense variant.[88] 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 histologic and functional characterization.[88] ALT, alanine transaminase; APBD, adult polyglucosan body disease; AR, autosomal recessive; AST, aspartate transferase; CK, creatine kinase; FBS, Fanconi–Bickel syndrome; GAA, acid alpha-glucosidase; GSD, glycogen storage disease; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; IOPD, NBS, newborn screening; PFK, phosphofructokinase; PGK1, phosphoglycerate kinase deficiency; PGM1-CDG, phosphoglucomutase 1 deficiency, a congenital disorder of glycosylation.

Supplemental Table 2. Epidemiology of GSDs

Condition	Overall frequency	Frequency in specific ethnicities	Variants common in specific ethnicities
GSD 0	Unknown	Unknown	Unknown
GSD I	Incidence ~1 in 100,000 (80% GSD Ia; 20% GSD Ib)[89,90]	Ashkenazi Jewish: Prevalence 1 in 20,000[90]	1) *G6PC1*; c.79delC (p.Gln27ArgfsTer9). 1 of 3 variants that comprise 21% of pathogenic variants in individuals of European ancestry.[90]
			2) *G6PC1;* c.247C>T (p.Arg83Cys). 32% of variants in European population[90,91] and 96% of variants in Jewish population (carrier frequency 1.4% in Ashkenazi Jewish population[92])
			3) *G6PC1;* c.248G>A (p.Arg83His). 38% of variants in Chinese population.[90]
			4) *G6PC1*; c.379_380dupTA (p.Tyr128ThrfsTer3). 50% of variants in Hispanic population.[90]
			5) *G6PC1*; c.562G>C (p.Gly188Arg). 1 of 3 variants that comprise 21% of pathogenic variants in individuals of European ancestry.[90]
			6) *G6PC1*; c.648G>T (p.Leu216Leu). Approximately 85-88% of variants in Japanese population and 36-40% of variants in Chinese population.[90,93-95]
			7) *G6PC1*; c.1039C>T (p.Gln347Ter). 1 of 3 variants that comprise 21% of pathogenic variants in individuals of European ancestry.[90,93]
			8) *SLC37A4*; c.352T>C (p.Trp118Arg). 37-50% of variants in Japanese population.[90,93,96]
			9) *SLC37A4*; c. 1015G>T (p.Gly339Cys). ~15-21% of variants in mixed European population and 29% in German population.[90,93]
			10) *SLC37A4*; c.1042_1043delCT (p.Leu348Valfs*53). ~27-31% of variants in mixed European population and 32% of variants in German population.[90,93]
GSD II (Pompe disease)	~1 in 40,000[16,97,98] historically (combined IOPD and LOPD), but the epidemiology of Pompe disease has been informed by NBS.[99] A population genetics approach estimated predicted genetic prevalence 1 in 23,232 overall.[99]	Infantile form appears to have higher incidence in African-American and Chinese ancestry.[16]	1) *GAA*; c.-32-13T>G. ~60-90% of alleles in individuals with LOPD (the variant is more common in individuals of European ancestry).[100-104]

		LOPD appears to be more common in The Netherlands.[16,97,105]	2) *GAA*; c.525delT (p.Glu176ArgfsTer45). ~5% of pathogenic alleles in the US population[106]
		Population genetics study estimated prevalence of overall Pompe disease stratified by ethnicity.[99]	3) *GAA*; c.1935C>A (p.Asp645Glu). ~80% frequency of variant in Chinese patients with IOPD.[107,108]
			4) *GAA*; c.2482_2646del (p.Gly828_Asn882del). ~26% of affected Europeans (~13% of alleles).[109]
			5) *GAA*; c.2560C>T (p.Arg854Ter). Common variant among individuals of African ancestry (in one study, ~47% of alleles)[110]
GSD III	Prevalence 1 in 100,000 (85% GSD IIIa; 15% GSD IIIb)[32]	Nunavik Inuit prevalence: ~1 in 2,500[111]	1) *AGL*; c.2590C>T (p.Arg864Ter). Approximately 10.3% of pathogenic variants in the US.[112,113]
		Faroe Islands prevalence: ~1 in 3,100[114]	2) *AGL*; c.4260-12A>G. Approximately 5.5% of pathogenic variants in the US.[113,115]
		Prevalence among individuals of North African Jewish ancestry in Israel: 1 in 5,400[27,116]	3) *AGL*; c.3965delT (p.Val1322AlafsTer27). Approximately 6.7% of pathogenic variants in the US.[115]
			4) *AGL*; c.3682C>T (p.Arg1228Ter). Approximately 5.2% of pathogenic variants in the US.[27]
			5) *AGL*; c.1222C>T (p.Arg408Ter). Founder variant in the Faroe Islands.[114]
			6) *AGL*; c.4456delT (p.Ser1486ProfsTer18). Founder variant in individuals of Inuit ancestry[111] and North African Jewish ancestry.[116]
			7) *AGL*; c.2309-1G>A. 11.8% of alleles in individuals of European ancestry.[113]
			8)*AGL*; c.1384delG (p.Val462Ter). ~50% of alleles in individuals of Hispanic ancestry (2 of 4 individuals homozygous).[113]
GSD IV	~1 in 600,000 to 1 in 800,000.[33,35]	APBD prevalence is thought to be more common among individuals of Ashkenazi Jewish ancestry.[117]	1) *GBE1*; c.986A>C (p.Tyr329Ser). APBD founder variant in the Ashkenazi Jewish population.[117] The estimated carrier frequency is 1 in 48 among individuals of Ashkenazi Jewish ancestry.[33]
			2) *GBE1*; c.2053-5289_2053-5297delins TGTTTTTTACATGACAGGT. APBD founder variant in the Ashkenazi Jewish population.[117]

GSD V	Prevalence estimated to be 1 in 100,000 in Dallas/Fort Worth of USA.[37] Prevalence in Spain estimated ~139,543.[118]	Unknown	1) *PYGM*; c.148C>T (p.Arg50Ter). The most frequent variant seen in individuals of European ancestry. 31% of variants in Netherlands, 43% of variants in Italy, 55% of variants in Spain, 58% of variants in German, 60-63% of variants in US, 68-72% of variants in France, 77-81% of variants in UK.[119]^
			2) *PYGM*; c.613G>A (p.Gly205Ser). Varying reports of frequency in different populations.[119] 9% of variants in Spain.[118]
			3) *PYGM*; c.2392T>C (p.Trp798Arg). Seen in 10% of Spanish individuals with GSD V.[118]
			4) *PYGM*; c.2128_2130delTTC (p.Phe710del). 68% of variants in individuals of Japanese ancestry.[120]
			5)*PYGM*; c.1A>G (p.Met1Val). In one study of 67 patients from Turkey, this was the most common variant identified (27 patients from 11 families).[121]
GSD VI	Best prevalence estimate appears to be 1 in 100,000[40] but estimates vary.	Prevalence ~1 in 1,000 in Mennonite population.[43,122]	1) *PYGL*; c.1620+1G>A. Founder variant in Mennonite population.
GSD VII	Rare	Appears to be more common in individuals of Ashkenazi Jewish ancestry.[36]	2 common variants in affected individuals of Ashkenazi Jewish ancestry. One variant, affecting exon 5 splicing, comprises about 68% of pathogenic variants in this population.
GSD IX	Liver PhK deficiency has had estimated frequency of 1 in 100,000.[40,49] Muscle PhK deficiency appears rare.[49] *PHKA2* accounts for ~75% of hepatic GSD IX cases.[40,49] *PHKA2* is X-linked, and disease is more common in males.	Unknown	1) *PHKA2*; c.3614C>T (p.Pro1205Leu). Common variant in Dutch patients.[123]
GSD X	Rare	While most individuals reported have been of African American ancestry, affected individuals of other ethnicities have been described.[124]	Unknown. Although most affected African American individuals had the p.W78X variant, GSD X has been described in very few reports.
GSD XI (LDHA deficiency; note that FBS is sometimes called GSD XI also)	Rare	Unknown. One study of 3,776 individuals in Japan suggested a carrier frequency of 0.185%.[125]	Unknown. A 20 base pair deletion in exon 6 has been identified in multiple Japanese families.[126]
GSD XII	Rare	Unknown	Unknown
GSD XIII	Rare	Unknown	Unknown
GSD XV	Rare	Unknown	Too few individuals have been reported to confidently comment on the presence of a founder variant. In a paper describing 7

			unrelated individuals of different ancestries, 4 had the c.143+3G>C variant (2 homozygous and 2 compound heterozygous with c.143+3G>C on one allele).[73] 2 sisters of Italian ancestry whose parents were first cousins were homozygous for c.143+3G>C.[127] 5 patients (4 families) of Sardinian ancestry were reported as homozygous for c.143+3G>C.[74] It is possible c.143+3G>C could be a founder variant in individuals of Italian ancestry or other ancestry, but future reports may be informative.
FBS	Rare	Unknown	1) *SLC2A2*; c.157C>T (p.Arg53Ter) was reported to be homozygous in 6 unrelated patients in Sudan (the study included 11 patients from 10 families). It was suggested this may be a Sudanese founder variant.[128]

Supplemental Table 2. Different publications report different terms for epidemiology, such as prevalence and incidence, which have notable distinctions. We have tried to either use the nomenclature of the cited studies or a broad term. ^Numerous studies evaluating the frequency of the *PYGM* variant p.Arg50Ter in different countries are reviewed in the Nogales-Gadea et al. (2015) publication cited. GSD, glycogen storage disease; LOPD, late-onset Pompe disease; IOPD, infantile-onset Pompe disease; APBD, adult polyglucosan body disease; PhK, phosphorylase kinase; LDHA, lactate dehydrogenase subunit A; FBS, Fanconi–Bickel syndrome.

Supplemental Table 3. Summary of clinical practice guidelines and outpatient management of GSDs

Condition	Laboratory Tests	Imaging	Other Surveillance	Diet	Exercise	Regular outpatient treatment	Other considerations
GSD I[93,129,130]	Laboratory tests to monitor kidney and liver function and other disease sequelae are detailed in guidelines. Monitor MELD score. Lipids, uric acid, CBC, iron studies. In GSD Ib, differential to evaluate neutrophils.	Abdominal US in pediatric population is reasonable. Abdominal CT or MRI with contrast in older patients or pediatric patients with adenomas. Echocardiogram beginning at age 10 for pulmonary HTN. Renal US.	Consider CGM.	Avoid fasting. Feeding schedule, cornstarch dosing, and foods to avoid as per guidelines. Frequent small feedings high in complex carbohydrates. 60-70% carbohydrate, 10-15% protein, less than 30% fat when older than 2. Sucrose and lactose are often limited.	Age-appropriate sports encouraged. Avoid contact or competitive sports due to risk of liver injury.	For adenomas, there are multiple treatment possibilities. HLD management discussed in guidelines. ACEi or ARB consideration with hyperfiltration or proteinuria. Consider low-purine diet and allopurinol for gout. Consider citrate for hypocitraturia or thiazide for hypercalciuria. Treatment of anemia. In GSD Ib, guidelines for starting and following G-CSF therapy exist in neutropenia treatment.[130]	Avoid long-term use of nephrotoxic medications. Other medications to avoid or use with caution per guidelines. Monitor BP. Evaluating causes of severe anemia should include hepatic adenomas in GSD Ia and enterocolitis in GSD Ib. Considerations for liver transplantation are discussed in guidelines. In GSD Ib, consideration of empagliflozin.[131,132]
GSD II (Pompe disease)[16]	CK, AST, ALT, urine Glc4, IgG against recombinant protein when on enzyme replacement. BNP for cardiac involvement.	CXR and swallow assessments when indicated, DEXA, echocardiogram at regular intervals.	Age-appropriate physical therapy evaluations (assess function / motor capacity), 24-hour ambulatory EKG, supine / upright spirometry as part of pulmonary function tests, polysomnography as indicated, hearing evaluation.	High protein (20-25% protein)	Encourage exercise with guidance from PT.	ERT (alglucosidase alfa); in some countries, avalglucosidase alfa[133-135] has been approved for Pompe disease (Europe)[136] or LOPD (US).[137] Albuterol may be considered to augment ERT. [138] Consideration of ITI in CRIM negative individuals.	Respiratory muscle training can be beneficial in infantile-onset and late-onset Pompe disease. Maximize clearance of airway secretions.

GSD III[27]	LFTs, coagulation studies, lipids, CK. Monitor MELD score.	Abdominal US in pediatric population is reasonable. Abdominal CT/MRI with contrast in older patients. Echocardiogram.	Consider CGM. Serial EKG. Age appropriate PT evaluations.	Avoid fasting, small and frequent feeds. Introduce CS ~ age 1 year if hypoglycemia. High protein (25%) with low complex carbohydrates (< 50%), and avoid simple sugars.	Encourage exercise with guidance from PT.	Largely dietary, avoid hypoglycemia, and support muscle health.	
GSD IV[33]	<u>Pediatric-onset GSD IV</u>: every 3-6 months measure serum ALT, AST, GGT, direct and total bilirubin, albumin, PT/INR, platelets, ammonia, glucose, and 25-hydroxy vitamin D. Periodic measurement of AFP. <u>APBD</u>: Annually measure serum AST, ALT, GGT, direct and total bilirubin, albumin, PT/INR, and platelets (if abnormal, refer to hepatology). <u>All GSD IV (including APBD):</u> Periodic (~ annually) serum BNP or NT-proBNP.	<u>Pediatric-onset GSD IV</u>: Abdominal imaging of liver and spleen by ultrasound every 6 months and liver elastography (FibroScan or MRE) annually. <u>All GSD IV (including APBD):</u> echocardiogram annually (sooner with clinical change). Cardiac MRI at least every 3-5 years (sooner with clinical change).	<u>Pediatric-onset GSD IV</u>: Hepatic evaluation at diagnosis and ongoing follow-up. Abdominal Doppler ultrasound if new ascites on physical examination or if acute weight gain. Diagnostic paracentesis when abrupt development of ascites (rule out SBP). <u>All GSD IV (including APBD):</u> EKG and ambulatory rhythm monitor annually (sooner with clinical change. Imaging and cystoscopy if recurrent UTIs, hematuria, or concern for anatomic abnormalities.	Individualized dietary recommendations directed by a metabolic dietician. Maintain health body weight and provide nutrient-rich foods including complex carbohydrates (low glycemic index) and limiting simple carbohydrates. If liver disease, protein restriction is not recommended (unless there is persistent clinically significant hyperammonemia), supplement fat-soluble vitamins if there is cholestasis, restrict sodium and fluid if ascites and portal hypertension. High protein diet, bedtime snack, and tube feedings are recommended prior to liver	Exercise should be monitored including strengthening and/or optimizing movement and protection of fragile muscles.	Routine immunizations. Hepatitis A and B vaccinations. Monitor age-matched height and weight and weight/height ratio. Good dental hygiene and dental health monitoring. Annual vision exams. Monitor bone density, especially when there is myopathy. <u>Pediatric-onset GSD IV</u>: If compromised spleen function and neutropenia, prophylactic antibiotics for small bowel bacterial overgrowth and spontaneous bacterial peritonitis. <u>All GSD IV (including APBD):</u> Existing guidelines for lower urinary tract dysfunction may guide management. Routinely screen for dysphagia in APBD.	Factors when considering liver and/or heart transplantation are detailed in the guidelines. Physical rehabilitation recommendations are also detailed. <u>Pediatric-onset GSD IV:</u> If hepatic involvement, refer to pediatric hepatologist and liver transplantation center for an individualized approach to consideration of liver transplantation. <u>All GSD IV (including APBD):</u> Cardiac evaluation at diagnosis ongoing follow-up. Neurology evaluation at diagnosis and then periodically. Screen for urinary tract involvement at diagnosis and follow-up. Referral to PT/OT. <u>APBD:</u> Brain and spinal cord MRI without contrast every 2-5 years. Neurogenic bladder requires urology management. Referral to

				transplantation to optimize growth and nutrition. Use of parenteral nutrition discussed in guidelines.			ophthalmology if sudden vision changes.
GSD V[36]	Serum CK, uric acid, hemoglobin A1c, lipid profile.	Routine imaging is not part of practice guidelines in GSD V	Evaluate for weakness and muscle wasting.	Dietician involvement. Avoid excess weight. Sucrose supplementation (37 grams) 5-10 minutes before exercise with careful planning.	Aerobic exercise to improve cardiorespiratory function. Exercise at low to moderate intensity, at least 20 minutes 2 to 4 times per week preferably. Benefit and considerations for strength training and risk of contractures discussed in guidelines.	Largely dietary and exercise	Carbohydrate-rich diet has been suggested beneficial compared to protein-rich diet. Pre-exercise sucrose ingestion improves exercise tolerance. There is ongoing research regarding dietary management in GSD V. Assess ADLs and QoL. For contractures, stop the inciting activity until resolution. Avoid stretching for contractures. Acetaminophen may be taken after activity for help with episodic cramping. Exercise program should improve chronic pain; avoid opioids for chronic pain.

GSD VI[40]	AST, ALT, serum albumin, GGT, coagulation studies.	Abdominal US in children and abdominal CT/MRI in older individuals. Baseline DEXA and as indicated. Heart imaging if clinically indicated.	Monitoring blood glucose and serum beta-hydroxybutyrate	High protein (~20-25% of calories). Cornstarch may be required prior to bedtime. Carbohydrate and fat restrictions as per guidelines.	Avoid contact sports if there is hepatomegaly.	Dietary treatment and symptomatic management	
GSD VII[36]		Routine imaging is not part of practice guidelines in GSD VII.		Detailed studies to inform dietary management in GSD VII are needed.	Aerobic exercise to improve cardiorespiratory function. Exercise at low to moderate intensity, at least 20 minutes 2 to 4 times per week preferably.	Largely dietary and exercise	For contractures, stop the inciting activity until resolution. Avoid stretching for contractures. Acetaminophen may be taken after activity for help with episodic cramping. Exercise program should improve chronic pain; avoid opioids for chronic pain.
Hepatic GSD IX[40]	AST, ALT, serum albumin, GGT, coagulation studies.	Abdominal US in children and abdominal CT/MRI in older individuals. Baseline DEXA and as indicated. Heart imaging if clinically indicated.	Monitoring blood glucose and serum beta-hydroxybutyrate	High protein (~20-25% of calories). Cornstarch may be required prior to bedtime. Carbohydrate and fat restrictions as per guidelines.	Avoid contact sports if there is hepatomegaly.	Dietary treatment and symptomatic management	

PGM1-CDG[76]	Serum IGF-1, IGFBP3, TGB, TSH, free T4, ACTH, cortisol, glucose, transaminases and hepatic function, coagulation assessment. LC-MS platforms for monitoring therapeutic response to galactose (specific assays detailed in guidelines).	Noninvasive elastography to monitor liver fibrosis development. Other liver imaging and monitoring, cardiac screening, and neurology evaluations as per guidelines.	Monitor growth. Neurology assessment, ophthalmology assessment, and cardiac screening per guidelines. Early stimulation programs and psychometric tests with adapted education plans when indicated.	Nutritionist and speech therapist when cleft palate is present.		Oral D-galactose restores glycosylation and improves multiple symptoms.[139]	Guidelines provide recommendations for referral and evaluation when bifid uvula, cleft palate, or Pierre-Robin sequence are present. Early surgical intervention for midline malformations. Supportive treatment for strabismus. L-thyroxine to treat clinical hypothyroidism and cortisol to treat hypocortisolism. Growth hormone can be considered for growth impairment.

Supplemental Table 3. This table 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 (ACMG) and 2002 (ESGSD 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. GSD, (glycogen storage disease), RFP, (renal function panel), AST, (aspartate transferase), ALT, (alanine aminotransferase), GGT, (gamma-glutamyl transferase), CBC, (complete blood count), US, (ultrasonography; HTN, hypertension; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GCSF, granulocyte colony-stimulating factor; HCA, hepatocellular adenoma; Glc4, glucose tetrasaccharide; IgG, immunoglobulin G; EKG, electrocardiogram; PT, physical therapy; ERT, enzyme replacement therapy; LFTs, liver function tests; CK, creatine kinase; APBD, adult polyglucosan body disease; MELD, model for end-stage liver disease; QOL, quality of life; ADL, activities of daily living; DEXA, dual x-ray absorptiometry.

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