Glycogen metabolism and glycogen storage disorders

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Abstract: Glucose is the main energy fuel for the human brain. Maintenance of glucose homeostasis is therefore, crucial to meet cellular energy demands in both - normal physiological states and during stress or increased demands. Glucose is stored as glycogen primarily in the liver and skeletal muscle with a small amount stored in the brain. Liver glycogen primarily maintains blood glucose levels, while skeletal muscle glycogen is utilized during high-intensity exertion, and brain glycogen is an emergency cerebral energy source. Glycogen and glucose transform into one another through glycogen synthesis and degradation pathways. Thus, enzymatic defects along these pathways are associated with altered glucose metabolism and breakdown leading to hypoglycemia ± hepatomegaly and or liver disease in hepatic forms of glycogen storage disorder (GSD) and skeletal ± cardiac myopathy, depending on the site of the enzyme defects. Overall, defects in glycogen metabolism mainly present as GSDs and are a heterogenous group of inborn errors of carbohydrate metabolism. In this article we review the genetics, epidemiology, clinical and metabolic findings of various types of GSD, and glycolysis defects emphasizing current treatment and implications for future directions.

Keywords: Glycogen; glycogen storage disorder (GSD); hepatomegaly; hypoglycemia; rhabdomyolysis

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Introduction

Glycogen is a branched polymer of glucose stored predominantly in the liver and muscle during times of plenty only to be broken down and released as glucose during times of need. It appears as a densely branched snowflake in 3-D with Glycogen in, a glycosyltransferase enzyme in the center. Glycogen in, initiates the formation of glycogen by attaching glucose residues from UDP glucose and subsequent linear prolongation up to ten glucose molecules making the core unit. To this core unit, subsequent attachment of glucose occurs by enzymes such as glycogen synthase, which adds the alpha 1,4 linkages, and glycogen debranching enzyme, which adds the alpha 1,6 branch points every 12–13 glucose residues to elongate and form a globular granule of 30,000 glucose units (1,2). The degradation of glycogen into usable glucose molecules result from combined actions of glycogen phosphorylase, glycogen debranching enzyme, and phosphoglucomutase.

Glucose is stored as glycogen primarily in the cytoplasm of liver and muscle cellular tissue, and in small amounts in brain tissues. While glycogen in the liver acts as the main depot source that maintains blood glucose homeostasis, glycogen in skeletal muscles provides energy to muscles during high-intensity exertion.

Liver glycogen breaks down to maintain blood glucose concentrations on demand. Alternatively, post prandial excess blood glucose triggers insulin release, and glycogen synthesis and storage in the liver and muscles. During stress or short periods of fasting, glucagon signals the liver to

break down glycogen stores into glucose (glycogenolysis). Glucose is then released into the circulation maintaining blood glucose homeostasis during the times of high energy demands or fasting.

Skeletal muscles use glycogen in a similar manner, however, typically after several minutes of strenuous activity to keep up with its energy requirements.

Glucose and glycogen convert into one another via synthesis or degradation through various steps in the glycogen metabolism pathways as presented schematically in *Figure 1*.

Mutations in genes encoding individual enzymes in the glycogen metabolism pathway lead to a class of diseases named glycogen storage disorders (GSDs), whereas defects in glucose oxidation are identified as glycolysis defects. Depending on the enzyme defect and its relative expression in the liver, kidney, skeletal muscle, or heart, the clinical manifestations of GSDs varies from one disorder to the other. As a general rule, Liver GSDs commonly present with fasting hypoglycemia ± hepatomegaly. While muscle GSDs present in one of two different ways: exercise intolerance and rhabdomyolysis or fixed muscle weakness without rhabdomyolysis (3). Often exercise intolerance and rhabdomyolysis is seen in dynamic disorders like McArdle (GSD5) , and Tarui (GSD7) diseases , while fixed muscle weakness without rhabdomyolysis is seen in cytoplasmic disorders associated with glycogenolysis defects as debrancher defect (GSD3a) or lysosomal glycogen breakdown defects as Pompe disease (GSD2) (4). Genetic defects with clinical features and epidemiology of each disorder of the glycogen metabolism pathway are summarized in *Table 1*. We will review glycogenosis and GSDs involving the liver, muscle, brain and include the lysosomal storage of glycogen—Pompe disease.

Liver glycogenosis and GSDs

GSD type 0a (GSD0a)

Clinical

GSD0a, is liver glycogen synthase enzyme deficiency with impaired ability to incorporate UDP-glucose onto glycogen strands and elongate it within the liver. This leads a lack of hepatic glycogen storage, absence of hepatomegaly and lack of liver's ability to maintain glucose homeostasis during fasting leading to hallmark presentation of ketotic hypoglycemia after an overnight fast in the absence of hepatomegaly and hypoglycemic seizures (5-7).

Another consequence of glycogen synthase deficiency is excess of substrates of the glycolytic pathway due to a reduced flow into glycogenosis (see *Figure 1*). The net effect results in transient post- prandial hyperglycemia and hyperlactatemia (5,8). However, some affected individuals may be asymptomatic or go undiagnosed (6,9).

Metabolic findings and diagnosis

GSD0a main clinical presentations include fasting Ketotic hypoglycemia without hepatomegaly, supported by a low pre-prandial blood glucose level associated with high blood and urine ketones and a high post-prandial blood glucose, lactate and alanine levels. Ultimately diagnosis can be confirmed by non-invasive DNA analysis of the *GYS2* gene or invasive enzymatic analysis from liver biopsy (10).

Treatment

Current treatment for GSD0a includes avoiding fasting, and frequent meals that are high in protein, to promote gluconeogenesis and uncooked cornstarch (UCCS) as needed in the day and or at nighttime to prevent hypoglycemia (8,11). With proper management, GSD0a has good prognosis.

Genetics and epidemiology

GSD0a is an autosomal recessive disorder caused by a mutation in the *GYS2* gene located at 12p12.2 that codes for the hepatic isoform of glycogen synthase (12). There are less than 30 reported cases of GSD0a (13).

GSD type 1 (GSD1)

GSD1 is caused by defective glycogenolysis and gluconeogenesis and is subdivided into two types: GSD1a and GSD1b.

GSD1a

Clinical

GSD1a, also known as Von Gierke disease or Glucose-6-phosphatase (G6Pase) deficiency results from impaired ability of the hydrolase subunit of G6Pase, also known as G6Pase-α to hydrolyze G6P, leading to impaired function of G6Pase in removing the phosphate group from glucose-6-phosphate (G6P), thus, impairing free glucose availability in the last step of gluconeogenesis (see *Figure 1*); resulting in impaired glucose homeostasis and hypoglycemia. G6Pase-α is necessary to convert fructose and galactose into glucose and is expressed in the liver, kidney, and intestines.

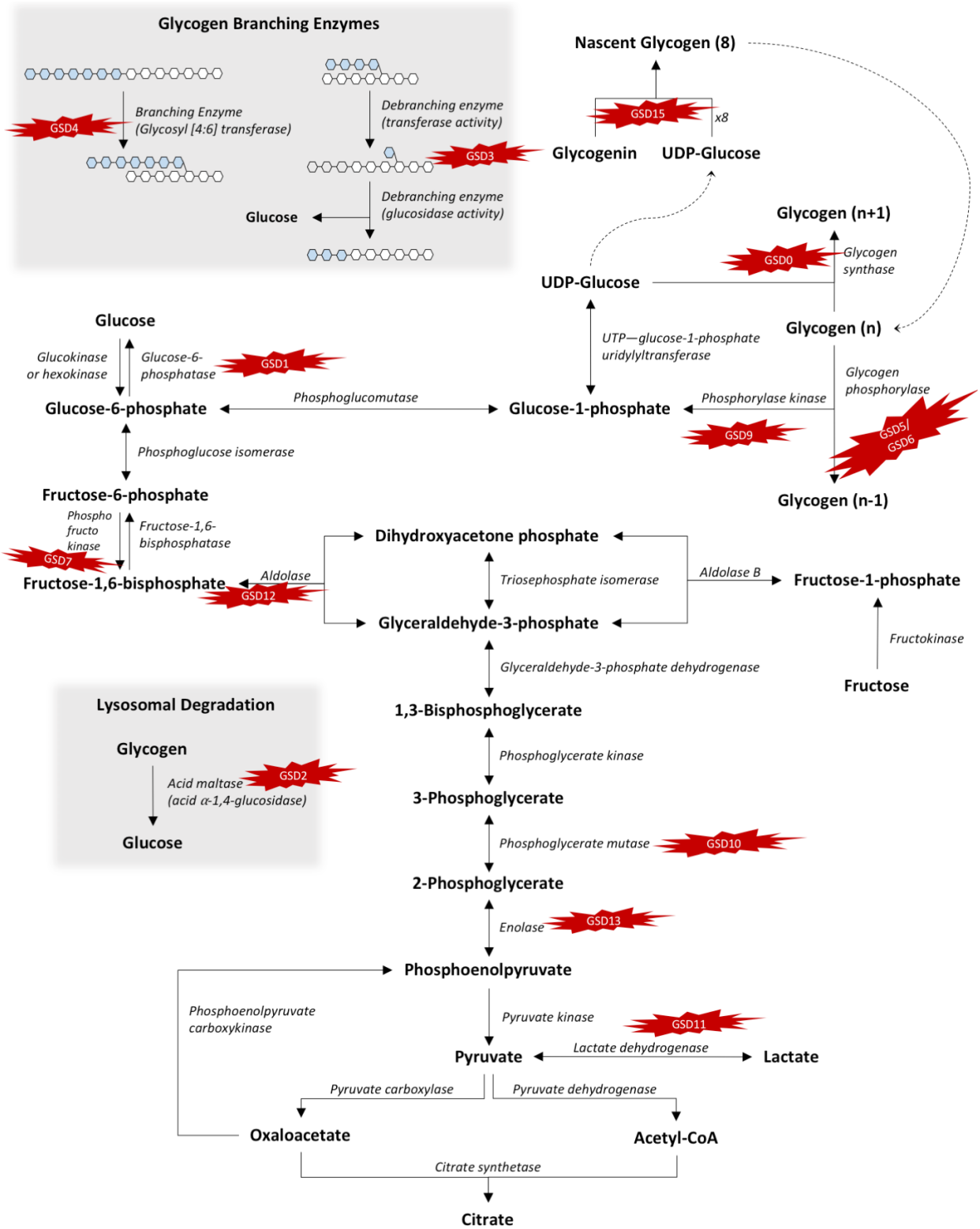

Figure 1 Glycogen metabolism pathway and defects. Enzyme affected are shown in italics and the correlating GSD are inserted in the star-shapes. GSD, glycogen storage disorder.

Table 1 Characteristics of inborn errors of glycogen metabolism

GSD type/name (phenotype MIM number)	Enzyme defect	Gene defect (OMIM number)	Chromosome location	Inheritance	Incidence	Clinical features
GSD0A/Liver GSD 0 (240600)	Liver glycogen synthase	GYS2 (138571)	12p12.1	AR	Unknown (<30 cases reported)	Fasting Ketotic hypoglycemia; hyperketonemia; hypoglycemic seizures; post-prandial hyperglycemia; post-prandial hyperlactatemia
GSD0B/Muscle GSD 0 (611556)	Muscle glycogen synthase	GYS1 (138570)	19q13.33	AR	Unknown (10 cases reported)	Muscle fatigue; seizures (rare); risk of cardiac arrest in childhood
GSD1A/Von Gierke/ Hepatorenal (232200)	Glucose-6-phosphatase	G6PC (613742)	17q21.31	AR	1 in 20,000 (Ashkenazi Jewish population)–1 in 100,000	Fasting hypoglycemia; lactic acidosis; hepatomegaly; growth delay/short stature; doll like facies; elevated liver enzymes; renal dysfunction; hyperuricemia; hypertriglyceridemia; osteoporosis; anemia; hepatic adenoma; hepatocellular carcinoma
GSD1B/G6P transport defect (232220)	Glucose-6-phosphate translocase	SLC37A4 (602671)	11q23.3	AR	Unknown	Recurrent bacterial infections; neutropenia; inflammatory bowel disease; oral/intestinal mucosal ulcers; fasting hypoglycemia; lactic acidosis; hepatomegaly; doll-like facies; anemia; growth delay/short stature; hyperlipidemia; xanthomas
GSD2/Pompe/Cardiac GSD (232300)	Acid maltase [alpha-1,4-glucosidase]	GAA (606800)	17q25.3	AR	1 in 8,684–1 in 40,000	Cardiomyopathy; muscular hypotonia; enlarged tongue; respiratory failure due to muscle weakness; adult onset limb girdle dystrophy
GSD3/Forbes/Cori/IIIa/IIIb	Glycogen debrancher [amylo-1,6 glucosidase]	AGL (610860)	1p21.2	AR	1 in 100,000	Hepatomegaly; hypoglycemia; fasting ketosis; failure to thrive; growth delay/short stature; myopathy; hypertrophic cardiomyopathy; doll like facies; hyperlipidemia; elevated liver enzymes
GSD4/Andersen/ Amylopectinosis/ Neuromuscular/ Polyglucosan (232500)	Glycogen brancher [amylo(1,4 to 1,6) transglucosidase]	GBE1 (607839)	3p12.2	AR	1 in 600,000–1 in 800,000	Failure to thrive; hepatosplenomegaly; progressive liver cirrhosis; fetal akinesia deformation sequence (FADS); hypotonia; muscle wasting/myopathy; cardiomyopathy; neurogenic bladder; peripheral neuropathy; leukodystrophy; cognitive impairment
GSD5/McArdle (232600)	Myophosphorylase	PYGM (608455)	11q13.1	AR	1 in 100,000–1 in 167,000	Skeletal muscle weakness; exercise-induced muscle cramping; rhabdomyolysis; myoglobinuria; “second wind” phenomenon
GSD6/Hers (232700)	Liver glycogen phosphorylase	PYGL (613741)	14q22.1	AR	1 in 1,000 (Mennonite population)–1 in 100,000	Hepatomegaly; growth retardation; mild hypoglycemia; fasting Ketotic hypoglycemia; fatigue; muscle hypotonia; motor developmental delay; osteoporosis

Table 1 (*continued*)

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GSD type/name (phenotype MIM number)	Enzyme defect	Gene defect (OMIM number)	Chromosome location	Inheritance	Incidence	Clinical features
GSD7/Tarui (232800)	Muscle phosphofructokinase	PFKM (610681)	12q13.11	AR	Unknown, but more prevalent among Ashkenazi Jewish population	Hemolytic anemia; muscle weakness; exercise-induced muscle cramping; exertional myopathy; gout/hyperuricemia
GSD9A1/XLG1/formerly GSD8 (306000)	Alpha-2 subunit of liver phosphorylase kinase	PHKA2 (300798)	Xp22.13	XLR	Unknown (~50 cases reported)	Hepatomegaly; growth retardation; motor developmental delay; hypercholesterolemia; hypertriglyceridemia; elevated liver enzymes; fasting hyperketosis
GSD9B/GSD IXb (261750)	Beta subunit of liver and muscle phosphorylase kinase	PHKB (172490)	16q12.1	AR	1 in 100,000	Short stature; hepatomegaly; diarrhea; muscle weakness; hypotonia
GSD9C/GSD IXc (613027)	Hepatic and testis isoform—gamma subunit of phosphorylase kinase	PHKG2 (172471)	16p11.2	AR	1 in 100,000	Growth retardation; hepatomegaly; hypotonia; cognitive delay
GSD9D/GSD IXd (300559)	Alpha subunit of muscle phosphorylase kinase	PHKA1 (311870)	Xq13.1	XLR	Unknown (only 7 cases reported)	Muscle weakness; exercise-induced muscle pain & stiffness; muscle atrophy; variable age onset, adults
GSD10/GSD X/PGAMM deficiency (261670)	Muscle phosphoglycerate mutase	PGAM2 (612931)	7p13	AR	Unknown (only 15 cases reported)	Exercise-induced muscle cramps & pain; exercise intolerance; rhabdomyolysis; myoglobinuria; hyperuricemia/gout; coronary arteriosclerosis; childhood or adolescence onset
GSD11/GSD XI/LDHA deficiency (612933)	Lactate dehydrogenase A	LDHA (150000)	11p15.1	AR	Unknown (only 12 cases reported)	Exercise-induced muscle cramps & pain; rhabdomyolysis; myoglobinuria; uterine muscle stiffness during pregnancy; psoriatic skin lesions; onset in childhood
GSD12/GSD XII/Aldolase deficiency (611881)	Fructose-1,6-bisphosphate aldolase A in red cell	ALDOA (103850)	16p11.2	AR	Unknown (<10 cases reported)	Short stature; myopathy; mental retardation; delayed puberty; hemolytic anemia; dysmorphic facies; hepatosplenomegaly; rhabdomyolysis with febrile illness
GSD13/GSD XIII/Enolase 3 deficiency (612932)	Beta-enolase	ENO3 (131370)	17p13.2	AR	Unknown (only 3 cases reported)	Exercise intolerance; myalgia; rhabdomyolysis

Table 1 (*continued*)

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GSD type/name (phenotype MIM number)	Enzyme defect	Gene defect (OMIM number)	Chromosome location	Inheritance	Incidence	Clinical features
GSD14/GSD XIV/CDG1t/ PGM1 deficiency (614921)	Phosphoglucomutase-1	PGM1 (171900)	1p31.3	AR	Unknown (only 22 cases reported)	Short stature; cleft palate; bifid uvula; Pierre Robin sequence; hepatopathy/chronic hepatitis; intermittent hypoglycemia; dilated cardiomyopathy; exercise intolerance; muscle weakness; rhabdomyolysis; hypogonadotropic hypogonadism; susceptibility to malignant hypothermia; hepatopathy/chronic hepatitis; intermittent hypoglycemia; variable phenotype
GSD15/GSD XV/GYG1 deficiency (613507)	Glycogenin-1	GYG1 (603942)	3q24	AR	Unknown (less than 20 cases reported)	Cardiac arrhythmias; muscle weakness
Fanconi-Bickel syndrome/ previously GSD XI (227810)	None (glucose transport defect)	GLUT2/SLC2A2 (138160)	3q26.2	AR	Unknown (200 cases reported)	Tubular nephropathy; hepatorenal glycogen storage; failure to thrive; polyuria; rickets; hyperuricemia; hyperaminoaciduria; hyperlipidemia; Ketotic hypoglycemia; hepatosplenomegaly
GSD Heart, lethal congenital (261740)	Gamma-2 subunit of AMP-activated protein kinase/cardiac muscle phosphorylase kinase	PRKAG2 (602743)	7q36.1	AD	Unknown (193 cases reported)	Hypoglycemia; heart failure; failure to thrive; cardiomegaly; cardiomyopathy; renomegaly; WPW syndrome; fatal in early infancy
Danon disease/lysosomal-associated membrane protein-2 deficiency/ formerly GSD2b or GSD IIb (300257)	[lysosomal-associated membrane protein-2 def-cy]	LAMP2 (309060)	Xq24	XLD	Unknown (171 cases reported)	Cardiomyopathy; skeletal myopathy; WPW syndrome; intellectual disability; hepatomegaly; retinopathy; arrhythmia
Brain GSD/Laforin deficiency (254780)	Laforin; E3 ligase	EPM2A (607566); NHLRC1/EPM2B (608072)	6q24.3; 6p22.3	AR; AR	Unknown; unknown	Epilepsy; hallucinations; dementia

AD, autosomal dominant; AR, autosomal recessive; XLD-X-linked dominant, XLR-X-linked recessive.

Patients typically present by 6 months of age with fasting hypoglycemia or hepatomegaly, and are found to have protuberant abdomen, stunted growth, and doll-like facies (14-16). Long term complication of from kidney glycogen accumulation include GSD nephropathy, chronic kidney disease, polycystic kidney and renal cancer, hyperuricemia associated with renal stones and renal tubular acidosis (16,17). Poor disease management or disease progression can lead to short stature, osteoporosis, anemia, polycystic ovarian syndrome, and hepatic adenomas which may be associated with the risk of transforming into hepatocellular carcinoma (16-20).

Metabolic findings and diagnosis

Patients with GSD1a typically have hypoglycemia from impaired last step of gluconeogenesis as discussed above, hyperuricemia and hypertriglyceridemia from excess G6P resulting in increased flux through pentose phosphate pathway and lipogenesis respectively, lactic acidosis from excess G6P over working the glycolytic pathway (16). GSD1a patients with hyperlipidemia seem to have increased fraction of apolipoprotein E (apoE) with suggested protective effect against atherosclerosis (21).

Initial clinical presentation of fasting hypoglycemia, lactic acidosis, hyperuricemia and hypertriglyceridemia can be confirmed by enzyme activity assay and or mutation analysis of both G6PC and SLC37A4 simultaneously due to the overlap of presentations seen in GSD1a and GSD1b (15,22).

Prenatal genetic diagnosis on chorionic villus sampling was reported in a family with known familial mutation (23).

Treatment

The main aim of treatment in GSD1a is to maintain normoglycemia or avoid hypoglycemia. ACMGG Consensus guidelines can be reviewed for further details on current guidelines on diagnosis and management of GSD1 (20). Nutritional approaches with frequent feedings of formula, meals, snacks, and UCCS including use of nasogastric and gastrostomy tubes are the cornerstone to maintain glucose homeostasis throughout the day and night (11). Glycosade, a modified form of cornstarch helps maintain normoglycemia overnight for a longer time in older children (24). Simple sugars as fructose, sucrose and galactose are restricted because of their contribution to lactic acidosis (11). A high-protein diet has been related to kidney damage and cannot be effectively converted into glucose because of the limited G6Pase activity (11). Hyperuricemia can improve with metabolic control or allopurinol (15). Hyperlipidemia may improve with metabolic control, but has historically been treated with fibrates, statins, niacin, fish oil, and medium-chain triglyceride milk (11).

Liver transplantation has been associated with favorable outcomes in severe disease (25). Liver transplantation corrects glucose homeostasis, but does not prevent renal dysfunction (16,25). However, based on the calculated liver disease score, GSD1a patients are typically low for liver transplant priority (26). Multiple studies using animal models have showed the efficiency of gene therapy in correcting glucose homeostasis and improved metabolic profiles (22). A clinical phase I/II trial (NCT03517085) using adeno-associated virus 8 (AAV8) to deliver G6Pase-α gene to the liver. in an attempt to correct defective G6PC (27) may help establish gene therapy as a promising future approach.

Genetics and epidemiology

GSD1a mode of inheritance is autosomal recessive; with mutations in the *G6PC* gene on chromosome 17p21.31 encoding α-glucose-6-phosphatase (G6Pase-α) enzyme (28). GSD1 incidence is about 1 in 100,000 with GSD1a accounting for 80% of diagnosis (16,22). Within the Ashkenazi Jewish population, the suggested incidence of GSD1a is 1 in 20,000 (29). No clear-cut genotype-phenotype correlation has been identified (20).

GSD1b

Clinical

GSD1b shares the same clinical presentation of GSD1a with, additional hallmark features: neutropenia and impaired neutrophil function; an inflammatory bowel disease (IBD) with a presentation similar to Crohn's disease, thyroid autoimmunity and hypothyroidism (30-32).

Metabolic findings and diagnosis

The G6PT enzyme is a transmembrane protein found within the endoplasmic reticulum and functions to move G6P into the endoplasmic reticulum. G6Pase-α and G6PT together as the G6Pase complex maintains glucose homeostasis. G6PT is ubiquitously expressed with G6Pase complexes throughout the body, while G6Pase-α is localized to the liver, kidney, and intestines, leads myeloid cell energy homeostasis disruption and the resulting neutropenia. Neutropenia can be severe, leading to recurrent infections and milder neutropenia with other features of GSD1b has been described with a homozygous mutation in *G6PC* gene (22,32).

Due to clinical presentation overlap seen in GSD1a and GSD1b, both G6PC and SLC37A4 should be analyzed

for mutations simultaneously in patients with suspected GSD1 (22).

Treatment

In addition to GSD1a treatment approaches, the only difference in GSD1b includes, addressing neutropenia and IBD with granulocyte colony-stimulating (G-CSF) to decreases the number and severity of infections and inflammation (31). Liver transplantation in GSD1b will correct glucose homeostasis, but effects on neutropenia and bowel disease are variable and less clear (25).

Genetics and epidemiology

GSD1b has autosomal recessive inheritance, with 92 different reported with 31 confirmed as pathogenic mutations in *SLC37A4* gene on chromosome 11q23 (33), encoding glucose-6-phosphate translocase (G6PT) enzyme (GDE); and no apparent genotype-phenotype relationship (15,22).

GSD type 6 (GSD6)

Clinical

GSD6, also known as Hers disease or liver phosphorylase enzyme deficiency, is a glycogenolysis defect with impaired interconversion of unphosphorylated form into active phosphorylated form of liver phosphorylase enzyme, necessary to remove the terminal branch glycosyl unit of glycogen to form glucose 1 phosphate (34). Varied clinical spectrum include mild to severe presentation of hepatomegaly, Ketotic hypoglycemia, with excessive glycogen accrual seen in liver biopsy (10). Though, considered a milder disease, long term complications are not well studied (35).

Metabolic findings and diagnosis

Ketotic hypoglycemia +/– hepatomegaly +/– growth delay presentation can be varied—Diagnostic confirmation includes molecular analysis of *PYGL* gene, liver biopsy measuring liver phosphorylase enzyme activity (36).

Treatment

Mainly is symptomatic, with frequent intake of complex carbohydrate, and high protein diet and avoiding fasting (10,11).

Genetics and epidemiology

GSD6 is an autosomal recessive disorder, with very few documented cases, and with mutation in *PYGL* gene on chromosome 14q22.1 (10,36,37).

GSD9A1 & GSD9A2

Clinical

GSD9A1 & GSD9A2 result from impaired phosphorylase kinase activity in the liver or erythrocyte (GSD9a1) or only liver (GSD9a2). They are reported more in males, and considered most common of all GSD9. Though, initially thought to be mild disease (38); severe presentations of liver cirrhosis are also reported. Common early childhood presentations include hepatomegaly, growth & motor developmental delay, hypercholesterolemia, hypertriglyceridemia, elevated liver enzymes, and fasting hyperketosis, which resolve with puberty (39).

Metabolic findings and diagnosis

Clinical suspicion in males with hepatomegaly and fasting hyperketosis, hyperlipidemia, elevated liver enzymes, and normal lactate & uric acid levels; should be confirmed with *PHKA2* gene molecular analysis and or erythrocyte phosphorylase kinase activity (39).

Treatment

Symptomatic to prevent hypoglycemia with frequent meals and snacks, high protein diet, and complex carbohydrates.

Genetics and epidemiology

GSD9a has X-linked inheritance with mutations in the *PHKA2* gene on chromosome Xp22.13 that encodes liver phosphorylase kinase (40).

GSD9c

Clinical

GSD9c results from impaired gamma unit of phosphorylase kinase enzyme function in liver and testis, with early childhood presentations of recurrent hypoglycemia, hepatomegaly progressing to liver cirrhosis and end stage liver disease; apart from motor delay, hepatosplenomegaly, renal tubular damage and muscle weakness (35). Because the gamma subunit contains the catalytic site of the enzyme, GSD9C typically has a more severe phenotype. In personal experience (SK unpublished data), a teenager presented with seizure disorder, microcephaly, intellectual disability, short stature apart from clinical presentations noted above.

Metabolic findings and diagnosis

Apart from clinical presentation noted above, elevated liver enzymes and lactate with severe fasting ketosis in setting of

normal triglycerides creatine kinase (CK) and uric acid can be seen. Measurement of enzyme activity in liver may help but diagnostic confirmation includes molecular analysis of *PHKG2* gene (41).

Treatment

Nutritional approaches to prevent recurrent hypoglycemia with high-protein and complex carbohydrates and symptomatic treatment and management for any hypoglycemia related complications may be helpful. In personal experience (SK unpublished data), teenage presentation of a GSD9c case with liver failure was treated successfully with liver transplantation and at 3-year post transplantation, showed improvement in cognitive abilities in late adolescence, to secure successful vocational training and employment, improved muscle strength, resolution of hepatosplenomegaly and seizures.

Genetics and epidemiology

GSD9C is an autosomal recessive disorder caused by mutations of the *PHKG2* gene which encodes the gamma subunit of phosphorylase kinase on chromosome 16p11.2 (42).

Liver & muscle glycogenosis and GSDs

GSD type 3

Clinical

GSD3, also known as Cori Disease or Forbes disease results from glycogen debrancher enzyme (GDE) deficiency with impaired glycogen breakdown and abnormal glycogen accumulation, affecting liver, skeletal and cardiac muscles (35,43). Clinical presentation in infancy is similar to GSD1 with hepatomegaly, fasting hypoglycemia, hyperlipidemia, growth delay/failure to thrive (44). However, significant liver enzyme elevations and lack of lactic acidosis in setting of fasting ketosis, CK elevation differentiates GSD3 in younger age; with absence of nephromegaly, presence of splenomegaly, improvement of liver size and function in adolescence; prior to progression to cirrhosis/liver failure later in life. Muscular symptoms become apparent during and after adolescence though hypertrophic cardiomyopathy seen in younger childhood (43,44).

Metabolic findings and diagnosis

As noted above, characteristic findings include fasting hypoglycemia with ketosis, hyperlipidemia, elevated CK, an inverse relationship between a patients age and liver enzymes, lack of lactic acidosis and hyperuricemia (35,43-45). A diagnosis can be made by mutation analysis of the *AGL* gene (46) or liver biopsy to detect the enzymatic defect.

Treatment

Best approaches are nutritional with frequent meals, with high protein content and lesser amounts of UCCS (than in GSD1), or bedtime glycosade helps growth during adolescence (43). Though there are suggestions that a modified Atkins diet improves myopathy symptoms (47).

Genetics and epidemiology

GSD3 has autosomal recessive inheritance, with 58 different reported mutations in the *AGL* gene on chromosome 1p21.2, encoding GDE; and an incidence of 1 in 100,000 (44).

GSD 4

Clinical

GSD4, also known as Andersen disease or Brancher deficiency, is a glycogenolysis defect with impaired and few α-1,6-glycosidic bonds along glycogen chain, resulting in abnormal glycogen with limited branch points (limited dextran) similar to amylopectin or polyglucosan (10). Clinical presentation is variable and historically classified as two hepatic and four neuromuscular forms based upon age of onset and severity (48). More recent studies suggest that GSD4 phenotypes should be considered a continuum of disease as opposed to discreet subtypes (49,50).

The classical hepatic GSD4 typically presents within 18 months of birth with patients having a failure to thrive, hepatosplenomegaly, and liver cirrhosis (51). As the disease progresses, liver failure ultimately results, leading to death by the age of 5 unless a liver transplant is performed (51). A non-progressive hepatic form with a similar presentation has also been described (52,53).

Neuromuscular variants range in onset from in utero presenting perinatally as fetal akinesia deformation sequence (FADS) to adulthood as adult polyglucosan body disease (APBD) with wide severity range from perinatal death to mild symptoms (49). Commonly seen features of the neuromuscular variant of disease includes: hypotonia, muscle atrophy, myopathy, cardiomyopathy, central nervous system (CNS), and peripheral nerve system (PNS) dysfunction (10).

Metabolic findings and diagnosis

Liver dysfunction with abnormal coagulation can be non-specific findings and amylopectin like material deposition can be seen in liver, heart, muscle, brain, spinal cord or reduced glycogen branching enzyme (GBE) activity seen in liver, muscle or leukocyte; but confirmation made by molecular analysis of *GBE1* gene (10).

Treatment

Unlike other liver GSDs, GSD4 has no specific treatment. Early liver transplant is indicated in patients with the classical hepatic form but only in absence of cardiac or CNS disease (10).

Genetics and epidemiology

GSD4 is rare and has autosomal recessive inheritance with mutations in the *GBE1* gene on chromosome 3p12.2 encoding GBE.

GSD9b

Clinical

GSD9B, also known as phosphorylase kinase deficiency of liver and muscle, have predominant hepatomegaly, short stature seen in early childhood and, sometimes in addition, muscle weakness and hypotonia (39).

Metabolic findings and diagnosis

Can be asymptomatic, but hypoglycemia and reduced enzyme activity can be seen. Diagnosis is mainly confirmed by mutation analysis of the *PHKB* gene.

Treatment

Symptomatic with prevention of hypoglycemia with hi-protein and complex carbohydrate diet; though there is no specific treatment for muscle disease (54).

Genetics and epidemiology

GSD9B is an autosomal recessive disorder caused by mutations of β subunit of *PHKB* gene on chromosome 16q12.1.

Muscle glycogenosis and GSDs

GSD0b

Clinical

GSD0b, also known as muscle glycogen synthase deficiency, is rare and seems to affect muscle mitochondrial structure and function apart from depleted glycogen (55). Known symptoms include muscle fatigue, exercise intolerance, recurrent exertional syncope, hypertrophic cardiomyopathy, sudden cardiac death without cardiomyopathy (55-57) .

Metabolic findings and diagnosis

Clinical suspicion with molecular analysis of *GYS1* gene provides diagnostic confirmation. Muscle biopsy can show depleted glycogen; oxidative fibers and abnormal mitochondria (55-57).

Treatment

No specific treatment, preventive measures, supportive therapy with high protein complex carbohydrates diet may help.

Genetics and epidemiology

GSD0b is an autosomal recessive disorder caused by mutations of *GSY1* gene on chromosome 19q13.33 (55).

GSD2

Clinical

GSD2, also known as Pompe disease or acid maltase deficiency results from impaired lysosomal acid-α-glucosidase (GAA) function and accumulation of lysosomal glycogen in skeletal, respiratory and cardiac muscle and often considered as lysosomal storage disorder (LSD) than GSD. It can present anytime from early infancy into adulthood, the most severe being the classic infantile-onset form, characterized by severe hypotonia, macroglossia, muscle and diaphragmatic weakness, hypertrophic cardiomyopathy with cardiomegaly +/– Wolf-Parkinson White arrhythmias , and hepatomegaly with fatality from cardiac failure in untreated patients within the first year of life (58). A non-classical infantile form shows slower symptom progression, is less severe with no cardiomyopathy (59). Late-onset Pompe disease (childhood, juvenile, and adult forms) is often used to describe patients who present after the first year of life with muscle weakness, and hypotonia (60).

Metabolic findings and diagnosis

Clinical suspicion as noted above with characteristic evidence of hypertrophic cardiomyopathy with EKG findings of shortened PR interval and high QRS complexes and elevated CK is seen in the infantile-onset form. While,

proximal myopathy with diaphragmatic weakness is seen in late-onset disease. Elevated blood aminotransferases and CK are common but diagnostic confirmation noted with deficient GAA enzyme activity in lymphocytes, fibroblasts, and muscle or molecular analysis of biallelic *GAA* gene (61). GAA activity is usually absent (in infantile-onset disease) or decreased (in late-onset disease). Some genotype—phenotype correlations exist and determined by the type of the mutation (62,63). Dried blood spot testing measuring GAA enzyme activity has helped GSD2 to be included in Newborn Screening (64). Evaluation of the CRIM status is important, since CRIM negative status is associated with poor response to ERT and poor prognosis, if immunomodulation is not started early (62).

Results of newborn screening in Taiwan demonstrated significant long-term benefits from the early identification and treatment of patients with infantile Pompe disease before symptoms appeared making an argument for its inclusion in newborn screening panels in many states in the U.S. and trialed in several countries (65,66).

Treatment

Enzyme replacement therapy (ERT) using human recombinant acid α-glucosidase, the only approved treatment in the US and Europe since 2006, is based on its ability to degrade accumulated lysosomal glycogen and improve cardiac and skeletal muscle function (35). Though, a negative cross reacting immune material (CRIM)-negative status has high anti-rhGAA IgG antibodies development and resultant reduced ERT therapeutic effect with poor outcomes if not treated early with immunosuppression (65,67).

If early diagnosis of late-onset disease is made via newborn screening, the question of when to start treatment in an asymptomatic patient is debated. Improvement in pulmonary function is seen in symptomatic patients with late-onset disease (68).

Genetics and epidemiology

GSD2 is a pan-ethnic autosomal recessive disorder caused by mutations of the *GAA* gene on chromosome 17q25.3. The increasing list of *GAA* gene pathogenic mutations can be found at www.pompecenter.nl. The estimated prevalence is considered to be 1 in 5436 (35).

GSD5

Clinical

GSD5, also known as McArdle disease results from deficient muscle phosphorylase activity and results in impaired glycogenolysis leading to exercise intolerance, muscle weakness and cramping alleviated by rest, and exercise induced rhabdomyolysis. A common history of childhood onset exercise intolerance and a wide range of severity and age of onset reported with most serious complication being renal failure from myoglobinuria and rhabdomyolysis. A short low intensity warm up or 5–15 minutes interruption/break, to rest or "second wind" often necessary to resume exercise (69).

Metabolic findings and diagnosis

Apart from clinical suspicion, elevated CK, myoglobinuria and renal dysfunction as common biochemical markers with additional non-invasive diagnostic confirmation with molecular analysis of *PYGM* gene is indicated. Invasive muscle biopsy with negative muscle phosphorylase activity can help diagnosis too.

Treatment

Oral sucrose loading 30–40 minutes before exercise helps exercise tolerance as exogenous fuel source to help energy gap with lack of endogenous glucose from glycogenolysis and free fatty acids availability until ~10 minutes into exercising (70).

Regular exercise of moderate intensity helps maximize circulatory capacity and increase fuel delivery to muscles (71).

Genetics and epidemiology

GSD5 is an autosomal recessive disorder caused by mutations of *PYGM* gene on chromosome 11q13.1.

GSD7

Clinical

GSD7, also known as Tarui disease results from deficient muscle subunit of phosphofructokinase (PFK) enzyme as a rate limiting factor, with resultant impaired glycogenolysis and glycolysis. The classical form is characterized by exercise intolerance, (often with rhabdomyolysis), muscle cramps and pain. In some cases jaundice accompanied by increased serum bilirubin, exercise related elevated CK levels, myoglobinuria and myogenic hyperuricemia may also be seen (72,73). In addition, three other GSD7 subtypes are late-onset, infantile, and hemolytic. Late-onset GSD7 typically presents in later life with muscle cramps and myalgias although patients may show increased muscular weakness and fatigability in childhood. Patients

with severe infantile form of GSD7 present with hypotonia early after birth and often die within their first year of life. Arthrogryposis and mental retardation may be present in cases who survived early death. The hemolytic form is characterized by non-spherocytic hemolytic anemia without muscle symptoms (72).

GSD7 though clinically similar to GSD5, is different with the absence of a second wind phenomenon and a detrimental, as opposed to beneficial, effect of glucose administration due to impaired fatty acid oxidation in GSD7 (73).

Metabolic findings and diagnosis

Presentations can include hyperbilirubinemia, increased reticulocytes due to the elevation of hemolysis from partial loss of PFK activity in erythrocytes, elevated CK, lactate dehydrogenase, and aspartate transaminase following acute exercise (4). Non-invasive diagnostic confirmation includes molecular analysis of *PFKM* gene (72).

Muscle biopsy or forearm exercise test showing elevated ammonia but reduced lactate can confirm impaired glycolysis following anaerobic exercise can be supportive.

Treatment

Symptomatic and preventive with avoiding strenuous exercise, high protein intake during exercise and avoiding exercise related simple sugars as sucrose intake.

Genetics and epidemiology

GSD7 is an autosomal recessive disorder caused by mutations of the *PFKM* gene on chromosome 12q13.11.

GSD9D

Clinical

GSD9D, also known as muscle phosphorylase kinase deficiency or X-linked muscle glycogenosis results from impaired alpha subunit of the muscle phosphorylase kinase activity, associated with muscle weakness, atrophy, and exercise-induced pain and stiffness, with a variable age at onset, mainly seen in males, though can remain asymptomatic until intense exercise (39,74).

Metabolic findings and diagnosis

CK may be elevated, but, diagnosis is confirmed by mutation analysis of the *PHKA1* gene.

Treatment

Unknown but symptomatic hydration for muscle enzyme breakdown can help.

Genetics and epidemiology

GSD9D is an X-linked recessive disorder caused by mutations of the *PHKA1* gene which encodes the alpha subunit of muscle phosphorylase kinase on chromosome Xq13.1.

The overall prevalence of GSD9 is estimated to be 1 in 100,000 (54).

GSD10

Clinical

GSD10 also known as PGAMM deficiency results from impaired muscle phosphoglycerate mutase-2 activity essential for conversion of 3-phosphoglycerate to 2-phosphoglycerate during glycolysis and resultant childhood or adolescence presentation of muscle cramping, rhabdomyolysis, and myoglobinuria precipitated by bursts of vigorous exercise (75).

Metabolic findings and diagnosis

Elevated CK, myoglobinuria can be confirmed non-invasively with molecular analysis of *PGAM* gene (76). Enzymatic assay shows decreased muscle phosphoglycerate mutase-2 activity.

Treatment

Symptomatic myopathy management with hydration and avoidance of strenuous exercise.

Genetics and epidemiology

GSD10 is an autosomal recessive disorder caused by mutations of the *PGAM2* gene on chromosome 7p13. Of the 15 cases reported in the medical literature, a founder exon1 null mutation noted in African Americans (76,77).

GSD11

Clinical

GSD11 (78) also known as GSDXI results from impaired muscle(M) isoform of lactate dehydrogenase enzyme essential for interconversion of lactate and pyruvate in muscle glycolysis with resultant fatigue, exertional myoglobinuria and also uterine pain and stiffness during pregnancy and labor (79).

Metabolic findings and diagnosis

Biochemical findings of elevated CK, lactate and

myoglobinuria can be confirmed with molecular analysis of *LDHA* gene. LDH activity in red blood cells is low or absent.

Treatment

No specific treatment. In pregnant women with GSD11 planned cesarean section can avoid increased risk of dystocia during labor (79).

Genetics and epidemiology

Lactate dehydrogenase A deficiency is an autosomal recessive disorder caused by mutations of the *LDHA* gene on chromosome 11p15.1. The H isoform of LDH is found in the heart and encoded by the lactate dehydrogenase B gene on chromosome 12p12.1, but mutations found had no clinical significance (80).

Hepatorenal glycogenosis or Fanconi-Bickel Syndrome, listed as MIM# 227810, previously also known as GSD XI, is an autosomal recessive disorder with mutations in *SLC2A2* gene encoding *GLUT2* transporter, affecting glycogen accumulation in liver and kidney, proximal renal tubular dysfunction and defective glucose and galactose utilization (81).

GSD12

Clinical

GSD12 also known as ALDOA deficiency, results from impaired fructose-1,6-bisphosphate aldolase A activity, essential for interconversion of fructose-1,6-bisphosphate to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate in glycolysis, with resultant hereditary non-spherocytic hemolytic anemia and myopathy (82).

In contrast, overexpression of aldolase A is associated with multiple forms of cancer including squamous cell carcinoma of the lung, hepatocellular, and renal cancer suggestive that increased glycolysis promotes tumor growth in cells (83).

Metabolic findings and diagnosis

Findings of hemolytic anemia, rhabdomyolysis and myoglobinuria can be confirmed with molecular analysis of *ALDOA* gene. Red cells enzymatic assay can show decreased activity.

Treatment

No known specific except symptomatic and preventive management of myopathy and hemolytic anemia complications.

Genetics and epidemiology

GSD12 is a rare autosomal recessive disorder caused by mutations of *ALDOA* gene on chromosome 16p11.2

GSD13

Clinical

GSD13, also known as Enolase-beta deficiency results from impaired beta-enolase activity, necessary for interconversion of 2-phosphoglycerate and phosphoenolpyruvate The skeletal muscle isozyme impairments presents with adult-onset myalgia post exertion, with mildly elevated CK levels (84) to recurrent rhabdomyolysis (85).

Metabolic findings and diagnosis

Diagnostic confirmation requires molecular analysis of *ENO3* gene.

Treatment

No specific treatment described yet.

Genetics and epidemiology

GSD13 is a rare autosomal recessive disorder caused by mutations of the *ENO3* gene on chromosome 17p13.2.

GSD14

Clinical

GSD14, also known as phosphoglucomutase-1 deficiency or congenital disorder of glycosylation type It CDG-1T has wide clinical spectrum with predominantly milder myopathy form or severe form with multisystem involvement and congenital anomalies (86).

Metabolic findings and diagnosis

Diagnostic confirmation requires molecular analysis of the *PGM1* gene.

Treatment

In a small study, supplementation with up to 1.5 g/kg/day of oral D-galactose showed improvement or normalization of liver function, coagulation profile and transferrin profile (86).

Genetics and epidemiology

GSD14 is a rare autosomal recessive disorder caused by

mutations of the *PGM1* gene on chromosome 1p31.3 (87).

GSD15

Clinical

GSD15, also known as Glycogenin deficiency results from impaired glycosyltransferase necessary for short glucose polymer formation from UDP-glucose and glycogen formation, leading to depletion of glycogen in skeletal muscle and abnormal glycogen storage in the heart and resultant myopathy, cardiomyopathy and or arrhythmias (88).

Metabolic findings and diagnosis

Molecular analysis of *GYG1* gene provides definitive diagnosis. Low skeletal muscle glycogen or abnormal cardiac muscle glycogen in the heart in patients with cardiomyopathy (88).

Treatment

No known treatment but glucose infusion during exercise showed improved exercise tolerance (89).

Genetics and epidemiology

GSD15 is a rare autosomal recessive disorder caused by mutations of *GYG1* gene on chromosome 3q24.

Other cardiac glycogenosis

Danon disease

Diagnosed by mutations in *LAMP2* gene located on chromosome Xq24, affecting lysosomal associated membrane protein-2 function of hydrolase sequestration and resultant lysosomal autolytic functions; leads to glycogen and autophagic materials accumulation in muscles and presents with cardiomyopathy, skeletal myopathy, intellectual disability, retinopathy or maculopathy in adolescent and younger adult males mostly, and milder presentation in hemizygous females (90-92).

AMP activated protein kinase deficiency

Is a cardiac phosphorylase kinase deficiency impairing fatty acid oxidation, glycolysis and glucose oxidation in response to energy demands leading to glycogen storage in cardiac muscles; secondary to mutations in *PRKAG2* gene and has autosomal dominant inheritance. Presentations include lethal congenital or early childhood fatal (93) but can present in adolescence with Wolff-Parkinson-White syndrome (WPW on EKG) with progressive fatal cardiomyopathy; requiring pacemaker or cardiac transplantation.

Brain glycogenoses

Lafora disease

Is a progressive myoclonic epilepsy with neurodegeneration in mid childhood to adolescent, caused by mutation in the *EPM2* gene on chromosome 6q24.3, with autosomal recessive inheritance, leading to abnormal glycogen accumulation called Lafora bodies in neuronal axons and dendrites (94).

Thoughts on future directions

GSDs and glycogenosis defects, though, heterogenous and individually rare; predominantly affect liver, muscles, heart and in rare instance brain from infancy to adulthood. Heightened clinical suspicion can lead to GSD diagnosis in primary care and in-patient setting. Common laboratory biochemical evaluation or EKG with a timely referral to biochemical geneticist can help GSD diagnosis. Medical crises in most GSD are preventable with simple nutritional measures and prevention of energy deficiency triggers. Newborn Screening is changing the natural history of Pompe and lessons from ERT management still unfolding. In general, proactive symptomatic treatment and compliance using integrated behavior health model can help prevent co-morbidities such as intellectual disability, growth delay, organ failure or malignancy.

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Footnote

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