

Screening for galactosemia: is there a place for it?

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Abstract: Galactose is a hexose essential for production of energy, which has a prebiotic role and is essential for galactosylation of endogenous and exogenous proteins, ceramides, myelin sheath metabolism and others. The inability to metabolize galactose results in galactosemia. Galactosemia is an autosomal recessive disorder that affects newborns who are born asymptomatic, apparently well and healthy, then develop serious morbidity and mortality upon consuming milk that contains galactose. Those with galactosemia have a deficiency of an enzyme: classic galactosemia (type I) results from severe deficiency of galactose-1-uridylyltransferase, while galactosemia type II results from galactokinase deficiency and type III results from galactose epimerase deficiency. Many countries include neonatal screening for galactosemia in their national newborn screening program; however, others do not, as the condition is rather rare, with an incidence of 1:30,000–1:100,000, and screening may be seen as not cost-effective and logistically demanding. Early detection and intervention by restricting galactose is not curative but is very rewarding, as it prevents deaths, mental retardation, liver cell failure, renal tubular acidosis and neurological sequelae, and may lead to resolution of cataract formation. Hence, national newborn screening for galactosemia prevents serious potential life-long suffering, morbidity and mortality. Recent advances in communication and biotechnology promise facilitation of logistics of neonatal screening, including improved cost-effectiveness.

Keywords: galactosemia neonatal screening, galactose-1-phosphate uridylyltransferase, galactokinase, UDP galactose-4-epimerase, galactosylation

What are galactose and galactosemia?

Galactose is a monosaccharide which, when combined with glucose (another monosaccharide), yields the disaccharide lactose, which is abundant in human milk and other newborn feeding formulae.^{1,2} Galactose has many roles in vivo, e. g., it is essential for galactosylation of ceramide for synthesis of myelin sheath, other ceramides and Fc (the crystallizable fraction) of immunoglobulin G (IgG), is involved in heparin and heparan sulfate synthesis,³ and the Leloir pathway, to produce energy for various tissues of the body.⁴ Galactokinase (GALK) facilitates the phosphorylation of galactose into galactose-1-phosphate, which is then catalyzed into glucose-1-phosphate by galactose-1-uridylyltransferase (GALT), releasing uridine diphosphate galactose (UDP galactose). UDP galactose is converted to uridine diphosphate glucose (UDP glucose) by UDP galactose-4-epimerase (GALE) in mammals. These three enzymes are part of the degradation pathway known as the Leloir pathway for galactose (Figure 1).^{1,2}

UDP GALE also catalyzes the formation of UDP-N-acetylgalactosamine, which is an essential step in glycoprotein/glycolipid production.⁵

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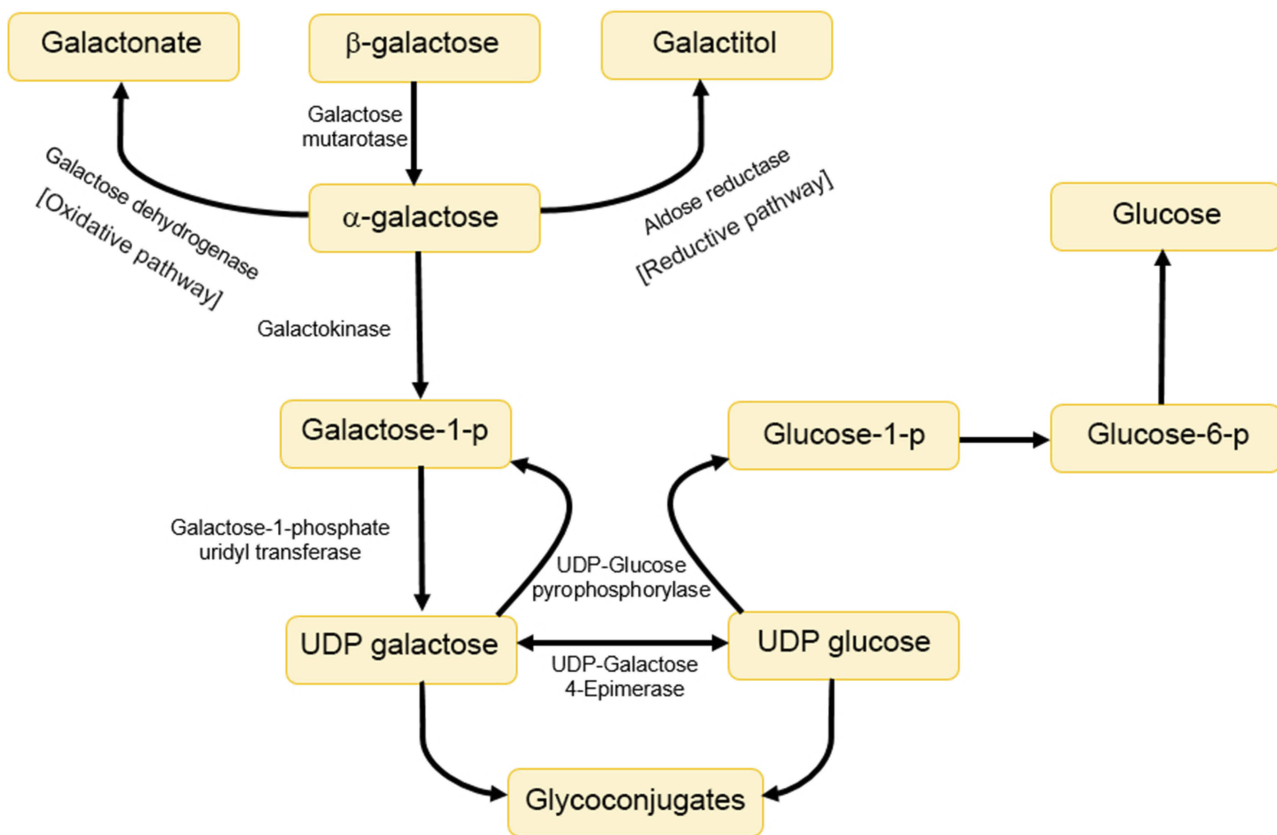


Figure 1 Galactose metabolism pathways; Leloir, oxidative and reductive galactose degradation pathways.

In the absence of the three enzymes described by Leloir,¹ galactose is forced to transform into the debatably toxic galactonate and notoriously toxic galactitol, which accumulate in various tissues⁶ (Figure 1).

Galactosemia is an autosomal recessive disorder that affects newborns who are born asymptomatic, apparently well and healthy, then develop serious morbidity upon consuming milk that contains galactose. They have a deficiency of one of the enzymes mentioned in the opening paragraph. Classic galactosemia (also known as type I) results from severe deficiency of GALT, galactosemia type II results from GALK deficiency and type III results from GALE deficiency.⁷

Newborns with galactosemia build up galactose, galactitol and galactonate, while being deprived of galactosylation, hence they develop serious acute and long-term morbidities of body systems, e.g., the nervous system, liver, kidneys and eyes, and premature mortality.^{2,7}

What is the role of galactose in vivo?

Galactose is essential for the production of energy^{1,8} and has a prebiotic role.⁹ Above all, it is essential for galactosylation

of proteins, ceramides essential for myelin sheath synthesis¹⁰ and other substances (Figure 2).

Galactosylation of ceramides

Ceramides comprise a family of lipids composed of sphingosine and fatty acids, which are essential for sphingomyelin synthesis. Ceramides in the plasma membrane of eukaryotic cells provide structural cellular support and participate in functional cellular signaling essential for differentiation, proliferation and apoptosis.¹¹ Galactosylation of ceramide by galactosylceramide synthase (GalCerS), also known as UDP galactose:ceramide galactosyltransferase, is distributed primarily in Schwann cells, oligodendrocytes and astrocytes, and is essential for production of galactosylceramide, the major sphingolipid of the myelin sheath.¹⁰

Galactosylation of IgG

Galactosylation of proteins aims to protect, stabilize and immobilize surface proteins to improve the structural stability of native proteins against inactivation by the interaction of water with hydrophobic clusters.¹² Galactosylation is

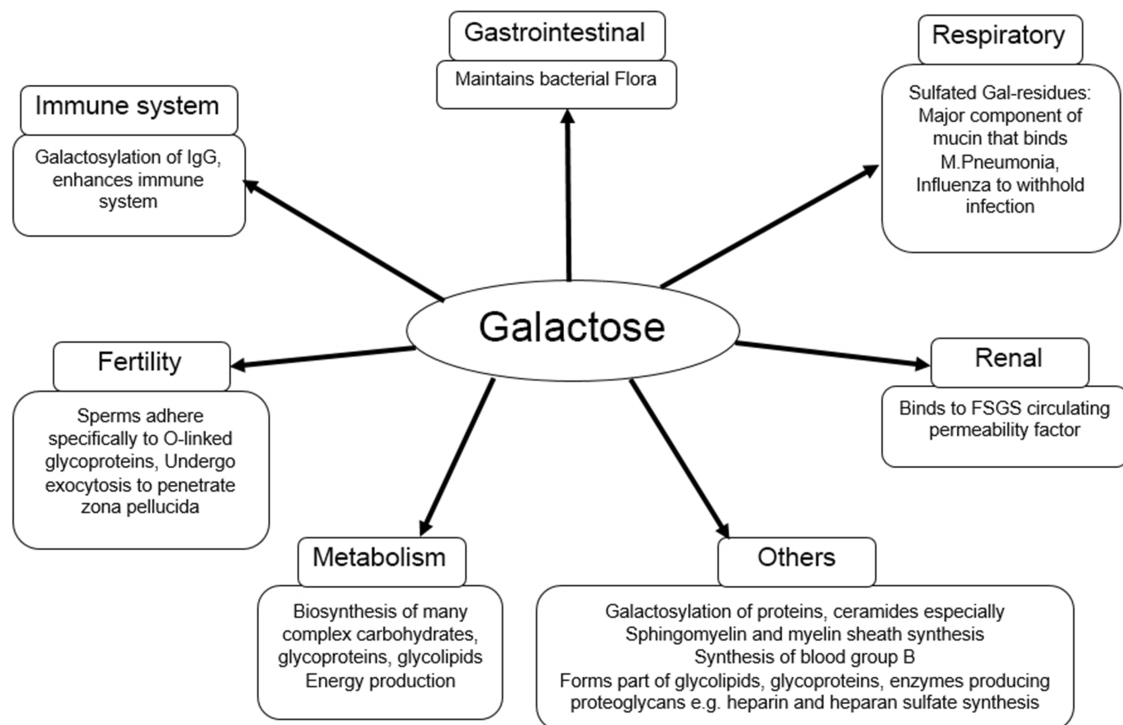


Figure 2 Role of galactose in vivo.

Abbreviations: FSGS, focal segmental glomerulosclerosis; *M. pneumoniae*, *Mycoplasma pneumoniae*.

performed by the enzyme galactosyltransferase in the Golgi apparatus.

IgG is the most abundant immunoglobulin found in plasma. It has four subclasses, IgG₁, IgG₂, IgG₃ and IgG₄, which are glycoproteins in nature. The organization of galactosylation takes place in the endoplasmic reticulum and the Golgi apparatus via galactosyltransferase.¹³ While IgG glycosylation involves fucosylation and sialylation,¹⁴ galactosylation remains an important step to achieve immune activation by autoantibodies through either complement (C1q) or Fc gamma receptors (FcγR).¹⁵ Agalactosylation decreases affinity for FcγRIII and decreases C1q binding and downstream activation. Agalactosylation has been shown to predispose toward and mediate immune diseases.¹⁶

Agalactosylation of IgG₃ is associated with severe forms of glomerulonephritis,¹⁷ lupus and other immune diseases.¹⁶

Galactosylation for synthesis of blood group B

Galactosylation is essential for biosynthesis of blood group B substances, which are substrates of the lysosomal alpha-galactosidase A. Weak blood group B expression is associated with abnormal red cell membranes.¹⁸

A key role of blood group B-antigens was reported in the biochemical and morphological pathology of the exocrine pancreas in Fabry disease patients with blood group B.¹⁹

Galactose binds to focal segmental glomerulosclerosis circulating permeability factor

Cytochemical and biochemical analysis of rat glomeruli, treated with puromycin to induce experimental necrosis, showed disrupted glomerular galactosylation of sialic acid residues.²⁰ Furthermore, galactose was found to decrease the focal sclerosis permeability factor in children with steroid-resistant nephrotic syndrome, with the most significant improvement found in those with post-transplant recurrence of focal segmental glomerulosclerosis. However, it failed to improve proteinuria.²¹

What controls the phenotype and outcome of galactosemia?

Classic galactosemia (type I), characterized by severe deficiency of GALT, is the most studied form. It is reported to present acutely with a sepsis-like picture in a previously apparently healthy newborn, which progresses rapidly to

liver cell failure and death after consuming lactose-containing milk.²² Yet, the clinical spectrum of galactosemia varies markedly, ranging from acute and early death within the first week or weeks of life to chronic neurodevelopmental, hepatic, renal and ocular morbidities, and mortality. Jaundice, convulsions, motor retardation, mental retardation, microcephaly, failure to thrive, hepatomegaly, splenomegaly, vomiting, diarrhea, liver cell failure, renal tubular acidosis, cataracts, autoimmune hepatitis, self-mutilation, combined immune deficiency, kernicterus⁷ and raised intracranial tension²³ have all been reported (Figure 3). Many factors control the phenotype and outcome of subjects with galactosemia, such as the type of enzyme deficiency of the Leloir pathway, residual enzyme activity, genotype, ontogeny of other accessory enzymes, accumulation of galactitol, other metabolites and the amount of lactose to which the individual was exposed. After the initiation of a galactose-restricted diet, subjects with

galactosemia mostly suffer mild neurological sequelae, primary ovarian failure and hypergonadotrophic hypogonadism, possibly leading to decreased fertility but are spared the serious morbidities and mortality associated with feeding galactose-containing diet.²⁴

Type of enzyme deficiency

The incidence of type I galactosemia with severe or total deficiency of GALT is reported to range from 1.2:10,000 to 1:60,000,^{25,26} while residual GALT enzyme activity of 14–25% has an incidence of 1:4000 and is named Duarte galactosemia.²⁶ Despite the inclination to assert that it is an asymptomatic disease or a mild disease, there are reports to the contrary.²⁷ GALK deficiency is reported to have a milder presentation, yet cataracts are prominent among affected individuals.^{28,29} GALE deficiency is reported both as a mild disease and as a severe

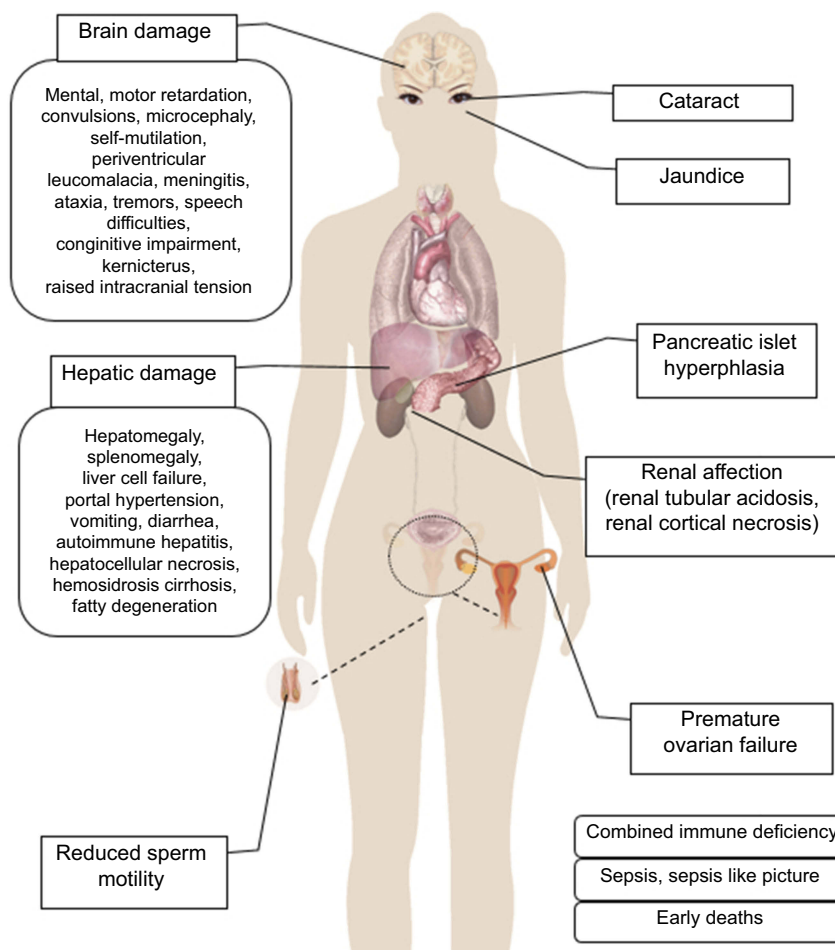


Figure 3 Complications of galactosemia. The spectrum of complications of galactosemia is dictated by the type of enzyme deficiency (GALT, GALK or GALE), residual enzyme activity, genotype, timing, amount and duration of exposure to galactose, endogenous galactose and galactitol production, intrauterine protection, institution of galactose-free versus galactose restriction and adult tolerance to galactose.

Abbreviations: GALE, galactose-4-epimerase; GALK, galactokinase; GALT, galactose-1-uridylyltransferase.

variant.^{30–32} It is quite rare, and more studies are needed to elucidate its true clinical picture and the factors controlling the phenotype and outcome.⁴

Genotype

The *GALT* gene (OMIM #230400) is located on chromosome 9p13. Classic galactosemia (*GALT* total deficiency) results from homozygous or compound heterozygous mutation in the *GALT* gene. A lot of mutations were reported, e.g., those associated with classic galactosemia, c.855G > T (K285N), c.584T > C (L195P), 626A > G (Tyr209Cys) and c.512T > C (Phe171Ser); that associated with the pathogenic variant c.404C > T (S135L); that associated with Duarte galactosemia, the clinical variant c.940A > G (N314D); and that associated with Ashkenazim 5.5 kb deletion (c.[–1041_751del;820+50_*790delinsGAATAGACCCCA]).^{26,33}

The clinical picture and response to a galactose-restricted diet have been noticed to be associated with specific genotypes/phenotypes. The classic galactosemia phenotype is associated with genotype Q188R/Q188R,³⁴ the clinical variant phenotype is an expression of genotype S135L/S135L and the biochemical variant phenotype is typified by N314D/Q188R.²¹

The classic/clinical variant/biochemical variant is classified according to residual erythrocyte *GALT* enzyme activity (e.g., Duarte galactosemia biochemical phenotype has a molecular genotype of N314D/N314D translated into 21–50% reduction of *GALT* activity), the levels of galactose metabolites (e.g., erythrocyte galactose-1-phosphate and urine galactitol) that are observed both off and on a lactose-restricted diet, and the risk of development of acute and chronic long-term complications. Yet, there are exceptions to the association of genotype/phenotype.^{21,34}

The *GALK1* gene is located on chromosome 17q25.1 (OMIM #230200 for homozygous mutations, and OMIM #604313 for phenotype of heterozygous mutations),²⁹ while the *GALE* gene (OMIM #230350) is located on chromosome 1p36,³⁰ with substantial evidence of emerging genotype/phenotype specificity,^{29,30} eg, heterozygous *GALK1* mutations were linked to early-onset cataracts (in 20–55-year-old adults) with no picture of other system effects.

Exposure to galactose

The timing, amount and duration of exposure to galactose affect the extent of damage in infants with galactosemia, with maximum damage incurred by early exposure to larger amounts for a longer duration.^{35,36} Morbidity during

the earliest 10 days of life was reported to reach up to 75% of neonates with galactosemia, with most deaths attributed to sepsis by *Escherichia coli*.³⁷ The damage incurred by the galactosemia–sepsis complex extends beyond hepatocellular necrosis, hemosiderosis, fatty degeneration and acinar formation of hepatocytes to pancreatic islet hyperplasia, renal cortical necrosis, periventricular leukomalacia and meningitis.^{38,39}

High blood galactose-1-phosphate was associated with a high risk of mortality, yet it is not the sole predictor.³⁹ Galactose was found to be toxic to canine and rat sperm and ovaries.⁴⁰

After discontinuation of galactose, some complications are reversed or ameliorated or their progression is halted. Hence, cataracts resolve in 73% of cases⁴¹ and epilepsy can become easier to manage. However, irreversible hepatocellular necrosis and cirrhosis, serious central nervous system injury, microcephaly and motor deficits are not regressive⁷ (Figure 4).

Endogenous galactose and galactitol production

Galactose metabolites, including red blood cell (RBC) galactitol and RBC galactonate, are increased in galactosemia. The accumulation of galactitol in the lens causes cataracts.⁴² Conflicting literature exists. In Duarte galactosemia, where increased concentrations of galactitol and galactonate are reported to correlate with galactose intake but not with any developmental or clinical pathology during early childhood, it is not necessary to adhere to a

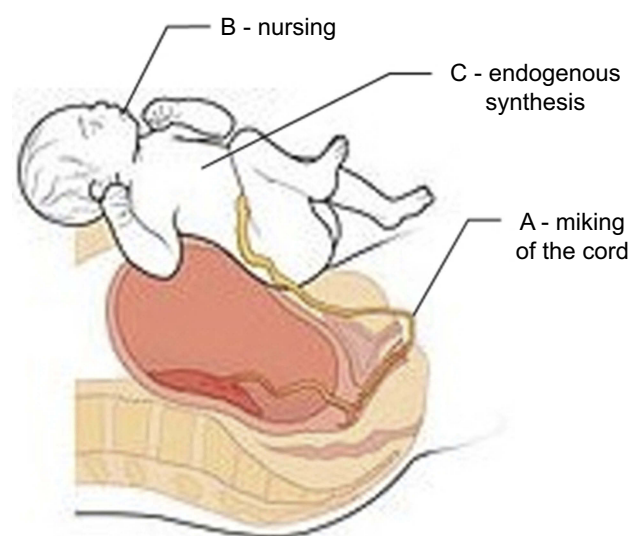


Figure 4 Routes of exposure to galactose in vivo. (A) Milking of the cord. (B) Nursing galactose containing milk. (C) Endogenous synthesis of galactose in vivo.

lactose-restricted diet.⁴³ Yet, idiopathic presenile cataract was reported to result from mutations, especially GALT N314D mutation and galactitol production.⁴⁴ Even with a very strict galactose-free diet, endogenous production of galactose will affect the phenotype, as endogenous galactose production from turnover of glycoproteins and glycolipids initiates a chronic “autointoxication” state^{45,46} (Figure 4).

Residual enzyme activity

While residual enzyme activity ameliorates the severity of galactosemia, it is not the only determining factor for complications, as the amount of ingested lactose is an unquantifiable confounder. Hence, neonates with GALT residual activity are still prone to lethal complications.⁷ Many children with galactosemia have speech, scholastic and behavioral difficulties with varying severity depending on residual GALT activity, which possibly also influences the severity of other long-term complications in classic galactosemia.⁴⁷

Intrauterine protection

It is intriguing that GALT purified from human placenta has the same kinetic parameters, heat stability characteristics and electrophoretic mobility of uridylyltransferase activity as the pure enzyme.⁴⁸ It seems that the placental GALT of a healthy mother protects the fetus with galactosemia during intrauterine life by metabolizing galactose. Hence, the baby is born with normal mentality and no galactosemia complications. Thereafter, the newborn will face the galactose burden, which it cannot handle as decreed by its genotype. As such, placental GALT not only seems to modify the phenotype of galactosemia, but also allows for the neonatal screening and early diagnosis of galactosemia in the newborn during the “window of opportunity” where the baby is phenotypically apparently healthy prior to the complicated phenotype of morbidity and mortality of galactosemia.

Maternal and cord blood contain the same amount of galactose.⁴⁹ It is not clear, however, whether the galactose in the milked cord of the newborn during delivery is related to the very early presentation of classic galactosemia. This argument is especially valid as the maternal galactose in cord blood will provide the earliest exposure to galactose in the newborn. Hence, the baby with galactosemia receiving galactose in cord milk will suffer a very early blow after being protected by the intrauterine placental galactosylation of IgG⁵⁰ and placental galactose limitation.⁵¹ On the other hand, cataract formation has been reported in utero, so placental protection is not

100%.⁵² While women with galactosemia are advised that pregnancy is possible, increases in galactose metabolites do occur. Although neither the mother nor her child is clinically affected in the short term (galactitol crosses the placenta but galactose-1-phosphate does not), long-term effects are yet to be investigated. Oocyte donation is a successful option in primary ovarian failure in galactosemia, that is foreseen to increase number of pregnancies and allow better understanding of placental role.⁵³

Galactose-free versus galactose-restricted diets

Galactosemia is not currently amenable to cure,⁵⁴ and there is no currently researched or approved enzyme replacement therapy.⁵⁵ Nevertheless, complications of galactosemia are potentially preventable by the early prompt introduction of a galactose-restricted diet.^{7,47} While a galactose-free diet was advocated initially, a galactose-restricted diet was recommended as being equally effective and reasonably more achievable as, in any case, the endogenously produced galactose does not allow a galactose-free setting. Moreover, evidence supports that when fruit and vegetables are not restricted from the diet, this does not result in new cataracts or liver diseases. Yet, relaxation of restriction is never recommended.⁵⁶ The galactose-induced feeding difficulties, hepatocellular dysfunction, hypoglycemia, renal tubular dysfunction, cataract and sepsis in the first weeks of life in newborns with galactosemia resolve with the prompt initiation of a galactose-restricted diet, and culminate in serious morbidities and mortality if the ingestion of galactose is not withheld.⁷ Early restriction is not the only determinant, as early detection and intervention do not completely prevent long-term complications, eg, growth delay and low bone mineral density in many patients, primary ovarian insufficiency in more than 80% of girls and young women, mild disorders of speech, cognition and behavior in at least 50% of all patients, and tremor and/or other movement problems in almost 40%.³⁵

Adult tolerance versus neonatal developing brain susceptibility to galactose

Adults with galactosemia develop a certain degree of tolerance to galactose toxicity, although it is not absolute. Hence, strenuous galactose restriction was relaxed to allow some vegetable and fruit galactose intake in adults with galactosemia.⁵⁷ This was an almost unanimous conclusion from different continents, where a spectrum of disabilities

developed in the majority of patients regardless of when treatment was initiated, how tightly the galactose-restricted diet was implemented, or close monitoring.⁵⁸

What is newborn screening?

A lot of diligent effort has been put into defining what qualifies for neonatal screening, as well as its achievable goals.^{59,60} Neonatal screening of apparently healthy infants aims to detect, in a timely fashion, those who are at risk, to provide prompt intervention and to minimize or alleviate the potential morbidity and early mortality of the screened-for disease, while not falsely labeling children. The necessary screening tools need to be evaluated, as the false-negative rate equals the number of sick subjects who will be falsely labeled as “not sick”, who will thus not be subject to early detection and intervention, thereby defeating the purpose of the screening. Not only does the rate of false-negative results miss the diagnosis of those with the disease, it will also make physicians reluctant to consider diagnosing an already screened-for disease as it has already been tested for.⁶¹ Newborn screening spans measurements of weight and height, clinical examination and sophisticated testing for specific diseases, such as phenylketonuria, hypothyroidism, medium-chain acyl-coenzyme dehydrogenase deficiency, cystic fibrosis, and hearing and visual defects. Since the introduction of newborn screening in the 1960s, it has been expanded by the US Department of Health and Human Services and the American College of Medical Genetics and Genomics to include screening for 34 core disorders and 26 secondary disorders.⁶² The development of new therapies and intrauterine diagnosis initiated the expansion of screened disorders. The successful response to the development of highly efficient enzyme replacement therapy for Pompe disease urged approval of newborn screening for Pompe disease in 2015 through a recommended uniform screening panel in the USA. However, the newborn screening has stringent guidelines, according to which samples should be collected within 48 hours and reach the laboratory within another 24 hours, and the results should be communicated to the physician within 5–7 days, depending on the type of screened disease.⁶⁰

Newborn screening has evolved to include a second tier of DNA confirmatory testing in motivated resourceful healthcare systems.⁶²

In developed countries, however, neonatal hyperbilirubinemia does not qualify for contemporary newborn screening despite being responsible for irreversible bilirubin-induced brain damage, because bilirubin-induced brain damage occurs only in the jaundiced baby who is already receiving

medical attention. As a result, screening of anicteric babies is seen as being of no value,⁶³ yet routine bilirubin assessment of neonates is common in hospital-based practice.⁶⁴

Does classic galactosemia qualify for newborn screening?

Galactosemia qualifies for newborn screening as it fulfills both the traditional and new criteria for screening.⁶⁵ Babies are born apparently healthy, with a window of opportunity, after which the baby develops serious morbidities and lethal consequences. Galactosemia is not curable, but its complications are potentially preventable.⁷ Decision-making in enrolling global galactosemia screening, or among specific populations, faces various other implementation challenges⁶⁰ (Figure 5).

Challenges facing newborn screening for galactosemia

Varying incidence of galactosemia across nations

The incidence of galactosemia type I varies across nations, ranging from 1:40,000 to 1:60,000. A higher incidence is reported among those of Irish descent (1:24,000) and the lowest incidence is found among those of Swedish descent, at 1:100,000, and Japanese, at 1:788,000. Many nations worldwide screen for galactosemia on either a governmental or non-governmental basis.^{66–68} The rarity of galactosemia in many societies renders it a low priority in decision-making for inclusion/exclusion in national neonatal screening programs. Galactosemia resulting from galactokinase and epimerase deficiency is even rarer.

Tests used to test/screen for galactosemia

RBC galactose level

Primary screening by assessment of total blood galactose in a dried blood sample is adopted alone or in combination with GALT activity as a screening tool. Total blood galactose assessment is suitable for mass screening, but, it carries high false-positive and false-negative results. Galactose-1-P more than 10 mg/%, is suggestive of galactosemia. Galactose tolerance tests were abandoned as they are ethically unacceptable, given that they induce complications in neonates with galactosemia.⁶⁹

Assessment of metabolic derangement products

Reducing substance in urine. Testing positive for reducing sugars other than glucose is suggestive of galactose, lactose, xylose and fructose. While the test would be positively true for galactosemia, it will also be positive

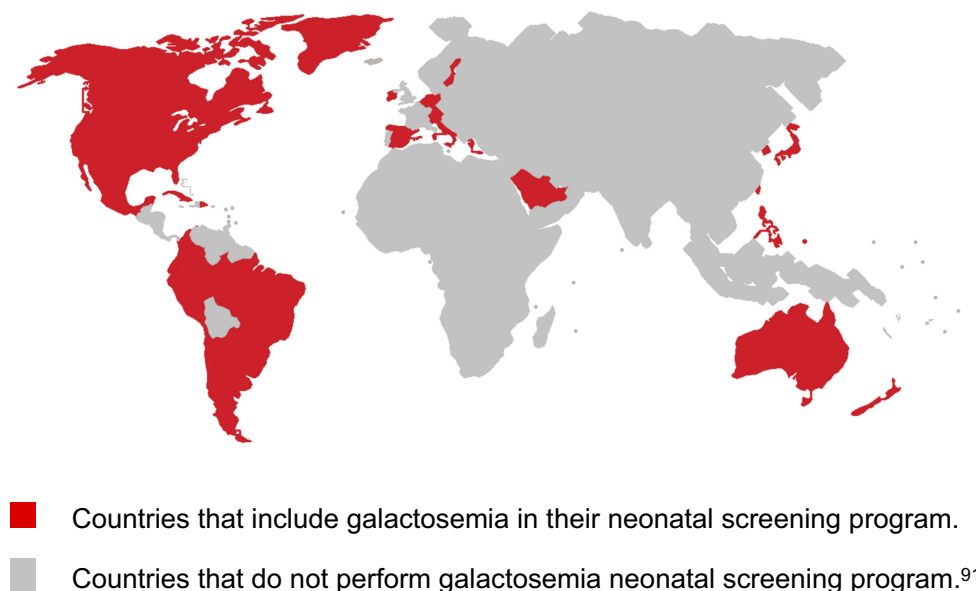


Figure 5 World map of countries screening for galactosemia in neonates.⁹¹

in prematurity,⁷⁰ renal tubular acidosis, in the presence of drugs, eg, valproic acid, amino acids, and in other metabolic diseases; hence, the test is non-specific.⁷¹

Galactitol excretion in urine. Galactitol is a serious neurotoxin that builds up in galactosemia. Boronic acid-based methods and multi-well-based arrays allow rapid detection of galactitol.⁷² It is positive in subjects with galactosemia, yet false-negative and false-positive results are encountered, and hence the tests are non-specific.⁷³ Assessment of galactitol excretion is advised to assure adherence to the galactose-restricted diet, rarely for prenatal diagnosis, and during pregnancy to project cataract development in the offspring of galactosemic expectant mothers.⁷⁴

Hypoglycemia, lactic acidosis and ketonuria. This triad is present in neonates with galactosemia challenged by galactose; however, these factors are present in many inborn errors of metabolism, such as organic acidemias, disorders of galactose metabolism and mitochondrial diseases.⁷⁵

RBC enzyme activity

GALT activity assessment, combined with galactose-1-phosphate in a dried blood spot, is adopted for neonatal screening in many nations, as it can directly detect those with disorders of GALT and indirectly detect those with Duarte galactosemia and disorders of GALK and GALE.⁷⁶

Genetic testing

DNA testing for mutations for galactosemia is available, and is provided for research, diagnostic and prognostic use. The *GALT* gene has 11 exons of 4.3 kb on chromosome 9p13 with more than 250 pathogenic variants, including deletions,

nonsense, missense, frameshift and splice-site variants. The majority (about 85%) have profound enzyme impairment consistent with classic galactosemia, with 61% being missense variants. Many patients (64%) of European descent have the c.563A > G (Q188R) variant. Almost always, the c.404C > T (S135L) variant is encountered in patients of African origin. Other variants associated with near or complete loss of enzyme activity include c.855G > T (K285N), c.626A > G (Y209C), c.413C > T (p.T138M), c.584T > C (L195P) and IVS2-2A > G.5 A deletion of approximately 5.5 kb is common among Ashkenazi Jewish individuals.⁶ The *GALK1* gene has 8 exons of 7.3 kb on chromosome 17q25.1.15. Variants include insertions, deletions and single base changes in RBCs. The variants may produce an insoluble enzyme, while milder phenotypes are characterized by a soluble enzyme with impaired catalytic function.⁷⁷ The *GALE* gene is located on chromosome 1p36.11.⁷⁸

Therefore, most countries rely on primary testing for galactose, galactose-1-phosphate and GALT in RBC activity detection. Whereas a raised sugar content with no GALT activity indicates classic galactosemia, raised sugar with some GALT activity indicates Duarte galactosemia and raised sugar with intact GALT points to galactokinase or epimerase deficiency, requiring further conclusive testing.

Galactosemia variants and false-positive results

Duarte galactosemia is a condition with reduced GALT activity, detected in 11.3–50.0% of galactosemia cases

detected by neonatal screening programs.⁷⁹ A large amount of conflicting literature exists on Duarte galactosemia; some reports consider it absolutely benign with no recommendation for further measures, whereas others demonize it and consider it a condition necessitating life-long galactose restriction.⁷ The knowledge gaps and the number of factors controlling the outcome, as presented earlier (see “What controls the phenotype and outcome of galactosemia?”), make Duarte galactosemia an area of theoretical debate, as those affected appear to be healthy. Hence, some countries advise one-year galactose restriction, while others do not.⁷⁹ Other studies report some differences in socio-emotional development, delayed recall and auditory processing speed between children with Duarte galactosemia and their unaffected siblings,⁸⁰ and more serious problems such as major hepatic, renal and central nervous system complications.⁷ It is not clear whether early exposure to galactose is the determining factor, or whether the restriction of galactose for a few days in those with an initial positive test requiring a second, confirmatory test until the results are available, protects against the serious complications of Duarte galactosemia. Other variants, such as clinical variant galactosemia, exist, albeit less often than Duarte. Despite the residual GALT activity, this condition necessitates a strict galactose-free/restricted diet. The dilemma of variants has led to suggestions of lowering the cut-offs for neonatal screening tests. False-positive tests include the detection of glycogen storage disease type XI.^{81,82}

Cost-effectiveness

An Iranian study estimated that the financial burden of galactosemia was reduced by two-thirds through the introduction of neonatal screening for galactosemia,⁶⁸ compared to 50% in the Philippines.⁸³ The Iranian study, published in 2017, reported that the cost of screening 81,837 neonates in 2010 cost 78,703 USD, saving 19,641 USD per patient annually. The authors estimated the burden of galactosemia with screening at 4222 USD and without screening at 12,615 USD per patient annually.⁶⁸ However, others reported that galactosemia screening was not cost effective but had overall individual and social positive effects in limiting the morbidity and mortality. They reported that each test cost 105 USD per person screened, which was 5 USD more than not testing per person; hence, it did not save money. Yet, the screening detects children who would have died, but who now incur lifetime costs that would not otherwise have been incurred. While this argument is very bold, they concluded that the

program saves 27% of lives that would have been lost, and allows improvement in quality of life that renders galactosemia screening seemingly effective.⁸⁴ Newer technologies with better sensitivity and specificity, with or without a change in the cut-off testing values,⁸² promise reductions in the cost of galactosemia screening. Hence, the question of cost-effectiveness is a relative one.

Outreach logistics

The very early presentation of rapid deterioration and premature mortality dictates a very prompt system of diagnosis and very early institution of galactose-restricted diets. A delay in diagnosis defeats the purpose of neonatal screening and does not prevent the early morbidity and mortality. Thus, program logistics must meet very early prompt screening. Thus, countries that implement screening at day 6 or later, and communicate the primary results within another week, would neither detect nor prevent the initial morbidity and mortality. Nevertheless, such screening would detect those who survived the early mortality to then suffer long-standing mental retardation, and pose personal and societal preventable disease-related ethical, social and financial burdens. The factors affecting sample preservation and transport also affect decision-making. Hence, in Japan, with the lowest incidence of galactosemia,⁸⁵ the galactosemia screening is enforced by law,⁸⁶ whereas in 1997 the UK excluded galactosemia from its national neonatal screening program, replacing it with clinically justified at-risk population screening.⁷⁹

Management shortcomings

A strictly adopted galactose-free diet does not secure the complete reversal or prevention of galactosemia morbidities and mortalities, e.g., primary ovarian insufficiency and speech problems. This provides potential justification against mass neonatal screening, to be replaced by at-risk population screening. Projected causes are the endogenously produced galactose,⁴⁵ the not completely reversible galactose-induced damage prior to diagnosis⁷ and the higher rate of susceptibility to galactosemia during rapid brain development during the first year of life compared to the adult brain.³⁴ The determinants of phenotype and outcome depend on many variables, as outlined earlier (see “What controls the phenotype and outcome of galactosemia?”), rendering compliance to diet a predictor of outcome, but not the only predictor of outcome. Whereas the unguaranteed management/diet–outcome correlation provides a justification and an argument against mass neonatal

screening, it provides more evidence that management/diet ameliorates and avoids a lot of suffering and prevents unnecessary deaths.⁵⁸

Contemporary healthcare: is there place for galactosemia screening?

Health and wealth usually occur together; hence, for societies with greater wealth, galactosemia screening, irrespective of cost, will remain an ethical obligation. The globalization of the world economy and the mutual interests among nations with diverse ethnicity and geography dictate a change in the rate of consanguinity as well as a change in patterns of international and transnational marriages.⁸⁷ These changes usher changes in the incidence of galactosemia in any given society. Advances in technology promise easier, cheaper and more prompt diagnosis of galactosemia. More countries have recently included galactosemia neonatal screening within their neonatal screening programs. It seems very unethical to discuss not screening for galactosemia under the pretext of economic burden, while 13.6 trillion dollars of the world economy is consumed by war.⁸⁸

Conclusion

Galactosemia is an inherited disease with potentially preventable grave suffering, morbidity and mortality that urges early diagnosis and intervention early in life; otherwise, the afflicted individuals, their family and society in general will suffer greatly. Despite the difficulties, challenges and complexities, galactosemia screening is advised. Galactosemia screening by testing galactose or galactose-1-phosphate and GALT detects classic galactosemia, and other forms, as whenever GALT is normal in the presence of high galactose, then subsequent testing for GALK and GALE follows. The future promises advances in technology and screening tests. Globally, many societies are collaborating to provide support worldwide for emerging neonatal screening programs.⁶⁶ More countries have recently adopted the inclusion of galactosemia screening within their national neonatal screening programs. In any society where national neonatal screening is not implemented, health authorities should consider screening the population at risk for galactosemia.

Abbreviations

GALE, galactose 4-epimerase; GALK, galactokinase; GALT, galactose-1-uridylyltransferase; IgG, immunoglobulin G; UDP, uridine diphosphate.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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