UK National Screening Committee

Screening for galactosaemia

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Executive Summary

This document reviews the literature published since 1997 relating to newborn screening for galactosaemia.

Galactosaemia is a genetically inherited metabolic condition in which an enzyme deficiency causes excessive amounts of galactose, a type of sugar commonly derived from lactose, to accumulate in the blood and other tissues. Adequate enzyme function is essential for the conversion of galactose to glucose.

An excessive amount of galactose can be toxic and cause acute illness such as vomiting and diarrhoea, liver failure and sepsis in the first weeks of life. As a consequence, galactosaemia is a cause of neonatal mortality. The condition can cause chronic problems such as cataracts, learning difficulties, growth retardation, speech and behaviour problems and, in women, premature ovarian insufficiency. A galactose restricted diet has been shown to reduce the severity of the neonatal symptoms. However, this is not case for the long term outcomes from galactosaemia.

Although deficiencies of three different enzymes can cause increased levels of galactose only one, galactose-1-phosphate uridyl transferase (GALT), is the main focus of discussion in relation to newborn screening. Some genetic variants can also result in more moderate reductions of GALT activity, the clinical significance of which is uncertain. The Duarte variant g is the most frequently observed, and detection of variants such as this has been an important dimension in discussions of newborn screening.

The current UK recommendation is that newborn screening for galactosaemia should not be implemented in the UK. This recommendation is based on a 1997 HTA report which identified a number of inter-related issues preventing the development of a screening programme. For example the HTA reported that:

- while GALT deficiency was sufficiently well understood, the incidence of variants of uncertain clinical significance was higher than that of GALT deficiency. As such, screening for galactosaemia may identify more cases of uncertain significance than the target condition.
- although the available tests for GALT deficiency appeared reliable, a proportion of affected babies would present with symptoms before the testing process was complete. This would limit the impact of newborn screening on the acute neonatal manifestations of the condition.
- a galactose restricted diet had not been shown to significantly improve long term outcomes from GALT deficiency, nor has early treatment as a consequence of screening been shown to improve outcomes compared to treatment following clinical detection of symptomatic cases.

This review explores the volume, quality and direction of the literature published since the HTA study and focuses on key questions relating to that study's conclusions. The aim of the review is to inform discussion on whether the recent evidence suggests a need to reconsider the current screening recommendation. The conclusion of the review is that this is not the case. The

volume of literature was very limited and, while it imposed limitations on the ability to draw clear conclusions, appeared to confirm the conclusions of the HTA review.

For example:

- no new evidence was identified to suggest that available dietary treatment can prevent long term clinical or developmental complications, either in screen or clinically detected classic GALT deficiency.
- it was not possible to identify a median age of symptomatic presentation of GALT because many of the publications were reports of screening programmes. In these reports the proportion of babies presenting before completion of the screening process ranged from 22% to 74%. Where newborn screening was not undertaken one paper reported that 47% of cases presented within eight days following birth.
- the reported rate of Duarte galactosaemia was lower than that reported in the HTA study, however, current testing options would continue to identify the Duarte variant for which no clinical guidelines were found, and the outcomes of which appear unaffected by treatment. Partial GALT deficiencies continue to be an area of uncertainty.
- the debate about newborn screening has changed considerably since the publication of the HTA study. There is now a focus on a wider range of benefits which screening may bring by reducing the diagnostic odyssey, informing future reproductive decisions and identifying potential research subjects. However the literature search did not identify any publications addressing these issues in the specific context of Galactosaemia. A UKNSC document exploring these themes more generally can be accessed at www.screening.nhs.uk/policydb_download.php?doc=455

The review suggests that the body of evidence identified by the literature search is an insufficient basis on which to change the current screening policy.

Introduction

This review will assess newborn screening for galactosaemia, a galactose metabolism disorder. Galactosaemia can arise due to inherited deficiencies in any of three enzymes along the galactose metabolic pathway: galactose-1-phosphate uridyl transferase (GALT), galactokinase (GALK), and UDP-galactose 4- epimerase (GALE). Mutations in the genes coding for these enzymes can cause a substantial reduction in enzyme activity, and an associated increase in galactose and other metabolites. This review will specifically address screening for classical galactosaemia due to GALT deficiency, and examine the impact of screening programmes as they relate to partial GALT deficiency.

In 1997, classic galactosaemia was included in a Health Technology Assessment (HTA) review of newborn screening for inborn errors of metabolism[1]. The review assessed six main criteria to decide if galactosaemia should be included in newborn screening:

- Clinically and biochemically well defined disorder (met)
- Known incidence in populations relevant to the UK (met)
- Disorder associated with significant morbidity or mortality (met)
- Effective treatment available (not met)
- Period before onset during which intervention improves outcome (partially met)
- Ethical, safe, simple and robust screening test (partially met)

The 1997 HTA review concluded that neonatal screening was not justified based on the available evidence, as the incidence of galactosaemia in the UK was substantially lower than other inborn errors of metabolism (e.g. phenylketonuria [PKU], congenital hypothyroidism), and that the evidence, though limited, suggested that available treatments did not improve long-term outcomes or that earlier treatment following newborn screening programmes improved long-term outcomes. The review also identified conflicting reports regarding the ability of screening to prevent severe symptomatic presentation during the neonatal period, and uncertainties surrounding the identification and treatment of partial GALT deficiency as part of galactosaemia screening.

Following the 1997 review, the UK National Screening Committee (UK NSC) elected to not recommend newborn screening for galactosaemia, and the Scottish programme of routine testing of newborn bloodspot specimens for galactosaemia was discontinued as of March 2002. In the UK it is recommended that bloodspot specimens found to have both elevated phenylalanine and tyrosine levels should be tested for galactosaemia.

The current review will consider whether the volume and direction of the evidence produced since the 1997 HTA review suggests that the previous recommendation should be reconsidered. Five main criteria will be considered, with particular focus given to areas the 1997 review identified as uncertain, or supported by insufficient evidence. The main criteria and key questions are:

Criterion	Key Questions (KQ)	# KQ Studies Included
2 - The epidemiology and natural history of the	What is the median age at presentation of classic galactosaemia?	5

condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage		
5 - There should be a simple, safe, precise and validated screening test	Do current screening options identify newborns with partial GALT deficiencies (e.g. those of uncertain clinical significance)?	7
10 - There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment	Has evidence been produced since the 1997 HTA report that demonstrates that treating screen detected GALT deficiency improves short and long term outcomes compared with clinically detected GALT deficiency?	4
	Is there any evidence of benefit from treatment of partial GALT deficiency?	2
11 - There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	Are agreed evidence based policies available covering the treatment of screen detected infants with partial GALT deficiency (e.g. those with over 5% of normal GALT enzyme activity)?	2
15 - The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)	Have any papers been identified which draw attention to the wider benefits of newborn screening for galactosaemia for example is there clear evidence that the information gained from screening affects reproductive decision making?	0

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

1. The condition should be an important health problem

Galactosaemia is an autosomal recessive disorder that affects the galactose metabolic pathway, also known as the Leloir pathway. Classic GALT deficiency reduces the ability to convert galactose to glucose, and results in raised blood galactose, galactose-1-phospate and other metabolites.[1] The 1997 HTA report estimated the UK incidence of classic galactosaemia as 1:44,000, the incidence of partial galactosaemia reportedly ranged from 1:3,800 to 1:9,200.[1]

Main classic galactosaemia genotypes

Hundreds of genetic mutations have been described that are associated with classic galactosaemia due to GALT deficiency. The frequency of these mutations vary according to

population, with the Q188R mutation being the most frequent in Caucasian populations; other frequent classic galactosaemia mutations include K285N, which is common in Central Europe, S135L, which is frequent amongst African Americans and is associated with a milder form of the disorder, and L195P.[2, 3] The homozygotic *Q188R/Q188R* mutation results in a complete lack of GALT activity and poor clinical outcome, while compound heterozygotic forms are associated with varied, but still profound, reductions in GALT activity.[3]

The 1997 HTA review reported that galactosaemia is clinically and biochemically well defined but that the genotype / phenotype association is not well understood. [1] A 2006 narrative review of galactosaemia suggests, however, that there is "a clear genotype-phenotype relationship. p.Q188R is associated with a severe biochemical and clinical genotype, with nearly undetectable residual erythrocyte GALT activity in homozygotes, whereas the p.S135L mutation is associated with a milder clinical outcome, with no detectable GALT activity in erythrocytes but a residual activity of 5% in leukocytes."[4] Further information on the genotype-phenotype relationship for other GALT mutations was not presented in the narrative review. Uncertainty surrounding the genotype-phenotype relationship is not further explored in this report as it was not identified as a key focus for the current update review.

Clinical course of untreated classic galactosaemia

The natural history of classic galactosaemia is marked by lethargy, poor feeding, jaundice and hepatomegaly during the first days of life following ingestion of galactose from milk.[5] If untreated, classic galactosaemia is life threatening, with acute toxicity symptoms leading to clinical presentation including hepatocellular insufficiency, hypoglycaemia, renal tubular dysfunction, muscle hypotonia, and *E. coli* septicaemia by the second week of life[3-5].

Galactosaemia variants

Partial galactosaemia is more frequent than classic GALT deficiency, and is most commonly due to the Duarte variant (i.e. N314D mutation), which can take two forms: the less severe Duarte-1 (Los Angeles mutation) or the Duarte-2.[3] Newborns with partial galactosaemia tend to be compound heterozygous for a Duarte mutation and a classic galactosaemia mutation (e.g. *Q188R/N314D*).[6] These patients, referred to as D/G variants, are reported to exhibit approximately 14-25% GALT activity.[2, 7]

Clinical course of partial galactosaemia

Patients with partial GALT deficiencies (e.g. Duarte galactosaemia) do not exhibit the acute neonatal symptoms associated with classical galactosaemia, despite reduced enzyme activity. The 1997 HTA reported that "these partial deficiencies are of doubtful clinical significance",[1] although this assertion is debated in the literature. While galactose tolerance is reduced, and blood galactose and galactose-1-phosphate levels may be elevated during infancy, the previous review reported that adults with partial GALT deficiencies appear healthy. However, the review quoted two studies, with divergent views of treatment of partial GALT deficiencies, one of which recommended treatment to avoid litigation, the other which found no evidence of benefit following four months of lactose restriction.[1]

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Frequency, distribution and populations at high risk for GALT deficient galactosaemia

The previous evidence review for galactosaemia screening reported a UK incidence of GALT deficient galactosaemia of 1:44,000.[1] No UK specific incidence or prevalence figures were identified in the updated search, however, based on studies identified in European and North American populations, the incidence of classic galactosaemia ranged in screened populations from 1:16,476 to 1:103,000. The reported frequency of partial or Duarte variant galactosaemia was substantially lower than that reported in the 1997 HTA report (1:7,736 to 1:171,429 vs. 1:3,800 to 1:9,200); the current review figures reflect frequency of screen detected partial or Duarte galactosaemia, and are thus influenced not only by the true population frequency, but also by the screening methods and cut-off values utilised in each individual programme.

Table 1. Frequency of classic and variant galactosaemia

Country	Overall or classic GALT deficiency		Partial or D/G GALT deficiency	
	1997 HTA[1]	Current review (screen detected)	1997 HTA[1]	Current review (screen detected)
UK	1:44,000	-	-	-
Ireland	1:26,000	1:16,476[8] to 1:23,000[9]	-	1:171,429[9]
Sweden	1:89,000	1:103,000[10]	-	-
Germany	1:44,000	-	1:9,200	-
Greece	-	1:22,182[11]	-	1:33,273 (D/G)[11] 1:49,910 (D/D)[11]
Estonia		1:19,700[12]		
Australia	1:35,000	-	1:3,800	-
Canada	-	1:36,200[13]	-	1:36,200[13] probable 1:82,742[13] confirmed
USA	-	1:47,765[14]	-	1:144,444 (D/G)[15] 1:7,736[6]
Japan	1:667,000	1:1,116,306*[16]	-	1:14,640 (partial)[17] 1:53,681 (D/G)[17]
Philippines	-	1:88,495[18]	-	1:15,710[18]
Iran	-	1:6,000[19]		
Egypt		1:1,794[20]		

* Galactosaemia types reported as Type I, Type II, and Type III; taken based on OMIM naming conventions to refer to GALT, GALK and GALE deficient galactosaemia, respectively. Type II (assumed GALK deficiency) frequency reported as 1:637,889.

The 1997 HTA review reported that partial galactosaemia variants are 5 to 10 times more common than total GALT deficiency, and that the detection of these partial variants was a key uncertainty of galactosaemia screening programmes.[1] Across the European and North American

NBS programmes identified in the current review, 11.3% to 50.0% of screen detected galactosaemia cases were partial GALT or Duarte variants.

Table 2. Clinical presentation and distribution of classic galactosaemia and partial variants across positive screen results

Country	Day of screening	Median age at clinical presentation (days)	% of cases symptomatic at diagnosis	Total detected GALT deficiencies	Classic galactosaemia (%)	Partial or Duarte variants (%)
Ireland[9]	NR (3-5 days in other report of Irish NBS programme[8])	8 (at diagnosis, routine screening) 2.5 (at diagnosis, high risk screening)	74.5%	62	55 (88.7%)	7 (11.3%)
USA[15]	-	-	-	32	23 (71.9%)	9 (28.1%)
Canada[13]	-	-	-	32	16 (50.0%)	16 (50.0%) probable; 7 of which confirmed (21.9% of total cases)
Greece[11]	3-5	NR	22.2%	17	9 (52.9%)	8 (47.1%)
Germany[21]	5	NR	28.3%			
Non universal screening approaches						
Canada[22]	NA (selective screening, all hospitalised newborns)	8 presented within first 2 weeks of life	94.4%	-	-	-
Turkey[23]	NA (clinical detection)	Median 13 (range 3 to 23)	NA	-	-	-

Two major high risk groups were identified in the literature. In Ireland, traveller populations are at greater risk for classic galactosaemia than non-traveller populations (1:430[8] and 1:700[9] vs. 1:23,000[9] to 1:33,917[8]). Consanguinity also increases the risk for classic galactosaemia, with data from Turkey[23], Egypt[20] and Iran[19] indicating that 59%[23] to 89.5%[20] of cases were born to consanguineous parents.

Key question: age at clinical presentation

UK screening practice is to collect bloodspot specimens at 5 to 8 days of age, with transport to the screening laboratory in no more than 4 days and return of results to the Child Health Record Department in no more than 4 days. As the natural history of classic galactosaemia is marked by acute toxicity symptoms within the first two weeks of life,[3, 4] a key question addressed by the current evidence review surrounds the median age at clinical presentation for classic galactosaemia, to evaluate whether current UK DBS practices will detect pre-symptomatic cases.

Thirty publications were assessed at full text for relevance to Criterion 2; 12 of these were included for context and frequency of classic and partial GALT deficiencies, and five were included for the key question regarding age of clinical presentation. The key question studies were observational designs and included four retrospective cohort studies[9, 11, 22, 23] and one before and after study[21].

This represents a limited number of studies reporting the median age of clinical presentation for classic galactosaemia, or the proportion of cases that were symptomatic at diagnosis. Three NBS programmes in Europe performed galactosaemia screening on day 3 to 5 of life (i.e. earlier than the current UK screening process), and reported that 22.2% to 74.5% of cases were symptomatic at time of diagnosis (see Table 2).

The study with the highest proportion of cases exhibiting clinical galactosaemia symptoms at diagnosis was based on selective testing of all hospitalised newborns under 2 weeks of age.[22] The focus on high risk patients in a hospital setting would influenced the high proportion of symptomatic cases seen. No studies were identified that assessed mean age at clinical presentation in unscreened populations, although one study found that 47% of classic galactosaemia patients detected through selective testing upon hospital admission were symptomatic within the first two weeks of life. Additionally, no studies were identified that reported mean age of symptomatic cases at diagnosis in populations screened at days 5 to 8, as would occur if galactosaemia screening were introduced in the UK.

The identified evidence did not specify the nature or severity of symptoms among those presenting clinically prior to confirmation of screening results, nor did any of the publications report on the genotype-phenotype relationship amongst the screen detected cases.

Overall, the identified evidence was limited, but suggests that a substantial proportion of screen detected galactosaemia cases will be symptomatic by the time screen results are confirmed and diagnosis is made.

Summary Criterion 2: Partially met. The 1997 HTA review suggested that the clinical and biochemical features of galactosaemia had been described, and the frequency and distribution of classic galactosaemia in the UK had been established. The reported frequency of partial galactosaemia appears to be lower than that reported by the 1997 HTA review in European and North American studies. No studies exploring the UK epidemiology were identified by the literature search.

The key question in this section concerned the mean age of clinical presentation of classic galactosaemia. There is very little evidence on this issue in the absence of a population wide screening programme. Most of the limited body of evidence related to the percentage of screen detected cases that were symptomatic at diagnosis. This is based on reports from programmes that collect DBS specimens at 2 to 5 days, earlier than current UK practice. Based on the identified evidence, there is uncertainty surrounding the mean age of clinical presentation and on the impact of later screening protocols on the percentage of cases that would have presented clinically prior to the receipt of screen results in the UK.

5. There should be a simple, safe, precise and validated screening test

GALT deficient galactosaemia screening markers

Several markers have been used in galactosaemia screening programmes. The enzyme deficiency that causes galactosaemia leads to an accumulation of two main metabolites, galactose (Gal) and galactose-1-phospate (Gal-1-P). Serum Gal and Gal-1-P levels are frequently used as either primary or secondary screening targets using bacterial inhibition assays, fluorescence assays or colorimetric enzymatic assays.[9-11, 14, 17-21] Use of Gal and Gal-1-P as markers will result in the inclusion of galactosaemia due to GALK and GALE deficiencies, and can result in false negatives due to feeding behaviours (e.g. difficulty feeding, use of soya or other lactose-free formula). The 1997 HTA report suggested that colourimetric enzymatic microassays for serum Gal and Gal-1-P, and a fluorescent enzymatic assay for the same markers performed well. The review suggested, however, that a proportion of compound heterozygotes would be identified as well, including Duarte galactosaemia (D/G) variants.

An alternative marker is measurement of the enzyme itself. Galactose-1-phosphate uridyl transferase (GALT) activity has been increasingly used as a either a primary or secondary screening marker (alone or in combination with Gal and Gal-1-P levels), assessed by the Beutler assay.[6, 9, 10, 15, 22] Use of GALT activity as a primary screening marker excludes the detection of GALK and GALE deficient galactosaemia, and detection of partial galactosaemia will depend on the threshold selected for the testing strategy. While the test is not affected by galactose intake/feeding behaviours, sample degradation due to temperature and humidity has, however, been reported as a potential issue with this marker.[24]

Assessing dried blood spot (DBS) samples directly for common GALT mutations (e.g. Q188R , S135L, K285N, L195P and the N314D Duarte variant mutation) has been proposed as a potential testing strategy for newborn screening programmes,[25] however no studies were identified that assessed the performance of such a strategy in current screening practices.

While reliable detection of classic GALT deficiency remains important, the key uncertainty emerging from the 1997 HTA review was regarding the detection of newborns with partial GALT deficiencies that may be of uncertain clinical significance (e.g. those with 5% to 20% GALT activity). This section covers the performance of screening techniques in terms of detection of classic GALT deficient galactosaemia, but focuses the detection of compound heterozygous and Duarte variants among positive screen results.

Detection of classic GALT

The reported testing strategies were broadly in keeping with those reported in the HTA. These were Gal / Gal-1-P or GALT activity testing strategies alone or in combination. No new options such as tandem mass spectrometry (MS/MS) were identified in existing screening programmes,

although a multiplex enzyme assay for galactosaemia using ultra performance liquid chromatography (UPLC) MS/MS has been reported in laboratory studies.[26]

Twenty publications were assessed at full text for relevance to Criterion 5, seven of which were included. Cohort studies that assessed the performance of various tests as part of newborn screening programmes for galactosaemia were included, with emphasis given to those studies that assessed the performance of these tests in terms of detecting partial galactosaemia. Laboratory based studies that assessed the detection capacity of new tests or techniques on a sample of galactosaemia patients (i.e. not in a screening context), or which evaluated post-screening diagnostic tests were excluded.

The number of studies included represents a low volume of evidence; two papers reported on programmes that screened for Gal and Gal-1-P,[11, 18] three papers assessed a GALT activity testing strategy,[10, 15, 21] the remaining two papers[9, 27] did not specify the screening marker, although based on the use of the bacterial inhibition assay, it is assumed that Gal and Gal-1-P levels were the primary target.

The studies reported the experience of implemented screening programmes and were not test accuracy studies per se. They included five retrospective cohort studies,[9-11, 15, 27] one prospective cohort study,[18] and one before and after study.[21]

Lack of sufficient data was the main limitation of the evidence identified regarding screening tests for classic GALT deficiency. The majority of studies provided limited information on the test utilised and its cut-off value, or insufficient information on the number of neonates screened and the distribution of positive and negative results. As such, assessing test performance (sensitivity, specificity, positive predictive value or negative predictive value) and synthesising performance across test options was not possible (see table 3).

In addition the categorisation of galactosaemia variants was unclear in some studies and outcome reporting was complicated by the inclusion of GALK and GALE in others.

Detection of Duarte galactosaemia

Four of the seven identified studies provided sufficient information to assess the proportion of Duarte galactosaemia (either D/G or D/D) cases among positive screen results (see Table 3).

The two programmes that employed either primary or simultaneous GALT activity measurement reported lower detection of D/G or D/D cases among positive screens (11.3% to 13.0%), while the two programmes that assessed Gal and/or Gal-1-P reported a higher proportion of screen positive results as having Duarte variants (45.5% to 66.7%).

However, a number of factors affect the reliability of these conclusions. For example lack of confirmatory genotyping across all studies meant that some partial galactosaemia cases were reportedly as likely Duarte variants. In some studies no information on the detection of any Duarte variants was provided and it is unclear whether this is because no D/G cases were detected or due to selective reporting of classic galactosaemia cases only. The inclusion of GALK and GALE in the screening and diagnostic process was reported to detect additional cases of Duarte variants in one study**.**[15]

Table 3. Performance of seven screening tests for galactosaemia and detection of partial variants

Country	Test timing	Test	Cut-off value(s)	Sn (%)	Sp (%)	PPV (%)	NPV (%)	% Duarte among positives
	Gal and Gal-1-P							
Greece[11] NB. Programme screened for GALE deficiency as well.	3-5d	Gal and Gal-1-P (Colourimetric microassay)	1. ≥6.5mg/dL 2. 4.47 to 6.49 mg/dL re-test 3. Enzyme analysis (confirmatory; method NR)	-	99.75%*	-	-	45.5%
Philippines[18]	48-72h	1. Gal and Gal-1-P (test NR) Confirmatory test GALT activity (Beutler) and galactose metabolites (TLC)	1. ≥1.5mmol/L with feeding OR ≥1.0mmol/L without feeding			16.7%*∫	-	66.7%*∫
	GALT Activity							
Sweden[10]	To 2007 ASAP post-72h After 2007 ASAP post-48h	*1986 to 1991* 1. GALT activity (Beutler) 2. Gal, Gal-1-P *1992 to 2010* 1. GALT activity (Beutler) 2. GAL-DH Gal, Gal-1-P (confirmatory)	*1986 to 1991* 1. <30% 2. >0.6mmol/L, >0.60mmol/L *1992 to 2010* 1. <15% 2. ≥2mM Gal Confirmatory: >0.5mmol/L, >1.5mmol/L	- -	- -	3.6%* 64.3%*	- -	-

USA[15] NB. Total Gal cut-off used for GALK and GALE detection as well	NR	1.1 Total Gal (free Gal plus Gal-1-P) 1.2 GALT activity (simultaneous testing) 2. Genotype (confirmatory)	1.1 ≥1.110 mmol/L 1.2 ≤40µmol/L 2. NA	-	-	87.0%*	-	13.0% of GALT testing portion* 4.3% of total screen positives*
Germany[21]	5d	GALT activity (Beutler) Some use of: Substrate test (Paigen) Gal and Gal-1-P (Colourimetric microassay)	NR	98.0%*	-	-	-	-
	Unknown screening regimen							
USA[27] 1993 and 1994 all values for classic galactosaemia	NR	NR	NR	*1993* 100% *1994* 100%	*1993* 99.7% *1993* 99.7%	*1993* 0.57% *1994* 0.53%	- -	-
Ireland[9]	NR	Gal and Gal-1-P (targets assumed, bacterial Inhibition assay used) GALT activity (Beutler test) for high risk neonates and as confirmatory test for others	NR	91.7%*	-	-	-	11.3%*
* **Reviewer calculated;** ∫ Includes 1 GALK case in denominator								

Summary: Criterion 5 uncertain. The 1997 HTA review suggested that testing options for classic GALT deficiency were reliable. The studies identified in the current review report results of comparable approaches to screening. However insufficient data was presented in the studies to assess the key test characteristics or performance criteria. In addition partial galactosaemia variants continue to be detected by current screening options.

Screening primarily for galactose and galactose-1-phosphate via colourimetric microassays or other tests can lead to low positive predictive value and a high proportion of D/G variants among the positive screen results. Testing primarily for reduced GALT activity using the Beutler test (either alone or in combination with Gal and Gal-1-P testing) appears to be associated with an increased positive predictive value and a reduced proportion D/G cases among positive screen results. Lower GALT activity threshold (e.g. 15% vs. 30%), or higher Gal and Gal-1-P thresholds (Gal >0.5mmol/L, Gal-1-P >1.5mmol/L) may improve test performance in terms of PPV and reduced detection of Duarte galactosaemia and other variants of uncertain clinical significance. No studies were identified which explored the possibility of excluding variants of uncertain significance.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The treatment for classic galactosaemia centres on dietary restriction of galactose, primarily via lactose restriction. The 1997 HTA report found that such a diet leads to the resolution of early manifestations of the disease, including cataracts and organ dysfunction, and can prevent their recurrence. The review suggested that the main benefit of screening, for those detected prior to onset of symptoms, would be prevention of acute neonatal presentation but that this has little long term benefit in comparison to outcomes in those identified clinically; this may be due to endogenous production of galactose that would not be altered by dietary galactose restrictions.[1] It has also been suggested that the reduced cognitive function among galactosaemics "may be initiated by an *in utero* toxicity of endogenously formed galactose"[28], however, no studies were identified that tested this hypothesis.

The 1997 HTA report concluded that there was not an effective treatment in terms of the development of long term outcomes for classic GALT deficiency and that there were uncertainties relating to the treatment of partial GALT deficiency. This was a key consideration in the report's conclusion that screening was not justified. As such, this review addresses two main questions surrounding treatment for classic galactosaemia and any partial galactosaemia variants detected by a screening programme.

Twenty-five publications were assessed at full text for relevancy to Criterion 10, seven of which were included. Studies that evaluated the effect/association of galactosaemia treatment (i.e. galactose restricted diet) on short- and long- term outcomes (including clinical, developmental, functional and health related quality of life outcomes) were selected. Particular emphasis was given to studies that compared treatment and outcomes between screen and clinically detected patients. Studies which reported only biochemical outcomes only (i.e. treatment effect on Gal, Gal-1-P, galactitol or other metabolites, or GALT activity) were excluded.

Key Question 10.1: Has evidence been produced since the 1997 HTA report that demonstrates that treating screen detected GALT deficiency improves short and long term outcomes compared with clinically detected GALT deficiency?

No studies were identified that statistically compared the effect of dietary galactose restriction on short and long term outcomes between screen and clinically detected classic galactosaemia patients. Four studies (one prospective cohort, one retrospective cohort, one before and after study and one case series) were identified that assessed the impact of dietary galactose restriction on clinical, cognitive and developmental outcomes among patients with classic galactosaemia.

Overall, these studies indicate that screen detection of classic galactosaemia and subsequent dietary galactose restriction:

- appears to reduce neonatal mortality compared to clinical detection and treatment,[21]
- is not associated with longer term developmental outcomes including IQ[8, 21, 28], speech or language disorders[8], or Hypergonadotrophic Hypergonadism (HH) among older females.[8]

The limited number of studies were observational, and generally retrospective in nature, providing a low level of evidence for the dietary treatments of this condition.

In addition to the quantity of studies, several key limitations across the body of evidence exist. First, limitations related to study design and analysis included the small number of cases in each study (n= range: 5 to 148), and the main analyses being descriptive only, with limited statistical comparisons. One study suggested that timing of treatment affected long term developmental outcomes, but did not provide statistical comparisons or delineation of results by timing of treatment or screening group, so the impact of screening and treatment on long term developmental outcomes is unclear.

Second, due to limited reporting on study methodology, it is unclear how well the participants adhered to the diet, and whether adherence had an impact of patient outcomes. Furthermore, some studies included participants from before and after the introduction of newborn screening programmes, but did not sufficiently report the detection status of patients for whom long-term results were presented.

Overall, the limited body of evidence suggests that newborn screening and subsequent dietary treatment may be associated with improvements in terms of mortality during the neonatal period. The benefit of dietary galactose restriction in terms of preventing long term developmental, hormonal and other complications has not been established since the 1997 HTA review.

Table 4. Outcomes among screen detected classic galactosaemia patients on a galactose restricted diet
Source: Coss et al (2013)[8]

Outcome (age group)	Prevalence (%)		
	Overall	Non-Traveller	Traveller
Speech or language disorders (≥2.5y)	49.6%	47.6%	51.9%

Osteopenia and osteoporosis (≥10y)	NR	39.6%*	14.7%*
Below average IQ (6 to 12y)	100%	NR	NR
Below average IQ (≥12y)	73.3%	NR	NR
HH (females ≥13y)	91.2%	87.0%	100.0%

* Significant difference between Non-Traveller and Traveller patients

Table 5. Outcomes among five selective-screening detected classic galactosaemia patients treated with a less restrictive galactose-limited diet
Source: Krabbi et al (2011)[29]

Patient	Age at Dx	Developmental	Ophthalmological	FSH levels
1	Prenatal	Normal	Normal	-
2	8 days	Normal	Normal	Premature ovarian insufficiency
3	2 weeks	Mild speech delay, Cognitive function deficit, Focal epilepsy (Dx at 4y)	Normal	-
4	4 weeks	Normal	Normal	NA (male)
5	6 weeks	Moderate mental retardation, Verbal dyspraxia, Ataxia	Bilateral cataracts	-

Summary: Criterion 10.1 Unchanged since previous review for classical GALT deficiency. No studies were identified that directly compared the efficacy of dietary galactose restriction as treatment for screen vs. clinically detected classic GALT deficiency, the 1997 HTA review found that this treatment was effective at reversing acute complications during the neonatal period, but that there was limited evidence of long term benefit. No new evidence was identified since the previous review to suggest that available dietary treatment can prevent long term clinical or developmental complications, either in screen or clinically detected individuals.

Key Question 10.2: Is there any evidence of benefit from treatment of partial GALT deficiency?

The 1997 HTA concluded that there were uncertainties regarding the clinical significance and treatment of partial GALT deficiencies. As some partial galactosaemia cases are detected by current screening strategies (see Criterion 5), determining the effect of treatment is a key focus of the current review.

Two retrospective cohort studies[2, 6] were identified that assessed the impact of dietary galactose restriction for the first year of life on clinical, cognitive and/or developmental outcomes among patients with Duarte galactosaemia. Overall, these studies found that:

- A lactose free diet for the first year of life is not associated with improvement in either short- or long-term clinical or developmental outcomes up to age 6[2]

- A higher percentage of Duarte galactosaemia patients may utilise special education services up to age 10 compared to the general population, despite galactose restriction during the first year of life[6]

Again, this represents a limited body of evidence on the impact of treatment, which does not include treatment for other forms of partial galactosaemia. Several additional limitations were identified across the studies:

Both studies were small (n= range: 28 to 59), and neither provided follow-up of patients into adulthood. The single significant outcome observed across the two studies is likely influenced by reporting bias, as the assessment was based on parental report and not objective measures.

The validity of outcome assessments was a limitation in both studies, due to the use of standardised developmental tests in a young participant group (validity of IQ tests in this age group not confirmed)[2] and the use of educational enrolment databases as a proxy for speech and other developmental deficits.[6]

Statistical analysis was provided in one study only, and it is unclear whether the non-significance of the differences reported in this study were due to the small number of participants, the validity of developmental outcome assessment measures or if it represents a true lack of difference between the treated and untreated groups.[2]

Neither study provided information on diet adherence, so the influence of this factor on assessed outcomes is unknown.

Overall, the limited body of evidence suggests that a lactose free diet in the first year of life may not be associated with short- or longer-term clinical or developmental outcomes among children with Duarte galactosaemia. Given the limited evidence identified, uncertainty remains regarding the benefits of treatment for partial GALT deficiency due to the lack of randomised controlled trials or high quality prospective cohort studies with robust statistical analysis of clinical and developmental outcomes in this population.

Summary: Criterion 10.2 not met for partial GALT deficiency. Data is limited but suggests that dietary treatment initiated within the first 10 days of life and maintained throughout the first year seems to have no effect on clinical or developmental outcomes among Duarte galactosaemia patients aged 1 to 6 years. Due to a lack of comparison with untreated Duarte galactosaemia patients, it is uncertain whether use of special education services varies according to treatment status, or if this outcome is unrelated to treatment in Duarte galactosaemia patients.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Four publications were assessed at full text for relevancy to Criterion 11, two of which were included. Policies, consensus statements and guidance published by government bodies or professional organisations were included.

A 1999 report from the UK Galactosaemia Steering Group[30] and a 2006 brief from the American Academy of Pediatrics (AAP)[31] provide treatment recommendations for galactosaemia. The reports both recommend immediate dietary galactose exclusion (i.e. galactose free formula)

upon suspicion of galactosaemia, and that initial management should include supportive care as required, based on the scope and severity of presenting symptoms.

Upon confirmed diagnosis, the UK Steering Group and the AAP recommend following continued lifelong galactose exclusion from dietary sources and checking of medications for galactose content. Outpatient review every three months until age 1 year, every four months until age 2 years, every six months until age 14 years, and annually thereafter. After age 1, nutritional monitoring to ensure adequate calcium intake and increased monitoring of females late in childhood and during adolescents is recommended to monitor pubertal development.[30]

Both groups suggest that the evidence for dietary exclusion of fruits and vegetables is insufficient to support consensus recommendations, as endogenous galactose synthesis at levels greater than that found in these foods has been reported.[30, 31]

No evidence based policies were identified regarding the treatment of screen detected infants with partial GALT deficiency.

Summary Criterion 11: Partially met. Agreed policies have been published in the UK and USA regarding the monitoring and treatment of classic galactosaemia. No published guidelines or policies were identified regarding evidence based treatments for screen detected partial galactosaemia.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

Summary Criterion 15: No studies were identified.

Implications for policy

This report assesses newborn screening for GALT deficient galactosaemia against the UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This topic was last reviewed by the Health Technology Assessment (HTA) NHS R&D HTA Programme in 1997.[1] The review concluded that neonatal screening was not justified based on the available evidence, as the incidence of galactosaemia in the UK was substantially lower than other inborn errors of metabolism, there was limited evidence that available treatments improved long-term outcomes or that earlier treatment following newborn screening programmes improved long-term outcomes , and there were uncertainties surrounding the identification and treatment of partial GALT deficiency as part of galactosaemia screening, as well as conflicting reports regarding the impact of screening in terms of prevention of severe clinical presentation during the neonatal period.

This review assessed key questions surrounding the clinical presentation of classic galactosaemia, the detection of partial GALT deficiency by available testing strategies, and the long term effectiveness of available treatment options. Overall, the identified evidence for each key question was limited in quantity and comprised mainly of observational studies with varying risk of bias. The limited body of evidence largely supported the findings of the 1997 HTA.

A summary of key findings for each of these criteria is provided below:

- **Effective treatment available –** The current review identified a limited body of evidence regarding the treatment of classic and partial GALT deficient galactosaemia. Overall, no new evidence was identified to suggest that available dietary treatment can prevent long term clinical or developmental complications, either in screen or clinically detected classic GALT deficiency. Outcomes in children with Duarte galactosaemia appear unaffected by dietary galactose restriction during the first year of life, although the evidence is limited.
- **Period before onset during which intervention improves outcome –** No UK studies were identified that reported the mean age of clinical presentation of galactosaemia, and limited evidence was identified from other countries' newborn screening programmes regarding either the mean age at clinical presentation (if before screen test results are available) or the proportion of positive tests that were symptomatic at diagnosis. The mean age of clinical presentation could not be determined based on the available evidence, although the evidence indicates that a proportion of screen positive cases were symptomatic at the time of diagnosis. Additionally, the three mass screening studies identified that reported this data all conducted dried blood spot sampling earlier than done in the UK. Whether classic galactosaemia patients are likely to present clinically prior to receiving screen test results in the UK is unclear based on this limited body of evidence.

  In terms of early treatment following screen detected galactosaemia, the limited body of evidence suggests that newborn screening and subsequent dietary treatment may be associated with improvements in terms of mortality during the neonatal period. The benefit of dietary galactose restriction in terms of preventing long term developmental, hormonal and other complications has not been established since the 1997 HTA review.
- **Ethical, safe, simple and robust screening test –** Screening primarily for galactose and galactose-1-phosphate via colourimetric microassays or other tests can lead to low positive predictive value and a high proportion of D/G variants among the positive screen results. Testing primarily for reduced GALT activity using the Beutler test (either alone or in combination with Gal and Gal-1-P testing) appears to be associated with increased positive predictive value of the screening programmes and reduce the proportion D/G cases among positive screen results.

  A key limitation for this criterion was insufficient reporting of main screening programme components, including the test utilised and its cut-off value, limited information on the number of neonates screened and the distribution of positive and negative results. This limited the ability to fully assess and compare screening performance (e.g. sensitivity, specificity, positive predictive value or negative predictive value) across different tests and cut-off values. The identified tests detect some partial galactosaemia cases (e.g. D/G variants) of uncertain clinical significance, and no evidence based treatment strategies were identified regarding these detected cases.

Implications for research

Given the limited evidence identified for each of the key questions, additional high quality studies in the following areas would be useful in order to resolve uncertainties regarding newborn screening for galactosaemia:

- Studies that establish the mean age at clinical presentation in the UK would be useful to determine whether current DBS sample timing (5-8 days) would allow for the early detection of classic galactosaemia patients.
- Studies to establish the number of Galactosaemia cases detected in babies with raised phenylalanine and tyrosine levels
- New assays that test for common GALT mutations or provide a quantitative evaluation of GALT activity have been proposed, however, evidence regarding their performance in a screening context is needed.
- High quality RCTs to determine the effect of treating partial galactosaemia (e.g. Duarte variants) would be useful to develop evidence-based guidelines on the treatment of screen detected cases of uncertain clinical significance.

Methodology

Search strategy

NSC knowledge update: Newborn screening for Galactosaemia

1. Search Strategy

1.1 Search strategy

Medline

Q2 Age at presentation search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy: 09/04/14

---

1 Galactosemias/ (1929)

2 galactos?emia.ti,ab. (1581)

3 (GALT and deficien*).ti,ab. (196)

4 1 or 2 or 3 (2517)

5 (identif* or diagnos* or present* or detect*).ti,ab. (6330271)

6 exp Diagnosis/ (6415396)

7 5 or 6 (10396562)

8 4 and 7 (1340)

9 Galactosemias/di [Diagnosis] (477)

10 8 or 9 (1429)

11 (age* or day* or month* or year*).ti,ab. (5125011)

12 10 and 11 (380)

13 limit 12 to (english language and yr="1996 -Current") (197)

14 case report.tw. or letter/ or historical article/ or comment/ or editorial/ or (animal/ not (animal/ and human/)) (5569154)

15 13 not 14 (152)

Q5, 10b and 11 variants search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy: 10/04/14
---
1 Galactosemias/ (1930)
2 galactos?emia.ti,ab. (1582)
3 (GALT and deficien*).ti,ab. (196)
4 1 or 2 or 3 (2518)
5 (variant* or partial or Type II or Type 2 or Type III or Type 3).ti,ab. (716990)
6 4 and 5 (196)
7 (GALK or GALE or galactokinase or galactose epimerase or UDP-Galactose-4-epimerase).ti,ab. (1539)
8 deficien*.ti,ab. (367041)
9 7 and 8 (259)
10 Duarte.ti,ab. (194)
11 6 or 9 or 10 (554)
12 limit 11 to (english language and yr="1996 -Current") (260)
13 case report.ti,ab. or letter/ or historical article/ or comment/ or editorial/ or (animal/ not (animal/ and human/)) (5572182)
14 12 not 13 (217)

Screening search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:09/04/14
---
1. Mass Screening/ or neonatal screening/
2. screen$3.ti,ab.
3. (test or tests or testing).ti,ab.
4. False Positive Reactions/
5. False Negative Reactions/
6. false negative.ti,ab.
7. false positive.ti,ab.
8. "Sensitivity and specificity"/
9. (sensitivity or specificity).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Galactosemias/
12. galactos?emia.ti,ab.
13. (GALT and deficien*).ti,ab.
14. 11 or 12 or 13
15. 10 and 14

16. Galactosemias/di [Diagnosis]
17. 15 or 16
18. limit 17 to (english language and yr="1996 -Current")
19. case report.tw. or letter/ or historical article/ or comment/ or editorial/ or (animal/ not (animal/ and human/))
20. 18 not 19 (274)

Treatment and outcomes search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:09/04/14
---
1. exp Therapeutics/
2. (treatment* or therap*).ti,ab.
3. outcome*.ti,ab.
4. 1 or 2 or 3
5. Galactosemias/
6. galactos?emia.ti,ab.
7. (GALT and deficien*).ti,ab.
8. 5 or 6 or 7
9. 4 and 8
10. Galactosemias/co, dh, dt, mo, pc, th [Complications, Diet Therapy, Drug Therapy, Mortality, Prevention & Control, Therapy]
11. 9 or 10
12. limit 11 to (english language and yr="1996 -Current")
13. case report.tw. or letter/ or historical article/ or comment/ or editorial/ or (animal/ not (animal/ and human/))
14. 12 not 13 (264)

Epidemiology search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:10/04/14
---
1 epidemiology/ or incidence/ or prevalence/ (354954)
2 (epidemiolog* or inciden* or prevalen* or morbid* or burden*).ti,ab. (1440485)
3 1 or 2 (1544162)
4 Galactosemias/ (1930)
5 (galactos?emia or Duarte).ti,ab. (1689)
6 (GALT and deficien*).ti,ab. (196)
7 4 or 5 or 6 (2611)

8 (GALK or GALE or galactokinase or galactose epimerase or UDP-Galactose-4-epimerase).ti,ab. (1539)
9 deficien*.ti,ab. (367041)
10 8 and 9 (259)
11 Galactosemias/ep, et, mo [Epidemiology, Etiology, Mortality] (171)
12 3 and (7 or 10) (184)
13 11 or 12 (312)
14 limit 13 to (english language and yr="1996 -Current") (134)

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EMBASE
Q2 Age at presentation search
Database: Embase <1996 to 2014 April 09>
Run 09/04/14
1. Galactosemia/
2. galactos?emia.ti,ab.
3. (GALT and deficien*).ti,ab.
4. 1 or 2 or 3
5. (identif* or diagnos* or present* or detect*).ti,ab.
6. exp Diagnosis/
7. 5 or 6
8. 4 and 7
9. Galactosemia/di [Diagnosis]
10. 8 or 9
11. (age* or day* or month* or year*).ti,ab.
12. 10 and 11
13. limit 12 to (english language and yr="1996 -Current")
14. limit 13 to exclude medline journals (24)

Q5, 10b and 11 variants search
Database: Embase <1996 to 2014 April 09>
Search Strategy:10/04/14
---
1 Galactosemia/ (1150)
2 galactos?emia.ti,ab. (856)
3 (GALT and deficien*).ti,ab. (228)
4 1 or 2 or 3 (1374)
5 (variant* or partial or Type II or Type 2 or Type III or Type 3).ti,ab. (645272)
6 4 and 5 (150)
7 (GALK or GALE or galactokinase or galactose epimerase or UDP-Galactose-4-epimerase).ti,ab. (736)
8 deficien*.ti,ab. (304777)

9 7 and 8 (116)
10 Duarte.ti,ab. (181)
11 6 or 9 or 10 (386)
12 limit 11 to (english language and yr="1996 -Current") (369)
13 limit 12 to exclude medline journals (20)

Screening search
Database: Embase <1996 to 2014 April 09>
Run 09/04/14
1. Mass Screening/ or newborn screening/
2. screen$3.ti,ab.
3. (test or tests or testing).ti,ab.
4. false negative.ti,ab.
5. false positive.ti,ab.
6. "Sensitivity and specificity"/
7. (sensitivity or specificity).ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Galactosemia/
10. galactos?emia.ti,ab.
11. (GALT and deficien*).ti,ab.
12. 9 or 10 or 11
13. 8 and 12
14. Galactosemia/di [Diagnosis]
15. 13 or 14
16. limit 15 to (english language and exclude medline journals and yr="1996 -Current") (51)

Treatment and outcomes search
Database: Embase <1996 to 2014 April 09>
Run 09/04/14
1. exp therapy/
2. (treatment* or therap*).ti,ab.
3. outcome*.ti,ab.
4. 1 or 2 or 3
5. Galactosemia/
6. galactos?emia.ti,ab.
7. (GALT and deficien*).ti,ab.
8. 5 or 6 or 7
9. 4 and 8
10. Galactosemia/co, dm, dt, pc, th
11. 9 or 10
12. limit 11 to (english language and yr="1996 -Current")
13. limit 12 to exclude medline journals (58)

Epidemiology search
Database: Embase <1996 to 2014 April 09>
Run 10/04/14
---
1 exp epidemiology/ or exp incidence/ or exp prevalence/ (1585107)
2 (epidemiolog* or inciden* or prevalen* or morbid* or burden*).ti,ab. (1442735)
3 1 or 2 (2299255)
4 Galactosemia/ (1150)
5 (galactos?emia or Duarte).ti,ab. (980)
6 (GALT and deficien*).ti,ab. (228)
7 4 or 5 or 6 (1492)
8 (GALK or GALE or galactokinase or galactose epimerase or UDP-Galactose-4-epimerase).ti,ab. (736)
9 deficien*.ti,ab. (304777)
10 8 and 9 (116)
11 Galactosemia/ep, et (209)
12 3 and (7 or 10) (291)
13 11 or 12 (449)
14 limit 13 to (english language and yr="1996 -Current") (410)
15 limit 14 to exclude medline journals (38)

Cochrane library (CDSR, CENTRAL, DARE, HTA, NHSEED)
Search Name: NSC Galactosaemia 070414
Last Saved: 07/04/2014 10:51:24.746
Description:
ID Search
#1 MeSH descriptor: [Galactosemias] explode all trees
#2 (galactosemia or galactosaemia):ti,ab
#3 (GALT or GALK):ti,ab
#4 Duarte:ti,ab
#5 #1 or #2 or #3 or #4 Publication Date from 1996 to 2014 (Word variations have been searched)

CRD (HTA, NHS EED, DARE)
1 MeSH DESCRIPTOR galactosemias EXPLODE ALL TREES IN DARE,NHSEED,HTA 2
2 (galactosaemia) OR (galactosemia) OR (Duarte) 25
3 (galk) OR (galt) 1
4 #1 OR #2 OR #3 26
No publication date limit set

The above search strategies retrieved 741 references in total, after duplicate references were removed. The title and abstracts of the remaining citations were sifted for relevance to screening for galactosaemia; 222 references were deemed to be relevant.

A second title and abstract sift of these 222 references was conducted by the reviewer; 63 studies were selected for appraisal at full text, 23 of which were selected for inclusion in the review.

Quality

Studies not in English, conference abstracts, non-systematic reviews, editorials, other opinion pieces, and those with nonhuman data were excluded. Case series and experimental studies of fewer than three patients with GALT deficiency were excluded except where they reported cases missed by screening. Studies solely relevant to GALK or GALE deficient galactosaemia were excluded. Additional relevant references identified during the preparation of the report were also included.

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Appendices

Appendix number	1

Relevant criteria	2, 5
Publication details	[18] Lee JY, Padilla CD, Chua EL. Screening for galactosemia: Philippines experience. Newborn Screening Study Group. Southeast Asian Journal of Tropical Medicine & Public Health. 1999;30:Suppl-8
Study details	Prospective cohort study, Philippines, healthcare setting not reported
Study objectives	Galactosaemia incidence, review of screening programme results
Inclusions	Newborns screened as part of the Philippines pilot NBS programme for galactosaemia.
Exclusions	Not reported
Population	n=62,841 newborns from 37 participating hospitals screened for galactosaemia (due to GALT, GALK and GALE deficiency) as part of the Philippines pilot NBS programme between June 1996 and June 1998.
Intervention	Gal and Gal-1-P DBS test between 48 and 72 hours old. Test enzymatically detects galactose metabolites that can indicate galactosaemia due to GALT, GALK or GALE deficiency. Positive screen cut-offs: ≥1.5mmol/L or ≥1.0mmol/L without feeding Positive screen cases underwent confirmatory testing of GALT activity via the Beutler test, and of galactose metabolites via thin layer chromatography.
Comparator	NA
Study results / outcomes	*Criterion2:* **Weighted overall incidence classic galactosaemia (GALK and GALT deficiency):** 1:38,022 **Weighted incidence classic galactosaemia:** 1:88,495 **2 year incidence partial galactosaemia:** 1:15,710 **Timing of clinical presentation of GALT deficiency** One patient was identified with GLAT deficient galactosaemia. DBS testing was conducted on Day 3, with positive screen results returned on Day 10 and confirmatory testing available on Day 16 (elevated metabolites and no enzyme

	activity). The patient presented clinically with fever and jaundice at Day 4, and was discharged at Day 5. Patient was started on lactose free formula following receipt of confirmatory testing on Day 16. *Criterion 5:* 62,528 NB screened; 6 positive screens; 1 classic GALT deficiency, 1 GALK deficiency, 4 partial galactosaemia (likely Duarte variants). 66% of screen positive results were partial galactosaemia
Comments	Detected partial galactosaemia patients noted as 'most likely Duarte variants' based on phenotype. Reported weighted incidence rates are based on the approximately 6 million population wide births; during the pilot period 62,528 NB were screened (this number was used for the 2 year incidence of partial galactosaemia, which may result in an overestimation compared to the reported weighted incidence of classic galactosaemia.

Appendix number	2
Relevant criteria	10
Publication details	[28] Schadewaldt, P., et al., *Longitudinal assessment of intellectual achievement in patients with classical galactosemia.* Pediatrics, 2010. **125**(2): p. e374-e381.
Study details	Prospective cohort study, Germany, healthcare setting not reported
Study objectives	To assess the long term cognitive outcomes in classical galactosaemia.
Inclusions	Previous clinical assessment of IQ by study authors, absence of acute or chronic illnesses other than galactosaemia, no problems with German as a native language, GALT deficiency <0.35µmol/L RBS (characteristic of classic galactosaemia), evidence of good lactose-restricted dietary compliance.
Exclusions	Not reported.
Population	n=23 (12 male/11 female), mean (SD) age 25.7y (5.3) classic galactosaemia patients (unclear if screen or clinically detected). Genotypes: twelve *Q188R/Q188R*, three *Q188R/K285N*, one *Q188R/L195P*, two *Q188R/Q54X,* one *K285N /H114P*, one *K285N /V151A*, one *K285N /V168M*, one *L195P / L195P*, one *L195P/F117C* (distribution described as representative of genotype variability in white classic galactosaemia patients)
Intervention	All patients complied with lactose-restricted diet; no further information reported.
Comparator	Previous IQ scores completed at mean (SD) age 10.8y (5.2)
Study results / outcomes	*Criterion 10:* <u>Cognitive outcomes</u> **Mean (SD) Total IQ**

	Previous score: 78 (14) Current score: 73 (15) Difference: NS **Mean (SD) Performance IQ** Previous score: 73 (17) Current score: 74 (17) Difference: NS **Mean (SD) Verbal IQ** Previous score: 86 (11) Current score: 77 (13) Difference: -9 (10); p<0.01 <u>Narrative description of individual change overtime</u> **Total IQ (TIQ)** Six patients had significant changes in TIQ (5 decreased, 1 increased). The remaining 17 patients exhibited stable TIQ scores. **Performance IQ (PIQ) and Verbal IQ (VIQ)** 17% of participants had significant increases and 52% had significant decreases in PIQ or VIQ with age. **Hierarchic cluster analysis** Two significant clusters were observed: Cluster 1 had 13 patients with TIQ scores <79 at both time points. Cluster 2 had 10 patients with TIQ scores ≥79 at both assessments, and generally had at least one TIQ assessment in the normal range. Difference in TIQ between clusters 1 and 2 was significant at p<0.001. No statistically significant effects of gender or *Q118R/Q118R* homozygotic status on TIQ, PIQ, or VIQ scores were observed.
Comments	Inclusion criteria based on previous study (conducted in 1989/1990); only 27.4% of the original cohort were eligible and included in the current review. Whether there were significant differences in cognitive outcomes between participants and non-participants is not known.

Appendix number	3
Relevant criteria	2
Publication details	[16] Aoki K. Long term follow-up of patients with inborn errors of metabolism detected by the newborn screening program in Japan. Southeast Asian Journal of Tropical Medicine & Public Health. 2003;34 Suppl 3:19-23.
Study details	Retrospective cohort study, Japan, healthcare setting not reported
Study objectives	Incidence of galactosaemia following twenty years of NBS in Japan
Inclusions	Not reported
Exclusions	Not reported
Population	n=23,579,309 newborns (92.8% of all births in Japan) between 1977 and 1994
Intervention	Blood sample taken on 5th day of life, filter paper sent to local screening laboratories and tested using the Guthrie method.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence of galactosaemia** Overall: 1:110,525 Galactosaemia Type 1: 1:1,116,306 Galactosaemia Type 2: 1:637,889 Galactosaemia Type 3: 1:115,878
Comments	Minimal information provided on identified cases; only incidence data was available. No data provided for screening marker or cut-off values, change in values overtime, or impact on case detection. Galactosaemia subtypes not specified in publication; based on identified conventions, Type 1 likely to indicate GALT deficient, Type 2 GALK deficient and Type 3 GALE deficient galactosaemia (OMIM 230400, 230200, and 230350)

Appendix number	4
Relevant criteria	2
Publication details	[13] Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. Pediatrics. 2000;105(1):e10.
Study details	Retrospective cohort study, Canada, healthcare setting not reported
Study objectives	Incidence of several inborn errors of metabolism, included classic galactosaemia
Inclusions	Not reported
Exclusions	Not reported
Population	n=579,196 births British Columbia, Canada 1984 – 1996

Intervention	Screening programme commenced in 1984, test methodology not reported.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Cases and incidence of classic galactosaemia:** 16 cases 1:36,200 2.8 per 100,000 births **Cases and incidence of probable Duarte variants:** 16 cases 1:36,200 (RC) 2.8 per 100,000 births (RC) **Cases and incidence of genotype confirmed Duarte variants:** 7 cases 1:82,742 (RC) 1.2 per 100,000 births (RC)
Comments	Cases identified during screening programme and confirmed via lack of erythrocyte GALT activity; Duarte variants are not included in the above incidence figures. Probable Duarte/classical galactosaemia compound heterozygotes (D/G) had low erythrocyte GALT activity and high Gal-1-P levels; genotype could only be confirmed in 7 cases (all carried the N314D mutation), but DNA analysis was unavailable for the remaining cases. Authors did not include probable Duarte variants in their analysis. Above incidence figures based on reviewer calculations.

Appendix number	5
Relevant criteria	2, 5
Publication details	[9] Badawi N, Cahalane SF, McDonald M, et al. Galactosaemia--a controversial disorder. Screening & outcome. Ireland 1972-1992. Irish Medical Journal. 1996;89(1):16-7.
Study details	Retrospective cohort study, Ireland, healthcare setting not reported
Study objectives	Examine 20 year population based screening for galactosaemia in Ireland.
Inclusions	Not reported
Exclusions	Not reported

Population	1.2 million newborns born in Ireland between 1972 and 1992.
Intervention	Screening test: Bacterial Inhibition Assay; the Beutler test was introduced in 1976 as a confirmatory test. High risk neonates (new sibling to a known case, ill neonate) are screened with the Beutler test. No information provided on cut-off values for positive test results.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Prevalence** Classic galactosaemia: 1:23,000 Classic plus Duarte galactosaemia: 1:20,000 Duarte galactosaemia: 1:171,429 (reviewer calculated based on 1.2m screen) Irish Travellers: 1:700 Mean age of diagnosis 6.9 days overall (8 days routine screen group; 2.5 days high-risk group) 41 of 55 (74.5%) of detected classic galactosaemia cases were symptomatic at the time of diagnosis; galactosaemia was suspected in 10 of the 41 (24.4%) symptomatic cases. None of the screen detected Duarte galactosaemia patients were symptomatic at diagnosis. *Criterion 5:* 55 cases classic galactosaemia (88.7% of all cases) 7 cases Duarte galactosaemia (11.3% of all cases) 5 false negatives (3 due to poor feeding, 2 due to use of soya formula)
Comments	No precise data is provided on the total number of screened newborns, or on false-positive rates, making the calculation of Sp, PPV and NPV impossible. No data provided on cut-off values for either the bacterial inhibition assay or the Beutler test; thus, results cannot be compared across programmes.

Appendix number	6
Relevant criteria	2, 10
Publication details	[8] Coss, K.P., et al., *Classical Galactosaemia in Ireland: incidence, complications and outcomes of treatment.* Journal of Inherited Metabolic Disease, 2013. **36**(1): p. 21-27.
Study details	Retrospective cohort, Ireland, healthcare setting not reported
Study objectives	Incidence of galactosaemia in general Irish and Irish Traveller populations Long-term outcomes following screen detection and dietary galactose restriction (Full scale IQ scores, presence of speech and language disorders, ataxia, hypergonadotrophic hypogonadism, cataracts, osteopenia and osteoporosis).
Inclusions	Patients born after 1972 with screen detected classical galactosaemia and attending National Centre for Inherited Metabolic Disorders (NCIMD)
Exclusions	Not reported
Population	n=130 screen detected patients (61 non-Traveller Irish, 63 Irish Travellers, 1 English, 2 Irish-American, 1 Irish-Jewish, 1 African, 1 unknown Irish population) detected since the 1972 introduction of a national screening programme, and being managed at the NCIMD. 122 patients were detected as part of the screening programme, three were born prior to the programme, and five were born in the UK and diagnosed clinically. 113 of 130 (87.0%) were genotyped and 92% of (figure not reported) followed-up patients were genotyped as *Q188R/Q188R*.* *As genotyping was part of the follow-up diagnostic process, this is unlikely to represent the true proportion of classical galactosaemia captured by the screen test.
Intervention	Blood spot tests conducted at 72 to 120 hours after birth for all newborns; Beutler test followed by quantitative GALT enzyme assay is performed, followed by mutation analysis. Beutler test replaced with galactose quantitation as the initial screening test. Screening with the Beutler test at day 1 to 2 was introduced in 1996 for all high-risk Traveller neonates. All patients received a galactose restricted diet (daily galactose intake estimated as <50mg; documented galactose intake up to 300mg/day in some patients).
Comparator	Several outcomes compared between non-Traveller Irish and Traveller Irish participants
Study results / outcomes	*Criterion 2:* **Incidence of classical galactosaemia (excluding Duarte variants)** Total Irish population, mean (1982 to 2011): 1:16,476

	Non-Irish Traveller population, mean (1982 to 2011): 1:33,917 Irish Traveller population, mean (1997 to 2011): 1:430 *Criterion 10:* Prevalence of complications **Speech and language disorders in patients aged ≥2.5y** (assessed disorders include verbal dyspraxia, speech delay or difficulties, no speech or severe speech delays, verbal comprehension problems) Overall: 49.6% Non-Traveller Irish: 47.6% Traveller Irish: 51.9% Difference NS **Hypergonadotrophic hypergonadism (HH) (in females aged ≥13y)** Overall: 91.2% Non-Traveller Irish: 87% Traveller Irish: 100% Difference NS **Osteopenia and osteoporosis (in patients aged ≥10y)** Overall: NR Non-Traveller Irish: 39.6% Traveller Irish: 14.7% p=0.028 **IQ (in patients aged ≥6y; n=85)** Exceptionally low (FSIQ<70): 30.6% Low borderline (FSIQ 70-79): 25.9% Low average (FSIQ 80-89): 24.7% Average (FSIQ 90-109): 11.8% High average (FSIQ 110-119): 7.1% **Below average IQ (FSIQ ≤89)**

	Patients aged 6-12y (n=25): 100% Patients aged >12y (n=60): 73.3%
Comments	Retrospective study of patients screened, diagnosed and followed up in clinic; does not provide information on screen detection of galactosaemia variants, and provides limited data on outcomes. No information is provided on adherence to galactosaemia restricted diet, and variations in outcomes cannot be assessed based on diet exposure.

Appendix number	7
Relevant criteria	List of criteria to which the study relates *and* from which reference to the study is made
Publication details	[20] Fateen E, el-Shafei S, el-Karaksy H, et al. Diagnosis and management of galactosemia: an Egyptian experience. Bratislavske Lekarske Listy. 2004;105(9):303-9.
Study details	Retrospective cohort study, Egypt, healthcare setting not reported
Study objectives	Projected outcomes of the study
Inclusions	Screening: Neonates recruited from the Obstetrics and Gynaecology Department in Cairo and Ains Shams Universities High risk: Neonates selected from outpatient genetics or hepatology clinics presenting with failure to thrive, vomiting, jaundice, liver disease, cataracts.
Exclusions	Not reported
Population	Screening: n=1,794 neonates born between January 1998 and June 2003 in Cairo, Egypt High risk: n=374 patients, aged 4 days to 1.5 years, born between January 1998 and June 2003 in Cairo, Egypt attending outpatient clinics.
Intervention	Screening: Mass screening programme for galactosaemia using enzymatic colorimetric testing of DBS for Gal and Gal-1-P; collected during the first week of life (day of life not reported). High risk: screening using enzymatic colorimetric testing of DBS for Gal and Gal-1-P, as well as radioactive enzyme assay of GALT, GALK, and GALE erythrocyte activity.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence of GALT deficient galactosaemia, screening population:** 1:1,794 **Age at clinical presentation GALT deficient galactosaemia**

	26 of 374 high risk neonates were galactosaemic; 18 GALT deficient, 8 GALE deficient. Age at diagnosis ranged from 4 days to 18 months; mean age 3.8 months **Risk factors** 17 of the 19 (89.5%)GALT deficient galactosaemia cases (screen detected and high risk) were born to consanguineous parents. 5 of the 18 GALT deficient cases in the high risk group had a positive family history of an affected sibling who died of the condition.
Comments	Small screening group (<2,000), not clear whether the program was a population wide NBS. The high frequency (1:1,754) is reported as likely due to high rate of consanguineous marriage in the population (28.9 to 36.8% estimated).

Appendix number	8
Relevant criteria	10
Publication details	[2] Ficicioglu, C., et al. (2008). "Duarte (DG) galactosaemia: a pilot study of biochemical and neurodevelopmental assessment in children detected by newborn screening." Molecular Genetics & Metabolism 95(4): 206-212.
Study details	Retrospective cohort study, USA, paediatric hospital
Study objectives	To compare the clinical, developmental and biochemical outcomes up to age 6 years between individuals with partial galactosaemia (DG galactosaemia) treated with a lactose restricted diet during the first year of life vs. an unrestricted diet.
Inclusions	Diagnosis of Duarte galactosaemia (DG variant).
Exclusions	None reported.
Population	28 children (13 male/15 female) with DG galactosaemia. Mean age 2.96 years (SD 1.31; range 1 to 6 years). Group division based on a history of lactose restriction during the first year of life. All patients were on a regular diet at the time of the study visit. **Group I** lactose restricted diet: n=17 (11 male/6 female), mean age 3.5y (SD 1.16; range 1.3 to 6.0 years) **Group II** no dietary restriction: n=11 (6 male/5 female), mean age 2.28y (SD 1.3; range 1.1 to 5.0)
Intervention	Group I patients followed a lactose restricted diet for the first year, which was initiated within the first 10 days of life.
Comparator	Group II patients were on a regular diet since birth.

Study results / outcomes	*Criterion 10:* Clinical outcomes (at study visit) **Mean (SD) follicle stimulating hormone (FSH), females** **Group I:** 2.96 (1.49) **Group II:** 3.16 (1.85) p=0.84 **Liver function (prothrombin time [PT] and partial thromboplastin time [PTT] values)** No data provided; none of the patients had abnormal liver function at time of diagnosis or at the study visit, all had normal PT and PTT values. **Cataracts** No data provided; slit lamp exam for cataracts at the time of study visit revealed no abnormalities among patients in either group. Cognitive and developmental outcomes (at study visit) **Mean (SD) overall IQ score** Bayley Scales of Infant Development – Third Edition for children aged 12 to 35 months; Wechsler Preschool and Primary Scale of Intelligence – Third Edition for children aged >35 months **Group I:** 108.24 (9.3) **Group II:** 102.55 (11.17) p=0.16 **Mean (SD) language development score** Bayley Scales of Infant Development – Third Edition for children aged 12 to 35 months; Wechsler Preschool and Primary Scale of Intelligence – Third Edition for children aged >35 months **Group I:** 109.41 (13.58) **Group II:** 109.36 (16.53) p=0.99 **Mean (SD) adaptive functioning score** Parent report

	Group I: 100.12 (13.74) **Group II:** 112.41 (14.03) p=0.027 Overall, the study suggests that a lactose free diet in the first year of life is not associated with short- or long-term clinical or developmental outcomes up to age 6 years among children with Duarte galactosaemia. All participants had IQ scores within the normal range, and there were no significant differences between the restricted and non-restricted diet groups.
Comments	Retrospective assessment with no information on diet adherence. Included participants were young which may reduce validity of IQ tests; longer term follow-up needed. There was some evidence of residual galactose restriction in Group 1 (galactose intake lower than comparator group during follow-up assessment). Adaptive functioning is not amenable to standardised testing in this age group, and was ascertained via parental report, which may introduce bias.

Appendix number	9
Relevant criteria	2, 5
Publication details	[15] Freer DE, Ficicioglu C, Finegold D. Newborn screening for galactosemia: a review of 5 years of data and audit of a revised reporting approach. Clinical Chemistry. 2010;56(3):437-44.
Study details	Retrospective cohort study, USA, healthcare setting not reported
Study objectives	Assessment of specificity of newborn galactosaemia screening.
Inclusions	Participation in Pennsylvania's newborn galactosaemia screening programme between 2001 to 2008
Exclusions	Not reported.
Population	2001 to 2006 (phase I): n=1,300,000 2007 to 2008 (phase II): n=274,960
Intervention	Phase I: DBS samples were tested for total Gal (free Gal plus Gal-1-P), modified Gal, and GALT activity. % Gal-1-P was assessed for further screening for GALK and GALE deficiency; this aspect of the screening programme is discussed further only as it resulted in the identification of individuals with D/G galactosaemia. Samples with elevated Gal and/or reduced GALT activity underwent qualitative DNA testing for 4 common mutations (Q188R, K285N, L195P, S135L) and the Duarte-2 variant (N314D). Screening cut-off values: Gal ≥1.110 mmol/L (≥20mg/dL)

	GALT ≤40µmol/L Phase II: Same procedure, revised cut-off values: Gal ≥1.665 mmol/L (≥15mg/dL) GALT ≤40µmol/L
Comparator	NA
Study results / outcomes	*Criterion 2:* **5 year Incidence screen detected classic GALT deficiency (2001-2006)** 1:65,000 **5 year Incidence screen detected Duarte galactosaemia (2001-2006)** 1:144,444 *Criterion 5:* <u>Phase I results</u> 209 samples had a Gal concentration Gal ≥1.110 mmol/L (≥20mg/dL) or GALT ≤40µmol/L. 23 of these had GALT ≤40µmol/L; the remainder flowed into screening for GALK or GALE deficient galactosaemia. **DNA analysis of 23 screen positives** 14 cases had two copies of mutations responsible for GALT deficiency (11 homozygous, 3 compound heterozygous). Five cases were compound heterozygous G; all had clinically confirmed classic GALT deficiency. One case had no detectable mutations, but was confirmed as classic GALT deficiency symptomatically. **Screen detected partial GALT deficiency** Three cases were D/G heterozygous (13.0% of screen positive cases) Six additional cases of D/G heterozygous galactosaemia were identified during the additional screening for GALK and GALE deficiency (Gal concentration Gal ≥1.110 mmol/L (≥20mg/dL) or GALT >40µmol/L.)
Comments	GALT cut-off of ≤40µmol/L seems to be sufficiently high to detect classic GALT deficiency, yet suitably low to not detect the majority of D/G galactosaemia (3 of

	9 cases were detected at this cut-off between 2001 and 2006). Insufficient information was provided to report or calculate Sn, Sp, PPV, NPV of the Gal and GALT screen tests at the described cut-offs; narrative assessment of detection of classic vs. partial galactosaemia only.

Appendix number	10
Relevant criteria	2
Publication details	[23] Karadag N, Zenciroglu A, Eminoglu FT, et al. Literature review and outcome of classic galactosemia diagnosed in the neonatal period. [Review]. Clinical Laboratory. 2013;59(9-10):1139-46.
Study details	Retrospective cohort study, Turkey, healthcare setting not reported
Study objectives	To define characteristics and outcomes of children with clinically detected galactosaemia in Turkey.
Inclusions	Paediatric patients followed up in a NICU at a hospital in Ankara, Turkey, from January 2005 to January 2011.
Exclusions	Not reported
Population	n=22 children
Intervention	NA
Comparator	NA
Study results / outcomes	*Criterion 2:* **Median age at clinical presentation (admission)** 13 days (range 3 to 23 days) **% Cases born to consanguineous parents, n= (%)** 13 (59%) **% Cases with a positive family history, n= (%)** 1 (4%)
Comments	Information provided on day of admission, with no information on time to diagnosis.

Appendix number	11
Relevant criteria	2, 5
Publication details	[27] Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. Archives of Pediatrics & Adolescent Medicine.

	2000;154(7):714-8
Study details	Retrospective cohort study, USA, healthcare setting not reported
Study objectives	Assess the sensitivity, specificity, PPV, and relative incidence of classic galactosaemia (and other conditions) using national screening data.
Inclusions	All newborns screened in the USA between 1993 and 1994 with data in reports published by the Council of Regional Networks for Genetic Services.
Exclusions	Not reported.
Population	Not reported.
Intervention	Screening procedures not reported.
Comparator	NA.
Study results / outcomes	*Criterion 2:* **Relative incidence rate (95% CI)** 1993: 1:54,900 (1:44,200 to 1:72,400) 1994: 1:62,800 (1:55,500 to 1:72,400) Overall 1:58,850 *Criterion 5:* **1993** / **1994** **Screen positive (n)** 9,221 / 10,210 **Confirmed cases (n)** 53 / 54 **Sensitivity** 100% / 100% **Specificity** 99.7% / 99.7% **PPV** 0.57% / 0.53%
Comments	No information provided on total number of newborns screened, screening procedures for galactosaemia, nor the cut-off values for any tests performed. Study based on a national dataset; however, some states were removed from the analyses due to missing or incongruous data.

Appendix number	12
Relevant criteria	2, 5
Publication details	[10] Ohlsson A, Guthenberg C, von DU. Galactosemia screening with low false-positive recall rate: the Swedish experience. Jimd Reports. 2012;2:113-7.
Study details	Cohort study, Sweden, healthcare setting not reported

Study objectives	Assess the impact of a two-tier methodology on false-positive rates in a NBS programme for GALT deficiency.
Inclusions	Not reported
Exclusions	Not reported
Population	**Number screened** 1967 to 1985: 1,780,600 1986 to 1991: 677,900 1992 to 2010: 1,973,400 Total: 4,401,900 From 1985 to 2009, diagnosis occurred at an average of 6.5 days (range: 4 to 14 days). Pre-2007, DBS sampling recommended as soon as possible after 72h of age. Since 2007, expanded MS/MS screening techniques changed that recommendation to as soon as possible after 48h of age.
Intervention	Screening procedure 1992 to 2010: Tier 1 – Beutler spot test, a semi-quantitative fluorometric method of testing GALT activity Cut-off value: absolute <15% (<10% triggers immediate tier 2 analysis; 10-15% triggers retest of GALT activity). Tier 2 – rapid galactose dehydrogenase test (GAL-DH), a semi-quantitative fluorometric spot test that visually approximates total galactose (Gal). Cut-off value: approximately ≥2mM galactose Two tier procedure allows for same day confirmation (upon sample arrival at laboratory. Quantitative analysis of Gal and Gal-1-P is performed the following day. Cut-off values: >0.5mmol/L Gal, >1.5mmol/L Gal-1-P
Comparator	Screening procedure 1967 to 1985: Bacterial inhibition assay (based on Guthrie method of screening for PKU); Beutler spot test added as a second tier test from 1983 to 1985. Cut-off values: >0.6mmol/L Gal, >0.60mmol/L Gal-1-P Screening procedure 1986 to 1991: Tier 1 – Beutler spot test for GALT activity Cut-off value: 30% Tier 2 – quantitative analysis of galactose (Gal) and galactose-1-phosphate (Gal-1-P) levels

	Cut-off values: >0.6mmol/L Gal, >0.60mmol/L Gal-1-P
Study results / outcomes	*Criterion 2:* **True positives:** 1967 to 1985: 22 of 1,780,600 screened 1986 to 1991: 3 of 677,900 screened 1992 to 2010: 18 of 1,973,400 screened Total: 43 of 4,401,900 screened **Incidence of classic galactosaemia (1967 to 2010)** 1967 to 1985: 1:81,000 1986 to 1991: 1:226,000 1992 to 2010: 1:108,000 Total: 1:103,000 *Criterion 5:* **Number false positives:** 1967 to 1985: 336 of 1,780,600 screened 1986 to 1991: 80 of 677,900 screened 1992 to 2010: 10 of 1,973,400 screened Total: 424 of 4,401,900 screened **Incidence of false positive screen results (1967 to 2010)** 1967 to 1985: 1:5,300 1986 to 1991: 1:8,500 1992 to 2010: 1:194,000 Total: 1:10,000
Comments	Long-term analysis of national NBS screening programme for classic GALT deficiency. Reveals variation in false positive rates using different screening tests and positive result thresholds. Unclear if rapid Gal-DH tier is responsible for drop in false positive rates or if this is primarily due to lower GALT activity and higher Gal-1-P thresholds. The main benefit of GAL-DH testing appears to be a confirmed diagnosis at the time of recall.

Appendix number	13
Relevant criteria	2
Publication details	[17] Ono H, Mawatari H, Mizoguchi N, et al. Transient galactosemia detected by neonatal mass screening. Pediatrics International. 1999;41(3):281-4.
Study details	Retrospective cohort study, Japan, healthcare system not reported
Study objectives	Detection of transient galactosaemia during NBS for galactose metabolism disorders; diagnosis and clinical course of transient cases
Inclusions	Transient galactosaemia detected by neonatal mass screening for galactosaemia between 1986 and 1996 in Hiroshima, Japan
Exclusions	Not reported
Population	n=322,087 neonates screened
Intervention	Screening of blood galactose levels via Paigen method (positive screen cut-off >0.44mmol/L) at approximately five days of age
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence of GALT deficient galactosaemia and its variants** No patients with homozygous GALT deficient galactosaemia were identified. 22 cases of partial GALT deficiency were identified; 16 heterozygous GALT deficiency (genotype not specified) and 6 Duarte variant GALT deficiency. All 22 cases were transient (blood galactose levels <0.44mmol/L by age 2 months with no treatment).
Comments	

Appendix number	14
Relevant criteria	2
Publication details	[12] Ounap K, Joost K, Temberg T, et al. Classical galactosemia in Estonia: selective neonatal screening, incidence, and genotype/phenotype data of diagnosed patients. Journal of Inherited Metabolic Disease. 2010;33(2):175-6.
Study details	Retrospective cohort study, Estonia, healthcare setting not reported
Study objectives	Incidence of classic galactosaemia in Estonia
Inclusions	Not reported.
Exclusions	Not reported.
Population	n=4,000 screening tests
Intervention	Selective screening for GALT deficient galactosaemia, 1996 – 2008; all sick neonates received a urinary screening test for reducing substances (Benedickt reaction); when positive, serum and urine HPLC and DNA analysis for the Q188R

	mutation were performed. Heterozygous Q188R or no mutation triggered assessment of GALT activity using the Beutler test, and then GALT gene sequencing.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence of GALT deficient galactosaemia** 1:19,700
Comments	Related to Krabbi et al. citation, covers longer period.

Appendix number	15
Relevant criteria	2, 10
Publication details	[6] Powell, K.K., et al., Long-term speech and language developmental issues among children with Duarte galactosemia. Genetics in Medicine, 2009. 11(12): p. 874-879.
Study details	Retrospective cohort, USA, healthcare setting not reported
Study objectives	Describe developmental disabilities associated with screen detected Duarte galactosaemia compared to a population based
Inclusions	Children born between 1988 and 2001 diagnosed with Duarte galactosaemia following a positive screen result through the Georgia Newborn Screening Program, and living in the five-county area surrounding Atlanta, Georgia USA at birth and from ages 3 to 10 years. All participants must have data in the population based Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP) and the Special Education Database of Metropolitan Atlanta (SEDMA).
Exclusions	Children who were not followed clinically by the Division of Medical Genetics at Emory University in Atlanta, Georgia.
Population	n=59 (79% of screen detected Duarte galactosaemia patients born between 1988 and 2001). Age and sex not reported. Galactose restriction initiated at mean age of 23 days (range 16 to 34 days) for five children in special education services, and at mean age of 29 days (range 1 to 101 days) for non-special education Duarte patients.
Intervention	Newborn screening for galactosaemia returned a positive result in the absence of fluorescence on the Beutler assay (1988 to 1990), plus total galactose >10mg/dL on the Hill assay. Confirmatory diagnostic tests based o Gal-1-P and urine galactitol levels, GALT activity and mutation analysis. Duarte galactosaemia patients treated with galactose restricted diet (primarily via lactose restriction) until 1 year of age. Children generally seen at age 4 to 6

	months for monitoring prior to initiating solids, and at age 10 to 12 months after a milk challenge until more regular monitoring was indicated. Monitoring was discontinued in Gal-1-P levels were within the normal range on a normal diet (not further defined).
Comparator	General population Special Education service use prevalence in 1998 for 1-year survivors in 1988 to 1995 birth cohorts.
Study results / outcomes	*Criterion 2:* **Incidence of Duarte Galactosaemia** 1:7,736 *Criterion 10:* **Developmental disabilities (identified during treatment or monitored by MADDSP) including intellectual disability, cerebral palsy, ASDs** No developmental disabilities were identified in any children during treatment period (to age 1y). No child had a developmental disability monitored by MADDSP. **Use of special education services aged 3 to 10y, n (%)** Duarte group: 5 of 59 (8.5%) General population: 13,187 of 295,939 (4.5%) **Use of special education services age 8y, n (%) (age cut-off not defined *a priori*)** Duarte group: 5 of 33 (15.2%) General population: 2,264 of 38,328 (5.9%) **Special education services among DG children** 3 of 5 – learning disabilities (not further defined) 4 of 5 – speech/language impairments (specified for two patients: moderate to severe articulation disorder and mild to moderate language disorder)
Comments	Descriptive statistics only; no statistical comparisons of special education service use were reported. Assessment of developmental outcomes based on review of databases and special education records and not primary evaluation of speech/language and other functioning; may lead to a misrepresentation of actual frequency of these outcomes. Due to exclusion criteria related to data linkage and residency, only 79% of

	screen detected Duarte galactosaemia patients born between 1988 and 2001 were included in the study; it is unclear whether developmental disabilities and special education service use differed between included and excluded DG patients.

Appendix number	16
Relevant criteria	2, 5
Publication details	[11] Schulpis K, Papakonstantinou ED, Michelakakis H, et al. Screening for galactosaemia in Greece. Paediatric and Perinatal Epidemiology. 1997;11(4):436-40.
Study details	Retrospective cohort study, Greece, healthcare setting not reported
Study objectives	To evaluate a newborn screening programme for galactosaemia in Greece.
Inclusions	Not reported
Exclusions	Not reported
Population	n=199,642 newborns aged 3 to 5 days Programme started in 1994; duration not reported.
Intervention	Screening of total Gal and Gal-1-P using a colorimetric microassay. Dried blood samples taken at age 3 to 5 days via routine heel puncture onto Guthrie cards. Cut-offs: <4.46mg/dL – no action 4.47 to 6.49 mg/dL – second Guthrie card witching 24 hours; if second test is less than cut-off (not further defined) no action, if higher than cut-off (not further defined) enzyme analysis and switch to soya milk. ≥6.5mg/dL – second Guthrie card and switch to soya milk; if second test is less than cut-off (not further defined) resumed natural milk feeding, if greater than cut-off(not further defined) enzyme analysis and maintain soya milk.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence among screened population** Classic galactosaemia: 1:22,182 Compound heterozygote D/G: 1:33,273 Duarte galactosaemia D/D: 1:49,910 Of 9 neonates with screen detected classic galactosaemia, 7 were asymptomatic at time of diagnosis.

	Criterion 5: **Galactosaemia screening programme figures** 199,642 neonates screened 9 detected cases of classic GALT deficient, 3 cases of GALE deficient, 6 cases of compound heterozygote D/G, and 2 cases of homozygote D/D galactosaemia. Reported 0.25% false positive rate (unclear whether D/G and D/D cases were counted as false positives).
Comments	Short descriptive study of the galactosaemia screening programme. Limited information on screening results makes calculation of sensitivity, specificity and PPV impossible. False positive rate is reported as low (0.25%), however, no further information is provided on the calculation of this rate. 6 cases of D/G and 2 cases of D/D galactosaemia were detected; no information was provided on the screening results for these patients, or whether they were considered true positives or false positives. 2 cases of GALE deficient galactosaemia were detected (no further information reported).

Appendix number	17
Relevant criteria	2
Publication details	[22] Shah V, Friedman S, Moore AM, et al. Selective screening for neonatal galactosemia: an alternative approach. Acta Paediatrica. 2001;90(8):948-9.
Study details	Retrospective cohort study, Canada, Paediatric hospital
Study objectives	To assess the impact of a selective screening programme for galactosaemia as an alternative to a population wide NBS programme.
Inclusions	Screen tests conducted between 1977 to 1998 at the Hospital for Sick Children in Toronto, Canada.
Exclusions	Case testing due to positive family history.
Population	n=25,099 tests
Intervention	Beutler/Baluda test for erythrocyte GALT activity for all children under the age of 2 weeks who are hospitalised for any reason are screened for galactosaemia; hospitalised children over 2 weeks of age are tested if galactosaemia is clinically suspected. Cut-off values not reported.
Comparator	NA

Study results / outcomes	*Criterion 2:* **Proportion of classic galactosaemia cases symptomatic at diagnosis** 17 of 18 confirmed cases (94.4%) 13 of 17 (76%) presented with galactosaemia related symptoms before 4 weeks; 8 of these presented in the first 2 weeks (47% of symptomatic).
Comments	The cut-off value for high risk screening and case finding was not reported; the authors suggest that mild galactosaemia or D/G compound heterozygotes would be unlikely to be detected by the approach (no data is provided on any detected D/G variants). A population wide newborn screening programme with 100% sensitivity and results available within the first two weeks of life would have detected five cases prior to clinical presentation in the current cohort (assuming complete coverage). Single asymptomatic case was diagnosed at day 2 prior to pacemaker insertion.

Appendix number	18
Relevant criteria	2
Publication details	[14] Strahan JE, Canfield MA, Drummond-Borg LM, et al. Ethnic and gender patterns for the five congenital disorders in Texas from 1992 through 1998. Texas Medicine. 2002;98(9):80-6.
Study details	Retrospective cohort study, USA, healthcare setting not reported
Study objectives	To determine the prevalence of galactosaemia in Texas, 1992 to 1998
Inclusions	All newborns screened as part of the Texas Department of Health NBS programme, 1992 to 1998.
Exclusions	Not reported.
Population	n=2,292,698 newborns screened (>94% of newborns in Texas during the time period.
Intervention	DBS sampling at 72 hours of life, with a follow-up screen at 1 to 2 weeks. Guthrie bacterial inhibition assays used as primary and confirmatory test. GALT activity is used as diagnostic test for classic galactosaemia, and unspecified specialist diagnosis for variant galactosaemia.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Annual prevalence rate of galactosaemia** 0.21 per 10,000 live births (95% CI 0.15 to 0.28) 1:47,765 **Detection method of galactosaemia (13 cases overall) in 1999, n= (% of annual**

	cases) First screen: 8 (61.5%) Second screen: 4 (30.8%) Clinical presentation: 1 (7.7%)
Comments	Information provided for true positives only; no data provided for false positives or false negatives. No data provided on type (GALT, GALK, GALE) or variants (homozygous, compound heterozygous or D/G) of detected cases. Authors suggest that in general, partial variants are more likely to be detected at the second screen, however, as no information is provided on test cut-off values at either the 72h or 1-2 week screening test, the reasons for this variation cannot be conclusively determined.

Appendix number	19
Relevant criteria	2
Publication details	[19] Senemar S, Ganjekarimi A, Senemar S, et al. The prevalence and clinical study of galactosemia disease in a pilot screening program of neonates, southern iran. Iranian Journal of Public Health. 2011;40(4):99-104.
Study details	Cross sectional study, Iran, healthcare setting not reported
Study objectives	Determine epidemiology of galactosaemia in Iran following a two year pilot screening programme
Inclusions	All newborns in the Fars Province with samples referred to the newborn Laboratory of Paramedical School, Shiraz University of Medical Sciences, Iran
Exclusions	Not reported.
Population	n=24,000 newborns
Intervention	Screening of Gal and Gal-1-P serum levels via colorimetric enzymatic test on DBS
Comparator	NA
Study results / outcomes	*Criterion 2:* **Incidence of galactosaemia** Overall: 1:6,000
Comments	Type (GALT, GALE, GALK) and variant (homozygous, compound heterozygous, D/G) of positive cases was not reported. Classic GALT was reported in 3 of the 5 cases, however, as the stratification appeared to be based on serum Gal-1-P and not GALT activity, the frequency of variants have not been calculated for this report. Information was provided for presumed true positives only; no information on the

	detection of partial GALT deficiency was reported. Four of the five screen detected cases were born to consanguineous parents

Appendix number	20
Relevant criteria	Criterion 2, 5, 10
Publication details	[21] Schweitzer-Krantz, S., *Early diagnosis of inherited metabolic disorders towards improving outcome: the controversial issue of galactosaemia.].* European Journal of Pediatrics, 2003. **162 Suppl 1**: p. S50-S53.
Study details	Before and after study, Germany, healthcare setting not reported
Study objectives	To describe short- and long-term outcomes for patients with GALT deficiency born before and after the introduction of a national screening programme.
Inclusions	Patients without residual GALT activity born between 1955 and 1995.
Exclusions	Not reported
Population	n=148 (81 males/67 females), 49 born between 1955 and 1977 (before screening programme), 99 born between 1978 and 1995 (during screening programme). Genotypes not reported.
Intervention	Screening programme between 1978 usually performed at day 5 using the Beutler test for enzyme activity and sometimes the additional use of Paigen test as a substrate screening test. During the 1990's some laboratories conducted screening using a colorimetric test (dehydrogenase-based method) and alkaline phosphate to determine free galactose and galactose derived from galactose-1-phosphate. Dietary galactose restriction from day 1 in 11 of 128 patients due to positive family history; between days 2 to 7 in 21 patients; between days 8 to 14 in 53 patients; between days 15 to 28 in 22 patients; between day 29 to week 8 in 9 patients; after 8 weeks in 14 patients (9^{th} week one patient., 10^{th} week one patient., 3^{rd} month nine patients, 5^{th} month one patient, 11 years one patient., 16 years one patient). Treatment initiation by screening group not reported.
Comparator	NA
Study results / outcomes	*Criterion 2:* **Diagnosis following screening programme** 28 of 99 (28.3%) GALT deficient patients born after the introduction of the screening programme were presented clinically and were diagnosed prior to the positive screening test result. 52 of 99 (52.5%) were diagnosed due to the positive screen result only, despite the presence of clinical abnormalities (not further described). 5 of 99 (5.1%) patients were clinically asymptomatic (unclear if these patients had partial or Duarte galactosaemia).

	14 of 99 (14.1%) patients were diagnosed due to a positive family history. *Criterion 5:* **False-negative results** 2 of 99 patients (2.0%) had false-negative screen results on the Beutler fluorescence test (due to transfusions). *Criterion 10:* **Mortality due to galactosaemia** Unscreened: 19 patients; 15 prior to diagnosis*, 2 after initiation of dietary - galactose restriction. Four patients died aged 7-14 days, five aged 15-21 days, nine aged 4 to 9 weeks, one aged 3 years. * case histories reviewed following the birth of an affected sibling. Screened: 1 patients, following initiation of galactose restricted diet **Dietary treatment** 128 of 148 patients (86.5%) (all surviving patients) were treated with a galactose restricted diet. **Long term neurological outcomes** For patients treated with a galactose restricted diet initiated prior to 8 weeks of age, there was no significant correlation between developmental quotient or IQ. There was a correlation among the 14 patients who did not initiate treatment until after the 8th week. IQ declined significantly with age in all patients assessed (r=0.69; n=98, group allocation NR).
Comments	Narrative description only, no quantitative analysis provided. Between group comparisons not conducted (different source populations for screened vs. not screened patients). Main outcome of interest (long-term outcomes) not described separately for screened and clinically detected groups.

Appendix number	21
Relevant criteria	2, 10
Publication details	[29] Krabbi, K., et al., *Long-term complications in Estonian galactosemia patients with a less strict lactose-free diet and metabolic control.* Molecular Genetics & Metabolism, 2011. **103**(3): p. 249-253.
Study details	Retrospective case series, Estonia, healthcare setting not reported
Study objectives	Describe the long-term complications and outcomes classic galactosaemia

	patients, identified through a selective screening programme, on a less restricted diet.
Inclusions	Not reported.
Exclusions	Not reported.
Population	n=5 (1 male/4 female) classic galactosaemia patients diagnosed during a selective screening programme from 1996 to 2003. Age range 7 to 14 years. Genotype: one *Q188R/Q188R*, three *Q188R/R272C*, one *Q188R/H114P*
Intervention	Galactose restricted diet (prohibited items: human milk, cows' milk and their products except hard cheeses, butter, margarine containing milk protein, milk chocolate; allowed items: lactose-free formulas for infants, soya products, mature hardened cheeses [e.g. gouda, emmantaler], no restrictions of meat/ fish/ eggs/ cereals/ fruit/ vegetables/ sugar.
Comparator	NA.
Study results / outcomes	*Criterion 2:* **Timing of diagnostic confirmation** One prenatal, one at 8 days, one at 2 weeks, one at 4 weeks and one at 6 weeks. *Criterion 10:* **Developmental outcomes** Three patients (diagnosed prenatally, *Q188R/R272C;* at 8 days, *Q188R/Q188R*; and at 4 weeks, *Q188R/H114P*) had normal mental and speech development One patient (diagnosed at 6 weeks, *Q188R/R272C*) had moderate mental retardation, verbal dyspraxia, and extrapyramidal signs with ataxia and stereotypical movements. One patient (diagnosed at 2 weeks, *Q188R/R272C*) had mild speech delay and cognitive function deficit and focal epilepsy (diagnosed at age 4). **FSH levels (four female patients)** One patient (diagnosed at 8 days, *Q188R/Q188R*) had premature ovarian insufficiency with increased FSH levels at age 12. **Ophthalmological outcomes** One patient (diagnosed at 6 weeks, *Q188R/R272C*) had bilateral cataracts (stabilised by last follow-up)
Comments	Small, retrospective study with no information available on actual galactose exposures; minimum daily intake estimated retrospectively as at least 50mg/day (method of assessment/estimation NR).

	Specifics of screening programme not described (test, thresholds, methods); unclear what the characteristics of the selective screening programme (target population etc.) Initiation of dietary therapy varied across patients. Prenatal diagnosis in one patient due to an affected older sibling (also in the study, diagnosed at 6 weeks).