UK National Screening Committee

Screening for Gaucher disease in newborns

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

Version: 2

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Contents

Plain English summary

Gaucher disease is a rare genetic disease. In 2016 about 300 people in the UK were known to have the disease. Gaucher disease varies in how it develops in different people. It can range from mild with no symptoms to life threatening and causing death in early childhood. Some people have symptoms at birth whilst others develop symptoms later in childhood or as adults. There are 3 different types of Gaucher disease with type 1 affecting most people.

Newborn Screening for Gaucher disease in babies identifies all children with the disease whether or not they have symptoms.

This review looks at whether children with type 1 Gaucher disease benefit from treatment before symptoms develop.
The UK National Screening Committee (UK NSC) published its last review in 2013. This recommended against introducing a UK newborn screening programme for Gaucher disease. This was because:

- there was not agreement on how the screening test should be used,
- there was some treatment for people with type 1 Gaucher disease but it was not clear if it was better to treat someone sooner rather than later
- there was no treatment for people with type 2 Gaucher disease
- the results of treating people with type 3 Gaucher Disease varied with some improving but others not finding any benefit

This review did not find any studies about whether people who have type 1 Gaucher disease, but do not have any symptoms, improve more than people who receive treatment when symptoms develop.

For this reason the UK NSC still cannot recommend newborn screening for Gaucher disease.

Executive summary

Purpose of the review

This evidence summary reviews newborn screening for type 1 Gaucher disease (GD) against selected UK National Screening Committee (UK NSC) criteria and updates the previous review in 2013. The aim of a newborn screening programme for GD would be to identify newborns with the disease and inform future treatment decisions. The review looks for evidence of whether treatment of type 1 Gaucher disease at a pre-symptomatic phase is more beneficial than later treatment following symptomatic presentation.

Background

Gaucher disease is a lysosomal storage disorder (LSD) which is inherited as an autosomal recessive condition with an estimated birth frequency of 1:50,000 to 1:100,000 in the European population, with a higher incidence of 1:500 to 1:1000 live births in the Ashkenazi Jewish population. The Gauchers Association in the UK, report that in 2016 they knew of 310 people with GD in the UK and Ireland (293 adults and children in Scotland, England and Wales, and 17 in all of Ireland).

GD is caused by mutations of the GBA1 gene which encodes for the enzyme glucocerebrosidase. Reduced enzyme function results in the over storage of glucosylceramide in white blood cells known as macrophages that accumulate primarily in the bone marrow, liver, spleen, and secondarily in the lungs and brain. The different sites of accumulation result in multi-system disease and diverse clinical symptoms. The phenotypic presentation of the condition ranges from almost asymptomatic to severe, life-threatening and fatal. There are 3 different types of GD with type 1 affecting 95% of those diagnosed in Europe, the US and Canada.

Type 1 GD is the non-neuronopathic form of the condition with phenotypic presentation ranging from mild to severe and life threatening. The onset of symptoms may occur at any time from childhood into adulthood with

people with identical mutations manifesting as variations in overall severity and organ involvement. Patients who present in early childhood generally go on to have more severe symptoms than those who present later in adulthood.

Type 2 GD accounts for 1% of GD cases and is a fatal neuronopathic form of the condition with neonatal-infantile onset which is rapidly progressive, leading to death typically by the age of 2.

Type 3 GD (also known as the chronic neuronopathic form), accounts for 4% of GD cases. Symptoms develop in childhood with progressive neurological deterioration that may result in death during the second decade, although some patients with non-progressive disease have survived into their fourth decade. This review only concerns type 1 GD.

Newborn screening for GD is in place in some states in the US and Taiwan. An initial test for reduced enzyme activity of glucocerebrosidase followed by confirmatory testing and genotyping is used to confirm the diagnosis of GD.

Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are used to reduce the severity of symptoms in children with type 1 GD.

Focus of the review

The aim of the current review is to update the evidence in a key area identified in the previous review. The key question addressed in the current review is:

- does the treatment of type 1 Gaucher disease at a pre-symptomatic phase result in better health outcomes?

Recommendation under review

The current UK NSC policy is that systematic newborn screening for GD is not recommended. The previous UK NSC external review of screening for GD considered literature published up to October 2012. This concluded that:

- an appropriate cut-off level for the screening test had not yet been agreed

- there was evidence that ERT is effective in mitigating the effects of type 1 Gaucher disease however evidence was limited about whether earlier treatment of type 1 GD is any more effective than later treatment
- some studies had investigated ERT or a combination of ERT and SRT as a treatment for type 3 GD, however the results were ambivalent with some studies demonstrating some improvement and others not able to demonstrate any beneficial results. There was no specific therapy for patients with type 2 GD.

Findings and gaps in the evidence of this review

The 1 key question in this review is concerned with the effectiveness of treatment for pre-symptomatic type 1 GD in children, however no studies were identified that met the inclusion criteria for this question.

Recommendations on screening

Based on the lack of studies about the effectiveness of treating children who have pre-symptomatic type 1 GD, the current recommendation not to introduce a UK newborn screening programme for Gaucher disease should be retained.

Limitations

A limitation of this review is the lack of any evidence about whether treating children who have pre-symptomatic type 1 GD is effective in ameliorating possible future symptoms.

This rapid review process was conducted over a condensed period of time (approximately 8 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by 1 information scientist, and further appraisal and study selection by 1 reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Evidence uncertainties

There is a lack of evidence about the harms or benefits of treating children who have pre-symptomatic GD. Currently treatment varies between countries as experts develop their own consensus guidelines in the absence of published evidence. The rarity of GD and variability of how the condition will progress in individuals over time makes research in this area particularly challenging.

Introduction and approach

This evidence summary reviews newborn screening for Gaucher disease against selected UK National Screening Committee criteria and updates the previous review in 2013[1]. The aim of a newborn screening programme for GD would be to identify newborns with the disease and inform future treatment decisions. The review looks for evidence of whether treatment of type 1 Gaucher disease at a pre-symptomatic phase is more beneficial than later treatment following symptomatic presentation.[2]

Background

Gaucher disease (GD) is a lysosomal storage disorder (LSD) which is inherited as an autosomal recessive condition with an estimated birth frequency of 1:50,000 to 1:100,000 in the European population with a higher incidence of 1:500 to 1:1000 live births in the Ashkenazi Jewish population[3]. The Gauchers Association in the UK report that in 2016 they knew of 310 people with Gaucher disease in the UK and Ireland (293 adults and children in Scotland England and Wales and 17 in all of Ireland)[4].

GD is caused by mutations of the GBA1 gene which encodes for the enzyme glucocerebrosidase resulting in reduced enzyme function. More than 300 mutations, including point mutations, deletions, insertions, splicing aberrations and various rearrangements, have been described in the GBA gene region as the cause of GD[5]. The gene mutations have been divided broadly into three groups according to their phenotypic effect: null, severe, and mild. Patients carrying at least one mild mutation have non-neuronopathic disease (GD type 1), while patients carrying two severe mutations or a severe and a null mutation usually develop neurological symptoms (GD types 2 and 3). In some cases people with the same mutations will develop different types of GD. Modifier genes[i]

i Genetic modifiers are genes, other than the GBA1 gene which may directly or indirectly have an affect on how the body responds to the conditions that develop as the result of the GBA1 mutation.

that if expressed might cause different phenotypic expression of GD is one current theory to account for the heterogeneity of the condition[6].

Reduced glucocerebrosidase enzyme function results in the over storage of glucosylceramide in white blood cells known as macrophages, that accumulate primarily in the bone marrow, liver, spleen, and secondarily in the lungs and brain. The different sites of accumulation result in multi-system disease and diverse clinical symptoms. The phenotypic presentation of the condition ranges from almost asymptomatic to severe, life-threatening and fatal[7,8].

The UK NSC's previous review in 2013[1] outlined the natural history of the condition with a description of the 3 types of GD with their varied signs and symptoms (Table 1)[9]. The review concluded that there was uncertainty about the natural history of the condition, specifically predicting how severely different individuals will be affected who might be identified through a newborn screening programme.

Table 1: Characteristics of Gaucher disease subtypes[9,10,11]

	Type 1	Type 2	Type 3
Phenotype	Accounts for 95% of GD cases. Diverse phenotypes among patients with identical GBA mutations manifests as variations in the overall severity of the disease, as well as in the pattern of organ involvement Childhood or adult onset varying from asymptomatic to life threatening symptoms.	Accounts for 1% of GD cases. Typically neonatal-infantile onset with a rapidly progressive fatal course. The median age of death is 9 months	Accounts for 4% of GD cases. Typically infantile-childhood onset; sub-acute and slowly progressive may result in death during the second decade although some have survived to their 4th decade.
Visceral symptoms	Hepatomegaly (>80% of patients), splenomegaly (>90% of patients), interstitial lung disease and pulmonary hypertension	Hepatomegaly, splenomegaly, hydrops fetalis (neonatal presentation) and interstitial lung disease	Hepatomegaly, splenomegaly and interstitial lung disease
Hematopoietic symptoms	Anaemia and thrombocytopenia	Anaemia and thrombocytopenia	Anaemia and thrombocytopenia
Orthopaedic symptoms	Bony pain crisis, osteopenia, aseptic necrosis of femoral	Arthrogryposis in severe cases, and generally death	Bony pain crisis, osteopenia, aseptic necrosis of femoral

	head, bony lytic lesions, bony infarctions and pathological fractures	before bony abnormality	head, bony lytic lesions, bony infarctions and pathological fractures
Neurologic symptoms	No CNS involvement and no cognitive regression except for an increased risk in Parkinson's disease	Bulbar palsies, hypertonicity, abnormal ocular saccades and cognitive impairment	Oculomotor apraxia, myoclonic epilepsy, generalized tonic-clonic seizures, and cognitive impairment

The newborn screening test for Gaucher disease involves demonstrating insufficient β-glucocerebrosidase activity using tandem mass spectrometry or digital microfluidic fluorometry from a single dried blood spot. This is followed by confirmatory testing and genotyping. These methods identify all 3 types of the disease. The previous UK NSC review in 2013[1] did not find any evidence that an appropriate screening test cut-off had been defined and agreed.

The UK NSC review in 2013[1] reported that there were newborn screening programmes for Gaucher disease in Taiwan and the US. Results from the Illinois newborn screening programme have been subsequently published by Burton et al (2017)[12] and report that of 219,793 newborns tested, 5 (of 117 screen positives) had a confirmed positive result and 2 had an undetermined 'possible' Gaucher disease phenotype. In the Missouri newborn screening programme of 308,000 infants tested, 5 (of 37 screen positives) had a confirmed positive result and 2 were unconfirmed (patients were lost to follow up, refused, or died)[13]. In the Illinois newborn screening programme none of the confirmed cases had any clinical manifestations or started treatment at diagnosis but were followed up with the intention of commencing treatment when and if symptoms developed[12]. The outcomes of newborn screening for this group of patients have yet to be demonstrated and Burton et al (2017)[12] suggest it will take years of long term follow up to clearly understand the risks and benefits of the programme.

The previous review in 2013[1] described how the development of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) have made GD treatable with the exception of the neurological deterioration associated with types 2 and 3[7]. ERT aims to replace the defective or missing enzyme with a functional protein that is infused into the bloodstream and taken up into cellular lysosomes[14]. ERT targets the underlying metabolic deficit rather than providing symptomatic

management[15]. SRT targets the failure of the lysosomal metabolic pathway by inhibiting the production of glucosylceramide and thereby reducing its accumulation in the lysosomes and the likelihood of subsequent multi organ dysfunction[3].

The 2013 UK NSC review[1] found limited evidence about whether earlier treatment of type 1 GD is more effective than later treatment. UK consensus guidelines published in 2012 recommend that children who are pre-symptomatic are treated immediately following diagnosis with the rationale that skeletal disease is difficult to diagnose clinically and radiologically subtle changes could be missed[16]. This would result in people who may have been identified through cascade testing receiving lifelong treatment prior to the onset of symptoms despite not knowing the future severity of their particular phenotype. This situation is avoided in US newborn screening programmes where individuals who are pre-symptomatic are monitored until symptoms emerge (which may be many years) and then treated.

There is no specific reference to newborn screening in the UK consensus guidelines.

The 2013 UK NSC review[1] reported that evidence for the effectiveness of treatment for type 2 and type 3 forms of the condition was less clear than for type 1. Some studies have investigated ERT or a combination of ERT and SRT as a treatment for type 3 Gaucher disease, however the results have been ambivalent with some studies demonstrating some improvement and others not able to demonstrate any beneficial results. There is no specific therapy for patients with type 2 Gaucher disease due to the rapid clinical progression of the disease[1.]

Current policy context and previous reviews

The current UK NSC policy is that systematic newborn screening for Gaucher disease is not recommended. The previous UK NSC external review of screening for Gaucher disease[1] considered literature published up to October 2012. This concluded that:

- an appropriate cut-off level for the screening test had not yet been agreed
- there was evidence that ERT is effective in mitigating the effects of type 1 Gaucher disease however evidence was limited about whether

earlier treatment of type 1 Gaucher disease is any more effective than later treatment

- some studies had investigated ERT or a combination of ERT and SRT as a treatment for type 3 Gaucher disease, however the results were unclear with some studies demonstrating some improvement and others not able to demonstrate any beneficial results. There was no specific therapy for patients with type 2 Gaucher disease.

Objectives

The aim of the current review is to update the evidence in a key area identified in the previous review. The key question addressed in the current review was developed by the UK NSC with input from Solutions for Public Health.

The key question and the UK NSC criterion that it relates to is presented in Table 2 below.

Table 2. Key question for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	Does the treatment of type 1 Gaucher disease at a pre-symptomatic phase result in better health outcomes?	0

Methods

The current review was conducted by Solutions for Public Health, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 1st August 2018 to identify studies relevant to the question detailed in Table 2.

Eligibility for inclusion in the review

The following review process was followed:

1. each abstract was reviewed against the inclusion/exclusion criteria by 1 reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured.
2. full-text articles required for the full-text review stage were acquired
3. each full-text article was reviewed against the inclusion/exclusion criteria by 1 reviewer, who determined whether the article was relevant to 1 or more of the review questions
4. any queries at the abstract or full-text stage were resolved through discussion with a second reviewer
5. the review was quality assured by a second senior reviewer, not involved with the writing of the review in accordance with SPH's quality assurance process.

Eligibility criteria for the question is presented in Table 3 below.

A total of 668 unique references were identified and sifted by an information scientist by title and abstract for potential relevance to the review. An SPH reviewer assessed 57 titles and abstracts for further appraisal and possible inclusion in the final review.

Overall, 17 studies were identified as possibly relevant during title and abstract sifting and further assessed at full text (see Appendix 2 for study flow).

Eligibility criteria for the question is presented in Table 3 below.

Table 3. Inclusion and exclusion criteria for the key question

Key question	Inclusion criteria							Exclusion criteria
	Population	**Target condition**	**Intervention**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	
Does the treatment of type 1 Gaucher disease at a pre-symptomatic phase result in better health outcomes?	Children diagnosed with type 1 Gaucher disease	Type 1 Gaucher disease	Treatment with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) in pre-symptomatically detected populations	N/a	Treatment in symptomatic type 1 Gaucher disease populations	Reduction or resolution of the following symptoms: • visceral (hepatomegaly, splenomegaly, interstitial lung disease, pulmonary hypertension) • hematopoietic (anaemia, thrombocytopenia) • orthopaedic (bony pain crisis, osteopenia, aseptic necrosis of femoral head, bony lytic lesions, bony infarctions, pathological fractures)	RCTs, cohort studies, systematic reviews	N/a

Databases/sources searched

A systematic search of 3 databases (Medline, Embase and Cochrane) was conducted on 1st August 2018 to identify studies relevant to the question detailed in Table 3. The search strategy is presented in Appendix 1.

Question level synthesis

Criterion 9

There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

Question 1 – Does the treatment of type 1 Gaucher disease at a pre-symptomatic phase result in better health outcomes?

The UK NSC review in 2013[1] concluded that there was evidence from a Health Technology Assessment by Wyatt et al (2012)[17] for an effective treatment in the form of ERT for symptomatic type 1 Gaucher disease. There was an association between time on ERT and:

- a clinically significant improvement in platelet count and haemoglobin in children and adults, regardless of whether they had undergone splenectomy.
- a clinically important decrease in the likelihood of having an enlarged spleen or liver.
- reduced aspartate transaminase (AST) levels (a test of liver function) and a lower risk of having an abnormal AST level.
- some evidence for a reduced risk of bone pain in adults and children.

Wyatt et al (2012)[17] found that substantial improvements were seen over the first 5 to 10 years of treatment followed by a plateauing of the effect. However the authors also noted the wide confidence intervals around the effect sizes associated with longer periods on ERT.

The UK NSC review in 2013[1] found a lack of studies examining whether pre-symptomatic treatment was effective.

Eligibility for inclusion in the review

- population – children diagnosed with type 1 Gaucher disease
- intervention – treatment with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) in pre-symptomatically detected populations
- comparator – treatment in symptomatic type 1 Gaucher disease populations
- outcomes – reduction or resolution of the following symptoms:
    - visceral (hepatomegaly, splenomegaly, interstitial lung disease, pulmonary hypertension)
    - hematopoietic (anaemia, thrombocytopenia)
    - orthopaedic (bony pain crisis, osteopenia, aseptic necrosis of femoral head, bony lytic lesions, bony infarctions, pathological fractures)
- study design – RCTs, cohort studies, systematic reviews
- date and language – studies published in the English language after October 2012.

Description of the evidence

Database searches yielded 668 results, of which 57 were judged to be relevant to this question and 17 abstracts met the criteria for full text review. After review of the full texts, no studies met the inclusion criteria for this question ie they did not report the outcomes of interventions in children with pre-symptomatic type 1 Gaucher disease. The reasons for exclusion of the 17 studies were:

- the study population were symptomatic (16 studies)
- the study population were symptomatic children and the publication had been included in Wyatt et al (2012) and reported in the previous review(1).

0contains a full PRISMA flow diagram (Figure 1).

Discussion of findings

No studies examining the effectiveness of interventions for children with pre-symptomatic type 1 Gaucher disease were identified.

Summary of Findings Relevant to Criterion 9: Criterion not met[2]

The question for this criterion concerned the effectiveness of interventions for children with pre-symptomatic type 1 Gaucher disease. No studies were identified that specifically examined the effectiveness of interventions in a pre-symptomatic population of children with this condition.

In the absence of evidence of the effectiveness of interventions in pre-symptomatic paediatric populations this criterion is not met.

[2] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Review summary

Conclusions and implications for policy

This report is an update review on newborn screening for type 1 Gaucher disease against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed 1 key question to determine if new evidence published since 2013 suggests that reconsideration of the current recommendation for screening for Gaucher disease in the UK is required.

The 1 key question in this review is concerned with the effectiveness of interventions for pre-symptomatic type 1 Gaucher disease in children who might be detected via a newborn screening programme, however no studies were identified that met the inclusion criteria for this question.

The current recommendation not to introduce a UK newborn screening programme for Gaucher disease should be retained.

Limitations

A limitation of this review is the lack of any evidence about whether treating children who have pre-symptomatic type 1 Gaucher disease is effective in ameliorating possible future symptoms.

This rapid review process was conducted over a condensed period of time (approximately 8 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by 1 information scientist, and further appraisal and study selection by 1 reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 4. MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase.

Table 4. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE	Ovid SP	1st August 2018	2012 to Present
Embase	Ovid SP	1st August 2018	2012 to Present
The Cochrane Library	Wiley Online	1st August 2018	2012 to Present

Search Terms

Search terms for MEDLINE are shown in Table 5. A similar search was conducted for Embase (Table 6). Search terms for the Cochrane Library databases are shown in Table 7.

Table 5. Search strategy for MEDLINE

#	Search terms	Results
Search 1		
1	Gaucher Disease/	4401
2	gaucher*.ti,ab.	4946
3	1 or 2	5577
4	Gaucher Disease/dt, th [Drug Therapy, Therapy]	1239
5	exp Enzyme Therapy/	1711
6	((enzyme* or substrate) adj3 (therap* or treat*)).ti,ab.	16475
7	(therap* or treat* or manage*).ti.	2272483
8	4 or 5 or 6 or 7	2283804
9	3 and 8	1766
10	limit 3 to "reviews (maximizes specificity)"	26
11	9 or 10	1777
12	limit 11 to (english language and yr="2012 -Current")	494
13	exp animals/ not humans.sh.	4478492
14	12 not 13	484
Search 2		
1	GAUCHER DISEASE/	4401
2	gaucher*.ti,ab.	4948
3	1 or 2	5579
4	(miglustat or eliglustat).mp.	453
5	(taliglucerase or imiglucerase or velaglucerase).mp.	411
6	4 or 5	807
7	3 and 6	513

8	limit 7 to (english language and yr="2012 -Current")	192
9	exp animals/ not humans.sh.	4479136
10	8 not 9	184

Table 6. Search strategy for Embase

#	Search terms	Results
Search 1		
1	Gaucher Disease/	7449
2	gaucher*.ti,ab.	6534
3	1 or 2	8372
4	Gaucher disease/dm, dt, th	1990
5	exp Enzyme Therapy/	10090
6	((enzyme* or substrate) adj3 (therap* or treat*)).ti,ab.	22044
7	(therap* or treat* or manage*).ti.	2866983
8	4 or 5 or 6 or 7	2883937
9	3 and 8	3355
10	limit 3 to "reviews (maximizes specificity)"	30
11	9 or 10	3371
12	limit 11 to (english language and yr="2012 -Current")	1199
13	(exp animals/ or nonhuman/) not human/	6497291
14	12 not 13	1160
15	conference*.pt.	3889232
16	14 not 15	751
Search 2		
1	Gaucher Disease/	7449
2	gaucher*.ti,ab.	6534
3	1 or 2	8372
4	(miglustat or eliglustat).mp.	1437
5	(taliglucerase or imiglucerase or velaglucerase).mp.	1488
6	4 or 5	2609
7	3 and 6	1626
8	limit 7 to (english language and yr="2012 -Current")	704
9	(exp animals/ or nonhuman/) not human/	6497913
10	8 not 9	689
11	conference*.pt.	3890473
12	10 not 11	443

Table 7. Search strategy for the Cochrane Library Databases

#	Search terms	Results
#1	gaucher*:ti,ab,kw (Word variations have been searched)	0

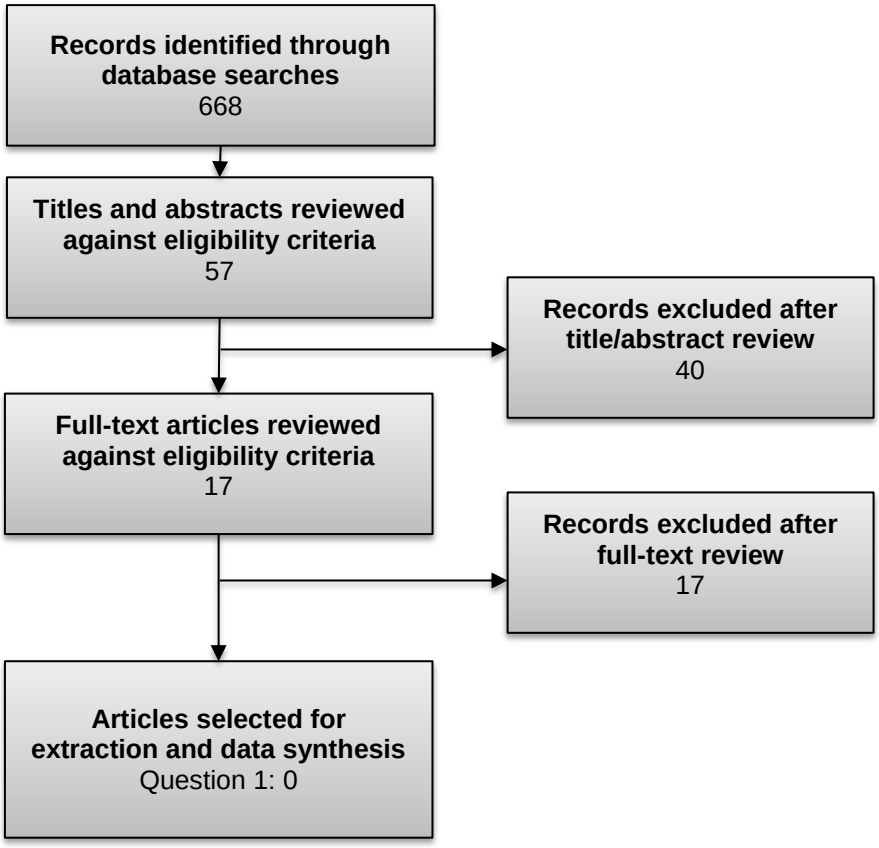
Duplicate references were removed.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. 17 publications were ultimately judged to be relevant to the review question and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

There were no publications included after review of full-texts.

Appendix 3 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 8.

Table 8. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	4
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	5
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review	9

		methods used.	
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	18
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	N/A
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	16
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	21
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	14
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION) N/A		
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	18
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	19
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each	19

		question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	20
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	20

References

1 Solutions for Public Health, Screening for Gaucher Disease, A report for the UK National Screening Committee. December 2013

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