DRAFT FOR CONSULTATION

Appraisal of Screening for Gaucher Disease

A draft report for the
UK National Screening Committee

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Summary

Gaucher disease is the most common of the inherited lysosomal storage diseases (LSD). It is caused by an enzyme deficiency from a mutation in the gene that codes for the lysosomal enzyme acid β-glucosidase (glucocerebrosidase (GBA1)). Newborn screening for Gaucher disease is being implemented in a few areas of the world as treatments for lysosomal storage diseases are becoming more effective. No screening programmes have been put in place just for this one condition, other LSDs such as Fabrys, Pompes and Niemann-Pick disorders are typically included using a multiplex assay.

This report reviews newborn screening for Gaucher disease against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search conducted by the NSC in October 2012.

Gaucher disease is an important, albeit rare, condition with an estimated 925 people carrying the underlying predisposing mutations for the disease in the UK and 325 with symptoms. In the UK Ashkenazi Jewish population of around 300,000 there is a higher prevalence of the condition with around 300 people with the underlying predisposing mutations and 90 with symptoms. We have not been able to identify a published estimate of the prevalence or birth incidence of Gaucher disease in the UK. Applying the results from an Austrian study of newborn screening for Gaucher disease to the number of UK live births for 2012 (729,674) suggests that we might expect 84 positive screening tests and 42 cases confirmed to have underlying predisposing mutations for Gaucher disease each year from a UK screening programme. However, it should be noted that there is a higher proportion of Jewish people in the UK population than the Austrian population. The number of positive screening tests and cases confirmed to have predisposing mutations in the UK could therefore be more in the region of 120 and 60 respectively.

The spectrum of Gaucher disease ranges from asymptomatic and less severely affected patients to severely affected and fatal in utero disease. There are a number of uncertainties in the natural history of Gaucher disease, specifically around predicting how severely different individuals will be affected.

It would be possible to identify individuals with low GBA enzyme levels through a newborn screening test, although an appropriate cut-off level for the screening test has not yet been agreed.

There is evidence that enzyme replacement therapy (ERT) is effective in mitigating the effects of type 1 Gaucher disease however evidence is limited about whether earlier treatment of type 1 Gaucher disease is more effective than later treatment. Any screening programme will currently also identify newborns with type 2 and type 3 Gaucher disease. Some studies have investigated ERT or a combination of ERT and substrate reduction therapy 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.

Due to several important UK NSC criteria not being met it is not recommended that a formal UK NSC screening programme is implemented at the current time. As research continues and treatments develop it will be important to reassess Gaucher disease against the UK NSC criteria in the future.

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The main areas where research would be beneficial include:

- A better understanding of the link between genotype and phenotype to allow the identification of which pre-symptomatic individuals are likely to develop symptoms that would impact on their quality of life and would benefit from treatment
- Exploring whether starting enzyme replacement therapy earlier (before the appearance of symptoms) is more beneficial than later treatment
- Developing treatments for the neurological aspects of type 3 Gaucher disease.

Introduction

1. This report reviews newborn screening for Gaucher disease against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (NSC 2003). It is based on a literature search conducted by the NSC in October 2012 (Coles 2012). Full details of the search strategy are set out in Appendix A.

2. Gaucher disease is the most common of the inherited lysosomal storage diseases (LSD). It is caused by an enzyme deficiency from a mutation in the gene that codes for the lysosomal enzyme acid β-glucosidase (glucocerebrosidase (GBA1)) (Connock et al 2006). The spectrum of Gaucher disease ranges from asymptomatic and less severely affected patients to severely affected and fatal in utero disease (Wang et al 2011).

3. Gaucher disease is traditionally classified into three broad phenotypic categories, type 1 non-neuronopathic disease, type 2 fulminant neuronopathic disease and type 3 chronic neuronopathic disease (Mistry et al 2011). An exception to the non-neuronopathic classification of type 1 disease is an increased risk of Parkinson's disease in these patients (Wang et al 2011).

4. More than 90% of patients have type 1 Gaucher disease and it has the broadest phenotypic spectrum for age of onset, rate of progression and organs affected (Mistry et al 2011).

5. It has been suggested that the terms type 2 and type 3 should be replaced by acute neuronopathic and chronic neuronopathic Gaucher disease[1] to take account of the wide spectrum of phenotypes within neuronopathic Gaucher disease (Vellodi et al 2009). However we have used the terms type 2 and 3 in this report in line with current common practice in most of the literature cited.

6. United Kingdom (UK) national guidelines for adult Gaucher disease (Deegan et al 2005) were published in 2005. A paediatric guideline for England (Vellodi et al 2012) was published in 2012.

7. Newborn screening for Gaucher disease has not previously been assessed against the UK NSC criteria.

[1] Acute neuronopathic Gaucher disease refers to onset at ≤1 year of age of progressive bulbar involvement (stridor, squint, swallowing difficulty) and pyramidal involvement (opisthotonus, head retroflexion, spasticity, trismus). Cognitive impairment may or may not be present. Chronic neuronopathic Gaucher disease refers to all patients with neuronopathic disease who do not have acute disease (Vellodi et al 2009).

The Condition

The condition should be an important health problem

8. Estimates for the prevalence of type 1 Gaucher disease vary from 1 in 40,000 to 1 in 60,000 [1.7 per 100,000 to 2.5 per 100,000]. However, the disease prevalence in the Ashkenazi Jewish population has been calculated at 1 in 800 [125 per 100,000] (Wang et al 2011).

9. The worldwide prevalence of type 1 Gaucher disease is 1 in 50,000-100,000, with a prevalence of approximately 1 in 850 [118 per 100,000] amongst people of Ashkenazi heritage (Mistry et al 2011). Type 2 and 3 Gaucher disease comprises less than 10% of the total number of cases and these types do not have increased prevalence in the Ashkenazi Jewish populations.

10. Many of the autosomal recessive disorders in the Ashkenazi Jewish population are attributed to mutations thought to arise in a single individual many generations ago. Due to the way in which the Ashkenazi Jewish population has migrated and expanded these mutations have become more common. Known as the founder effect, this type of genetic drift has been proposed as the reason why Gaucher disease is more common in the Ashkenazi Jewish population (Zhang et al 2004). There is a theory that the high frequency of these mutations is due to people carrying them having a better reproductive or survival advantage such as increased resistance to infectious pathogens (Zhang et al 2004).

11. We have not been able to identify a published estimate of the prevalence or birth incidence of Gaucher disease in the UK. In England a cohort study involving all seven of the designated LSD treatment centres identified that there were 272 patients with Gaucher disease (known to these centres) in 2006 (Wyatt et al 2012), however this may underestimate the actual figure.

12. The UK Gaucher Association (webpage last updated in 2004[2]) estimated that there are 590 people in the non-Ashkenazi UK population with underlying predisposing mutations for Gaucher disease, of which 235 would have symptoms. Amongst the UK Ashkenazi population (estimated as approximately 300,000 people by Burton et al 2009) there were estimated to be about 335 people with underlying predisposing mutations for Gaucher disease, of which 90 would have symptoms. These estimates would equate to a total of 925 people in the UK with underlying predisposing mutations for Gaucher disease, of which 325 would have symptoms (approximately 35%).

13. Using the estimated 2004 UK population figure of 59.8 million (ONS 2011) the Gaucher Association figures would suggest a prevalence of 1.5 per 100,000 population for people with a biallelic recessive genetic markers (mutations on both copies) for Gaucher disease in the UK and 0.5 per 100,000 population for people in the UK with symptoms.

14. An Austrian study (Mechtler et al 2012) tested 34,736 bloodspots from newborn babies from which 4 cases (1 in 8,684) had a positive screening result with 2 cases (1 in 17,368) confirmed to have underlying predisposing mutations for Gaucher disease after mutation analysis. Applying these figures crudely to the number of UK live births for 2012 (729,674) suggests that we might expect 84 positive screening tests and 42 cases confirmed to have underlying predisposing mutations for Gaucher disease each year from a UK screening programme. However, it should be noted that there is a higher proportion of Ashkenazi Jews in the UK population (0.5%) than in the Austrian population (0.1%) (Pergola 2005). Adjusting for the higher proportion of Ashkenazi Jews in the UK suggests

[2] http://www.gaucherdisease.org.uk/genetic.htm

that the number of positive screening tests and cases confirmed to have predisposing mutations for Gaucher disease in the UK could therefore be more in the region of 120 and 60 respectively.

15. Data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry found that North America (96%) and Latin America (95%) had the highest proportion of patients with type 1 Gaucher disease and that Asia-Pacific (10%), Europe (14%) and the Middle East/ Africa (16%) had higher percentages of patients with type 3 Gaucher disease (Weinreb et al 2010).

16. Patients with type 1 disease can experience growth retardation, delayed puberty, leukopenia, impairment of pulmonary gas exchange, destruction of vertebral bodies with secondary neurologic complications and have an increased risk for multiple myeloma and Parkinson's disease. Patients with type 1 disease who present in childhood generally have more pronounced visceral and bony disease manifestations (Wang et al 2011).

17. Type 2 disease has a neonatal-infantile onset and a rapidly progressive fatal course (Wang et al 2011). The median age of death for type 2 disease is 9 months (Grabowski 2008).

18. Type 3 disease has an infantile-childhood onset with sub-acute, slowly progressive disease (Wang et al 2011). In type 3 disease, progressive neurological deterioration may result in death during the second decade, however some patients with non-progressive disease have survived into their fourth decade without specific treatment other than splenectomy (Deegan et al 2005). Type 3 disease is often divided into 3 sub-types (Wang et al 2011).

19. Further details of the symptoms associated with the three Gaucher disease subtypes are presented in appendix B.

20. Clinicians with experience in the management of Gaucher disease have reported consistent patterns of previous misdiagnoses in their patients. Such misdiagnosis can lead to complications such as avascular necrosis, osteopenia, liver disease and bleeding complications and can also result in inappropriate procedures being performed such as splenectomy, liver biopsy and empirical corticosteroid therapy (Mistry et al 2011).

21. Gaucher disease is an important, albeit rare, condition so this criterion is met.

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

22. The severity of symptoms and rate of progression for Gaucher disease varies between patients, ranging from asymptomatic to severe with early death. This variability is partly related to genotype, with over 300 different mutations identified (Grabowski 2008). However, there are five which account for approximately 90% of disease alleles in people of Ashkenazi Jewish ancestry and approximately 50% of people who are not of Ashkenazi descent (Mistry et al 2011).

23. Table 1 summarises the genotype/phenotype correlations in Gaucher disease.

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Table 1: Phenotype-genotype correlations in Gaucher disease (Adapted from Wang et al 2011)

Genotype	Phenotype
p.N370S / any	Type 1 Gaucher disease
p.L444P/p.L444P p.D409H/p.D409H	Type 3 Gaucher disease
p.L444P/recombinant Recombinant/recombinant	Type 2 Gaucher disease

24. In populations of European descent the most frequent type 1 Gaucher disease genotype is thought to be N370S/L444P, which generally leads to more severe disease compared to N370S homozygosity (Mistry et al 2011).

25. Mutations that cause a complete loss of enzyme activity usually result in a severe phenotype with early onset of disease (Wyatt et al 2012).

26. However, prediction of the clinical course of an individual patient based on genotype is uncertain (Connock et al 2006) and there is 'extreme phenotype diversity' in patients with the same disease genotype and within affected sibling pairs. For example, a genotype of N370S/N370S accounts for approximately 70% of disease alleles in the Ashkenazi Jewish population and is associated with atypical presentation in adults, however a minority of people with this genotype may present with classic manifestations in childhood (Mistry et al 2011).

27. For the 4,936 patients with Gaucher disease enrolled in the ICGG Gaucher Registry between 1991 and 2007, the mean age at diagnosis was 19 years, with the majority of people being diagnosed between the age four and 30 years (Vom Dahl et al 2009). About 50% of patients in the Gaucher Registry presented during childhood or adolescence (Vellodi et al 2012).The percentage of these patients presenting with various symptoms at diagnosis is summarised in table 2.

Table 2: Symptoms present at diagnosis for patients enrolled in the ICGG Gaucher Registry between 1991 and 2007 (Vom Dahl et al 2009)

Symptom	Percentage of patients
Moderate to severe thrombocytopaenia	60%
Anemia	37%
Splenomegaly	86%
Hepatomegaly	65%
Radiologic bone disease	83%
Bone pain	34%

28. A study at one clinic in New York involved 8,069 individuals who had requested prenatal carrier testing for genetic diseases affecting the Ashkenazi Jewish population. This study identified 524 people who were heterozygous Gaucher disease carriers (1 in 15) and nine who were homozygous for Gaucher disease (1 in 897) (Balwani et al 2010).

29. Balwani et al (2010) conducted a range of tests on six of the nine people who were homozygous for Gaucher disease identified by their clinic plus a further 31 people identified by other prenatal carrier programmes in the wider New York area. All 37 patients were aged between 17 and 40 years. Twelve patients had clinically significant disease manifestations and were recommended to have enzyme replacement therapy (ERT), however all 37 patients had some Gaucher disease manifestations identified on

clinical, laboratory and/or imaging testing. A summary of the findings for this group is provided in table 3.

Table 3: Evaluation of 37 people identified as being homozygous for Gaucher disease by prenatal carrier programmes in New York (Balwani et al 2010)

Assessment	Symptom	Number of patients (%)
Self-report	No Gaucher disease related symptoms	24 (65%)
	Bone pain	3 (8%)
	Fatigue	2 (5%)
	Easy bruisability	12 (32%)
Clinical assessment	Anemia	4 (11%)
	Thrombocytopenia	Total: 16 (43%) *Of which:* *Moderate: 6 (16%)* *Severe: 1 (3%)*
MRI or CT scan of the abdomen (n=29)	Splenomegaly	Total: 29 (96%) *Of which:* *Mild: 25 (86%)* *Moderate: 3 (10%)*
	Hepatomegaly	Total: 16 (55%) *Of which:* *Moderate: 7 (24%)*
Imaging studies to assess skeletal involvement (n=29)	Marrow infiltration of the spine and/or femur	29 (100%)
	Bone infarction (on MRI)	4 (14%)
Skeletal radiographs (n=23)	Erlenmeyer flask deformity (due to failure of bone remodeling)	10 (43%)
	Lucencies	5 (22%)
	Osteopenia	13 (57%)
Baseline bone marrow density (BMD) (n=25)	Low BMD at the hip, spine and/or forearm	15 (60%)
	Osteopenia	13 (52%)
	Osteoporosis	2 (8%)

30. Balwani et al (2010) continued to follow 21 patients to determine whether these Gaucher disease homozygotes identified through prenatal carrier screening remain mostly asymptomatic or whether they show disease progression and receive treatment later in life. However, only limited information on this follow up is available at present. In their 2010 publication Balwani et al reported that the oldest patient in their cohort (who was 50 at last follow up) had showed no disease progression in ten years after their initial assessment had shown mild splenomegaly and minimal bone involvement. However, 13 patients who either had clinically significant disease at initial assessment or evidence of disease progression over a nine-year observation period were recommended to have ERT.

31. There are a number of uncertainties in the natural history of Gaucher disease, specifically around the difficulty in predicting how severely different individuals will be affected. This criterion is therefore not met.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

32. Not applicable to Gaucher disease.

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

33. Newborn screening for Gaucher disease would not identify heterozygous carriers.

The Test

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

34. The literature on newborn screening in this area has tended to focus on the development of multiplex assays which test for multiple LSDs from a single dried bloodspot using tandem mass spectrometry. We did not identify any studies in which a newborn screening test was only performed for Gaucher disease, as opposed to testing for multiple LSDs.

35. Screening tests for Gaucher disease involve demonstrating insufficient acid β-glucosidase (GBA) enzyme activity in peripheral blood leukocytes or a dried bloodspot on filter paper. This method cannot reliably predict disease phenotype or identify people who are carriers (heterozygote) for Gaucher disease (Wang et al 2011).

36. Two pilot studies on newborn screening for LSDs (including Gaucher disease) were identified. Both tested for Gaucher disease by assaying GBA enzyme activity, however there were differences in the approach and cut-off levels used.

37. A prospective national study in Austria assessed the feasibility of newborn screening for several LSDs including Gaucher disease (Mechtler et al 2012). Blood spot samples were collected from 34,736 neonates between January and July 2010 and were subjected to a direct multiplex assay to test for multiple LSDs. The test for Gaucher disease involved assessing deficiencies in GBA activity with a cut-off level of 4μmol/L/h. Mutation analysis was performed for neonates with a positive screening result. Four neonates had a positive screening result (<4μmol/L per h). Gaucher disease was confirmed by mutation analysis for two of these neonates giving a positive predictive value of 50% (95%CI 7-93).

38. In a pilot regional newborn screening programme in Italy 3,403 newborns from the Umbria region were screened for four LSDs, including Gaucher disease, between January 2010 and June 2012. The cut-off level for a positive test for Gaucher disease was GBA enzyme activity below 25% of the average control activities (i.e. 24.5nmol/h/ml). Eight neonates (0.24%) were found to have low GBA levels on the first test and four (0.12%) of these were found to have low GBA levels on re-testing using a second blood spot (Paciotti et al 2012).

39. A whole blood sample was assayed for GBA enzyme activity in purified lymphocytes for the four neonates who had low levels of GBA activity on the second blood spot test. Only one neonate was confirmed as having decreased GBA activity (2.81 nmol/h/mg protein, compared to a normal mean of 14.1±5nmol/h/mg protein). Following genetic sequencing this one neonate was identified as a potential Gaucher patient, due to the presence of the N370S causing-disease mutation and the E388K mutation which has not currently been correlated to the onset of Gaucher disease but has been described in patients affected by Parkinson's disease or dementia with Lewy bodies. Both this child and a four-year old sibling who was found to have the same genotype were asymptomatic (Paciotti et al 2012).

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40. There is a screening test for Gaucher disease however we did not find any evidence to suggest that an appropriate cut-off level has been defined and agreed. This criterion is therefore not met.

The test should be acceptable to the population

41. There is already an established newborn screening programme in the UK which uses the same dried blood spot testing as would be used in a newborn screening programme for Gaucher disease. The uptake of the existing newborn blood spot screening is high, with the UK Newborn Screening Programme Centre reporting that local figures suggest that more than 99% of babies born each year are screened[3].

42. This criterion is met.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

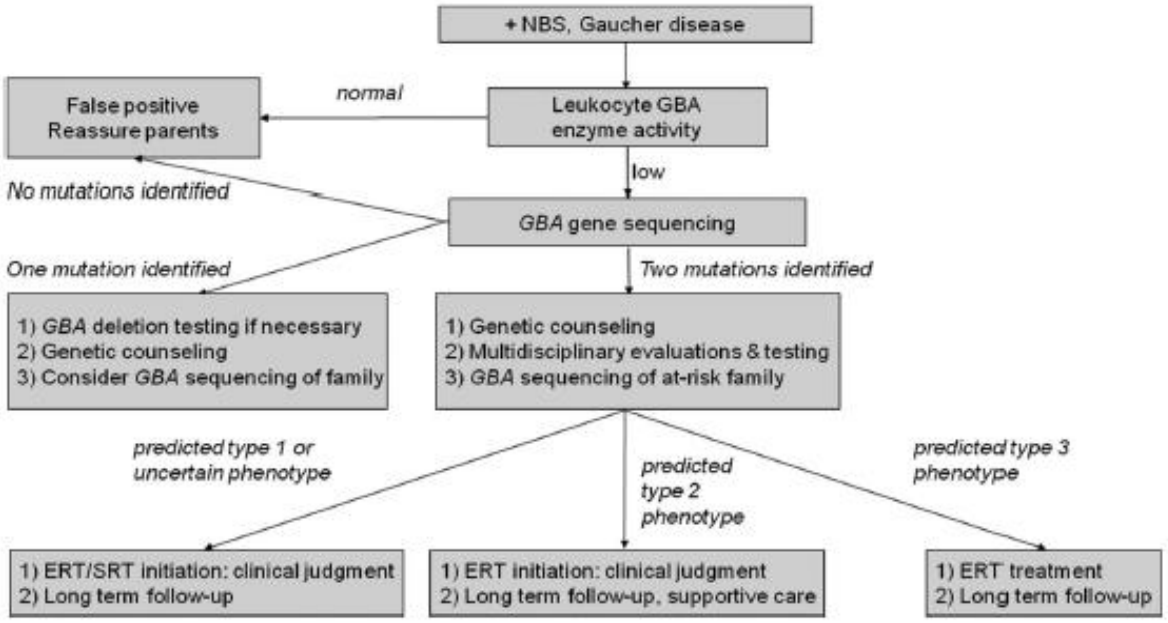
43. The definitive method for diagnosing Gaucher disease is to sequence the GBA gene (Wang et al 2011).

44. There are UK/ English national guidelines of the diagnosis and treatment of clinically-detected adults and children with Gaucher disease (Deegan et al 2005; Vellodi et al 2012). We did not identify a UK policy specifically addressing the management of individuals identified as having Gaucher disease though a newborn screening programme.

45. Wang et al (2011) produced a recommended algorithm for the diagnostic confirmation of Gaucher disease for the American College of Medical Genetics. The first step in this algorithm is to repeat the test for enzyme activity. The recommended procedure following this repeat test is described in figure 1:

[3] http://newbornbloodspot.screening.nhs.uk/public

Figure 1: Diagnostic algorithm for newborn screening for Gaucher disease (Wang et al 2011)



46. The detection of Gaucher disease during newborn screening would provide an opportunity for genetic counselling for the family (Hwu et al 2010).

47. There are US recommendations for policy on the further diagnostic investigation of individuals with a positive newborn screening result, however we did not identify any UK equivalent. This criteria is partially met.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

48. The screening test itself does not test for mutations, although neonates confirmed as having low enzyme activity would be referred for gene sequencing.

The Treatment

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

49. There are currently two recommended treatment options for patients with type 1 Gaucher disease. Enzyme replacement therapy (ERT) is the reference treatment with an alternative treatment of substrate reduction therapy (SRT) (Wang et al 2011).

50. Other potential treatments, such as pharmacological chaperone therapy and gene therapy are still in the early stages of clinical development (Wyatt et al 2012).

51. There is no specific therapy for patients with type 2 Gaucher disease due to the rapid clinical progression of the disease (Wang et al 2011).

52. The treatment of type 3 Gaucher disease is complicated by the need to cross the blood brain barrier. 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 (Wang et al 2011).

53. Due to the rarity of Gaucher disease there is very little evidence from randomised controlled trials.

Enzyme replacement therapy (ERT)

54. Enzyme replacement therapy (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 (Connock et al 2006). ERT targets the underlying metabolic deficit rather than providing symptomatic management (CADTH 2011).

55. ERT is given either weekly or biweekly by intravenous infusions, often administered in a patient's own home. Three ERGs are licensed for the treatment of Gaucher disease in the UK (alglucerase, imiglucerase and velglucerase alpha) (Wyatt et al 2012).

56. Wyatt et al (2012) conducted a cohort study of 175 patients with Gaucher disease which included 150 adults (average age at recruitment 46.4; range 16.8 to 83.1 years) and 25 children (average age at recruitment 9.74; range 1.14 to15.6 years). At recruitment, 131 adults and 24 children were receiving ERT with an average time on ERT of 10.8 years (range 0-17.8 years). A further eight adults and one child[4] were receiving SRT and 11 adults were not receiving ERT or SRT. Of the 175 patients 159 had type 1 disease and 16 had type 3 disease.

57. Wyatt et al (2012) concluded that 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.

58. There was no evidence for an association between duration of ERT and quality of life or fatigue in adults. However a statistically significant association was found for a worsening score on the social functioning subscale of the Pediatric Quality of Life Inventory. There were insufficient data to perform analysis on neurological involvement outcomes (Wyatt et al 2012).

59. Wyatt et al (2012) found that substantial improvements were seen over the first five to ten 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.

60. Wyatt et al performed Bayesian modelling on some of the outcomes achieved with time on ERT and concluded that there was no strong evidence to suggest that age at

[4] This patient had initially received ERT before receiving SRT

commencement of treatment affects the patient's ability to benefit in terms of platelet count, haemoglobin level or liver volume/size. Estimates did suggest an 83% probability that first ERT infusion at 45 years of age would result in a greater reduction in spleen volume than first infusion at 18 years, however Wyatt et al (2012) suggest that this may result from patients who are diagnosed in middle age having less aggressive disease and therefore responding better to treatment.

61. Piran & Amato (2010) conducted a systematic review and meta-analysis of the impact of treatment on bony complications in type 1 Gaucher disease. Meta-analysis of two studies (n=27) found that bone marrow involvement significantly decreased after ERT (weighted mean difference (WMD) -4.98, 95%CI -8.38 to -1.57; Z=2.87, p=0.004). However, a meta-analysis of three studies (n =54) showed that improvements in bone marrow density following ERT were not statistically significant for lumbar spine (WMD 0.37, 95%CI -0.05 to 0.79; Z=1.71, p=0.09) or femoral Z-scores (WMD 0.16, 95%CI -0.29 to 0.61; Z=0.70, p=0.48). The authors concluded that ERT is very effective in ameliorating bone marrow involvement, but that further research is needed to establish the effect of ERT on bone marrow density.

Substrate reduction therapy (SRT)

62. Substrate reduction therapy (SRT) targets the failure of the lysosomal metabolic pathway by reducing the level of the substrate to allow the residual degradative activity to prevent substrate accumulation in the lysosomes.

63. At present only one SRT (Miglustat) is licensed for use with adults (>18 years) in the UK. Miglustat (Zavesca®, Actelion Pharmaceuticals Ltd) is an oral drug that is administered daily. Miglustat does not have a European licence for use in children with any forms of Gaucher disease (Vellodi et al 2012).

64. SRT has been shown to be effective for hepatosplenomegaly, anaemia and thrombocytopenia (Wang et al 2011).

65. Piran & Amato's (2010) systematic review included three studies using different methods for quantifying bone marrow infiltration in type 1 Gaucher disease. There were no demonstrable significant effects for SRT on bone marrow involvement, but the review did note the very small sample sizes of the three studies. One study showed significant increases in bone marrow density after six, 12 and 24 months of SRT (Pastores et al 2007), however concerns about the study design led to the conclusion that more research on the effects of SRT on bone morrow density is required.

66. This criterion is only partially met. There is an effective treatment for type 1 Gaucher disease, but not for type 2 Gaucher disease. Studies on the treatment of type 3 Gaucher disease have had mixed results. The evidence for earlier treatment leading to better outcomes than later treatment is limited at present.

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

67. There is a UK guideline for the management of adult Gaucher disease (Deegan et al 2005) and an England guideline for paediatric Gaucher disease (Vellodi et al 2012). The recommendations in these guidelines are based on consensus and the personal experience of UK clinicians with experience of the treatment and management of Gaucher disease. No specific reference is made in these guidelines to children identified through a newborn screening programme.

68. The paediatric guideline (Vellodi et al 2012) recommends that all children with type 1 and type 3 Gaucher disease should commence treatment with ERT, even if they are apparently asymptomatic, on the grounds that a delay in commencing treatment may result in suboptimal peak bone mass being achieved. An exception may be made for children who are homozygous for the N370S allele who may remain asymptomatic for many years. Miglustat (an SRT) does not have a European licence for use in children with any form of Gaucher disease (Vellodi et al 2012).

69. The paediatric guideline also recommends follow-up assessment intervals for children who have been diagnosed with Gaucher disease. The follow-up intervals vary from every three months for some clinical and biochemistry assessments to every 24-36 months for a limited skeletal imaging survey (Vellodi et al 2012). No specific reference is made to monitoring children identified though newborn screening.

70. The American College of Medical Genetics have produced standards and guidelines for the diagnostic confirmation and management of pre-symptomatic individuals with lysosomal storage diseases (Wang et al 2011). These include a section on Gaucher disease which recommends that type 3 patients should be started on treatment immediately, type 2 patients should just receive supportive care due to a lack of effective treatments, and type 1 patients should start treatment if two or more manifestations of Gaucher disease are present (see table B in the appendix).

71. There are UK guidelines for the treatment of people with Gaucher disease but these do not specifically consider situations where an individual has been identified as having Gaucher disease through a newborn screening programme.

Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

72. There are seven centres in England which have been designated as lysosomal storage disorder treatment centres by the National Specialised Commissioning Group.

The Screening Programme

73. Screening for Gaucher disease already takes place in Taiwan. Pilot programmes for newborn screening for LSDs (including Gaucher disease) have been run in Austria and Italy in recent years.

74. Screening for Gaucher disease has recently been added to established newborn screening programmes in the US states of Illinois and Missouri (Wang et al 2011).

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

75. We did not identify any randomised controlled trials assessing newborn screening for Gaucher disease.

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There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

76. A newborn screening programme for Gaucher disease would use the same testing procedure (collection of a bloodspot from a heel prick) that is already used in the existing newborn screening programme in the UK.

77. There are several ethical considerations in screening for any LSD, including the fact that the clinical significance of the diagnosis is uncertain and that some patients with adult-onset variants will be identified who may never go on to develop symptoms or require therapy (Wang et al 2011).

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

78. No evidence was identified that set out clearly the benefits versus the physical and psychological harms of screening the population for Gaucher disease in the UK.

79. Type 2 Gaucher disease is severe, there is no specific treatment and babies often die in infancy.The psychological impact of detecting a baby with a fatal untreatable condition is likely to be significant for the parents (Hwu et al 2010).

80. Reporting false positive results will also have a significant impact on the parents (Green et al 2004). In Mechtlers (2012) study only two of the four neonates with a positive screening result were confirmed to have Gaucher disease on mutation analysis (a positive predictive value of 50%).

81. There is also likely to be a psychological impact on parents of children and the children themselves as they grow to adulthood who have a positive test result reported but who never go on to develop symptoms or require therapy (Wang 2011).

82. This criterion is not met as it is unclear whether the level of harm resulting from the programme would outweigh the benefits.

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).

83. Wyatt et al (2012) estimated the annual cost of caring for people with Gaucher disease (based on patient's self-reported health and social care service use) as approximately £3,000. The mean annual costs of therapy were calculated to be between £126,300 and £144,900 for ERT for an adult (depending on which drug is used) and between £107,400 and £187,800 for ERT for a child. The mean annual cost of SRT for an adult was £54,320. However, the authors do emphasize that due to limited evidence there is extreme uncertainty about the estimates.

84. This criteria is not met as there is no information about the opportunity cost of the whole screening programme and the study by Wyatt et al (2012) looking at costs of treatment was very uncertain about the estimates.

There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

85. There is already an established newborn screening programme in the UK which would be used as the structure for managing and monitoring the screening programme. A set of quality assurance standards is not currently available.

Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

86. Newborn screening for an LSD disease (such as Gaucher disease) requires laboratories that can conduct rapid, accurate enzymatic and molecular testing. In 2011, Wang et al (2011) reported that there are only a few laboratories around the world with the required expertise and experience, however a number of these labs are in the UK.

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

87. Presentation followed by a range of investigations often precedes accurate diagnosis and treatment due to the rarity of the disease. It is not clear what other interventions could be introduced within the current resources available to improve cost effectiveness.

Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

88. Evidence based information for parents would have to be developed and incorporated into the current newborn bloodspot screening information pack.

Conclusion

Gaucher disease is the most common of the inherited lysosomal storage diseases (LSD). It is caused by an enzyme deficiency from a mutation in the gene that codes for the lysosomal enzyme acid β-glucosidase (glucocerebrosidase (GBA1). Newborn screening for Gaucher disease is being implemented in a few areas of the world as treatments for Lysosomal storage diseases are becoming more effective. No screening programmes have been put in place just for this one condition, other LSDs such as Fabrys, Pompes and Niemann-Pick disorders are typically included using a multiplex assay.

This review outlines whether the condition meets the criteria set out by the UK National Screening Committee to test whether newborn screening for Gauchers disease has the potential to be part of an evidence based screening programme. There are several areas in which Gaucher disease meets or partially meets the NSC criteria for a screening programme:

- Gaucher disease is an important, albeit rare, condition with an estimated 925 people carrying underlying predisposing mutations for the disease in the UK and 325 with symptoms. In the UK Ashkenazi Jewish population of around 300,000 there is a higher prevalence of the condition with around 300 people with the underlying predisposing mutations and 90 with symptoms.

- We have not been able to identify a published estimate of the prevalence or birth incidence of Gaucher disease in the UK. Applying the results from an Austrian study of newborn screening for Gaucher disease to the number of UK live births for 2012 (729,674) suggests that we might expect 84 positive screening tests and 42 cases confirmed to have underlying predisposing mutations for Gaucher disease each year from a UK screening programme. However, given the higher proportion of Jewish people in the UK population than the Austrian population the number of positive screening tests and cases confirmed to have predisposing mutations in the UK could therefore be more in the region of 120 and 60 respectively.
- In terms of the screening test it would be possible to identify individuals with low GBA enzyme levels through a newborn screening test, although an appropriate cut-off level still needs to be established.
- There is an effective treatment for type 1 Gaucher disease using enzyme replacement therapy (ERT).

There are a number of areas in which Gaucher disease does not meet the UK NSC criteria for introducing a newborn screening programme at the present time.

- An appropriate cut-off level for the screening test has not yet been agreed.
- There is evidence that ERT is effective in mitigating the effects of type 1 Gaucher disease however evidence is limited about whether earlier treatment of type 1 Gaucher disease is any more effective than later treatment.
- Some studies have investigated ERT or a combination of ERT and substrate reduction therapy 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 several important UK NSC criteria not being met it is not recommended that a formal UK NSC screening programme is implemented at the current time. As research continues and treatments develop it will be important to reassess Gaucher disease against the UK NSC criteria in the future.

The main areas where research would be beneficial include:

- A better understanding of the link between genotype and phenotype to allow the identification of which pre-symptomatic individuals are likely to develop symptoms that would impact on their quality of life and would benefit from treatment
- Exploring whether starting enzyme replacement therapy earlier (before the appearance of symptoms) is more beneficial than later treatment
- Developing treatments for the neurological aspects of type 3 Gaucher disease.

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Appendix A

Knowledge update on newborn screening for Gaucher disease
Paula Coles, Information Scientist, October 2012

BACKGROUND: Gaucher disease has not previously been assessed against the UK NSC screening criteria. It was decided that the searches for this literature should start from 2002.

SOURCES SEARCHED: Medline (OvidSP), Embase, PsychINFO, Cinahl, Cochrane Library.
DATES OF SEARCH: January 2002 – October 2012 (All searches carried out on 1st October 2012).

SEARCH STRATEGY:

STRATEGY: Carried out in Medline (OvidSP)
1. Gaucher Disease/ (3561)
2. gaucher$.tw. (3852)
3. 1 or 2 (4444)
4. Neonatal Screening/ (6425)
5. (screen$3 or detect$3 or test or tests or testing).tw. (2763518)
6. (neonat$ or newborn).tw. (252405)
7. Infant, Newborn/ (468380)
8. 4 or 5 or 6 or 7 (3264926)
9. 3 and 8 (783)
10. Natural History/ (570)
11. prognosis/ or disease-free survival/ (353861)
12. (prevalen$ or inciden$).tw. (879351
13. (genotype or phenotype).tw. (282530)
14. Genotype/ (135340)
15. Phenotype/ (159287)
16. prognos?s.tw. (209914)
17. 10 or 11 or 12 or 13 or 14 or 15 or 16 (1706142)
18. 3 and 17 (798)
19. Gaucher Disease/dt [Drug Therapy] (609)
20. Enzyme Replacement Therapy/ (521)
21. ((enzyme replacement adj (therapy or treatment)) or ERT).tw. (3234)
22. clinical$ effective$.tw. (9118)
23. (substrate reduction adj (therapy or treatment)).tw. (113)
24. exp treatment outcome/ (565785)
25. ((treatment or therapy) and outcome$).tw. (317509)
26. ((stem cell or bone marrow) adj transplant$).tw. (49702)
27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (829645)
28. 3 and 27 (1024)
29. 9 or 18 or 28 (2006)
30. 29 (2006)
31. limit 30 to yr="2002 -Current" (1071)

Similar searches also carried out in Embase, PsycINFO, Cinahl, and Cochrane Library.

Medline	1,071
Embase	2,151
Cochrane Library	31
PsycINFO	54
Cinahl	150
Total	**3,457**

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Inclusions and exclusions

The above search strategies retrieved 3,457 references. After duplicate references were removed a total of 2,141 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to newborn screening for Gaucher disease:

Inclusions

- Type I, Type II and Type III, natural history, genotype-phenotype correlation
- Treatment
- Newborn screening

Exclusions

- Treatments that had not been tested in patients with Gaucher disease
- Genetic testing, preimplantation genetic diagnosis, prenatal screening/ testing

460 references were deemed to be relevant.

A simple search was also carried out for ongoing trials in the metaRegister of Controlled Trials: http://www.controlledtrials.com/mrct/ of the 25 results retrieved 5 were completed trials that had not been published and met the criteria for inclusion. These are included in the results below. 465 references are therefore included and are classified in to the categories below according to the NSC criteria. There will inevitably be some overlap between categories.

Systematic reviews and meta-analysis The condition (1) The treatment (12)	**13**
Guidelines and recommendations	**15**
General reviews	**24**
The condition Epidemiology (19) Genotype-phenotype correlation (43) Bone and skeletal (including musculoskeletal) manifestations (22) Parkinson's disease (16) Neurological manifestations (16) Haematological manifestations (14) Malignancies (8) Organ involvement (7) Audiological and/or visual manifestations (5) Cholesterol and gallstones (4) Dental manifestations (2) Clinical characteristics (6) Miscellaneous (5) Untreated or undiagnosed (4) Life expectancy or death (3) Quality of life (6) Ethics (1)	**181**
The test	**35**
The treatment Reviews (11) Enzyme replacement therapy (32) Enzyme replacement therapy – imiglucerase/ alglucerase (53) Enzyme replacement therapy – shortage of imiglucerase (12) Enzyme replacement therapy – velaglucerase alfa (18) Enzyme replacement therapy – taliglucerase alfa (9) Enzyme replacement therapy – costs (5) Enzyme replacement therapy and/or substrate reduction therapy (5) Substrate reduction therapy (2)	**185**

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Substrate reduction therapy – miglustat (15) Substrate reduction therapy – eliglustat (13) Chaperone treatment (4) Stem cell transplantation (5) Bone marrow transplantation (1)	
The screening programme Reviews (7) Pilot/ feasibility studies (5)	**12**
Total	**465**

Appendix B

Table B: Symptoms of Gaucher disease subtypes (Wang et al 2011)

	Type 1	**Type 2**	**Type 3**
General	95% of cases; childhood-adult onset; some symptomatic	1% of Gaucher cases; neonatal-infantile onset; rapidly progressive, fatal course	4% of Gaucher cases; infantile-childhood onset; sub-acute, slowly progressive
Visceral	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	Anaemia and thrombocytopenia	Anaemia and thrombocytopenia	Anaemia and thrombocytopenia
Orthopaedic	Bony pain crisis, osteopenia, aseptic necrosis of femoral head, bony lytic lesions, bony infarctions and pathological fractures	Arthrogryposis in severe cases, and generally death before bony abnormality	Bony pain crisis, osteopenia, aseptic necrosis of femoral head, bony lytic lesions, bony infarctions and pathological fractures
Neurologic	No CNS involvement* and no cognitive regression	Bulbar palsies, hypertonicity, abnormal ocular saccades and cognitive impairment	Oculomotor apraxia, myoclonic epilepsy, generalized tonic-clonic seizures, and cognitive impairment

*except for an increased risk of Parkinson's disease

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