# UK National Screening Committee

# Newborn screening for Gaucher disease

# 27 February 2019

**Aim**

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation based on the evidence presented in this document, on whether or not screening for Gaucher disease in newborns meets the UK NSC criteria for a systematic population screening programme.

**Current recommendation**

2. The 2013 UK NSC review of screening for Gaucher disease in newborns concluded that systematic population screening is not recommended. This was because:

    a) there were uncertainties about the natural history of Gaucher disease; specifically around predicting how severely an individual detected through screening might be affected by the condition

    b) for type 1 Gaucher disease, (which is the type that the vast majority of Gaucher disease patients have), it was uncertain whether earlier treatment following a screening test would deliver additional benefit over those treated following clinically presenting symptoms

    c) there was a lack of evidence showing benefit from treatment of cases of Gaucher disease types 2 and 3.

**Evidence Summary**

3. Screening for Gaucher disease in newborns was reviewed in accordance with the triennial review process https://legacyscreening.phe.org.uk/gauchers.

4. The current review focused on the criteria addressing the effectiveness of the intervention in a screen detected population; specifically whether the treatment for pre-symptomatic type

1 Gaucher disease in children results in better health outcomes than those experienced in symptomatically detected populations. The review was undertaken by Solutions for Public Health.

5. The current review concluded that the current recommendation on screening should not be reconsidered at this point. This was because no published studies which met the inclusion criteria for the review were identified. This means that it remains uncertain whether earlier treatment following screening would deliver additional benefit over those treated following clinically presenting symptoms. **Criterion 9 not met**

**Evidence map**

6. At the time of the previous review, enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) were the two recommended treatment options for patients with type 1 Gaucher disease. There were no specific treatments for type 2 Gaucher disease, and unclear results as to whether ERT and/ or a combination of ERT and SRT were effective treatments for type 3 Gaucher disease. The previous review also found that other potential treatments such as gene therapy and pharmacological chaperone therapy were in the early stages of clinical development.

7. An internal evidence map was conducted primarily to gauge the volume and type of literature on the advancement of the treatment of Gaucher disease, specifically:
   a) whether there have been treatment advances in gene therapy and/ or chaperone therapy for type 1 Gaucher disease.
   b) whether any treatments have been developed for type 2 Gaucher disease.
   c) whether any treatment has been developed to reduce and/ or reverse neurologic symptoms (which are experienced by those with type 3 Gaucher disease).

   The evidence map findings did not indicate that new treatments for the three types of Gaucher disease have been developed.

**Consultation**

8. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 15 stakeholder organisations (**Annex A**).

9. Responses were received from the following 5 stakeholders;

    - British Inherited Metabolic Diseases Group (BIMDG)
    - The Gauchers Association
    - Genetic Alliance UK
    - The Royal College of Midwives
    - Royal College of Paediatrics and Child Health

    All comments are in **Annex B**, below.

10. Most of the stakeholder responses acknowledged that there is a lack of evidence about pre-symptomatic treatment resulting in better outcomes than in those treated symptomatically. The Board of the Gauchers Association noted that research on this issue is due to report and may inform future reviews. However the Board of the Gauchers Association did agree that there needs to be more evidence for screening, and reported that they will begin formally gauging the views of their members on newborn screening for Gaucher disease later this year.

11. The following themes were raised across stakeholder comments:

    a. *That the value of newborn screening followed by surveillance for the onset of symptoms should be considered, as this will stop delayed diagnosis and may prevent adverse health implications related to this.*
    Response: This is a valid consideration when trying to identify the benefits of screening to the screened individual compared to usual care. Studies which demonstrate a benefit of treatment in screened individual in comparison to usual care will be of interest in future reviews. Any evidence on the benefits of screening should be evaluated for its applicability to the UK population.
    That the clinical significance of a Gaucher disease diagnosis is uncertain, (with some patients developing symptoms in adulthood and some remaining asymptomatic),

means that this important ethical consideration should be taken into account in a newborn screening scenario.

b. *That the scope should have been wider and included Gaucher disease types 2 and 3.* Response: The scope of the current review was limited to type 1 only, as an internal evidence map suggested that the volume and type of evidence on treatment developments had not moved significantly.

12. One stakeholder suggested that a recently published paper on a pilot newborn screening programme for lysosomal storage disorders in New York City should be included in the review document, (which mentions other United States lysosomal storage disorder screening programmes), for completeness.

    Response: The paper cited was published after the search date for this review. The paper reports that the screening pilot diagnosed 15 of the 17 Gaucher disease screen positive patients as having the condition. All 15 were identified as having a predicted late-onset phenotype. None of the individuals diagnosed with the lysosomal storage disorders identified in the pilot programme had been receiving disease specific-treatment. As this paper was published outside of the search dates for the current review, it will be eligible for inclusion when the literature search for the next review on this screening topic is undertaken.

**Recommendation**

13. The committee is asked to approve the following recommendation:

*A systematic population screening programme for Gaucher disease in newborns is not recommended.*

Based upon the UK NSC criteria to recommend a population screening programme, evidence was appraised against the following criterion.

| | Criterion | Met / Not met |
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| **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 should not be further considered. | Not met ✖ |

**Annex A**

**List of organisations contacted:**

1. British Association of Perinatal Medicine
2. British Inherited Metabolic Disease Group
3. Faculty of Public Health
4. Gauchers Association
5. Genetic Alliance UK
6. Metabolic Support UK
7. MetBio
8. MPS Society
9. Royal College of General Practitioners
10. Royal College of Midwives
11. Royal College of Paediatrics and Child Health
12. Royal College of Physicians
13. Royal College of Physicians and Surgeons of Glasgow
14. Royal College of Physicians of Edinburgh
15. Save Babies Through Screening Foundation UK

**UK National Screening Committee**
**Screening for Gaucher disease in newborns**

**Consultation comments pro-forma**

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| **Name:** | Rachel Scanlan | **Email address:** | xxxx xxxx |
| **Organisation (if appropriate):** | Royal College of Midwives | | |
| **Role:** | **Practice and Standards Advisor** | | |

**Do you consent to your name being published on the UK NSC website alongside your response?**

**Yes x☐ No ☐**

| **Section and / or page number** | **Text or issue to which comments relate** | **Comment**<br>*Please use a new row for each comment and add extra rows as required.* |
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| | General Comment | RCM supports the UK NSC in the decision not to recommend newborn screening for Gaucher Disease due to the lack of further research. |
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**UK National Screening Committee**
**Screening for Gaucher disease in newborns**

**Consultation comments pro-forma**

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| **Name:** | Dr James Davison | **Email address:** | xxxx xxxx |
| **Organisation (if appropriate):** | British Inherited Metabolic Diseases Group | | |
| **Role:** | Consultant in Paediatric Metabolic Medicine | | |

**Do you consent to your name being published on the UK NSC website alongside your response?**

**Yes** ☒ **No** ☐

| Section and / or page number | Text or issue to which comments relate | Comment<br>*Please use a new row for each comment and add extra rows as required.* |
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| P19 | Summary of Findings | We concur with the finding that there is no published evidence examining whether presymptomatic treatment of paediatric patients with Gaucher disease type 1 confers greater clinical benefit than commencing treatment at time of (symptomatic) diagnosis. |

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| | Point 20 in original consultation | Although not the focus of the current 2018 Review, the original consultation commented that misdiagnosis (i.e. late diagnosis) after onset of symptoms can lead to clinical deterioration that would have been avoided if NBS had identified patients and appropriate surveillance commenced. This could form focus of future evidence review to determine frequency of mis- or late diagnosis. |
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The Association would recommend to the NSC to widen the remit of the review to include all types of Gaucher disease and not just type 1.

The Association would like to request that a review of the pre-screening of Gaucher disease, be held in 3 years' time, rather than 5 years. The Association feels that in regard to patient research, pharmaceutical advances and our own consultation of our members, there will be more evidence for the NSC to make a more well informed review for NBS for all types of Gaucher disease.

Jane Jones

Chief Executive

Gaucher Association

UK National Screening Committee

**UK National Screening Committee**
**Screening for Gaucher disease in newborns**

**Consultation comments pro-forma**

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| **Name:** | Comments on behalf of Martin Peter Ward-Platt, Saikat Santra and Eugene Strehle | **Email address:** | xxxx xxxx |
| **Organisation (if appropriate):** | Royal College of Paediatrics and Child Health | | |
| **Role:** | | | |

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**Yes** ☒ **No** ☐

| Section and / or page number | Text or issue to which comments relate | Comment<br>*Please use a new row for each comment and add extra rows as required.* |
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| | | Screening for Gaucher disease does not fulfil even basic criteria for population-based newborn screening |
| | | It cannot be denied that there are no published studies examining the effect of treating presymptomatic children with |

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| | | Gaucher Disease Type 1 and comparing this to treating such patients at the onset of symptoms.<br><br>As this very specific question was the focus of the review from the outset the review decision is agreed with. |
| | | There are a few points to record here:<br>• The review comments on the published data from Illinois and Missouri states' NBS programs. But New York State's NBS program for LSDs has also been recently published and this review for completeness should acknowledge this data as well: [The New York pilot newborn screening program for lysosomal storage diseases: Report of the First 65,000 Infants. Wasserstein MP, Caggana M, Bailey SM, Desnick RJ, Edelmann L, Estrella L, Holzman I, Kelly NR, Kornreich R, Kupchik SG, Martin M, Nafday SM, Wasserman R, Yang A, Yu C, Orsini JJ. Genet Med. 2018 Aug 10. doi: 10.1038/s41436-018-0129-y. [Epub ahead of print]<br>• It is unlikely that the answer to the question posed in this review will ever be answered systematically. The only way this will be answered will be by a study of newborn screening for Gaucher Disease coupled with a randomised allocation of identified babies to either presymptomatic or symptomatic ERT. Seeing as NBS is currently only performed in a small selection of sites across the World, which follow-up identified babies closely rather than allocating to early ERT data from these sites won't answer the question posed.<br>An alternative question that may be worth exploring in the future is whether long term follow-up of an affected baby leads to earlier commencement of ERT even when waiting for |

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| | | symptoms. i.e. are symptoms detected earlier if the diagnosis is known? This could be answered from comparing UK registry data with the US programs' long term follow-up and also studies like [Early manifestations of type 1 Gaucher disease in presymptomatic children diagnosed after parental carrier screening. Yang AC, Bier L, Overbey JR, Cohen-Pfeffer J, Desai K, Desnick RJ, Balwani M.Genet Med. 2017 Jun;19(6):652-658. doi: 10.1038/gim.2016.159. Epub 2016 Oct 13. PMID: 27735925] where only 4 out of 38 children detected were actually treated. The question may remain, however, as to whether delayed diagnosis without screening (e.g. from initial misdiagnosis) actually leads to preventable and irreversible harm. |
| | | As discussed above the equality issue that could be raised by the Gaucher Disease community is that the UK is only reviewing the merits of newborn screening with neonatal ERT treatment for Type 1 patients. The community could argue that this is not on a par with the existing sites worldwide that are evaluating NBS for Gaucher Disease which are doing so with a view not to immediate treatment but to close follow-up and early detection of symptoms.<br><br>One other issue which is more difficult to perhaps include in the review is that the published data are heavily focussed on the mutations which are common in the Ashkenazi Jewish population (such as N409S) and the natural history of patients with those genotypes is well established. In other geographical areas (including many areas of the UK) such patients are not the majority of those treated and it is likely that patients will be diagnosed from a NBS program with greater genotypic diversity and the natural history would not necessarily be so clear-cut. Hence it follows that a NBS |

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| | | programme in the UK would be more likely to be one that follows up affected patients for early diagnosis of symptoms and commencement of symptomatic ERT than advocating for early presymptomatic ERT anyway. |
| | | The outcome of this review is agreed with. |

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**Screening for Gaucher disease in newborns**

**Consultation comments pro-forma**

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| **Name:** | Dr Jayne Spink | **Email address:** | XXXX XXXX |
| **Organisation (if appropriate):** | Genetic Alliance UK<br>Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic, rare and undiagnosed conditions. We are an alliance of over 200 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine.<br>Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working towards the delivery and implementation of a national strategy for rare diseases in the UK. The UK Strategy for Rare Diseases was published in November 2013. Pertinent to this consultation, the Strategy includes a commitment from all four Governments of the UK to: "Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes." Commitment 9, The UK Strategy for Rare Diseases, November 2013.<br>This commitment recognises the value that the rare disease community places on early diagnosis, not only for the benefits it can bring to an affected individual but because of the impact it can have on improving the quality of life for their whole family. | | |
| **Role:** | Chief Executive | | |

| Do you consent to your name being published on the UK NSC website alongside your response?<br><br>Yes ☒ No ☐ | | |
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| **Section and / or page number** | **Text or issue to which comments relate** | **Comment**<br>*Please use a new row for each comment and add extra rows as required.* |
| p9 | '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.' | We question the decision to restrict this evidence review to consideration of criterion 9 only.<br>Though the previous evidence review was unclear, it appears to have regarded criteria 1, 5, 11, 13 and 14 as not met, and criteria 7, 9 and possibly 10 as partially met. The decision not to determine whether there have been significant developments in the evidence base on these other key questions does not appear to fit with the UK NSC's published evidence review process. |
| p14 | Section headed 'Eligibility for inclusion in the review' | Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. While information from clinicians and patients may not be published, it represents the most recent and relevant information on a condition coming from those that either directly manage or are affected by the condition today.<br>NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency all have facility to consider evidence from patients and clinicians that is not sourced from peer reviewed literature. These agencies have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common |

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| | | conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community. We believe the UK NSC should take steps to do the same. |
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