UK National Screening Committee

Gaucher Disease Screening in Newborn

26 November 2014

Aim

1. This document provides background on the item addressing Gaucher disease.

Current policy

2. This is the first time the UK National Screening Committee (UKNSC) has reviewed newborn screening for Gaucher disease.

Review

3. The current review was undertaken by Solutions for Public Health (SPH) following a literature search by the UK NSC Information Scientist considering literature from January 2002 to October 2012.

4. The review found that Gaucher disease was an important, albeit rare genetic condition with a wide spectrum of disease. While the genetic variation is common to all those with Gaucher disease it doesn't affect people in the same way. This leads to different manifestations of the disease (types 1, 2 and 3). There is evidence that treatment by enzyme replacement therapy (ERT) can mitigate the effects of Gaucher disease type 1 but there are several limitations in the current evidence base to support screening.

5. The review came to the conclusion that, on the balance of the evidence, universal screening should not be recommended.

6. Key findings to support that conclusion were:

- Uncertainties around the natural history of Gaucher disease; specifically around predicting how severely an individual, detected through screening, might be affected by the condition.
- Limited evidence; that earlier treatment following a screening test would deliver additional benefit over those treated following clinically presenting symptoms.

- The lack of evidence showing benefit from treatment of cases of Gaucher disease types 2 and 3. Type 2 patients progress very rapidly. There is no consensus about whether treatment for type 3 reduces neurological symptoms of the disease.

Consultation

8. A three month consultation was hosted on the UK NSC website and additionally promoted through the PHE Screening Twitter platform. The following organisations were contacted directly: British Inherited Metabolic Diseases Group, Children Living with Inherited Metabolic Diseases, Genetic Alliance UK, Royal College of Paediatrics and Child Health, Save Babies Through Screening Foundation UK and Society for Mucoplysaccharide Diseases. Members of the advisory board from the UK NSC Newborn Blood Spot programme were also contacted regarding the consultation.

9. Responses were received from the Gauchers Association (UK), Save Babies Through Screening Foundation (UK) (whose comments were additionally on behalf of the UK Patient Advocates for NBS Group) and Genetic Alliance UK.

10. The responses were supportive of the review conclusion not to recommend screening for any of the three types of Gaucher disease. Both Gauchers Association UK and Saving Babies Through Screening UK responses highlighted early detection and appropriate clinical management being essential to evaluating eligibility for treatment.

11. The response from Genetic Alliance UK suggested that: -

- An anticipatory screening programme should begin to be implemented before a new medicine is likely to be made available to ensure that those patients who could benefit from a treatment are not prevented from doing so due to the time it takes for the required screening programme to be put in place.
- In future reviews the UK NSC should examine the potential value of genetic testing for type-specific Gaucher disease screening and more consideration should be placed on screening and diagnosis to enable informed reproductive decision-making.
- While accepting the views of the Gauchers Association UK's survey of members, who did not feel screening should be recommend at present; Genetic Alliance UK also suggested that the UK NSC's focus on the published evidence may exclude the patient voice from being accounted for in its decision making.

The full consultation responses can be found in Annexe A.

13. Recommendation

The committee is asked to approve the following statement:

"*The UK NSC does not recommend universal newborn screening for Gaucher disease. "*

Annexe A –

Gaucher Disease Screening

Consultation Comments

1.

Name:	Pat Roberts	**Email address:**	xxxxxxxxxxxx
Organisation (if appropriate):	Save Babies Through Screening Foundation UK (and behalf of the UK Patient Advocates for NBS Group)		
Role:	Executive Director		

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** *Please use a new row for each comment and add extra rows as required.*
Appraisal of Screening for Gaucher Disease - Draft Report Summary	Page 4 Recommendation - Penultimate paragraph. Conclusions: Page 18.	We thank you for the opportunity to comment of the policy review on screening for Gaucher Disease. In considering this report and the recommendations contained within it we have consulted with the Gauchers Association Ltd. In their own consideration of the report and the recommendations, they do not at this time feel that NBS for any of the three types of Gaucher

		disease is appropriate in the UK. In light of this we have nothing to add on their own submission and the NBS recommendation. However I believe the Gaucher Association recognise that early detection and appropriate clinical management is essential to evaluating eligibility for treatment and have raised this point with yourselves.
The Test	Para 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.	We acknowledge that at this point the screening test in other countries will not necessarily meet the requirements to satisfy a screening programme decision for the UK. How in light of developments internationally, it would be helpful if the UK NSC could establish when this research could be carried out and consequently to establish a timely review date for this policy.
Conclusions: Page 18	Final paragraph – research	We note the main areas where it is suggested that research would be beneficial and PANS will be discussing with the Gaucher Association where we can assist or how we can move forward on this.

2.

Name:	Tanya Collin-Histed	**Email address:**	xxxxxxxxxxxx
Organisation (if appropriate):	Gauchers Association Ltd		
Role:	Chief Executive		

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** *Please use a new row for each comment and add extra rows as required.*
4	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	There are currently 301 Gaucher patients with symptoms being treated in the UK and All Ireland.
4	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	The Gauchers Association do not at this time feel that NBS for any of the three types of Gaucher disease is appropriate in the UK but recognise early detection and appropriate clinical management is essential to evaluating eligibility for treatment. There are currently three licensed products for Type 1 Gaucher disease in the UK and also for the visceral aspects of Type III. Patients with type I Gaucher disease can become symptomatic at any time from early childhood to old age, therefore NBS may inform someone that they have the disease but they may not show any symptoms till many years later or even in some cases may remain asymptomatic.

		Type III GD - research into treating the neurological aspects of the disease is underway and potential trials are being discussed. In the UK Patients are treated with ERT or SRT for their visceral disease and NBS would not alter their current treatment pathway. Following recent discussions with clinicians, the use of bone marrow transplantation for Type 3 Gaucher disease has been discussed as a possible treatment on a case by case basis in consultation with the patients and family. Sadly no treatment exists for Type II, although there is some gene therapy research being undertaken for Type II. If gene therapy is proven effective then NBS would be essential for Type II GD, as currently patients die by the time they are two years old due to severe brainstem involvement.

3.

Name:	Alastair Kent	**Email address:**	xxxxxxxxxxx
Organisation (if appropriate):	Genetic Alliance UK		
Role:	Director		

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** *Please use a new row for each comment and add extra rows as required.*
	About Genetic Alliance	Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 180 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. 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. 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.
Page 4	"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"	Genetic Alliance UK supports the recommendation of the Gaucher Association's response to this consultation that at this present time no formal Screening Programme should be implemented for Gaucher Disease. We note that the Gaucher Association have surveyed families affected by the three types of Gaucher disease and have reached this conclusion based on the results of their survey. It would be valuable to include two further issues in future considerations of screening programmes for Gaucher disease. **Genetic testing for type-specific Gaucher disease screening** Gaucher disease is divided into three phenotypes which have been distinguished genotypically. The potential impact on an individual and their family of obtaining a diagnosis at birth is in part

		dependent on which form of Gaucher disease they are diagnosed with and varies widely. Type 2 Gaucher disease has a neo-natal onset and is currently an untreatable, fatal condition. It is clear that early diagnosis would be essential if an effective treatment was developed for patients affected by type 2. As outlined in the response of the Gaucher Association, such a treatment is currently being developed. In our response to the UK NSC's triennial review of its methods and processes, Genetic Alliance UK supports the view that a screening programme should begin to be implemented before a new medicine is likely to be made available to ensure that those patients who could benefit from a treatment are not prevented from doing so due to the time it takes for the required screening programme to be put in place. Type 3 Gaucher disease has an infantile-childhood onset that can be fatal within 20 years. In some cases affected individuals can survive into their forties. As stated in the UK NSC's review, the paediatric guideline recommends that all children with "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." (Vellodi et al 2012).

Taken together, we believe it would be valuable for the UK NSC to examine the potential value of introducing a screening programme that looked to diagnose type 2 and type 3 affected individuals by testing for the genetic mutations that

have been linked to these conditions (see below, as taken from the UK NSC's review).

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

We would welcome further research in the relationship between genotype and phenotype in Gaucher disease, as recommended by the UK NSC and supported by the Gaucher Association. We hope that this would enable the future consideration of a Type 1 Gaucher screening programme based on the genetic identification of those

		individuals likely to develop symptoms within childhood and who could most benefit from early intervention, as recommended by the paediatric guideline on the treatment of Gaucher disease (Vellodi et al 2012). **Diagnosis to enable informed reproductive decision-making** For conditions with variable severity and age of onset, it is possible that the diagnosis of an individual at birth may offer little or no direct benefit, due to delayed onset of their symptoms. However, information about whether an individual is affected by a genetic condition, regardless of their symptom severity, can be immensely valuable for future reproductive choices, both for their parents and for themselves. There are well known cases of childhood-onset metabolic diseases where the family have had three affected children before the eldest child began to show symptoms, where newborn screening could have allowed the parents to consider their reproductive options at an earlier stage. Individuals with an asymptomatic form of a genetic condition will be at an increased risk of having a child affected by that condition, which may be more severe than their own. Being aware of their own genetic status may allow them to similarly consider their

		reproductive options from a more informed position. We have explored in more detail in our response to the UK NSC's triennial consultation the systematic issues we believe exist within the appraisal criteria for screening programmes that make them inappropriate for considering rare diseases. We also recognise the need to consider the particular views of the patient population in question when making decisions about specific screening programmes.
5	"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"	The Gaucher Association has consulted its members about this consultation and the results have informed their response. This valuable work has allowed the patient voice to be taken into consideration in this consultation process. As the community that have lived with the effects of Gaucher disease on their family, this is a vital group of stakeholders which should be included much more centrally in the process of the UK NSC's appraisal of screening programmes. The current methodology places a premium on peer reviewed literature to the exclusion of all other forms of evidence. We note with particular concern that in this instance the literature review is two years out of date.

		Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. This is out of step both with other institutions with responsibility for decisions regarding public health, such as NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency, and with accepted practice in dealing with rare disease issues. All three of these agencies, and more, 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 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. As the national organisation representing those affected by inherited conditions, Genetic Alliance UK would welcome a meeting to discuss where we could assist in this process.