UK National Screening Committee

14/360

UK National Screening Committee

Newborn Screening for Galactosaemia

19 March 2015

Aim

This paper provides background on the agenda item addressing newborn screening for Galactosaemia.

Current policy

The current policy is that screening for Galactosaemia is not recommended.

The last document produced on this subject was a 1997 HTA study (Seymour et al, Newborn screening for inborn errors of metabolism: a systematic review) in which screening for Galactosaemia was considered alongside a number of other conditions.

The HTA study identified a number of problematic issues such as uncertainty regarding the ability of screening to detect Galactosaemia prior to clinical presentation and evidence that long term outcomes were unaffected by the treatment or that early treatment did not lead to improved outcomes. This informed the withdrawal of the screening programme in Scotland in 2002. A CMO circular recommending increased clinical vigilance in the presence of signs and symptoms suggestive of Galactosaemia.

Bazian were asked to review the literature published since the previous review which focused on the issues covered in the HTA study. In addition the reviewers were asked to consider whether current testing options would detect partial GALT deficiency and whether there was evidence of benefit from treatment. To address the changing nature of the

debate on newborn bloodspot screening a final question related to whether any evidence had been published regarding the wider benefits of screening for Galactosaemia.

Review results

The review is attached, the main results were:

- no new evidence was identified to suggest that available dietary treatment can prevent long term clinical or developmental complications, either in screen or clinically detected classic GALT deficiency.
- it was not possible to identify a median age of symptomatic presentation of GALT because many of the publications were reports of screening programmes.
- the reported rate of Duarte galactosaemia was lower than that reported in the HTA study. But current testing options would continue to identify the Duarte variant, and other variants of uncertain significance, for which no clinical guidelines were found and the outcomes of which appear unaffected by treatment.
- the literature search did not identify any publications addressing the wider benefits of screening in the specific context of Galactosaemia. A UKNSC document exploring these themes more generally can be accessed at www.screening.nhs.uk/policydb_download.php?doc=455

Consultation

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 Disease Group, Children Living with Inherited Metabolic Diseases, Clinical Genetics Society, Galactosaemia Support Group, Genetic Alliance UK,

Institute of Child Health, Rare Disease UK, Royal College of Paediatrics and Child Health, Save Babies Through Screening Foundation UK and UK Newborn Screening Laboratories Network.

Four responses were received. These were submitted by Galactosaemia Support Group, Genetic Alliance UK, Royal College of Paediatrics and Child Health, Save Babies Through Screening Foundation UK / Patient Advocates for Newborn Screening Group (PANS).

The responses are attached to this document.

Responses

Overall the discussion of the evidence was not subject to particular criticism. One respondent noted that the review was comprehensive and had included the relevant papers published since 1997. However the responses clustered around two main themes:

- screening should be considered as a means of improving prevention and management of acute neonatal presentation and the reduction of neonatal mortality.

The Galactosaemia Support Group and RCPCH suggested that the review question on the age of clinical presentation may have been misplaced and the focus should have been on 'age at conventional diagnosis for infants with Galactosaemia as it is recognised that many infants may be symptomatic already by the time of a positive screening result but being cared for in a setting where Galactosaemia is not being considered as a possible cause.'

I. this would focus attention on the time difference between diagnosis in screen and non screen detected cases. But it also acknowledges the problem towards which the question was directed, that the benefit of screening would tend to be limited for a proportion of cases as they would require management of symptoms prior to completion of the screening and diagnostic process. A paper submitted by the

Galactosaemia Support Group and RCPCH estimated that, in the ten European screening programmes, this was ~50%, within the range of 22% - 74% described in the review. A paper submitted by Genetic Alliance UK highlighted the difficulty of diagnosis in some early presenting cases and drew attention to the need for awareness of Galactosaemia in the presence of neonatal liver failure even if a screening programme was in place. It is unclear whether any guidance addresses this issue

II. the responses varied on a number of points. Genetic Alliance UK suggested that an approach focusing on this would reduce parental stress caused by delayed diagnosis, prevent illness, and improve recovery and future development. However the responses from the RCPCH and the Galactosaemia Support Group noted that the evidence did not suggest an effect of treatment on long term outcomes. Similarly, the RCPCH and PANS suggested that an approach based on the prevention and management of neonatal complications would also need to consider the detection of variants of uncertain clinical significance which would arise with current testing options.

III. the review suggested that false negative test results would occur and this could further limit the ability of screening to impact on acute neonatal presentation.

IV. the situation in the UK is complicated as a proportion of Galactosaemia cases are detected through the current PKU screening programme.

The case for screening to prevent and improve management of acute presentation was proposed but no papers discussing the advantages were submitted. The case may be clearer if longer term outcomes improved through treatment, if the test did not detect clinically uncertain variants and if more was known about current clinical practice as it relates to the management of neonatal liver disease.

- That focusing on the published literature excludes the contribution of the patient and public voice and the experience of practicing clinicians

The Genetic Alliance UK recommended that the UKNSC adopts the same approach to qualitative evidence as NHSE, NICE and EMEA for rare diseases. A meeting is being set up to discuss this with Genetic Alliance UK and the UKNSC Secretariat will find out more about practice in other organisations. However published literature should remain the priority in the UKNSC review process.

Other issues raised by the responses included the need for a review of the timing of UK bloodspot screening and the need to find a way of pursuing the research recommendations.

FMCH discussion

The FMCH discussed and approved the recommendation not to screen at its March meeting. However there was concern about the situation as it relates to acute neonatal liver failure and uncertainty on the proportion of cases detected through current screening practice.

Action

It is recommended that the current policy on newborn screening for Galactosaemia should remain unchanged.

However the following work should be considered:

- quantification of the number of Galactosaemia cases currently detected through screening for PKU,
- review of current guidance, for example on the management of neonatal liver disease and / or early onset e-coli infection, and whether galactosaemia is included in this by relevant clinical organisations (eg RCPCH, BASL, NICE) and as an additional part of this,
- development guidance for Galactosaemia cases detected through the current screening programme.

The UKNSC is asked to consider the above and approve the recommendation.

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UK National Screening Committee

Screening for Galactosaemia- an evidence review

Consultation comments pro-forma

Name:	Pat Roberts	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	Save Babies Through Screening Foundation (and the Patient Advocates for Newborn Screening Group)		
Role:	**Executive Director of SBUK and Chair of PANS**		

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** *Please use a new row for each comment and add extra rows as required.*
General Comment	Lack of evidence raised throughout the external review document.	Lack of evidence is a theme throughout the review document. 10 EU Member states already screen for this disorder. The

		evidence review refers to published evidence on Galactosaemia in particular areas. However the fact that 10 EU Member states already screen for the disorder has to stand as some small piece of evidence of the benefits to children.
General Comment		
Executive Summary	A proportion of affected babies will present with symptoms before the screening process is complete	Screening for Galactosaemia may benefit from the review of the date on which the bloodspot sample is taken in the UK. This has been raised previously on policy reviews/consultations for other disorders. A promised review of the day of screening in the UK has yet to materialise. We need this review to be commissioned if we are to benefit children. The day of screening in the UK also impacts early diagnosis of children with other disorders.
Page 5 Para1	Is it an Important Health Problem	On the estimated UK incidence in the 1997 HTA report i.e. 1:44,000 this equates to at least 15 children a year. This is more patients at risk than in some disorders already included in the UK NBS programme. There is a question on whether screening would identify more cases of uncertain significance than the target condition. However this is a high incidence rate. Rather than dismiss the case for screening, this type of evidence can be established in a pilot screening programme in the UK. Early detection is about benefiting the child by better care at the earliest opportunity, to minimize damage/disability and thereby also reducing longer term care and intervention costs to the NHS.

Page 10	Epidemiology and natural history of the condition Age at clinical presentation.	The Galactosaemia Support Group registry has additional information on the mean age of diagnosis and we understand they will be including this information in their response to the consultation.
Page 20	Implications for Research	The policy review by the UK NSC team has identified a lack of evidence from other countries in a number of areas. The review has identified where studies in 4 areas may assist in driving out the necessary evidence to support screening for Galactosaemia. However no suggestion is made by the UK NSC of what work might be done and by who to obtain this evidence. Without suggestions on next steps the policy will be boxed forward for review in another few years and the same conclusion will be reached. Something concrete needs to happen to provide the necessary evidence.

Please return to Hugh Davis (Evidence Review & Policy Development Manager) screening.evidence@nhs.net **by 19th February 2015**

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UK National Screening Committee

Screening for Galactosaemia- an evidence review

Consultation comments pro-forma

Name:	Alastair Kent	**Email address:**	**xxxx xxxx**
Organisation (if appropriate):	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.		

Role:	

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.*
Page 10	"Overall, the identified evidence was limited, but suggests that a substantial proportion of screen detected galactosaemia cases will be symptomatic by the time screen results are confirmed and diagnosis is made."	Genetic Alliance UK supports the Galactosaemia Support Group's response to this consultation and their recommendation that a formal newborn screening programme should be implemented for galactosaemia. We note that the Galactosaemia Support Group have reached this conclusion based on patient experience and on the review held by their Medical Advisory Panel. The Galactosaemia Support Group's patient register shows that the mean age of diagnosis is between 13 and 17 days. This means that, on average, parents have to wait between five and nine days longer for their child to be diagnosed clinically than if a newborn screening programme was in place. This is an unnecessarily long time for parents to watch their child deteriorate when early diagnosis and intervention

		could be facilitated by implementing a screening programme. From our work with the undiagnosed patient community through our SWAN UK initiative, we know that for a parent not knowing the cause of their child's condition can make it more difficult to cope with, not only medically but psychologically and emotionally. Genetic Alliance UK therefore supports the view of the Galactosaemia Support Group that reducing the stress parents go through when they have a seriously ill baby without a diagnosis should be seen as a valuable potential benefit of newborn screening for galactosaemia. Another positive outcome from early diagnosis that the Galactosaemia Support Group highlight is the ability to prevent the child from becoming as ill in the first instance, improving the child's ability to recover and their future development. From working with patients and clinicians, the Galactosaemia Support Group supports the view that screening would prevent neonatal deaths and severe liver failure in undiagnosed babies, and avoid the cost implication of caring for these babies in specialist liver units. This view is supported by a recent published review of the condition that states: "If a lactose-free diet is provided during the first three to ten days of life, the signs resolve quickly and prognosis for prevention of liver failure, Escherichia coli sepsis, and neonatal death is

		good. Failure to implement effective newborn screening may have catastrophic consequences such as liver failure"[1]. The ability for newborn screening to prevent neonatal death and acute liver disease by detecting the condition at an earlier stage is critical and should form a central part of the UKNSC's consideration of the benefits and risks of adding galactosaemia to the list of conditions screened for at birth.
Page 3	"There is now a focus on a wider range of benefits which screening may bring by reducing the diagnostic odyssey, informing future reproductive decisions and identifying potential research subjects. However the literature search did not identify any publications addressing these issues in the specific context of Galactosaemia."	We welcome the statement made by the UKNSC in their consultation document that they are now focussing on the broader benefits that can be gained from earlier diagnosis through newborn screening. Unfortunately, by restricting themselves to gathering data from published literature, the UKNSC has failed to bring this new focus to bear on this appraisal of galactosaemia for newborn screening by not considering the valuable evidence provided by the Galactosaemia Support Group, which demonstrates the benefits of earlier diagnosis. The experience and knowledge of the Galactosaemia Support Group indicates that many newborns are not diagnosed within the first 10 days of life. This means that early intervention with treatment that could significantly improve clinical outcomes is currently not possible for many children with galactosaemia; and indicates that a newborn screening programme, where a

[1] Malone JI, Diaz-Thomas A, Swan K. Problems with the new born screen for galactosaemia. BMJ Case Rep. 2011 Jun 3;2011. pii: bcr0120113769

		diagnosis could be achieved within the first eight days of life, would significantly reduce the diagnostic odyssey for these children and their families.
Page 2 and 3	"This recommendation is based on a 1997 HTA report which identified a number of inter-related issues preventing the development of a screening programme" "The review suggests that the body of evidence identified by the literature search is an insufficient basis on which to change the current screening policy"	The current methodology used by the UKNSC when making decisions about whether the benefits of introducing a newborn screening programme for a condition outweighs the risks places a premium on peer reviewed literature to the exclusion of all other forms of evidence. We note with concern that in the UKNSC's review of screening for galactosaemia against their programme appraisal criteria, nearly a third of the literature included in the review was published before 2000. In particular, we are concerned that the Health Technology Assessment review on which the UKNSC have based their decision was published in 1997 and is nearly 20 years out of date. 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. Not taking this type of information into account during a review of the evidence 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.

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Screening for Galactosaemia

Evidence review

(Comments due 5pm, Friday 6 February 2015)

Name	Dr Saikat Santra
Position	Consultant in Clinical IMD
Specialty group, special interest group or CSAC Please specify if you are responding on behalf of a group/committee	Metabolic Medicine CSAC / BIMDG / Galactosaemia Support Group Medical Advisory Panel

Section and / or page number	Text or issue to which comments relate	Comments *Please use a new row for each comment and add extra rows as required.*
Page 19 and Page 4	Incidence	The statements "the incidence of galactosaemia in the UK was substantially lower than other inborn errors of metabolism" refer to PKU and MCADD which might have been an acceptable comparator in 1997. Following the successful pilot of expanded newborn screening for rarer IEMs including GA1, IVA, MSUD and HCU it is important for this review to put the incidence of galactosaemia in the current context of conditions included in the NBS programme. It is

		no longer correct to state that "the incidence of galactosaemia in the UK is substantially lower than other inborn errors of metabolism" being screened for – it is much more frequent than MSUD for example. Whilst the use of these phrases in the review do relate to the 1997 review – I think it would be helpful for this to be a separate key finding in favour of screening for galactosaemia at this point in time (though the validity of the rest of the review is unchanged)
Page 10/11	Mean age at clinical presentation	The review mentions several individual studies about the percentage of patients who are symptomatic at presentation in individual screening programmes/countries. It does not include, I think, Burgard et al J Inherit Metab Dis (2012) 35:613–625 which includes the pooled questionnaire results of several European countries – 10 of whom provided data on galactosaemia and nearly 50% of patients were symptomatic at diagnosis
Pages 10/11 and 20/21	Mean age at clinical presentation	The review does focus on mean age at clinical presentation – although one could argue that the key question is not so much the age at clinical presentation but rather the age at conventional diagnosis. There is certainly a precedent for this with the approval of screening for MSUD – where one would expect most babies already to be symptomatic but not necessarily undergoing the correct diagnostic tests. The interim report of the Galactosaemia Register produced by the RCPCH in 2002 showed that • 167 babies were born between 1994-2002 with galactosaemia • 8 cases died (4% mortality) • Mean age at diagnosis was 14 days (when there was no prior family history) • Mean age at starting a lactose free diet was 17 days Therefore there is still an argument for considering screening for galactosaemia to reduce neonatal mortality and improve the time to diagnosis and treatment.
Page 18/19	Agreed policies	There are also published European recommendations for the management of galactosaemia including some long-term outcomes such as prevention of osteoporosis. Although this does not specifically address the question of whether or not to screen, it does demonstrate wider international agreement on the management of galactosaemia (Panis et al J Inherit Metab Dis. 2007 Nov;30(6):982)
	General	I agree there has not been any significant new evidence published to support the argument for screening for galactosaemia in order to reduce long term complications of the disease – and no studies comparing screened vs non-screened outcomes. An argument for screening would therefore need to be focussed on early outcomes (mortality and morbidity) and factoring in the implications of detecting atypical variants.

You may add extra pages as needed.

Please email this form to clinical.standards@rcpch.ac.uk by 5pm, Friday 6 February 2015.

Our deadline is set before that of UKNSC to allow time to consider all comments received and to draft an official response with review from the RCPCH Clinical Standards Committee. Responses received after this deadline will not be included in the RCPCH response to this consultation. We reserve the right to summarise and edit comments received, or not to include them.

Reg. Charity No. 1020167

xxxx xxxx
xxxx xxxx
xxxx xxxx
xxxx xxxx
xxxx xxxx

Email : xxxx xxxx
Website : www.galactosaemia.org

To whom it may concern,

I am writing on behalf of the Galactosaemia Support Group in response to the UKNSC's consultation on including screening for Galactosaemia in the newborn screening programme.

The Galactosaemia Support Group is a registered charity dedicated to supporting parents, families and patients affected by this devastating condition which if unrecognised can lead to severe liver failure and death. These could be prevented in some babies by newborn screening and we feel it is vital to have galactosaemia included in future screening.

As a parent myself, and through my work with the support group, I understand at first hand the stress of having a seriously ill baby. This stress could be lessened through screening giving an earlier diagnosis. For a parent the worst part is not knowing what is causing your child's illness. The earlier diagnosis, giving parents a "name" and reason for their child's problems, would help so much; their child would not become so ill in the first place, decreasing the stress period for the parents and helping the child immensely in their recovery and future development.

The information on our Galactosaemia register shows the mean age of diagnosis is between 13 and 17 days. That is a long time for parents to watch their child deteriorate whilst waiting for a diagnosis when it could be so greatly reduced through screening.

Preventing neonatal deaths and acute liver disease through detecting the condition at an earlier stage through screening has to be a major consideration. The cost of these babies being cared for in liver units cannot be underestimated. Please see appendix which is a short review written by a member of our medical advisory panel which supports the GSG request for newborn screening. I hope you will consider our comments.

Yours faithfully

Sue Bevington
Galactosaemia Support Group

APPENDIX
To whom it may concern,
I am writing on behalf of the Medical Advisory Panel to the Galactosaemia Support Group in response to the UKNSC's consultation on including screening for Galactosaemia in the newborn screening programme.

I also have had the opportunity to assess the External Review against programme appraisal criteria produced by Bazian Ltd in June 2014 on behalf of the Royal College of Paediatrics and Child Health, so you may already have seen much of what I write here.

When Galactosaemia was last assessed in a Health Technology Assessment Review (1997), it was concluded that neonatal screening for Galactosaemia was not justified based on the available evidence as:

1. The incidence of galactosaemia in the UK was substantially lower than other inborn errors of metabolism

2. The limited evidence suggested that available treatments (and their earlier use) did not improve long-term outcomes

3. There were conflicting reports regarding the ability of screening to prevent severe symptomatic presentation in neonates

4. There were uncertainties surrounding the identification and treatment of partial deficiencies.

The current evidence review is certainly comprehensive and has identified the majority of the relevant published literature since 1997. As is often the case with rare diseases, published literature can be quite sparse, but there are certainly some issues to consider when reassessing the merits of screening for Galactosaemia.

1. Following the successful pilot of expanded newborn screening for rarer Inborn Errors of Metabolism including Glutaric Aciduria Type 1, Isovaleric Acidaemia, Maple Syrup Urine Disease (MSUD) and Homocystinuria, it is important to put the incidence of galactosaemia (estimated at 1:44,000 in the UK) in the

current context of conditions included in the Newborn Screening programme. It is no longer correct to state that “the incidence of galactosaemia in the UK is substantially lower than other inborn errors of metabolism” being screened for – it is much more frequent than MSUD for example.

2. I agree there has not been any significant new evidence published to support the argument for screening for galactosaemia in order to reduce long term complications of the disease – and no studies comparing screened versus non-screened outcomes. However an argument for screening could still be made focussed on early outcomes (neonatal mortality and morbidity) and Mrs Bevington will have written to you separately with insight into the distress this can cause families of newly diagnosed infants.

3. The External Review concentrates much discussion around a key question about the mean age at clinical presentation and presence of symptoms at the time of diagnosis. The review mentions several individual studies about the percentage of patients who are symptomatic at presentation in individual screening programmes/countries. It does not though include, I think, Burgard et al J Inherit Metab Dis (2012) 35:613–625, which includes the pooled questionnaire results of several European countries – 10 of whom provided data on galactosaemia and nearly 50% of patients were symptomatic at diagnosis. One could argue, though, that the key question is not so much the age at clinical presentation but rather the age at conventional diagnosis for infants with Galactosaemia as it is recognised that many infants may be symptomatic already by the time of a positive screening result but being cared for in a setting where Galactosaemia is not being considered as a possible cause. There is certainly a precedent for this with the approval of screening for MSUD – where one would expect most babies already to be symptomatic but not necessarily undergoing the correct diagnostic tests. The interim report of the Galactosaemia Register produced by the RCPCH in 2002 showed that

- 167 babies were born between 1994-2002 with galactosaemia
- 8 cases died (4% mortality)
- Mean age at diagnosis was 14 days (when there was no prior family history)

- Mean age at starting a lactose free diet was 17 days
- Therefore there is still an argument for considering screening for galactosaemia to reduce neonatal mortality and improve the time to diagnosis and treatment.

4. The external review acknowledges that in published data from countries already undertaking newborn screening for Galactosaemia, the numbers of “false-positive” screens and patients with partial enzyme deficiencies detected has been lower than initially expected and there is no reason to believe this to experience to prove different in the UK.

5. The external review also acknowledges the publication of several UK and US guidelines for the management of Galactosaemia. There are also published

European recommendations for the management of galactosaemia including some long-term outcomes such as the prevention of osteoporosis. Although this does not specifically address the question of whether or not to screen, it does demonstrate wider international agreement on the management of galactosaemia (Panis et al J Inherit Metab Dis. 2007 Nov;30(6):982) It is of the view of the Galactosaemia Support Group that further consideration be made of the case for screening for Galactosaemia. As the external review rightly identifies, there are technical issues regarding screening for Galactosaemia at 5-8 days of age and it is likely that many infants so detected would already be unwell. However, it is certainly likely that many infants would be unwell in a non-specialist centre where the diagnosis of Galactosaemia is not being seriously considered. An earlier diagnosis through newborn screening does, then, have the potential to reduce neonatal mortality and morbidity from this serious condition. We hope you will consider our comments.

Yours faithfully

Dr Saikat Santra
Medical Advisor to the Galactosaemia Support Group
Consultant Paediatrician in Metabolic Medicine,
Birmingham Children's Hospital