UK National Screening Committee

UK National Screening Committee

Newborn Screening for Tyrosinaemia Type 1

Aim

1. To ask the UK National Screening Committee (UK NSC) to recommend newborn screening for tyrosinaemia type 1.

Current Recommendation

2. The UK NSC currently does not recommend newborn screening for tyrosinaemia type 1. The Committee made this recommendation in 2017 based on the evidence provided by a review carried out by the University of Warwick. However the Committee recommended that a modelling project should be undertaken to evaluate the clinical and cost effectiveness of screening compared to current UK practice.

Modelling project

3. The modelling project was undertaken by University of Warwick. The resulting model has been received by the FMCH at several meetings. The modelling and a summary description have been circulated with this paper.

4. The model estimated that screening would do more good than harm. This was primarily based on its estimate that screening would increase the number of babies receiving nitisinone and dietary management in the presymptomatic phase. These interventions would reduce neurological crises, liver disease and the need for liver transplantation.

5. The base case estimate was that the cost per additional QALY gained compared to current practice (incremental cost effectiveness ratio (ICER)) was £61,756. Sensitivity analysis suggested this was uncertain. However there was greater certainty that the ICER would be less than £100,000.

6. As such the modelling exercise concluded that newborn screening was unlikely to be cost effective according to the standard ICER threshold of £20,000 - £30,000 used by NICE. However this is not a precise or fixed maximum ICER above which an intervention would automatically be categorised as not cost effective. NICE have a flexible approach based on consideration of a number of decision making modifiers. These are factors and value judgements which cannot be included in a QALY estimate. Application of modifiers is used to justify investment in interventions which exceed the standard ICER threshold. They are considered qualitatively through committee discussion or quantitatively through QALY weighting.

7. The approach to cost effectiveness evaluation in screening has not been defined and the application of NICE thresholds and decision making modifiers in the evaluation of screening programmes has not been formally considered or approved. However the approach taken by NICE has been used as a reference point to help structure discussion of newborn screening for tyrosinaemia type 1.

8. An earlier version of this paper was received by the FMCH at its meeting in May 2022.

Consultation

9. A 3-month consultation was hosted on the UK NSC website. Direct emails were sent to 19 stakeholders.

10. The initial public consultation closed in March 2022. This was extended until 2 May 2022 because of the low response rate. The total number of consultation responses received was 5. The consultation comments received are presented below in Appendix 3.

11. Comments were received from the following stakeholders:

- British Association for the Study of the Liver (BASL)
- Royal College of Paediatrics and Child Health
- Royal College of General Practitioners

- Genetic Alliance UK
- Metabolic Support UK

12. Stakeholders were invited to:

- make an overall statement of their views on screening for the condition being reviewed and on the standard of the review
- draw attention to disagreements with the review's recommendations or with particular aspects of a review
- highlight potential inconsistencies in the interpretation of the evidence which has been included in the review
- alert the Committee to questions or evidence which may have been omitted by a review and which may contribute to the recommendation
- suggest amendments to important errors in the wording of the review document
- comment on whether screening should be recommended given the estimated cost associated with health outcomes and the uncertainty of the evidence

13. Comments relating directly to the high ICER:

- GAUK acknowledged the high ICER. GAUK pointed to the higher ICER threshold used by NICE as a modifier for highly specialised technologies (HST). HSTs refer to 'highly specialised medicines and treatments within the NHS in England'. In evaluations of HSTs, where an intervention results in the addition of less than 10 QALYs / patient, NICE apply a maximum ICER of £100,00. This fits the outcome of UK NSC evaluation of screening for tyrosinaemia type 1 in which approximately 8 QALYs were gained by each affected baby identified by screening.

However the fit between both newborn screening and tyrosinaemia type 1 and HSTs has not been formally considered. NHS England distinguishes highly specialised services from specialised services as those provided to 'usually no more than 500 patients a year'. Screening is offered to the whole neonatal population and clearly exceeds this number. However the endpoint of newborn screening for tyrosinaemia type 1 is the identification and treatment of a condition with an incidence of about 1/100,000. Also, in England, tyrosinaemia type 1 is grouped with other metabolic diseases and delivered as a specialised service rather than a highly specialised service. However the impact of screening is estimated to be primarily on liver disease and transplantation and these are delivered as highly specialised services.

These considerations and the absence of ground rules for decision making in screening prevent direct application of the NICE modifier for HSTs. However the modifier may provide a useful reference point for perspective when considering the high ICER associated with screening for tyrosinaemia type 1.

- The RCPCH also acknowledged the high ICER. However the College pointed out that interventions with a high cost per patient are not uncommon in ultra rare disease settings. The College considered the cost associated with screening for tryosinaemia type 1 to be acceptable.

  Cost per patient is not a recognised measure of cost effectiveness and no analysis was undertaken to compare with other interventions.

- Metabolic Support UK (MSUK) raised two points which may be relevant to the way in which the high ICER is considered. This patient organisation highlighted the negative impact of tyrosinaemia type 1 on the parents and carers of affected babies. However, a health decrement in parents and carers was not factored into the cost effectiveness evaluation. As such, this aspect of the condition was not incorporated into the model. This is an area of active research interest[1] which may affect the estimated QALY gain from screening.

[1] Simon et al. Health utilities and parental quality of life effects for three rare conditions tested in newborns, Journal of Patient-Reported Outcomes (2019) 3:4

For example, MSUK emphasises the stress and anxiety experienced during a route to diagnosis based on clinical symptoms. If screening eliminates this, as it does in the model, there may be an uncaptured benefit of screening which would lower the ICER by increasing the QALY gain at no extra monetary cost. However, the model also estimated that early nitisinone treatment following screening may increase the number of babies with tyrosinaemia who would experience learning difficulties. This may have an impact on any parental QALYs gained through the elimination of symptomatic clinical presentation. This outcome was considered very uncertain and its impact on parental / carer experience is unknown. A 'spillover' impact on the QALY estimate is therefore difficult to gauge and whether parental QALYs should be included in future evaluations has not been established. However the potential for this to affect the outcome of the evaluation of tyrosinaemia type 1 might be a helpful point to consider.

- MSUK also pointed out that, in the West Midlands, there is a higher prevalence of tyrosinaemia type 1 in the Pakistani population compared with other populations. Because of this, screening may be relevant to the reduction of health inequalities. NICE do not currently apply a decision making modifier based on inequalities. However, NICE's recent consultation on this issue highlighted that there is a 'strong case for introducing a modifier into decision making that allows [NICE] committees to give greater importance to technologies that help to reduce health inequalities.' The main issue preventing this was uncertainty about an approach which would ensure a modifier was applied consistently. Work is ongoing to address this and awareness of this might be helpful.

- In addition to these issues raised by stakeholders, it might be noted that NICE recently extended their modifiers to include severe chronic conditions affecting younger patient populations. This is termed the 'severity modifier'.[2] This is applied when conditions lead to a significant QALY shortfall in affected people compared to unaffected people of the same age and sex. The QALY shortfall is calculated as 'the expected total QALYs that people living with a condition would be expected to have with current treatment … subtracted from the total QALYs that the general population with the same age and sex distribution would be expected to have.' As the QALY shortfall increases a higher weighting is applied to any QALYs gained from a new intervention. This effectively increases the ICER threshold.

[2] NICE health technology evaluations: the manual, January 2022

The UK NSC evaluation of newborn screening for tyrosinaemia type 1 was not set up to undertake a QALY shortfall calculation. However, awareness of this emphasis on childhood conditions may be of use when considering the high ICER.

14. Other comments:

- MSUK sent two publications which were published after the literature search dates.
- Das A. M. (2017). Clinical utility of nitisinone for the treatment of hereditary tyrosinemia type-1 (HT-1). The application of clinical genetics, 10, 43–48.

  This is a review of studies which were overwhelmingly published within the search dates of the Warwick reviews. Relevant papers were captured in these reviews and / or the model. The small number of papers published after the search dates do not appear to relate to newborn screening for tyrosinaemia or nitisinone treatment.

- Ute Spiekerkoetter, Maria L Couce, Anibh M Das, et al, Long-term safety and outcomes in hereditary tyrosinaemia type 1 with nitisinone treatment: a 15-year non-interventional, multicentre study, The Lancet Diabetes & Endocrinology, Volume 9, Issue 7, 2021, Pages 427-435
  This paper was published after the search dates of the Warwick reviews and has not been incorporated into the analyses informing the UK NSC recommendation. The paper provides data which could be incorporated into future reviews and / or iterations of the model.

  Of note, the paper reports an incidence of cognitive and neurodevelopmental events which is lower than that reported in the papers informing the modelling exercise. It also reports a rate of liver transplantation which suggests that the model may have overestimated the number of tyrosinaemia related transplants in the no screening arm.

  The paper provides some useful pointers for further post implementation monitoring.

- BASL suggested including cardiac outcomes and the cost of (or avoidance of) post transplant immunosuppressive drugs and long term clinical follow up in the evaluation. Future reviews or iterations of the model would provide an opportunity to explore these issues further.

- The RCGP response suggested that the consultation proposal was not to recommend screening. However this misunderstood the purpose of the consultation.

- GAUK welcomed the modelling approach as potentially useful methodology. The UK NSC Secretariat would look forward to working with GAUK to develop and improve the approach.

FMCH meeting in May 2022

15. The FMCH considered the above points and recommended the following to the UK NSC:

- tyrosinaemia type 1 should be added to the UK newborn blood spot screening panel

- work should be undertaken to scope the requirements to implement this recommendation, for example to define the case definition for screening potentially to align with European practice, identify and validate laboratory methods, specify resource requirements and develop pathways, standards and the relevant information for the public and professionals

- a mechanism to collect and report on key clinical outcomes should be identified to try to establish the effect of screening over time. This might be considered in relation to the hypothesis presented by the modelling exercise by, for example, including a focus on liver transplantation and learning difficulties

- work to consider the UK NSC's approach to cost effectiveness would be helpful for decision making in future evaluations and

- consideration of the methodological and resourcing issues affecting modelling in rare diseases could help improve the quality and efficiency of future evaluations in this area

In discussion, individual FMCH members suggested that careful consideration should be given to the way in which the cost effectiveness of screening for ultra rare diseases was evaluated. This was particularly the case where a drug had been found to be cost effective.

16. Action

The UK NSC is asked to consider the papers relating to newborn screening for tyrosinaemia type 1 and the recommendations agreed by the FMCH.

UK National Screening Committee

Appendix 1

Summary of the evaluation of the cost effectiveness of newborn screening for tyrosinaemia type 1

Tyrosinaemia type 1 (TYR1) is a very rare, genetically inherited, disorder where a person has raised blood levels of tyrosine. Tyrosine is an amino acid, that is an important building block of proteins in the body. Early symptoms can include failure to gain weight, diarrhoea and jaundice. These may appear within the first few months of life. Over time, people with TYR1 are at an increased risk of learning difficulties, liver cirrhosis and cancer. TYR1 can also lead to liver and kidney failure. Globally, one person in 100,000 is affected with TYR1 but it may be more common in some areas. In the UK, approximately 7 babies are born each year with TYR1.

There is no cure for TYR1. A special diet and a drug called nitisinone are available as treatment which continues for life. If left untreated, death from liver failure or liver cancer usually occurs before the age of 10 years. Evidence suggests that earlier health care leads to better health than later treatment. Very rarely people who inherit the genetic mutation which causes TYR1 do not develop symptoms, even without treatment.

In the UK, current practice to detect newborns with TYR1 includes:

- testing babies when there is a family member with the condition (cascade testing),
- testing babies who have a positive phenylketonuria (PKU) screening test as some have TYR1 not PKU (incidental detection),
- testing babies who have symptoms (clinical detection).

Newborn screening for TYR1 at 5 days of age with tandem mass spectrometry (TMS), using raised levels of a chemical compound called succinylacetone (SUAC) as the test , may help to improve the health of those affected by TYR1. The UKNSC team looked for research that directly compared the health (good and bad) in babies found by screening with those found through current practice. . This kind of research is very difficult in such rare diseases as there are very few babies with TYR1. In these

circumstances, other methods such as ‘models’ are useful. These are simulated comparisons between different interventions and use data and information from many sources. For example, they incorporate expert opinion, data from other countries or from research that didn’t look at screening. Models can help assess the clinical effect of a screening programme on health outcomes such as severe illness or death.

To develop and run a screening programme, it must offer good value for money as well as being clinically effective. Models also provide the information needed to estimate the cost-effectiveness of screening and care . This enables policy makers to decide whether the same money would help more people if used in another area of health or social care.

The University of Warwick developed a model on behalf of the UK NSC to compare current practice in the UK with a newborn screening programme for TYR1. The model compared health and costs for both these approaches in a hypothetical one-year group of new babies in the UK. An expert group acted as a reference group for the modelling study. The group discussed the details of the 2 pathways, the health outcomes of interest, the data inputs required and the assumptions that needed to be made in the absence of evidence.

The health issues included in the economic model were:

- liver disease (cirrhosis and cancer)
- liver transplant
- kidney problems
- learning difficulties
- neurological crises (seizures, vomiting, limb pain)

The model’s main findings were:

- how many extra correctly identified babies with TYR1 were found

- how many extra years babies with TYR1 lived? Known as life years gained (LYG)
- what the quality of those extra life years was, known as quality-adjusted life-years (QALY)

The QALY is a way of summarising the length and quality of life gained (or lost) as a result of an intervention (in this case a screening programme)

These findings help to show the short-term and long-term benefits and costs of introducing newborn screening for TYR1.

Extra babies found early

The number of babies with TYR1 found early is important because it shows how effective screening will be in identifying babies with TYR1 before they develop symptoms.

The model estimated that 7 babies would be born each year with TYR1. Using current UK practice as described above

- four would be identified before symptoms develop. Three of them because they had a sibling with the disease (cascade testing)
- one baby would be found ‘incidentally’ following a positive PKU screening test
- the remaining 3 babies would be detected following the onset of symptoms usually by about 6 months of age

When comparing this with newborn screening undertaken when a baby is 5 days old using SUAC as the marker for TYR1, the expert group made the following assumptions:

- cascade screening would continue as normal as it would be unethical not to test siblings as soon as possible

- assessment of babies with PKU screen positive results for TYR1 would stop as screening for TYR1 would be offered for all newborns

The model estimated that all 7 babies with TYR1 would be detected before developing symptoms. The model also estimated that replacing current practice with screening for TYR1 would mean that 89 babies would avoid receiving an incorrect diagnosis as they do not have TYR1 (referred to as false positive results). This would avoid unnecessary worry and stress for their parents.

The model estimated that the annual cost of adding SUAC to the current panel of markers would be about £430,000. This includes the costs of the screening, testing and diagnostic pathway up to the point of detection. This means that it would cost an additional £144,000 to detect a baby with TYR1 compared to current practice.

There are some uncertainties about these estimates. For example, no test is perfect and not everyone accepts the offer of screening. In addition, although rare, some babies with TYR1 will develop symptoms before the screening test result is available. This means that, even with newborn screening, some babies will still present clinically with symptoms of TYR1.

Another uncertainty is the number of babies affected by TYR1. This can vary year on year. The number of affected babies can also vary between those detected within the cascade testing, incidental and clinical detection pathways. This means that the number of cases detected by screening may also vary and this could have an impact on the cost per case detected.

Finally, the cost of the test is unknown so the model tried two or three costs and this changed the estimated cost per case found: . For example, when using current commercial products in the testing process, the model estimated that the cost per case detected may be about £260,000.

Improvements in health

To evaluate the impact of screening, it is important to understand the health benefits gained by detecting a disease earlier.

The model estimated that, overall, detection and starting a special diet and nitisinone treatment in babies without symptoms led to better health , both short- and long-term, compared to treatment after symptoms had already developed.

In the short-term, newborn screening at 5 days of age meant that the 3 babies that would remain undetected in current practice would largely avoid the early symptoms of TYR1. These 3 babies would also avoid neurological crises and be less likely to develop kidney disease.

The main gain was avoidance of liver disease. In the model, newborn screening and earlier intervention with diet and nitisinone, reduced the risk of liver cirrhosis, liver cancer and, as a consequence, the need for liver transplantation. By comparison, without newborn screening, 2 of the 3 babies who developed symptoms went on to require liver transplantation at a later point in their lives.

Health interventions can cause harm as well as giving benefits. In the model it was assumed that learning difficulties were more likely in those babies treated early with nitisinone compared to those treated later after symptoms developed. Because newborn screening meant more babies with TYR1 were being treated earlier, this also led to an increase in the number of babies experiencing learning difficulties.

However, because the expert group (and therefore the model) placed a higher health value on avoiding liver disease than avoiding learning difficulties , the total estimate (QALYS) was that the benefits of screening outweighed the potential harms. This is reflected in the conclusion that screening would result in a gain of 24 QALYs in 679,000 live births. This means that each of the 3 additional babies detected by screening would gain about 8 QALYs over the course of their lives. Finally, it was estimated that early detection through newborn screening would not lead to a significant increase in the life expectancy of those with TYR1. Screening led to a gain of 6 – 12 months per case detected compared with current practice. This was because some babies with TYR1 are already detected before symptoms develop and people with TYR1 can expect a normal life expectancy after a successful liver transplant.

Therefore the cost per additional QALY gained was estimated to be £61,756. This is based on a comparison of the lifetime costs, quality and length of life in current practice and in newborn screening. An example of the increase in costs due to screening is the assumption that lifelong treatment with nitisinone is not required following liver transplantation. This meant that while avoiding liver transplantation led to an improvement in quality of life, this also led to an increase in costs.

There are some uncertainties about these estimates. Better health outcomes in TYR1 depend on good compliance with treatment and diet schedules[3]. The expert groups assumed a that all babies and families exactly followed the treatment all the time. Life isn't always like that so this assumption might mean that the benefits are overestimated. However, this assumption applies to both current practice and screening, so the effect of this would be unlikely to affect the comparison between the 2 strategies.

In addition, the assumption that nitisinone treatment would not be needed following liver transplantation may not be 100% all the time and may not be accepted by those who work with people affected by TYR1. .[4] If nitisinone is used in babies who have had liver transplant this would increase the cost of current practice and reduce the cost difference between current practice and screening.

There is no consensus on whether learning difficulties are due to early treatment with nitisinone or TYR1 itself. Therefore, the assumption that early nitisinone treatment causes learning difficulties is very uncertain. But again, this assumption is made in both current practice and screening. It is difficult to know how clear evidence to resolve this question would affect either strategy in terms of the practical care of people with TYR1.

Value for money

In the UK, QALYs are used a standard way of assessing the health value of an intervention. The cost per additional QALY gained (the incremental cost effectiveness ratio (ICER)) from screening for TYR1 compared to current practice is above the thresholds that the National Institute for Health and Care Excellence (NICE) recommend for standard conditions. But the value is within the accepted threshold for treatment of very rare or 'orphan' diseases. This threshold is an ICER of £100,000 per QALY gained. However, it is not clear whether this threshold applies to screening programmes for very rare diseases.

Extra analyses were carried out. The team varied some of the data for the particular issues where there is uncertainty. This is standard practice in such models. As many pieces of information are based on opinion (albeit highly expert opinion) rather than

[3] C Dawson, R Ramachandran, S Safdar, Severe neurological crisis in adult patients with Tyrosinemia type 1, Ann Clin Transl Neurol. 2020 Sep; 7(9): 1732–1737.

[4] J M Chinsky, R Singh, C Ficicioglu, Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations, Genet Med. 2017 Dec; 19(12)

scientific evidence, varying the numbers in the model slightly is done to see how such changes affect the final result and therefore how reliable the result is. . For example, for one analysis all the uncertainties were brought together, then the results were recalculated 10,000 times. These results showed that the model's main estimate, an ICER of £61,756,

was very uncertain and that the 'true' ICER is likely to be higher. The model is more certain that the ICER will be lower than £100,000. However, due to limited evidence, there is a need for further research to refine these results.

In conclusion

Work was done to bring together research, clinical evidence and expert opinion to compare a hypothetical screening programme for TYR1 with usual NHS services. The aim of the work was to see if a screening programme for early detection and care of babies with TYR1 was better than current arrangements in the NHS.

The work came to the conclusion that such a programme would do more good than harm to babies but the cost of doing so was high by comparison with NICE thresholds. The work also showed that there are many gaps in the evidence so the conclusion of the work is not certain.

UK National Screening Committee

Appendix 2: List of organisations contacted

1. ArchAngel MLD Trust
2. British Association of Perinatal Medicine
3. British Inherited Metabolic Disease Group
4. Clinical Genetics Society
5. Faculty of Public Health
6. Genetic Alliance UK
7. Institute of Child Health
8. Metabolic Support UK
9. MetBio
10. Royal College of General Practitioners
11. Royal College of Midwives
12. Royal College of Paediatrics and Child Health
13. Royal College of Physicians
14. Royal College of Physicians and Surgeons of Glasgow
15. Royal College of Physicians of Edinburgh
16. UK Newborn Screening Laboratories Network
17. British Association for the Study of the Liver
18. The British Liver Trust

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19. Children's Liver Trust

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UK National Screening Committee (UK NSC)

Screening for tyrosinaemia

Consultation comments pro-forma

Name:	Jak Swain
Email address:	xxxx xxxx
Organisation (if appropriate):	Metabolic Support UK
Role:	Policy & Advocacy Manager

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

Yes

Section and / or page number	Text or issue to which comments relate	Comment
Incidence in the UK	Overall incidence Incidence by ethnic sub populations	In terms of incidence of the condition in the UK, we would prefer the data to be more recent than 2014 but we do not have any evidence to add to this. It was noted in this section that the incidence is unevenly distributed amongst ethnic sub populations in the UK. We are aware of a higher incidence of TYR1 in the Pakistani population in the West Midlands 1

		1.Angileri, Francesca et al. “Geographical and Ethnic Distribution of Mutations of the Fumarylacetoacetate Hydrolase Gene in Hereditary Tyrosinemia Type 1.” *JIMD reports* vol. 19 (2015): 43-58. https://doi.org/10.1007/8904_2014_363
Impact of early diagnosis		Tyrosinaemia type 1 (TYR1) is a devastating condition where diagnosis as soon as possible after birth is essential to the positive outcomes of the person with the condition. Case studies demonstrate the impact of receiving the diagnosis following the onset of symptoms, rather than at birth. One family describes their anguish at wishing that the illness was spotted at an earlier stage given they could have prevented the elevated tyrosine levels and liver problems that this child had developed by the time the diagnosis was received. A mother of a child with TYR1 states “our wish is that our kids live a normal healthy life, even if that means shortening mine”. A further parent described her child’s diagnosis at 3 months of age as “a very lonely experience” with her child displaying symptoms one week after birth including nose bleeds, failure to thrive, and a distended stomach with secondary ascites”. From our long-standing experience of speaking with families, we know that the route to diagnosis can be challenging and that from the child being sent home for the first time since birth there is a parental instinct that something is “not quite right”, initiating numerous consultations with healthcare professionals to try and gain answers which puts an enormous stress, anxiety, and burden on new parents.

Treatment		Since the last review in 2017, further research has emerged which demonstrates how early diagnosis is essential to the onset of treatment, with nitisinone being essential in allowing those with TYR1 to live life to their fullest. Research demonstrates that the occurrence of liver transplantation or death is more frequent the later that nitisinone treatment was initiated and that most patients are reported to have good overall clinical condition throughout this treatment[1]. Research also indicates how nitisinone has completely changed the clinical course of patients suffering from TYR1 who used to die in the first few months to years of life from liver failure, renal dysfunction, and/or hepatocellular carcinoma (HCC). It is recommended that nitisinone therapy is started as early in life as possible to avoid the emergence of symptoms and that beginning treatment in the new-born period is ideal[2] Families describe how the nitisinone treatment is of low burden and easy to administer and with accompanying dietary management and supplementation this contributes to good outcomes. The diet itself can be burdensome, however an earlier diagnosis improves the adherence to this and enables metabolic dietitians to work with parents and family members as part of existing clinical practice to develop confidence and the skills needed to manage this and to provide long-term support. This early intervention helps to instil a positive culture regarding the dietary treatment and offers early access to peer support networks and

		ongoing dietary support from patient organisations with in-depth knowledge of both specialist and non-specialist low protein foods. 1. *Ute Spiekerkoetter, Maria L Couce, Anibh M Das, Corinne de Laet, Carlo Dionisi-Vici, Allan M Lund, Manuel Schiff, Marco Spada, Erik Sparve, Johan Szamosi, Roshni Vara, Mattias Rudebeck,* ***Long-term safety and outcomes in hereditary tyrosinaemia type 1 with nitisinone treatment: a 15-year non-interventional, multicentre study***, *The Lancet Diabetes & Endocrinology, Volume 9, Issue 7, 2021, Pages 427-435, ISSN 2213-8587,* *https://doi.org/10.1016/S2213-8587(21)00092-9 .* *(https://www.sciencedirect.com/science/article/pii/S2213858721000929)* *2.* Das A. M. (2017). Clinical utility of nitisinone for the treatment of hereditary tyrosinemia type-1 (HT-1). The application of clinical genetics, 10, 43–48. https://doi.org/10.2147/TACG.S113310 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5533484/

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Recommendations		Overall, we agree with the recommendation provided that such a screening programme would do more good than harm and we would welcome a positive decision made of adding the condition to new-born screening.

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Name: xxxx xxxx
Email: consulation@rcpch.ac.uk
Organisation: Royal College of Paediatrics and Child health (RCPCH)
Role: Clinical Guidelines Manager

Condition: Tyrosinaemia

Response from the Paediatric metabolic medicine

The CSAC's overall view is supportive of screening for Tyrosinaemia Type 1 and welcomes the review and outputs of the workshop that conclude that screening "would do more good than harm". Whilst the ICER does appear high, in the context of treatments for rare diseases these costs per patient are in our view acceptable and comparable to other high cost interventions for ultra-rare diseases

No specific disagreements or inconsistencies noted.

We note that the evidence review suggests that 7 patients are diagnosed with Tyrosinaemia each year in the UK, of which 3 are found by sibling screening, 1 by incidental PKU screening and 3 present clinically by 6m age. The evidence

review discusses that these later diagnosed patients have higher incidence of kidney and liver disease and may require transplantation. We would like to point out that these later diagnosed (including later presenting) patients are in fact the ones at most risk of hepatocellular carcinoma even with Nitisinone treatment and this is the main reason for requiring transplantation – not just failure to respond to nitisinone. Not all patients with advanced cancer get to transplant – there have been children who have died from liver cancers and this should be considered a preventable situation by newborn screening which would get all these children onto nitisinone within a month of age and no child treated so early with nitisinone has yet developed cancer. This may be well be in the evidence review though.

We would also like to ensure that the review committee understands that nitisinone is now available generically in the UK which would not have been the case at the time of the previous evidence review therefore some of the additional cost of screening for Tyrosinaemia type 1 will be offset by the reduced lifelong cost of nitisinone therapy now.

No amendments suggested

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UK National Screening Committee (UK NSC)

Screening for tyrosinaemia

Consultation comments pro-forma

Name:	Jane Hartley
Email address:	xxxx xxxx
Organisation (if appropriate):	BASL
Role:	**Consultant hepatologist**

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

Yes

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 11	Cirrhosis and liver cancer develop needing transplant	Transplant may be needed for those when the initially present as they sometimes have a very severe presentation. In this case it is not the development of cancer that is determining the need for transplant. Incidentally in those patients who need a rapid transplant there can be a previously undetected cancer in the liver.

Page 79	Other healthcare professionals	In those presenting later cardiac disease may also occur which does improve with time / treatment but will require cardiology input with ECHO and ECH and Consultant time
Pahe 80	Liver transplant -	Need tofactor in not just stopping treatment and diet but long term immunosuppressive drugs and long term liver follow up

UK National Screening Committee

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Name: xxxx xxxx
Email: xxxx xxxx
Organisation: Royal College of General Practitoners
Role: Clinical Policy Officer

Condition: Tyrosinaemia

The RCGP is supportive of the decision not to screen for tyrosinaemia.

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Name:	Sophie Peet
Email address:	xxxx xxxx
Organisation (if appropriate):	Genetic Alliance UK
Role:	Policy Analyst

UK National Screening Committee

Do you consent to your name being published on the UK NSC website alongside your response? Yes		
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		We welcome the modelling approach the UKNSC has used, we believe this is a useful and promising methodology.
p13	'that such a programme would do more good than harm to babies…'	We welcome the outcome 'that such a programme would do more good than harm to babies'. We see this as a central conclusion and would like to see this programme move forward and begin to address the barriers to delivery.
p12 p13	'The model is more certain that the ICER will be lower than £100,000' …but the cost of doing so was high by comparison with NICE thresholds'	The NICE HST appraisal considers ICER values between £100,000 and £300,00 a reasonable cost for rare conditions with significant QALY gain. Therefore, given that the model consistently estimates the ICER to be below £100,000, after 10,000 recalculations, it is not a high cost in comparison with NICE thresholds.

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p3 p11	‘this would improve the quality of life for people with TYR1, but early treatment may also increase the likelihood of learning difficulties’ ‘In the model it was assumed that learning difficulties were more likely in those babies treated early with nitisinone compared to those treated later after symptoms developed. Because newborn screening meant more babies with TYR1 were being treated earlier, this also led to an increase in the number of babies experiencing learning difficulties.’	The model clearly states its uncertainty around the cause of learning disabilities and the text implies early treatment causes learning disabilities. Nitisinone is currently used to treat other conditions, such as AKU, and we are not aware of learning disability side effects. If we identify babies with TYR1 earlier individuals can choose a treatment course. If we carry out a TYR1 screening programme we can gather clinical information that will refine the point at which nitisinone is delivered and better understand the relative dosing i.e with current levels of knowledge, screening will allow us to resolve uncertainties.
General		Up to 15 other EU countries currently screen for TYR1 and we would like to understand to what level the UKNSC has sought evidence of the value and cost effectiveness of their screening programmes for TYR1.