UK National Screening Committee

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Newborn Screening for Tyrosinaemia Type 1

Aim

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

Current Recommendation

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

The modelling project was undertaken by University of Warwick. The resulting model was received and discussed by the FMCH at several meetings and by the June 2022 UK NSC meeting.

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 compared with current practice. The model estimated that screening would not reduce mortality from tyrosinaemia type 1.

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. 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.

The UK NSC requested further analysis of the cost effectiveness evaluation with a view to making a recommendation at its next meeting (November 2022).

In the absence of specific guidance on cost effectiveness thresholds for screening or the use of modifiers in the presence of high ICERs, there was concern that approving newborn screening for tyrosinaemia may set a precedent across the range of conditions within the Committee's remit. Related to this, there was concern about

the opportunity cost which may be associated with the addition of this condition to the UK newborn screening programme.

Further analysis of the model was therefore requested to explore a number of options which might help the UK NSC discussion. A number of approaches were suggested following the meeting and these have been implemented by the Warwick University team. These are described and summarised in the appendix to this covernote.

Results of additional modelling

The most pronounced effect on the ICER was associated with reductions in the rate of liver transplantation in clinically presenting cases in the model. This was implemented with reference to the recent paper by Spiekerkoetter et al. The scenario analyses in which these rates were applied resulted in ICERs close to £20,000. This was because, compared to the model's base case, a reduction in the rate of liver transplantation in clinically presenting tyrosinaemia i) reduced the cost difference between the current practice and the screening arms and ii) slightly increased the QALY difference between the two arms.

The FMCH discussed the additional modelling and continue to advise that the UK NSC should recommend screening for this condition.

Summary

Newborn screening for tyrosinaemia has been considered very closely through a modelling exercise informed by an expert group. This has been through a public consultation in line with the UK NSC review process and stakeholders indicated their support for screening.

The original model suggested that there would be a limited clinical gain from screening compared to current practice. In particular, the model estimated that there would be no reduction in mortality. The main gains were associated with the avoidance of liver disease in the first months of life and avoidance of liver transplantation.

The base case ICER associated with these gains was considered to be both high and uncertain. New evidence on the long term effect of nitisinone treatment, submitted as part of the consultation, was used to inform the construction of additional scenarios. These resulted in ICERs which were much closer to £20,000.

These scenarios and the data informing them have not been incorporated into the model. This would require significant changes to the model which could not be achieved in the timescale. This means that the impact on the base case estimate and the overall conclusion of the original evaluation cannot be gauged. However the

analyses broaden the range of ICERs compared to the original model. They also change the discussion about the potential clinical gains of screening.

The lower ICERs are associated with scenarios in which there is a less pronounced difference between screening and current practice in terms of reduction of liver transplantation. In these scenarios the main gain of screening is limited to avoidance of liver disease in the early months of life with little impact on the longer term outcome.

Conversely, the higher ICERs are associated with scenarios in which the main gains of screening combine avoidance of liver disease in the early months of life and avoidance of liver transplantation at a later point.

Potential justifications for the higher ICER were discussed at the recent FMCH meeting and in the public consultation:

- the FMCH considered that, although liver transplantation is considered curative, it is usually undertaken as a result of severe deterioration of health which can be protracted. The intervention requires ongoing monitoring and care and can also result in complications. Avoidance of this was considered an important outcome from a clinical perspective
- in the public consultation stakeholders suggested that the UK NSC should use the same threshold for screening for tyrosinaemia as NICE apply in highly specialised technology assessments. It was also suggested that decision modifiers such as uncaptured benefits in patients and carers should be considered. Another suggestion was that screening may address a health inequality as the prevalence of tyrosinaemia is thought to be higher in the Pakistani population compared to other populations

In terms of the Committee's concerns about setting a precedent and opportunity cost, it might be noted that the absolute cost of screening in the model is low in the context of healthcare expenditure as a whole. However, tyrosinaemia is one candidate for newborn screening among many. The gains of screening for other conditions may be similarly limited and / or difficult to quantify. There is therefore a risk that increasing the number of conditions on the screening panel may unreasonably increase the opportunity cost to the detriment of life saving interventions elsewhere.

This highlights the importance of careful consideration of the benefits and harms of candidate conditions for newborn screening, the need for guidance on cost effectiveness in screening and for dialogue with stakeholders about the selection of conditions for the screening panel.

Proposed recommendation

It is proposed that:

- 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 this should include the place of opportunity cost in the decision making process
- 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

Action

The UK NSC is asked to consider and approve the proposed recommendation.

UK National Screening Committee

APPENDIX

Cost-effectiveness of newborn blood spot screening for Tyrosinaemia type 1 using tandem mass spectrometry – Additional scenario analyses August 2022

This report was prepared by Peter Auguste and Sian Taylor-Phillips, with significant input on specific sections from John Marshall, Chris Hyde and David Elliman.

Summary

Additional scenario analyses were undertaken in the evaluation of cost-effectiveness of screening for Tyrosinemia Type 1 with SUAC. Reducing the costs of the Nitisinone treatment or the Succinylacetone (SUAC) test were not found to be viable strategies to achieve cost-effectiveness at a threshold of £20k to £30k per quality adjusted life year (QALY). Reducing the discount rate for health benefits to 1.5% reduced the cost per QALY to £40,600. Reducing the rate of liver transplant in symptomatically detected people with liver disease using data from Spiekerkoetter et al. was highly influential on cost effectiveness, giving estimates of £19,600 and £22,400 per QALY. However, these estimates are likely to be optimistic due to differences between the metrics reported in the paper and those required in the model.

Background

Several additional scenario analyses were suggested at the UK National Screening Committee in June 2022. To meet the rapid turnaround required for initial results we have undertaken some preliminary analyses. In this document we report preliminary results for the four of the proposed scenario analyses. The four chosen were those for which data were immediately available.

Methods

The rationale and methods for each scenario analysis are as follows:

- To determine whether negotiating a discount to the price of Nitisinone with manufacturers would reduce the cost per QALY, we reduced the cost of Nitisinone until the overall cost/QALY of SUAC screening was £20,000 (and repeated for £30,000)
- To determine whether procuring a cheaper SUAC test would reduce the cost per QALY to under £30,000, we reduced the cost of testing in the SUAC screening arm from 60p more than the current practice arm, to costing no more than the current practice arm.
- To determine whether incorporating new data from a recent registry study by Spiekerkoetter et al., 2021 affects cost effectiveness, we used that paper to replace the incidence of liver transplantation in people who were symptomatically detected and have liver disease in the model. The paper reported transplantation incidences which were lower than those used in the model from a registry study sample which was much larger than the

papers used in the original model. These incidences were derived from data from two phases of the registry's operation undertaken in analyses of two datasets. The first, 'complete set', combined cases from the period 2005 – 2013 (when the registry operated as a post marketing surveillance programme) and 2013 – 2019 (when the registry operated as a formal observational safety study). This dataset excluded cases who stopped nitisinone treatment in the first phase due to death, transplantation or who withdrew for other reasons which were unstated. To compensate for potential under-reporting of death and transplantation in this set the study constructed a second, 'extended', dataset which included the complete set plus the excluded deaths and transplanted cases.

However, Spiekerkoetter et al. do not report the incidence of liver transplantation in people who are symptomatically detected and have liver disease. Instead, they report the incidence of liver transplantation in people with Tyrosinemia Type 1 who have received Nitisinone treatment initiated at different ages. These treatment groups are, <28 days, ≥28 days to <6 months, ≥6 months to <12 months, >12 months. We used the subset initiating Nitisinone treatment ≥28 days to <6 months as a proxy for the cases presenting symptomatically with liver disease in the model. The study's treatment group consisted of people who were detected through neonatal screening and people who were detected following symptomatic presentation.

However, route to diagnosis was not reported in 36% of the cohort and neither 'neonatal screening' or 'clinical detection' were clearly defined in the paper. For example, 20% of the whole cohort were reported to be detected by neonatal screening but the proportion of those detected through this route was not reported for any of the treatment groups. 'Neonatal screening' could include both cascade testing in the presence of a family history of tyrosinaemia, as in the McKiernan study from the UK, and SUAC based population screening. Therefore, a proportion of babies starting treatment ≥28 days to <6 months were detected presymptomatically. In terms of the symptomatically presenting cases, although liver disease is the most common presenting feature in tyrosinaemia, there is uncertainty whether this applies to all the clinically detected cases in the treatment group.

In addition to these two reporting limitations, death and transplantation were reported as a composite outcome. However no deaths occurred in the ≥28 days to <6 months treatment group in either dataset. This scenario analysis is therefore likely to overestimate cost effectiveness of SUAC population screening because it is likely to underestimate the incidence of liver transplant in symptomatically presenting tyrosinaemia , and liver transplant significantly reduces costs through no ongoing requirement for Nitisinone treatment.

Because of the reporting uncertainties, it is not possible to quantify the magnitude of this overestimation. Spierkerkoetter et all report 4 (4% of the ≥28 days to <6 months treatment group) events of death or liver transplant in the 'complete set' and 6 (6% of the ≥28 days to <6 months treatment group) in the 'extended set'. We undertook scenario analyses for both values to account for the uncertainty surrounding the characteristics of the treatment group. The extended set may be more appropriate because liver transplant was a reason to exclude from the complete set, and the extended set added back in those who died or had liver transplant but did not add back in people excluded for other reasons. Finally, person years of

follow up is only reported for the complete set (1174.1 person years), so we assumed follow up time was the same in the extended set (this will be an underestimate due to missing follow up time in the extra people in the extended set).

- We explored the effect of discounting on health benefits because the extension of life could be considerable, and so highly sensitive to the rate of discounting used. There is precedent on the importance of doing this from NICE's interim guidance on Highly Specialised Technologies where the issue of prolonged extension of life also occurs. They specifically suggest 1.5% per annum as the alternative discount rate. So we discounted costs at 3.5% and health benefits at only 1.5%

We also undertook further exploration of whether introducing SUAC screening would reduce the number of false positive results from the current PKU screening.

Results

Descriptions of the four scenario analyses undertaken are given in table 1, with further details in appendix 1.

Table 1: Scenario analyses undertaken based on changes to model inputs

Scenario analysis	Original value	New value	Scenario analysis result
1. Further discount to the cost of nitisinone treatment to see at what discount to nitisinone would the ICER reach £20,000 and £30,000 per QALY.	Up to £50,526 per year dependent on age and sex (detailed in table 13 on page 40 of original report).	90% discount to reach lower threshold. 70% discount to reach upper threshold	£19,800 per QALY £29,200 per QALY
2. At what cost (if any) to the MS/MS screening test would see the ICER reach £20,000 per QALY and £30,000 per QALY	Overall cost was £3.30, which is 60p more expensive than current screening protocols.	Assumed the same cost of £2.70 as the comparator.	£45,100 per QALY
3. Rate of liver transplants in cases with liver disease for symptomatically detected cases	4-month transition probability (0.012) 6-month transition probability (0.018) McKiernan et al.	'Complete set' data 4-month transition probability (0.0011) 6-month transition probability (0.0017) 'extended set' data 4-month transition probability (0.0017) 6-month transition probability (0.0026)	£19,600 per QALY £22,400 per QALY

		Proxy derived from Spiekerkoetter et al., 2021. This will give an overly optimistic cost per QALY, see methods.	
4. Discount rates of 3.5% and 1.5% applied to costs and health benefits, respectively	3.5% applied to both costs and benefits	Discounting future costs and benefits by 3.5% and 1.5%, respectively	£40,600 per QALY

Further exploration of English data indicated that there were 15 uncertain results from PKU screening in 2020-2021 (see appendix 2), which received further testing for a range of conditions including Tyrosinemia Type 1. Of these 4 had normal phenylalanine on repeating the assay in duplicate, but abnormal tyrosine so would be tested for potential Tyrosinemia type 1 and other conditions. Therefore, if SUAC screening were introduced, the removal of testing for Tyrosine in babies with normal phenylalanine could result in, at most, four fewer false positives in the PKU pathway. However, the clinical and laboratory advisors indicated uncertainty about the acceptability of such a change.

Discussion

The largest impact on cost effectiveness is from changing the rate of liver transplant in symptomatically detected cases. This is because the model (based on clinical advice) assumes that there is no requirement for Nitisinone after liver transplant. This reduces costs in the current practice arm through detecting Tyrosinemia later when liver transplant is required, therefore removing the requirement for lifetime Nitisinone treatment, but through the child becoming ill enough to require liver transplant. This makes the SUAC screening arm more costly, and less cost-effective, through avoidance of liver transplant in screen detected cases, and subsequent cost of lifetime Nitisinone treatment. So here early detection significantly increases overall treatment costs through cost of a drug given for rare diseases, and that drives the high cost per QALY. In this circumstance it may be worth considering what the appropriate cost-effectiveness threshold may be, and how this unusual mechanism of action affects decision-making.

The Spiekerkoetter paper was not considered for inclusion in the original model due to its date of publication after the search dates. We have not undertaken formal quality appraisal, but it is a large retrospective and prospective cohort, with manufacturer involvement in conduct and authorship. The major limitation is the format of results does not fit into the current model structure well. Most importantly Spiekerkoetter report incidence of liver transplant in people with Tyrosinemia Type 1 detected between 28 days and 6 months taking Nitisinone, and we have assumed in this new scenario analysis that this is equivalent to incidence of liver transplant in symptomatically detected people with Tyrosinemia Type 1 who already have liver disease. This will clearly overestimate cost-effectiveness due to the different denominator (here we are applying an estimated incidence of liver transplant in people with Tyrosinemia to people with Tyrosinemia and liver disease, so the incidence will be an underestimate.) This scenario analysis does clearly highlight the mechanisms driving cost

effectiveness as described above, and the dependence of the cost effectiveness on difference in the incidence of liver transplant between arms.

UK National Screening Committee

References

McKiernan P (2017) Liver Transplantation for Hereditary Tyrosinaemia Type 1 in the United Kingdom. Advances in Experimental Medicine & Biology 959, 85-91.

Spiekerkoetter, Ute, 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 9.7 (2021): 427-435.

UK National Screening Committee

Appendix 1: More details of scenario analysis results

Table A1 shows the results of the additional scenario using in a hypothetical UK cohort of 100,000 live-born babies considering all costs related to TYR1 detection, treatment and management in relation to the expected QALYs.

Table A1: Summary of the additional scenario analyses. Results based costs and measures of effect in QALYs in 100,000 live births

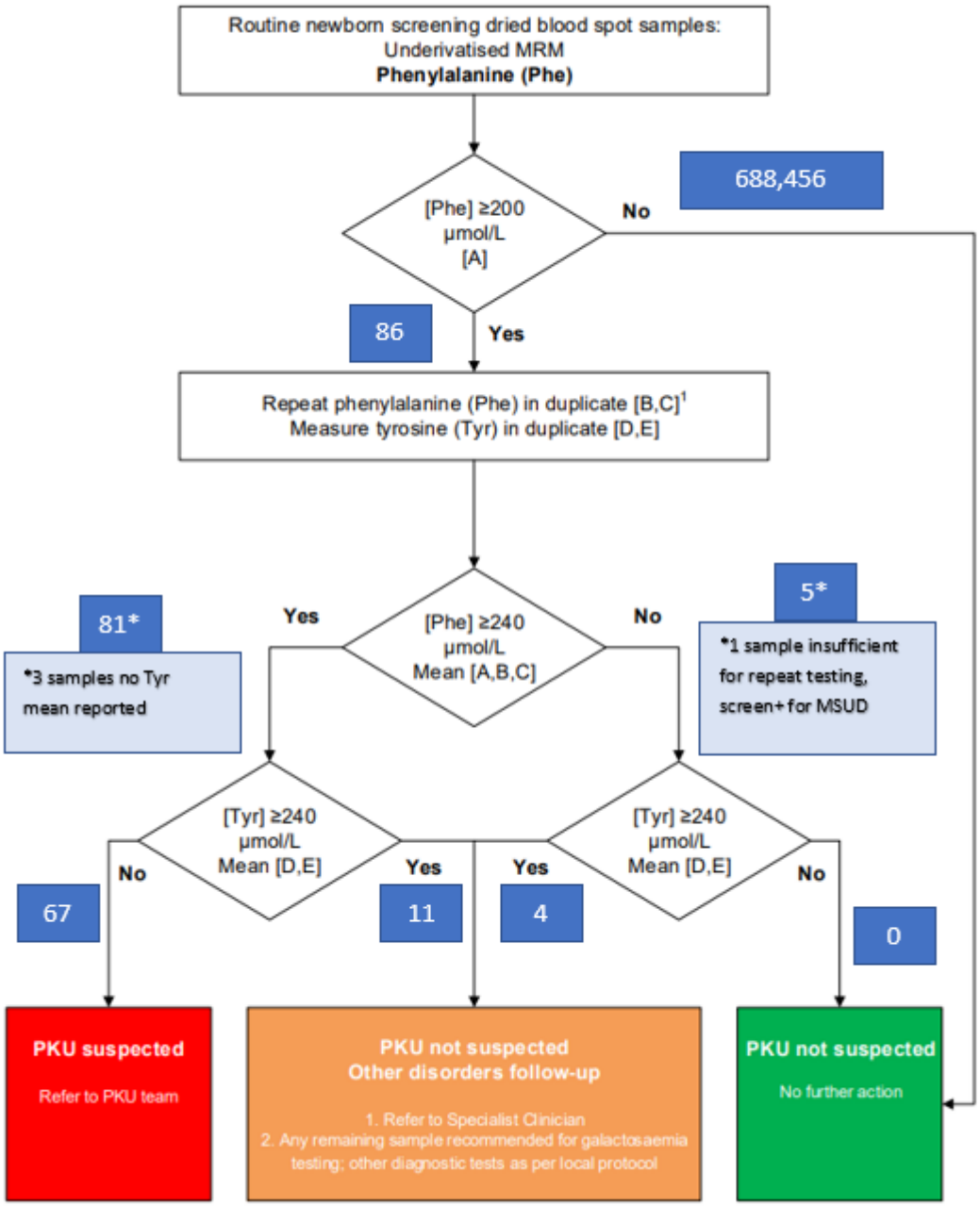
Screening strategy	Expected total costs (£)[a]	Incremental costs (£)[a]	Expected QALYs discounted	Incremental QALYs [a]	ICER (£) per QALY gained
Base-case results					
No universal screening for TYR1	1,831,475	-	26.67386	-	-
Universal screening for TYR1	2,045,569	214,094	26.67390	3.5	61,756
90% discount applied to nitisinone					
No universal screening for TYR1	704,049	-	26.67386	-	-
Universal screening for TYR1	774,067	70,018	26.67390	3.5	20,000
Cost of MS/MS screening test is £2.70					
No universal screening for TYR1	1,831,475	-	26.67386	-	-
Universal screening for TYR1	1,987,669	156,194	26.67389	3.5	45,054
Liver transplant transition probability (4 liver transplants per 1174.1 patient years)					
No universal screening for TYR1	2,192,174	-	26.67383	-	-
Universal screening for TYR1	2,282,721	90,547	26.67388	4.5	19,610
Liver transplant transition probability (6 liver transplants per 1174.1 patient years)					
No universal screening for TYR1	2,160,900	-	26.67383	-	-
Universal screening for TYR1	2,262,231	101,331	26.67388	4.5	22,440
Discount: 3.5% to costs and 1.5% to benefits					
No universal screening for TYR1	1,831,475	-	44.3180	-	-
Universal screening for TYR1	2,045,569	214,094	44.3181	5.3	40,642

[a] Values have been multiplied by 100,000
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life-years; TYR1, tyrosinaemia type 1

UK National Screening Committee

Appendix 2: False positive results from PKU screening

Figure A1: Flowchart of results from PKU screening in United Kingdom in 2020-2021, source: David Elliman personal communication. Data collected from UK screening labs and flow chart constructed by Tessa Morgan



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