| | |
|---|---|
| **Title:** Decision to introduce a national screening programme for Hereditary Tyrosinaemia type 1 in the New-born Blood Spot (NBS) screening programme.<br>**IA No:**<br>**RPC Reference No:**<br>**Lead department or agency:**<br>**Other departments or agencies:** | **Impact Assessment (IA)**<br>**Date:** 12/02/2024<br>**Stage:** Development/Options<br>**Source of intervention:** Domestic<br>**Type of measure:** Primary legislation<br>**Contact for enquiries:** uknsc@dhsc.gov.uk |

## Summary: Intervention and Options

**RPC Opinion:** RPC Opinion Status

| Cost of Preferred (or more likely) Option | | | |
|---|---|---|---|
| **Total Net Present Social Value** | **Business Net Present Value** | **Net cost to business per year** | **Business Impact Target Status** |
| - £4.4m | NA | NA | Qualifying provision |

**What is the problem under consideration? Why is government action or intervention necessary?**

Hereditary Tyrosinaemia type 1 (HT1) is a rare genetic condition that affects approximately seven babies in the UK per year. Left untreated HT1 can lead to severe complications such as liver, kidneys, and nervous system damage, and in some cases requires liver transplant. There is no cure for HT1 however treatment can help prolong life. The UK National Screening Committee (NSC) recommends screening for HT1 due to the clinical benefit of early detection, diagnosis, and treatment of HT1 in new-borns immediately following confirmation of diagnosis.

This IA sets out economic analysis to inform the decision on whether to introduce screening for HT1 in the New-born Blood Spot screening programme, and whether to use lab developed or commercial assays as the screening approach. In addition to health benefits, implementing HT1 screening and adopting the commercial test kits also modernises the testing process in England and enhances the harmonisation of results between labs to reduce variation. The cost of modernising labs could be shared across related diagnostic tests in future, if the UK NSC recommends any other conditions covered by this test for screening.

**What are the policy objectives of the action or intervention and the intended effects?**

The objective is to identify and as a result begin treatment for individuals with HT1 at an earlier stage of life for all cases, through national screening for HT1. This will avert cases with severe symptoms such as liver, kidneys, and nervous system damage, which can result in liver transplant, and hospitalisations.

**What policy options have been considered, including any alternatives to regulation? Please justify preferred option (further details in Evidence Base)**

Option 0: Do nothing - no introduction of a national screening programme for HT1. Some cases will be detected through incidental or genetic screening. Additional cases will be identified by clinicians at a later stage in the condition where symptoms may be more severe.

Option 1: Introduce a national screening programme for HT1 in the New-born Blood Spot (NBS) screening programme as part of the day 5 New-born Blood Spot (NBS) test. NBS screening programme laboratories to continue with current practice and predominantly use lab-developed assays.

**Option 2 (preferred):** Introduce a national screening programme for HT1 in the New-born Blood Spot (NBS) screening programme as part of the blood spot test. All NBS screening programme laboratories to adopt a commercially available assay.

**Will the policy be reviewed?** It will be reviewed. **If applicable, set review date:** Month/Year

| | | | | |
|---|---|---|---|---|
| Is this measure likely to impact on international trade and investment? | | No | | |
| Are any of these organisations in scope? | **Micro** No | **Small** No | **Medium** No | **Large** Yes |
| What is the $CO_2$ equivalent change in greenhouse gas emissions? (Million tonnes $CO_2$ equivalent) | | **Traded:** NA | **Non-traded:** NA | |

***I have read the Impact Assessment and I am satisfied that, given the available evidence, it represents a reasonable view of the likely costs, benefits and impact of the leading options.***

Signed by the responsible SELECT SIGNATORY: ..... Date: 28/2/24

# Summary: Analysis & Evidence

Policy Option 0

**Description:**

**FULL ECONOMIC ASSESSMENT**

| **Price Base Year** 2023 | **PV Base Year** 2023 | **Time Period:** One year cohort with impacts assessed over their lifetime | **Net Benefit (Present Value (PV)) (£m)** | | |
|---|---|---|---|---|---|
| | | | **Low:** NA | **High:** NA | **Best Estimate:** 0 |

| **COSTS (£m)** | **Total Transition** (Constant Price) Years | | **Average Annual** (excl. Transition) (Constant Price) | **Total Cost** (Present Value) |
|---|---|---|---|---|
| **Low** | NA | | NA | NA |
| **High** | NA | | NA | NA |
| **Best Estimate** | 0 | | 0 | 0 |

**Description and scale of key monetised costs by 'main affected groups'**

Option 0 is modelled to have no monetised costs as it represents the "do nothing" option and would not require any specific action.

**Other key non-monetised costs by 'main affected groups'**

In practice the "costs" of this option relate to cases of HT1 that are symptomatically detected at a later stage in the condition where symptoms may be more severe and could be measured in terms of the costs to the NHS of treatment. These costs correspond to the cost savings in the other options.

| **BENEFITS (£m)** | **Total Transition** (Constant Price) Years | | **Average Annual** (excl. Transition) (Constant Price) | **Total Benefit** (Present Value) |
|---|---|---|---|---|
| **Low** | NA | | NA | NA |
| **High** | NA | | NA | NA |
| **Best Estimate** | 0 | | 0 | 0 |

**Description and scale of key monetised benefits by 'main affected groups'**

The "benefit" of Option 0 is cost savings from not introducing a national screening programme. This benefit is seen in the corresponding costs for screening for other options.

**Other key non-monetised benefits by 'main affected groups'**

Option 0 has no non-monetised benefits.

| **Discount rate (%)** | Costs: 3.5%<br>Benefits: 1.5% |
|---|---|

**Key assumptions/sensitivities/risks**

Continuing with current practise and not introducing national screening for HT1 will mean that babies with HT1 may be incidentally detected as a result of screening for phenylketonuria (PKU) or by genetic testing for new-borns with siblings living with HT1. This will likely identify around 4 babies per year.

Additional cases will be identified by clinicians at a later stage in the condition where symptoms may be more severe, and liver disease and liver transplant are more likely. Identifying these cases earlier would reduce severe cases and liver transplant instances.

There is also value to reducing uncertainty through diagnostics. A national screening programme would identify asymptomatic cases, removing the period of uncertainty for families between the onset of symptoms and the diagnosis of HT1 and avoiding the delays before diagnosis when the child is ill and not receiving treatment.

**BUSINESS ASSESSMENT (Option 1)**

| **Direct impact on business (Equivalent Annual) £m:** | | | **Score for Business Impact Target (qualifying provisions only) £m:** |
|---|---|---|---|
| **Costs: NA** | **Benefits: NA** | **Net: NA** | Not Applicable |

# Summary: Analysis & Evidence

Policy Option 1

**Description:**

**FULL ECONOMIC ASSESSMENT**

| **Price Base Year** 2023 | **PV Base Year** 2023 | **Time Period Years:** One year cohort with impacts assessed over their lifetime | **Net Benefit (Present Value (PV)) (£m)** | | |
|---|---|---|---|---|---|
| | | | **Low:** NA | **High:** NA | **Best Estimate:** - £4.8m |

| **COSTS (£m)** | **Total Transition** (Constant Price) Years | **Average Annual** (excl. Transition) (Constant Price) | **Total Cost** (Present Value) |
|---|---|---|---|
| **Low** | NA | NA | NA |
| **High** | NA | NA | NA |
| **Best Estimate** | 0 | 0 | £6.9m |

**Description and scale of key monetised costs by 'main affected groups'**

The costs of screening using a lab developed assay (incl additional staff costs) is estimated to be [redacted] per annum. The net lifetime discounted cost of screening and treatment for one birth cohort is £6.9m. These costs are measured in opportunity cost terms, on the assumption that this is not new health funding for NHSE and will be met from current budgets and resources. HT1 is treated using Nitisinone immediately following diagnosis and continuing over a patient's lifetime, unless a liver transplant is provided (for advanced liver damage), in which case Nitisinone is stopped. The main costs are not the screening itself but the additional use of Nitisinone, which is an approved treatment for this use. Early detection and treatment reduce the likelihood of requiring a transplant. There is uncertainty regarding liver transplant rates due to HT1 being a rare condition with few cases. Screening will produce cost savings from a reduction in liver transplants but an increase in the use of Nitisinone, resulting in a net lifetime treatment cost of [redacted] per additional case diagnosed through screening.

**Other key non-monetised costs by 'main affected groups'**

| **BENEFITS (£m)** | **Total Transition** (Constant Price) Years | **Average Annual** (excl. Transition) (Constant Price) | **Total Benefit** (Present Value) |
|---|---|---|---|
| **Low** | NA | NA | NA |
| **High** | NA | NA | NA |
| **Best Estimate** | NA | NA | £2.1m |

**Description and scale of key monetised benefits by 'main affected groups'**

The health benefits from one birth cohort are estimated to be 30 discounted QALYs, through the reduction in severe cases via early detection, based on the assumption that screening will detect 3 babies a year that would otherwise be symptomatically diagnosed at a later stage. It also includes the benefits of an ~88% reduction in the number of false positive results currently identified through PKU screening. The modelled health benefits are monetised at £2.1m based on the societal value of a QALY of £70,000.

**Other key non-monetised benefits by 'main affected groups'**

Only direct health benefits are quantified within the model produced by Auguste et al.

Non-monetised benefits include gains in future productivity due to better health outcomes, reduced impact on education in childhood and equity of access to treatments for very rare diseases. There will also be informal care costs and productivity impact on carers, out-of-pocket expenditures such as travel costs and over-the-counter medication for symptoms. Screening would also have the benefit of reducing uncertainty for families through asymptomatic diagnosis.

| **Key assumptions/sensitivities/risks** | **Discount rate (%)** | Costs: 3.5%, Benefits: 1.5% |
|---|---|---|

There is uncertainty around HT1 due to it being a rare disease, including the liver transplant rates and utility values for each health state, which presents challenges to quantifying the health benefits.

The cost of using a lab developed assay has significant uncertainty due to concerns on the viability of using lab tests, which will depend on the source of the internal standards used. There is also no lab developed test currently available to evaluate, as outlined in the main evidence base.

Risks include patent law, uncertainty regarding compliance with future In Vitro Diagnostic regulation (IVDR) requirements, and operational risks.

**BUSINESS ASSESSMENT (Option 2)**

| **Direct impact on business (Equivalent Annual) £m:** | | | **Score for Business Impact Target (qualifying provisions only) £m:** |
|---|---|---|---|
| **Costs: NA** | **Benefits: NA** | **Net: NA** | Not applicable |

# Summary: Analysis & Evidence

Policy Option 2

**Description:**

**FULL ECONOMIC ASSESSMENT**

| Price Base Year 2023 | PV Base Year 2023 | Time Period Years: One year cohort with impacts assessed over their lifetime | Net Benefit (Present Value (PV)) (£m) | | |
|---|---|---|---|---|---|
| | | | **Low:** NA | **High:** NA | **Best Estimate:** - £4.4m |

| COSTS (£m) | Total Transition (Constant Price) | Years | Average Annual (excl. Transition) (Constant Price) | Total Cost (Present Value) |
|---|---|---|---|---|
| **Low** | NA | | NA | NA |
| **High** | NA | | NA | NA |
| **Best Estimate** | 0 | | | £6.5m |

**Description and scale of key monetised costs by 'main affected groups'**

The costs of screening using a commercial assay is estimated to be [redacted] per annum. The net lifetime discounted cost of screening and treatment for one birth cohort is £6.5m. These costs are measured in opportunity cost terms, on the assumption that this is not new health funding for NHSE and will be met from current budgets and resources.

HT1 is treated using Nitisinone immediately following diagnosis and continuing over a patient's lifetime, unless a liver transplant is provided (for advanced liver damage), in which case Nitisinone is stopped. The main costs are not the screening itself but the additional use of Nitisinone, which is an approved treatment for this use. Early detection and treatment reduce the likelihood of requiring a transplant. Screening will produce cost savings from a reduction in liver transplants but an increase in patients receiving Nitisinone, resulting in a net lifetime treatment cost of [redacted] per additional case diagnosed through screening.

**Other key non-monetised costs by 'main affected groups'**

| BENEFITS (£m) | Total Transition (Constant Price) | Years | Average Annual (excl. Transition) (Constant Price) | Total Benefit (Present Value) |
|---|---|---|---|---|
| **Low** | NA | | NA | NA |
| **High** | NA | | NA | NA |
| **Best Estimate** | 0 | | NA | £2.1m |

**Description and scale of key monetised benefits by 'main affected groups'**

The health benefits from one birth cohort are estimated to be 30 discounted QALYs, through the reduction in severe cases via early detection, based on the assumption that screening will detect 3 babies a year that would otherwise be symptomatically diagnosed at a later stage. It also includes the benefits of an 88% reduction in the number of false positive results currently identified through PKU screening. The modelled health benefits are monetised at £2.1m based on the societal value of a QALY of £70,000.

**Other key non-monetised benefits by 'main affected groups'**

Only direct health benefits are quantified within the model produced by Auguste et al.

Non-monetised benefits include gains in future productivity due to better health outcomes, reduced impact on education in childhood and equity of access to treatments for very rare diseases. There will also be informal care costs and productivity impact on carers, out-of-pocket expenditures such as travel costs and over-the-counter medication for symptoms. Screening would also have the benefit of reducing uncertainty for families through asymptomatic diagnosis.

Wider societal benefits include modernising the testing process in England. The use of a commercial assay will enhance the harmonisation of results between labs and reduce lab to lab variation. The cost of modernising the NBS labs could be shared across related diagnostic tests in future if the UK NSC recommends any other conditions covered by this test for screening.

| Key assumptions/sensitivities/risks | Discount rate (%) | Costs: 3.5%, Benefits: 1.5% |
|---|---|---|

There is uncertainty around HT1 due to it being a rare disease, including the liver transplant rates and utility values for each health state, which presents challenges to quantifying the health benefits.

**BUSINESS ASSESSMENT (Option 3)**

| Direct impact on business (Equivalent Annual) £m: | | | Score for Business Impact Target (qualifying provisions only) £m: |
|---|---|---|---|
| **Costs: NA** | **Benefits: NA** | **Net: NA** | Not applicable |

## Summary

1. Hereditary Tyrosinaemia type 1 (HT1) is a rare genetic condition that affects 1 in 100,000 babies globally[1]. Left untreated, HT1 can lead to severe complications such as liver, kidneys, and nervous system damage, and may require liver transplant. There is no cure for HT1 however treatment, using a special diet and the drug Nitisinone, can help prolong life. Evidence is available and supports the clinical benefit of early detection and diagnosis of HT1 in new-borns to commence treatment of Nitisinone.

2. Auguste et al. conducted modelling in 2021[1] and 2022[2]. The base-case results showed that expanding the NBS programme to include screening for HT1 led to an increase in costs and benefits compared to the counterfactual of no HT1 screening. Auguste et al.[1], conducted sensitivity analyses including reducing the costs of treatment with the drug Nitisinone, reducing the costs of testing, and reducing the rate of liver transplants in symptomatically detected individuals with liver disease. This was presented to UK NSC and UK NSC recommended HT1 screening in 2022[2].

3. The net lifetime discounted cost of introducing national screening for HT1, for one birth cohort, is £1.4 million under the preferred option (Option 2). This includes [redacted] in screening programme costs, with the remaining [redacted] per birth cohort in net NHS treatment costs. Treatment costs include Nitisinone, diet, liver transplant costs and other follow up care such as blood, urine test and follow up appointments. The lifetime Social Net Present Value (SNPV) for the preferred option (Option 2) for one birth cohort is -£4.4m, after accounting for the opportunity cost value of the financial costs to the NHS.

4. Assessing the cost effectiveness of national HT1 screening is challenging because it would increase the duration of Nitisinone use, a very expensive drug that is available via highly specialised commissioning[3]. The additional use of Nitisinone treatment following earlier diagnosis through screening accounts for the majority of the cost of the screening programme. Nitisinone is currently approved by NICE. When first brought to market, Nitisinone was eligible for assessment under the NICE Highly Specialised Technologies (HST) programme, which applies a far higher cost-effectiveness threshold of £100,000 to service its aim of improving access to treatments for people with very rare diseases.

5. Only direct health benefits are quantified within the model. Wider non-monetised benefits include lifetime productivity, impact on parents, reduction in uncertainty through early diagnosis and lower probability of severe complications (such as liver transplants) later in life, and modernising the testing process. There is also the benefit of increasing equity in the treatment of this rare disease; screening would increase equity between those who currently are identified through genetic and incidental

[1] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[2] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)

[3] 7 Highly specialised technologies | NICE health technology evaluation topic selection: the manual | Guidance | NICE

screening strategies and those who are not detected through screening but later through symptomatic diagnosis, potentially resulting in worse health outcomes. There is a risk that the evaluation of HT1 screening will not sufficiently reflect society's preferences for how health spend is allocated. An additional ~£1.5 million in benefits per additional positive screen result is required for the programme to be a net societal benefit.

6. There is also uncertainty in the cost-effectiveness due to the nature of HT1 being a very rare disease and the resulting limitations in the available evidence, particularly regarding the liver transplant incidence rate. Sensitivity analysis using alternative transplant rate estimates from Spiekerkoetter et al[4], show HT1 screening to have net societal benefit.

7. In this IA, we report results according to HMT Green Book methodology[5]. We conclude that although the base case calculations suggest HT1 screening is not cost effective under HMT Green Book methodology, there are some plausible scenarios where HT1 screening is cost-effective; hence this uncertainty is an important consideration for decision-makers.

8. We also include an evaluation using NICE's Health Technology Appraisal (HTA) and Highly Specialised Technologies (HST) approach in the sensitivity analysis[6]. The estimated lifetime ICER is ~£60,900 per QALY gained, the ICER for the screening programme is above the £20,000 - £30,000 NICE HTA threshold, but below the NICE HST threshold of £100,000. HT1 universal screening is likely to attract the maximum severity modifier weighting of 1.7 as HT1 is a severe life-limiting condition in most cases when not diagnosed through existing screening and treated promptly. Applying this gives an ICER of ~£34,300, which is still above the £20,000 - £30,000 NICE HTA threshold.

9. It is anticipated that there will be several UK NSC recommendations in the coming years which could include screening for rare genetic diseases for high-cost treatments. The decision on HT1 screening could set an expectation for the evaluation of future screening programmes for rare diseases with expensive treatments facing similar challenges in assessing the cost effectiveness. All programmes should be judged on their individual impacts. The circumstances and conclusions here may or may not apply in similar cases. There is also a risk that, if HT1 screening is not introduced following the UK NSC recommendation, that this is perceived to be caused by inconsistencies between NICE and HMT Green Book evaluations and could decrease confidence in Government evaluation approaches.

[4] 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.

[5] The Green Book (publishing.service.gov.uk)

[6] NICE health technology evaluations: the manual

# Evidence Base

## Problem under consideration and rationale for intervention

### Screening for Hereditary Tyrosinaemia type 1

10. Hereditary Tyrosinaemia type 1 (HT1) is a rare genetic condition that affects 1 in 100,000 babies globally[7]. Around seven babies are born each year with HT1 in the UK. HT1 is one of three types of tyrosinemia affecting how tyrosine is processed by the body and prevents the body processing an amino acid called tyrosine found in many foods[8].

11. HT1 presents in two forms: Acute, characterised by early onset usually within the first months of life, and a Chronic form which is slower to develop. Left untreated, HT1 can lead to severe complications such as liver, kidneys, and nervous system damage before the age of ten years. There is no cure for HT1 however treatment, using a special diet and the drug Nitisinone, can help prolong life[9].

12. There is no national screening of new-borns for HT1 in the UK. Incidental detection of HT1 can happen as a result of screening for phenylketonuria (PKU)[10], which is another disease affecting amino-acid metabolism. Incidental screening identifies approximately 1 case per year. Additionally, new-borns with siblings living with HT1 are identified through genetic testing. Genetic testing identifies approximately 3 cases per year. The cases identified by PKU screening and genetic testing will immediately start treatment while asymptomatic following confirmatory diagnostic testing. Additional cases not detected through screening are usually identified by clinicians at a later stage in the condition where symptoms may be more severe. National screening of new-borns for HT1 would identify an additional 3 cases per year, or 7 cases per year in total, allowing these additional asymptomatic new-borns early access to treatment immediately following confirmation of diagnosis to reduce severe complications later in life.

13. The UK currently screens new-borns for nine other rare but serious conditions through the New-born Blood Spot (NBS)[11] at 5 days of age. These include Sickle cell disease, Cystic Fibrosis, and congenital hypothyroidism as well as six Inherited Metabolic Diseases (IMDs)[12]. HT1 would be the tenth condition and the seventh of which is an IMD.

14. Evidence is available and supports the clinical benefit of early detection and diagnosis of HT1 in new-borns. The main benefit to pre-symptomatic identification in babies is receiving Nitisinone and dietary management immediately following diagnosis to avoid liver disease and reduce the risk of needing a liver transplant, which has risks of

[7] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download
[8] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)
[9] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download
[10] Phenylketonuria - NHS (www.nhs.uk)
[11] New-born Blood Spot (NBS) screening data collection and performance analysis report 1 April 2018 to 31 March 2019 - GOV.UK (www.gov.uk)
[12] New-born Blood Spot (NBS) screening: programme handbook: 7. Conditions - GOV.UK (www.gov.uk)

complications and transplant availability, and the need for lifelong immunosuppressants.

## UK National Screening Committee (UK NSC) recommendation

15. The UK NSC provides independent scientific advice to the government regarding conditions that are suitable for a targeted or national screening approach[13]. As part of the process of making a recommendation for the implementation of a national screening programme, the UK NSC reviews the evidence put forward against a list of criteria appraising the viability, effectiveness, and appropriateness of a screening programme[14].

16. The UK NSC did not recommend new-born screening for HT1 in 2017 based on the evidence provided by a review carried out by the University of Warwick[15]. However, it made the recommendation to conduct modelling to evaluate the clinical and cost effectiveness of HT1 screening compared to current UK practice. The independent model brought together research, clinical evidence, and expert opinion to assess the impact and cost effectiveness of a national screening programme for HT1 in the NBS programme compared to current practice.

17. This work concluded that there was clinical benefit to a national screening programme for HT1, but in the base case scenario the cost of doing so was high in comparison to the National Institute for Health and Care Excellence (NICE) Health Technology Appraisal's (HTA) cost effectiveness thresholds[16]. The work also highlighted the gaps and uncertainty in the evidence base, primarily due to the rarity of the disease, particularly regarding the incidence of liver transplants in symptomatically detected cases. Sensitivity analysis using transplant probability rates derived from a study by Spiekerkoetter et al.[17], was then undertaken which concluded that HT1 screening could be cost effective under NICE's HTA methodology based on this study.

18. In November 2022, the UK NSC recommended the 4 nations implement Tyrosinaemia type 1 (HT1) screening into the existing New-born Blood Spot test (NBS), using tandem mass spectrometry measurements of succinyl acetone (SUAC)[18].

## New laboratory testing method for New-born screening

19. Currently laboratories in England that screen for Inherited Metabolic Diseases (IMDs) use a mixture of commercial and 'lab-developed' assays.

20. Expert advice from NHS England and UK new-born screening laboratories is that due to the complicated nature of the screening test for HT1, a commercial new-born screening assay may be required.

[13] GOV.UK. Role of the NSC (accessed 15 June 2023)
[14] NSC. Criteria for a targeted screening programme (accessed 5 July 2023)
[15] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)
[16] 7 Assessing cost effectiveness | The guidelines manual | Guidance | NICE
[17] 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.
[18] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)

21. Patent law together with uncertainty regarding future In Vitro Diagnostic Regulations (IVDR)[19], may prevent the use of laboratory developed tests for succinyl acetone needed to identity HT1. There are also increased staff costs associated with the use of a laboratory developed test which is likely to be significantly greater than when using a workflow optimised commercial option. The use of a commercial solution may also enhance the harmonisation of results between labs and reduce lab to lab variation.

22. To screen for HT1 will therefore require the NBS Screening Programme laboratories to change their current laboratory method. Tandem mass spectrometers will remain the equipment used but the reagents used will change.

23. Implementing HT1 screening and adopting the commercial test kits needed also brings the benefit of modernising the testing process in England. The initial investment in using commercial assays means that if the UK NSC recommends any other conditions covered by this test for screening, then the cost of implementing will be very low. New conditions simply need to be selected from the list of options when running the mass spectrometer and as most of them use the same reagent, this is all that is required. Kits can measure over 50 different analytes and conditions.

24. The cost of modernising the NBS labs could be shared across the overall programme or related diagnostic tests that may use commercial assays in the future, due to the risks and issues associated with continuing to use lab developed assays which may continue with future screening recommendations. There is also potential to recoup the additional costs if the NHS chooses to redesign the NBS lab services in the future. This is explored in the Sensitivity analysis.

25. Three commercially available assays are being scheduled for evaluation by NHS England in early 2024. These assays are readily available, already validated by the suppliers and should take 4 months to be evaluated.

**Rationale for intervention**

26. This IA estimates the costs and benefits of introducing a national screening programme for HT1, through either using lab developed testing or moving to use commercial assays.

27. A market for screening can exist in the private sector. Providing they have information on the disease risk and the cost and the benefits of screening, parents of new-borns could decide to privately take up HT1 screening. However, individuals are likely to under-estimate the benefits from screening due to it being a rare and genetic condition, or due to a lack of information on the condition and the risks and health impacts.

28. National screening of HT1 using the SUAC marker would identify fewer false positive results than current practise, reducing uncertainty in the diagnosis process and anxiety caused by false positive results.

[19] Regulating medical devices in the UK - GOV.UK (www.gov.uk)

29. Screening would increase equity in the treatment for HT1 between those who currently are identified through genetic and incidental screening strategies and those who are identified later through symptomatic diagnosis, resulting in worse health outcomes. There is evidence that society values providing greater parity in treatments for rare diseases, which could address inequality in the distribution of health[20].

30. Through early detection, screening will allow additional patients immediate access to treatment while asymptomatic. Therefore, screening may deliver benefits to health by preventing more severe symptoms later in life which may also be costly to the NHS such as liver transplants and other wider monetised and non-monetised impacts to the patient and their families.

31. There could therefore be a positive externality associated with screening by using less NHS resource in the future and enabling higher productivity due to screening reducing likelihood of liver transplants and improving health outcomes through early treatments.

32. These considerations – benefits under-estimation and the positive externalities of screening – suggest that screening for rare diseases should be treated as merit goods and that government should intervene to promote their use.

33. Another rationale for government provided screening programmes is social equity. Screening privately may be expensive and hence may not be accessible to the whole population. Coverage for New-born Blood Spot (NBS) screening in the UK was over 95% in 2018/19[21].

## Rationale and evidence to justify the level of analysis used in the IA (proportionality approach)

34. This IA appraises the costs, benefits, and risks of introducing national screening for HT1, as part of the New-born Blood Spot (NBS) screening programme.

35. Auguste et al. conducted modelling in 2021[22] and 2022[23]. The base-case results showed that expanding the NBS programme to include screening for HT1 led to an increase in costs and benefits compared to the counterfactual of no HT1 screening.

36. Auguste et al.[24], conducted sensitivity analyses including reducing the costs of treatment with the drug Nitisinone, reducing the costs of testing, and reducing the rate of liver transplants in symptomatically detected individuals with liver disease. This was presented to UK NSC and UK NSC recommended HT1 screening in 2022[25].

37. The analysis used the same evaluation methods as NICE Health Technology Appraisals (HTA). The results suggested significant uncertainty in whether screening

[20] Valuation of Treatment for Rare Diseases: A Systematic Literature Review of Societal Preference Studies, Dabbous et al., December 2022 Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies - PMC (nih.gov)

[21] Newborn blood spot screening data collection and performance analysis report 1 April 2018 to 31 March 2019 - GOV.UK (www.gov.uk)

[22] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[23] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)

[24] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[25] Tyrosinaemia - UK National Screening Committee (UK NSC) - GOV.UK (view-health-screening-recommendations.service.gov.uk)

would be cost effective under this evaluation framework. The largest impact on the cost effectiveness was reducing the rate of liver transplant in symptomatically detected cases using data from Spiekerkoetter et al.[26] However, there was uncertainty in the clinical evidence and literature on the rate of liver transplants due to HT1 being a rare condition with a small number of cases. There was also uncertainty in the costs for screening.

38. For this IA we ran new model scenarios which include several updated assumptions (particularly on screening costs), and we re-evaluate the screening programme using the HMT Green Book[27], while undertaking sensitivity analyses. More explanation can be found in the Sensitivity analysis section.

39. Further limitations and risks are outlined in Risks and assumptions.

## Description of options considered

40. The options considered are as follows:

    **Option 0: Do nothing.** No introduction of a national screening programme for HT1. New-borns with HT1 will either be identified through incidental detection, genetic testing due to having siblings with HT1, or identified by clinicians following the onset of symptoms at a later stage in the condition.

    **Option 1:** Introduce a national screening programme for HT1 in the New-born screening programme as part of the day 5 New-born Blood Spot (NBS) test. NBS Screening Programme laboratories to continue with current practise using lab-developed or commercial assays.

    **Option 2 (preferred):** Introduce a national screening programme for HT1 in the New-born screening programme as part of the day 5 New-born Blood Spot (NBS) test. All NBS Screening Programme laboratories to adopt a commercially available assay.

41. For all options, access to treatment (such as Nitisinone and diet) is made available to patients immediately following confirmation of HT1 diagnosis.

42. Modernisation of the NBS screening programme, by fully moving to use of commercially available assays in NBS screening labs would not likely be pursued on its own without HT1 screening.

### Risks: Option 1

43. Despite Option 1 allowing for the implementation of HT1 screening, there is a risk of significant delay, additional cost and that laboratory developed assays will not be viable.

44. Risks with option 1 include:

[26] 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

[27] The Green Book (publishing.service.gov.uk)

a. **Patent law.** Use of a laboratory developed assay may be present challenges in relation to patent law and subject to legal challenge if employed.

b. **Uncertainty regarding future IVDR requirements**. Use of a laboratory developed test may not be consistent with future IVDR requirements and may prevent the use of laboratory developed tests for succinyl acetone needed to identity HT1.

c. **Operational risks.** A laboratory developed test, if devised, would be significantly more demanding than the commercial solutions and may result in significant operational issues for NBS screening laboratories seeking to use such an assay.

d. **Harmonisation of results.** As a lab developed test would be unlikely to harmonise results between laboratories, this may make the adoption of a consistent national approach and implementation problematic.

e. **The increased staff costs.** It is expected that there will be an increase in staff costs associated with using lab developed assays. While difficult to quantify, at least 0.5 WTE person per laboratory would be required to utilise a laboratory developed assay for succinyl acetone.

f. **Supply risks.** There is potential for difficulties with production, supply and possible future withdrawal of products (these issues could also affect the components of commercial tests). However, this risk could be mitigated during the procurement process by seeking information on the supply chain.

45. Due to the risks raised, the UK NSC HT1 task force and oversight group decided to exclude this option in its test validation work.

46. Risks for Option 2 can be found in Risks and Assumptions.

## Policy objective

47. The intended outcome is to identify and treat individuals with HT1 at an earlier stage of life, to avert severe symptoms such as liver disease and reduce risk of liver transplants, and hospitalisations.

48. We can partially assess the outcomes of the intervention by monitoring individuals with HT1 and the rates of hospitalisations and deaths. It will also be recommended to monitor liver transplants, cancers related to the liver and neurodevelopmental cases. These results could inform future estimates of willingness to pay for national screening of HT1.

## Summary and preferred option with description of implementation plan

49. The preferred option (Option 2) is to introduce a national screening programme for HT1 in the New-born Blood Spot (NBS) screening programme as part of the blood spot test, where NBS screening laboratories will adopt the use of a suitable commercial assay if they have not already done so.

50. Three commercially available assays are being scheduled for evaluation by NHS England in early 2024. These assays are readily available, already validated by the suppliers and should take 4 months to be evaluated. These assays avoid the risks associated with Option 1.

51. NHS England will lead on the implementation of screening for HT1 within the existing NBS screening programme. NHS England will propose a go live date when they are confident the necessary IT changes to lab systems, child health systems and public and professional screening information has been produced and is available for use.

## Monetised and non-monetised costs and benefits of each option (including administrative burden)

### Cost effectiveness methodology

52. Screening provides health benefits in terms of improved quality of life, which is measured in terms of quality-adjusted life years (QALYs). One QALY represents one year of perfect health. By measuring the difference in the health and life expectancy for new-borns with and without the introduction of HT1 screening, we can estimate the QALYs gained from preventing morbidity and mortality.

53. Screening new-borns for HT1 will deliver financial savings due to averted treatment costs in the absence of severe illness that would have occurred without screening. However, screening also introduces costs through the earlier treatment of HT1 with Nitisinone (see below).

54. DHSC's standard approach to cost effectiveness uses a methodology and criteria that aligns with the HMT Green Book.

55. The UK NSC commissions cost effectiveness analysis as part of the evidence presented to their members when making screening recommendations. The framework they have typically used to date is the NICE HTA methodology, however they are not bound by any particular cost effectiveness methodology in their terms of reference. There are significant differences between the NICE HTA methodology and the HMT Green Book (Table 1); and by using a different methodology, there is always a possibility of reaching different cost-effectiveness conclusions.

56. HT1 is a very rare disease and treatment includes the drug Nitisinone, which is available on the NHS to any person with HT1 via the NHS's highly specialised commissioning (HSC) route. Treatment with Nitisinone has a high cost - the average cost for a male is ~£815,000 and ~£778,000 for a female by the time they turn 18 years old[28]. Nitisinone treatment costs are a main contributing factor to the overall HT1 screening programme costs. Nitisinone has been licensed for this use for some time, and there was no cost effectiveness analysis performed for its use for HT1 at the time of licensing (which pre-dates NICE's responsibility for HSC). Were it to be developed today, it is likely that the drug would be eligible for the Highly Specialised

[28] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

Technologies Programme. This programme applies a far higher cost effectiveness threshold of £100,000-£300,000 per QALY gained to service its aim of improving access to treatments for people with very rare diseases. More explanation on the Highly Specialised Technologies Programme (HST) can be found in Assessing cost effectiveness under NICE HST methodology section of this IA.

57. In this IA, we report results according to HMT Green Book methodology, however we also include an evaluation using NICE's Health Technology Appraisal (HTA) and Highly Specialised Technologies (HST) approach in the Sensitivity analysis. There is uncertainty in the cost-effectiveness of screening due to the nature of HT1 being a very rare disease. In particular there are limitations in the evidence regarding liver transplant instance rates, which has a significant impact on the cost-effectiveness of screening. We conclude that although the base case calculations suggest HT1 screening is not cost effective under HMT Green Book methodology, there are some plausible scenarios where HT1 screening is cost-effective; hence this uncertainty is an important consideration for decision-makers.

*Table 1: Comparison of Green Book and NICE Methodologies*

| | **HM Treasury Green Book** | **NICE HTA** | **NICE HST** |
|---|---|---|---|
| Scope | All societal costs and benefits | Healthcare costs/savings, QALYs | Healthcare costs/savings, QALYs |
| Discount rate | Costs: 3.5%<br>Benefits: 1.5% | Costs: 3.5%<br>Benefits: 3.5% | Costs: 3.5%<br>Benefits: 3.5% |
| Equity for very rare diseases | Allows it to be included if it can be quantified but no methodology has been established to do this | No allowance (if HST ruled out) | Exists to improve access for very rare diseases, reflected in threshold and QALY weighting |
| Possible QALY weightings | 1 | 1-1.7 (severity modifier) | 1-3[29] |
| Output | Societal Net Present Value (SNPV) where QALYs are valued at £70K and net health and social care costs are converted into opportunity costs at the margin | ICER (net health and social care costs have no adjustment for opportunity costs) | ICER (net health and social care costs have no adjustment for opportunity costs) |
| Threshold | SNPV should be +ve once all monetised and non-monetised factors are considered | £20,000-£30,000 per (weighted) QALY | £100,000 per (weighted) QALY |

[29] For this weight to be applied, there will need to be compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained. NICE health technology evaluations: the manual.

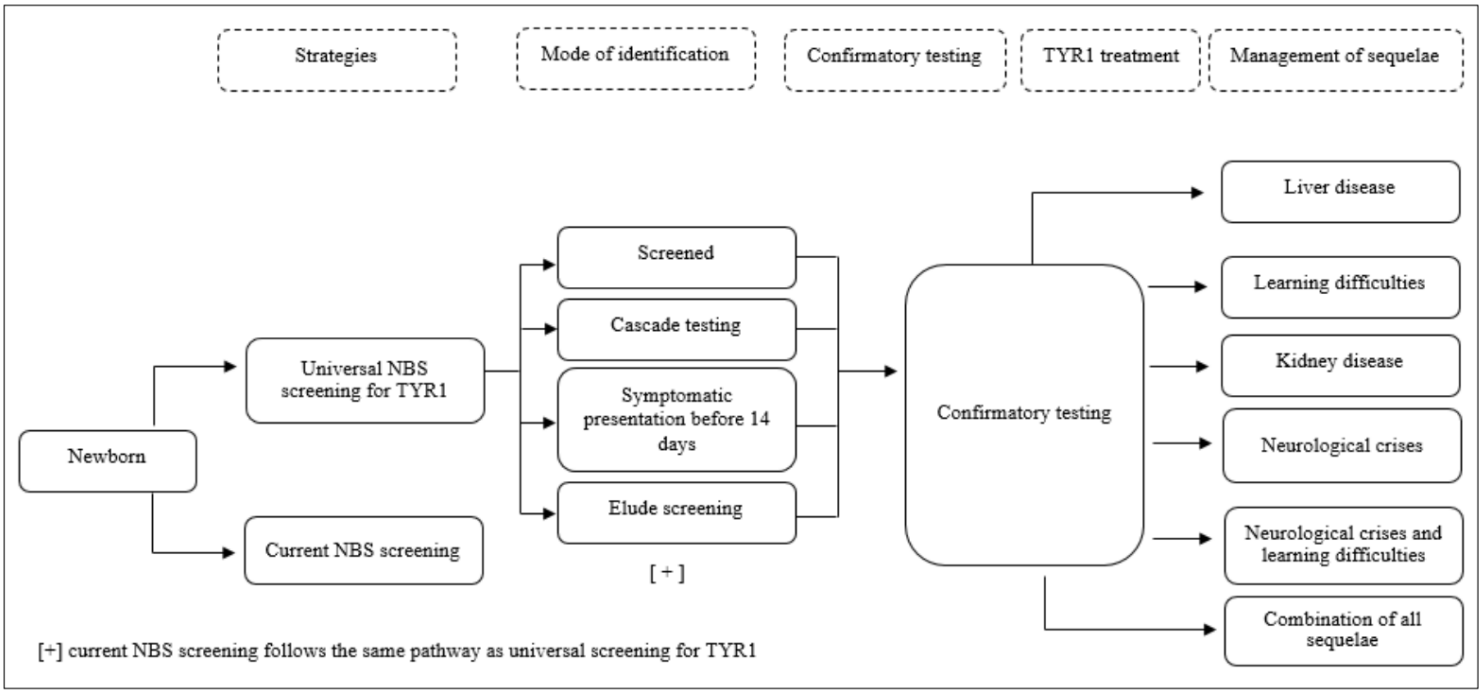
## HT1 model

58. Auguste et al.[30], developed an economic model incorporating clinical input to reflect the different pathways of babies being screened and treated for HT1.

59. The decision-analytical model comprised two stages. The first stage predicts the number of cases of HT1 identified under the current system (no national screening for HT1) and proposed NBS screening programme. The first stage uses a decision tree structure.

60. The second stage simulates the treatment and management of HT1 and its long-term sequelae[31]. This stage comprises of a Markov model structure. This structure of the pathways is illustrated in Figure 1 and a description of the clinical pathways is summarised in Table A1 in Annex B.

*Figure 1: Illustrative structure of the clinical pathways[30]*




61. For all clinical pathways new-borns are assumed to be treated with Nitisinone and diet immediately following confirmation of HT1, where there is assumed to be 100% compliance with treatment. The model assumes individuals may develop sequelae related HT1 or its treatment as they get older.

62. Auguste et al.[30], incorporated estimated annual transition probabilities to model the number of individuals entering each health state for long-term complications associated with HT1 and its treatment, including liver disease, renal dysfunction, learning difficulties, and neurological crises. These are presented in Table A2 in Annex B.

[30] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download
[31] A condition or symptoms as a result of a prior disease. E.g., Liver disease or neurological crises resulting from HT1.

63. Liver transplantation is required in some cases with liver disease. The incidence rate of transplants was derived from McKiernan et al.[32], and Bartlett et al.[33], where the health outcomes of children with HT1 treated early with Nitisinone following selective new-born screening are compared to the outcomes of siblings who had presented symptomatically and treated at a later stage. There are limitations in the evidence on liver transplant incidence rates due to HT1 being a very rare disease. This is explored further in the Sensitivity analysis section if this IA.

**Health benefits**

64. The main benefit of introducing a national screening programme for HT1, is treating pre-symptomatic new-borns with Nitisinone and through changes in diet at an earlier stage of life. This could avoid liver disease and reduce the risk of requiring a liver transplant. Liver transplant has risks of complications and transplant availability, and also requires lifelong use of immunosuppressants. Similarly, the associated hospitalisation costs from treating liver disease and other long-term complications associated with HT1 will fall if there is a reduction in the number severe cases through early detection as a result of screening new-borns.

65. The total QALYs also includes the benefits of a reduction in the number of false positive results currently identified through PKU screening. The model developed by Auguste et al. [34], estimated there would be an ~88% reduction in false positive screen results (from 89 to 11 new-borns having a false positive screen result based on a hypothetical UK cohort of 679k live-born babies per year in 2017) from introducing a national screening programme for HT1. Confirmatory diagnostic testing is done prior to starting treatment with Nitisinone. The model outputs presented in the Output summary of this IA are presented to reflect 2023 ONS birth estimates in England only[35] at ~569k per year. Screening would therefore reduce the impact of false positive and false negative tests. The QALY impacts of false positive tests are included within the model.

66. To derive QALYs, in each cycle of the model, a utility pay-off is assigned based on the health-state occupied. The sum of the QALYs is calculated over the model time horizon, which is over the period of a lifetime, and are discounted at 1.5% per annum.

67. As explained in Auguste et al[.36], utility values for each health state associated with HT1 were largely used from research by Tiwana et al.[37]. These utility values are shown in Table A3 in Annex B.

*Non-monetised benefits*

[32] Liver Transplantation for Hereditary Tyrosinaemia Type 1 in the United Kingdom. McKiernan, 2017, *Advances in Experimental Medicine & Biology*

[33] Early nitisinone treatment reduces the need for liver transplantation in children with tyrosinaemia type 1 and improves post-transplant renal function. Bartlett et al., 2014. *Journal of Inherited Metabolic Disease*

[34] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[35] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

[36] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[37] Tiwana SK, Rascati KL, Park H (2012) Cost-Effectiveness of Expanded New-born Screening in Texas. Value in Health 15, 613-621.

68. Only direct health benefits are quantified within the model. Earlier diagnosis followed by treatment with Nitisinone is shown to reduce severe health impacts including liver disease and liver transplant.

69. Additional non-monetised benefits include that more severe illness has productivity impacts directly through labour market participation and indirectly through lower educational attainment if time in school is missed due to ill health. It would additionally impact on parents and care givers, through out-of-pockets costs, and impacts on the economic productivity of carers. Their health and wellbeing may also be impacted.

70. There is also value to reducing uncertainty through the diagnostic stage. A national screening programme would identify asymptomatic cases, removing the often challenging period of uncertainty for families between the onset of symptoms and the diagnosis of HT1 and avoiding the delays before diagnosis when the child is ill and not receiving treatment. Screening may also reduce instances of liver transplant. While the costs of transplants and the utility value of the health state of the child are included in the model, the uncertainty of waiting for a transplant also has wider impacts on the family and carers of the child.

71. Option 2 has additional wider benefits which includes modernising the testing process in England. The use of a commercial assay will enhance the harmonisation of results between labs and reduce lab to lab variation.

72. These benefits may be considerable; however, it has not been possible to estimate them within this IA due to a lack of sufficient research on how to parametrise any estimates. This may underestimate the benefits of HT1 screening.

73. Wider benefits also include equity in treatments – the value which society puts on providing greater parity in treatments for rare diseases which could address inequality in the distribution of health. Screening would increase equity in the treatment for HT1 between those who currently are identified through the current genetic and incidental screening strategies and those who are not detected through screening but later through symptomatic diagnosis, resulting in worse health outcomes. Survey evidence and trade-off studies suggest that when holding the total health gain constant, the average person prefers to allocate resources towards the treatment of more severe uncommon diseases, which are often inherited and disproportionately affect the very young, even when the cost per unit of health benefit was greater[38]. This is not because of rarity per se, but primarily because of disease severity and lack of therapeutic alternatives typically associated with rare diseases[39]. While equity in treatments has not been monetised in this IA under HMT Green Book methodology, it is an important consideration for decision makers due to the unequal access to early Nitisinone treatment under current practice.

## Costs

[38] Valuation of Treatment for Rare Diseases: A Systematic Literature Review of Societal Preference Studies, Dabbous et al., December 2022 Valuation of Treatments for Rare Diseases: A Systematic Literature Review of Societal Preference Studies - PMC (nih.gov)

[39] Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers, Ollendorf et al., May 2018 Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers - Value in Health (valueinhealthjournal.com)

74. The costs associated with diagnosing and treating HT1 include index tests, diagnostic protocols, treatment costs with Nitisinone, diet and other costs associated with the treatment of babies and children with HT1 and long-term sequelae. In this Impact Assessment, costs are discounted at a rate of 3.5% per annum.

*Cost of incidental screening for HT1*

75. As discussed in Auguste et al.[40], the cost of PKU screening was used as a proxy for the cost of incidental detection of HT1. The cost of £2.70 per sample was based on using MS/MS to screen for PKU (and other conditions), inclusive of labour, capital, and consumables.

*Additional cost of using lab-developed assay for HT1*

76. The cost estimates to introduce a national screening programme for HT1 in the NBS programme as part of the day 5 blood spot test using lab-developed assays, Option 1, are set out in Table 2 below.

*Table 2: Costs with and without national screening for HT1 using lab developed assays, 2022/23 prices[41]*

| | Arithmetic mean | Range |
|---|---|---|
| Cost without HT1 | [redacted] | [redacted] |
| Cost with HT1 | [redacted] | [redacted] |
| Difference | [redacted] | [redacted] |

*n.b. these are reagent costs only and exclude staff costs*

77. The average additional cost to include HT1 in the current NBS programme using a lab-developed test is estimated to be around [redacted] per baby screened, excluding staff costs. The use of a lab-developed test would add additional steps to the existing screening programme, and as such would require additional staff time. This has been estimated as an additional [redacted] per baby screened, resulting in a total lab-developed test cost per baby screened of around [redacted]. However, there is uncertainty in this estimate as each lab developed test will depend on the source of the internal standards used which will vary across labs in each UK region.

78. There is no lab developed test currently available to evaluate nor is there a laboratory currently exploring the development of such a method. It may not be a viable option to use lab developed assays due to patent laws and potential difficulties in continuing to use lab-developed assays in a way that complies with the IVDR regulations. Other risks are mentioned in the Description of Options Considered section - Risks with Option 1, and under Risks and assumptions.

*Additional cost of using commercial assay for HT1*

[40] Cost-effectiveness of New-born Blood Spot (NBS) screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[41] Indicate estimates from NHSE. To use a lab developed test is dependent upon the source of the internal standards used which vary between [redacted] per baby screened. An arithmetic mean would suggest the existing cost of lab developed tests to be around [redacted]. Therefore, an average cost for a lab developed test to include HT1 may be around [redacted] per baby screened with a broad range of [redacted].

79. The estimated increase for introducing a national screening programme for HT1 in the NBS programme using commercial assays is around [redacted] per baby screened.

80. This is a one-off cost that would modernise the testing process in England. This cost would be shared across the overall programme and would enable screenings for additional conditions in the future or related diagnostic tests that currently use lab developed assays that soon may not comply with IVDR.

*Cost of diagnostic protocol*

81. To estimate a cost of the confirmatory diagnostic protocol of HT1 diagnosis, £257 was assumed as a proxy in Auguste et al.[43]. This is the cost of the confirmatory protocol for PKU in 2017/18 prices.

*Cost of treatment with Nitisinone*

82. The model developed by Auguste et al.[43] assumes new-borns are treated with Nitisinone immediately following confirmation of HT1 diagnosis regardless of whether they are symptomatic. The average dosage of Nitisinone is 1 mg per kg body weight per day and it is assumed children up to age 10 years will receive Nitisinone in its liquid form and those older than age 10 years will receive Nitisinone in the form of capsules. Estimated annual average costs for treating individuals with Nitisinone are presented and summarised in Table A4 in Annex B. Costs are presented in 2017/18 prices and are based on clinical expert opinion.

*Other costs*

83. As presented in Auguste et al.[43], other costs associated with the treatment of HT1 include inpatient stay, outpatient visits, contact with healthcare staff including dieticians, testing, diet, and costs associated with long-term conditions including liver transplant. These costs, based on clinical expert opinion, are presented in Table A5 in Annex B, in 2017/18 prices, and reflect the costs presented in Auguste et al.[43].

84. The costs of liver transplant include the liver transplantation surgery, inpatient stay, x-rays and ultrasounds, drugs, blood tests, parenteral nutrition, and staff time, including surgical and anaesthetic team costs. The cost savings of screening from a reduction in liver transplants were included within the costs calculations in the model produced by Auguste et al., [43].

85. A national screening programme would produce some NHS cost savings, primarily through the reduced likelihood of liver transplants through starting Nitisinone treatment.

## Output summary

86. This IA is a cost-benefit analysis where the net monetary benefit is used to determine whether a policy is economically viable. For completeness we have also included the

[42] The overall cost increase is [redacted] per baby tested. This figure is based on 2022/2023 workload (babies tested pa). The cost is for IMD screening to enable incorporation of succinylacetone.

[43] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

cost-effectiveness results, in the form of an incremental cost-effective ratio (ICER). The ICER is deemed cost-effective if its value is below the cost-effectiveness threshold.

87. The model by Auguste et al.[43], presented all costs in 2017/18 prices. To ensure consistency in the model the additional unit cost of using a lab developed assay and additional unit cost of using a commercial assay were deflated to 2017/18 prices, due to the complexity of inflating all the model cost components. These are presented and summarised in Table 3. The total costs and incremental costs in this IA have then been inflated to reflect 2022/23 prices.

88. The expected total costs, incremental costs, QALYs and the ICER for Option 1 and Option 2 are presented in Table 4. It also compares the outputs from two sets of model runs – the modelling conducted by Auguste et al.[43], and with updated parameters for this IA – according to the value parameters in Table 3. For this IA, cost effectiveness was assessed over a lifetime horizon of one birth cohort. Costs of screening were a one-off for one birth cohort and other costs such as treatment costs and health benefits were assessed in the same birth cohort over a lifetime horizon. Costs were discounted at 3.5% per annum and QALYs discounted at 1.5% per annum, and a £15,000 ICER threshold is used to evaluate cost effectiveness.

*Table 3: Comparison of the parameters used in the two sets of model runs*

| **Parameter** | **Warwick model: 2022 - NSC report** | **Warwick model: 2023 - updated values** |
|---|---|---|
| Additional unit cost of using a lab developed assay | £0.60 (2017/18 prices) | [redacted][44] (2022/23 prices), (2017/18 prices) |
| Additional unit cost of using a commercial assay | £1.16 (2017/18 prices) | [redacted][45] (2022/23 prices), (2017/18 prices) |
| Discount rate of future costs | 3.5% | 3.5% |
| Discount rate of future benefits | 3.5% | 1.5% |

89. The model developed by Auguste et al.[43], was based on a hypothetical UK cohort of ~679k in 2017. The model outputs in this IA, however, are presented to reflect 2023 ONS birth estimates in England only[46] at ~569k per year.

90. As presented in Table 4, the incremental QALYs are unchanged between Option 1 and Option 2 as the health benefits of introducing a national screening programme for HT1 are not impacted by the type of test. Conversely, the costs for using a commercial assay are lower than for using a lab developed assay. This impacts the total costs for introducing HT1 into the NBS screening programme leading to a lower cost per QALY gained for Option 2.

[44] For the model run 2023 with DHSC and NHSE values, the cost per screening test was deflated in order to get consistent ICER estimates due to the treatment costs all being in 2017/18 prices. The cost for using a lab developed assay in 2017/18 prices is [redacted]

[45] For the model run 2023 with DHSC and NHSE values, the cost per screening test was deflated in order to get consistent ICER estimates due to the treatment costs all being in 2017/18 prices. The cost for using a commercial assay in 2017/18 prices is [redacted]

[46] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

91. This lower ICER for Option 2 and the risks associated with using a lab developed assay (Option 1), mean this is the preferred option. There are also additional non-monetised benefits of using commercially available kits, including that it would allow the harmonisation of results by labs using the same kit as opposed to using different lab developed assays. Further non-monetised benefits are discussed in the Risks and assumptions section.

92. There are additional treatment costs from implementing national screening for HT1. These include the cost of additional Nitisinone treatment, diet supplements and other treatment costs such as routine blood tests and care visits. New-borns are assumed to commence treatment immediately following confirmation of HT1 and there is assumed to be 100% compliance with treatment. This means early detection of HT1 will identify need for treatment of HT1 sooner and therefore treatment (and the costs associated with treatment) for HT1 will start earlier in a patient's life.

93. Additionally, early detection and treatment with Nitisinone leads to lower rates of liver disease and liver transplants. HT1 requires lifetime treatment with Nitisinone, however the model assumes this is no longer administered following liver transplant. Therefore, a reduction in the rate of transplants results in an increase in the lifetime use of Nitisinone in these cases.

*Table 4: Deterministic results based on costs and QALYs per birth cohort* [47]

| Model run | Strategy | Expected total costs* | Incremental costs* | Incremental QALY* | ICER per QALY gained |
|---|---|---|---|---|---|
| **Warwick model: 2022 - NSC report** | **No national screening for HT1** | £10.43m | - | - | - |
| | **National screening for HT1 – Option 1** | £11.65m | £1.2m | 20 | £61,800** |
| | **National screening for HT1 – Option 2** | £11.96m | £1.5m | 20 | £71,300** |
| **Model run 2023 - new DHSC and NHSE values** | **No national screening for HT1** | £12.16m*** | - | - | - |
| | **National screening for HT1 – Option 1** | £13.64m*** | £1.5m*** | 30 | £42,300** |
| | **National screening for HT1 – Option 2** | £13.57m*** | £1.4m*** | 30 | £40,100** |
| **Values have been multiplied by ~569,000 to reflect the number of live births per year.* | | | | | |

[47] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

***Rounded to nearest 100.*
****Values have been uplifted to 2022/23 prices.*
*Exact results have been obtained from TreeAge.*

94. Table 5 summarises the total monetised costs and benefits for Option 1 and Option 2. The costs and benefits of Option 0 (maintaining status quo) are defined as zero, with the costs and benefits of Option 1 and Option 2 expressed relative to that baseline. Only direct health benefits are quantified within the model.

*Table 5: Summary of quantified costs and benefits; Option 1 and Option 2*

| | **Further Details** | **Value (2022/23 prices)** |
|---|---|---|
| **Option 1**<br>**Benefits** | | |
| Health benefits from the screening programme | Improved morbidity outcomes as a result of the screening programme. | Incremental QALYs: 30<br>Total: £2.1 million |
| **Costs** | | |
| Modelled total incremental costs | Includes screening and treatment costs, including Nitisinone and diet costs, liver transplant cost savings, and other treatments costs. | £1.5 million |
| Opportunity Cost | £1.5m x (£70,000/£15,000) Value of QALYs forgone due to lost NHS revenue assuming no additional funding is provided for this programme | £6.9 million |
| Net Present Value (excluding opportunity cost) | *Equals* Total benefits *minus* total financial costs to NHS | £0.65 million |
| **Net Present Value (including opportunity cost)** | *Equals* Total benefits *minus* Opportunity Cost | **-£4.8 million** |
| | | |
| **Option 2 – preferred**<br>**Benefits** | | |
| Health benefits from the screening programme | Improved mortality and morbidity outcomes as a result of the screening programme. | Incremental QALYs: 30<br>Total: £2.1 million |
| **Costs** | | |
| Modelled total incremental costs | Includes screening and treatment costs, including Nitisinone and diet costs, liver | £1.4 million |

| | | |
|---|---|---|
| | transplant cost savings, and other treatments costs. | |
| Opportunity Cost | £1.4m x (£70,000/£15,000) Value of QALYs forgone due to lost NHS revenue assuming no additional funding is provided for this programme | £6.5 million |
| Net Present Value (excluding opportunity cost) | *Equals* Total benefits *minus* total financial costs to NHS | £0.72 million |
| **Net Present Value (including opportunity cost)** | *Equals* Total benefits *minus* Opportunity Cost | **-£4.4 million** |

**Option 1**

95. The total net incremental discounted cost of introducing national screening for HT1, for one birth cohort, is ~£1.5 million. The cost of introducing the screening programme using lab-developed assays is estimated at [redacted] and the remaining [redacted] represents the net lifetime discounted costs of NHS treatments for HT1. The estimated lifetime ICER compared to the 'do-nothing' option is £42,300 per QALY gained.

96. The societal net present value (SNPV) is shown in Table 5. After accounting for the opportunity cost value of the financial costs to the NHS, it is estimated that the lifetime SNPV for one birth cohort is -£4.8m. Only health benefits are quantified in the model. Non-monetised benefits include lifetime productivity impacts to the child, impact on parents from caring for a sick child, modernisation of the New-born Blood Spot (NBS) screening programme, and reduced uncertainty through a reduction in liver transplants and early diagnosis. Wider benefits also include equity of access to treatments for very rare diseases.

97. It is important to note that while the costs, QALYs and ICER for using lab developed testing methods have been estimated, it may not be a viable option for laboratories to use lab developed assays due to the risks associated with this option. More information on the risks can be found in Risks and assumptions.

**Option 2:**

98. The total net incremental discounted cost of introducing national screening for HT1, for one birth cohort, is ~£1.4 million. The cost of introducing the screening programme using commercial assays is estimated at [redacted] and the remaining [redacted] represents the net lifetime discounted costs of NHS treatments for HT1 per birth cohort. The estimated lifetime ICER compared to the 'do-nothing' option is £40,100 per QALY gained.

99. The societal net present value (SNPV) is shown in Table 5. After accounting for the opportunity cost value of the financial costs to the NHS, it is estimated that the lifetime SNPV for one birth cohort is -£4.4m. As discussed, the modelling includes health benefits only and wider benefits are non-monetised, and therefore the monetised benefits are likely an underestimate of the benefits of HT1 screening.

100. The additional unquantified benefit per baby diagnosed with HT1 through screening needed in order for the programme to have a net societal benefit is included in the Break-even scenario in the Sensitivity analysis section of this IA.

101. Limitations of the modelling can be found in the Risks and assumptions section of this IA.

## Sensitivity analysis

### Liver transplant rate in symptomatically detected cases with liver disease

102. Sensitivity analysis was conducted by Auguste et al.[48], on the incidence of liver transplants in individuals who were symptomatically detected (under the current practice of no screening). There is uncertainty in the literature and studies on the instance of liver transplants in HT1 patients, largely due to the rarity of the condition.

103. The rates of liver transplants in the sensitivity analysis were derived from a registry study conducted by Spierkoetter et al.[49], which used data from two phases of the registry's operation undertaken in analyses of two datasets, across 17 countries. The first, 'complete set', combined cases from 2005 to 2013 (when the registry operated as a post marketing surveillance programme) and 2013 to 2019 (when the registry operated as a formal observational safety study). The 'complete set' 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.

104. Spiekerkoetter et al., do not directly report the incidence of liver transplants in symptomatically detected people. Instead, they report the incidence in people with HT1 who receive Nitisinone treatment initiated at different ages. The treatment group initiating treatment > 28 days to < 6 months of age is used as a proxy in the model for cases presenting symptomatically. Treatment groups initiating Nitisinone treatment > 6 months were not included.

105. As presented in Table 6, the original base case values for 4-month and 6-month transplant incidence probabilities were 0.012 and 0.018 respectively. For the sensitivity analysis the transplant incidence probabilities were lower; the 4-month and

[48] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[49] 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.

6-month transition probabilities were 0.0011 and 0.0017 respectively for the ‘complete set’ and 0.0017 and 0.0026 respectively for the ‘extended set’.

*Table 6: The original and new values for transplant incidence probabilities*

| | **Original value** | **New value** | |
|---|---|---|---|
| | | **Complete set** | **Extended set** |
| **4-month transition probability** | 0.012 | 0.0011 | 0.0017 |
| **6-month transition probability** | 0.018 | 0.0017 | 0.0026 |

*Table 7: Deterministic results based on costs and QALYs per birth cohort[50], using “complete set” values for liver transplants.*

| **Model run** | **Strategy** | **Expected total costs*** | **Incremental costs*** | **Incremental QALY*** | **ICER per QALY gained** |
|---|---|---|---|---|---|
| **Warwick model run 2022 - NSC report** | **No national screening for HT1** | £12.5m | - | - | - |
| | **National screening for HT1** | £13.0m | £0.5m | 26 | £19,600** |
| **Model run 2023 with new DHSC and NHSE values** | **No national screening for HT1** | £14.6m*** | - | - | - |
| | **National screening for HT1** | £15.1m*** | £0.6m*** | 44 | £11,200** |
| **Values have been multiplied by ~569,000 to reflect the number of live births per year*<br>***Rounded to nearest 100*<br>****Values have been uplifted to 2022/23 prices*<br>*Exact results have been obtained from TreeAge.* | | | | | |

106. The total net incremental discounted cost of introducing screening for HT1, for one birth cohort, is ~£0.6 million. The estimated lifetime ICER compared to the ‘do nothing’ option is £11,200 per QALY gained for the “complete set”, Table 7, and £13,000 for the “extended set”, Table 8, scenarios.

*Table 8: Deterministic results based on costs and QALYs per birth cohort[50], using “extended set” values for liver transplants.*

| **Model run** | **Strategy** | **Expected total costs*** | **Incremental costs*** | **Incremental QALY*** | **ICER per QALY gained** |
|---|---|---|---|---|---|

[50] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

| | | | | | |
|---|---|---|---|---|---|
| **Warwick model run 2022 - NSC report** | **No national screening for HT1** | £12.3m | - | - | - |
| | **National screening for HT1** | £12.9m | £0.6m | 26 | £22,400** |
| **Model run 2023 with new DHSC and NHSE values** | **No national screening for HT1** | £14.4m*** | - | - | - |
| | **National screening for HT1** | £15.0m*** | £0.7m*** | 43 | £13,000** |
| **Values have been multiplied by ~569,000 to reflect the number of live births per year*<br>***Rounded to nearest 100*<br>****Values have been uplifted to 2022/23 prices*<br>*Exact results have been obtained from TreeAge.* | | | | | |

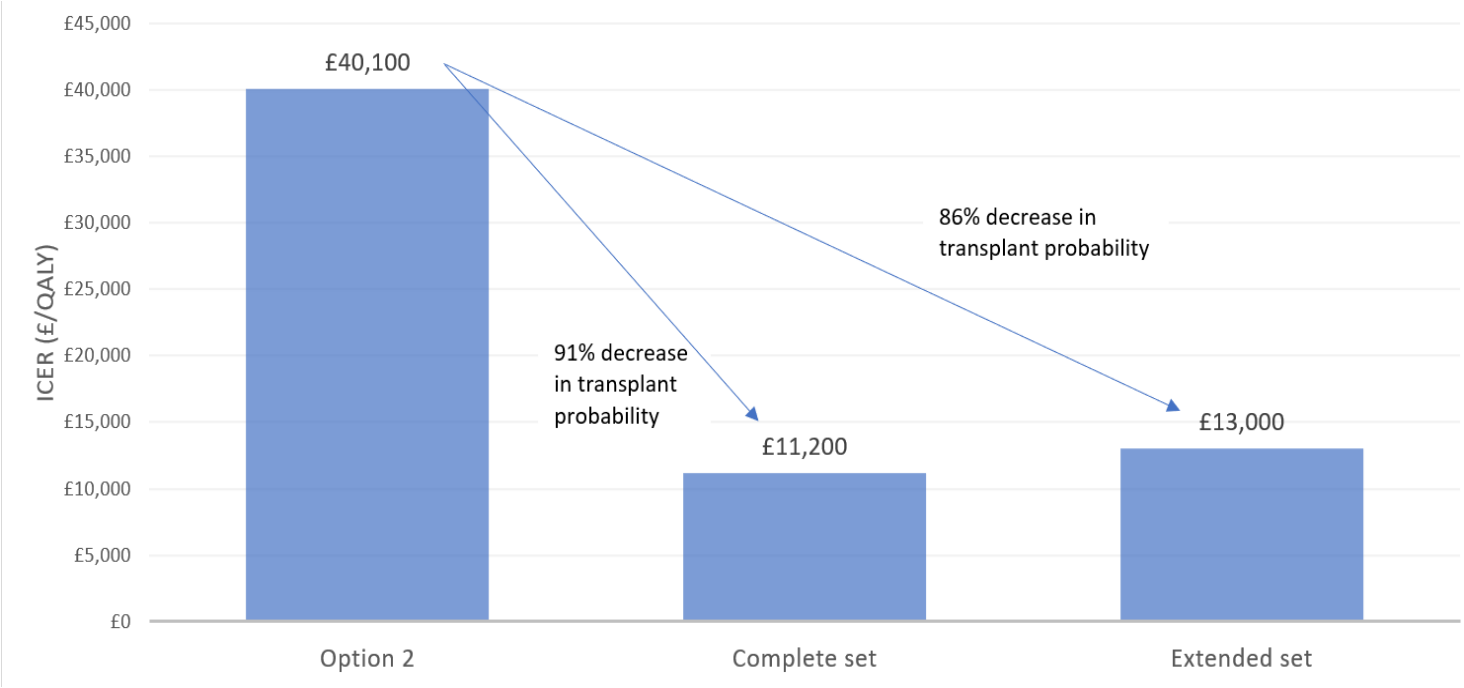
107. As presented in Figure 2 below, reducing the rate of transplant probabilities in symptomatically detected cases by 91% in the "complete set" leads to a reduction in the ICER to £11,200 (from £40,100), and reducing the rate of transplant probabilities by 86% in the "extended set" leads to a fall in the ICER to £13,000.

108. Costs of Nitisinone treatment are high and the model developed by Auguste et al. [51], assumes that there is no requirement for Nitisinone after a liver transplant. This reduces the costs under the current practice (no screening) when HT1 is detected later and liver transplant is required as it removes the need for lifetime Nitisinone treatment, but through the child becoming ill enough to require transplant. Overall, this means that early detection significantly increases overall treatment costs through the cost of Nitisinone, and that drives the high cost per QALY.

109. Reducing the rate of transplant probabilities under current practice (no screening), results in fewer transplants being prevented through screening, and therefore fewer additional cases requiring lifetime Nitisinone treatment as a result of screening. This reduces the cost per QALY. Screening in these scenarios still benefits individuals through earlier treatment and prevention of other long term health impacts.

*Figure 2: ICER values in the base case (Option 2) and sensitivity analysis under the "Complete set" and "Extended set" liver transplant incidence probabilities*

[51] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download




110. However, there are limitations of this sensitivity scenario, for instance, the modelling conducted by Auguste et al.[52], assumes that patients stop Nitisinone treatment after receiving a liver transplant and that transplant is successful for all individuals, however, in practise, this may not be the case and patients may still receive Nitisinone treatment even after they receive a liver transplant.

111. Additionally, Auguste et al. [52], assume that the transplant rate in the proxy group, where Nitisinone treatment is initiated >28 days to <6 months, is equivalent to the incidence of liver transplant in symptomatically detected people with HT1 who already have liver disease. This assumes that all cases detected pre-symptomatically through screening begin treatment < 28 days of age. Those detected pre-symptomatically under current practice are identified through cascade testing, or incidentally through PKU screening, and may begin treatment after 28 days. Therefore, some of the symptomatically detected group may have been detected pre-symptomatically through screening. The study also covers 17 countries, and screening practices and timelines of treatment may differ. The Spiekerkoetter et al.[53], estimation of the instance of liver transplant may underestimate the instance of transplants in symptomatically detected cases and overestimate the cost effectiveness of screening.

112. The societal net present values (SNPV) for this sensitivity analysis are presented in Table 9. After accounting for the opportunity cost value of the financial costs to the NHS, it is estimated that the lifetime SNPV for one birth cohort is £0.4m in the 'complete set' and -£0.1m in the 'extended set' scenario. As mentioned, the modelling includes health benefits only, wider benefits are non-monetised.

[52] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[53] 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.

*Table 9: Summary of societal net present value (SNPV) for the sensitivity analysis on changing the incidence of liver transplants in symptomatically detected individuals in the 'Complete set' and 'Extended set' scenario.*

| Sensitivity scenario | SNPV 2022/23 values |
|---|---|
| Complete set | £0.4m |
| Extended set | -£0.1m |

**Incremental cost of additional assays to commercial assays**

113. Implementing HT1 screening and adopting the commercial test kits needed would modernise the testing process in England. The initial investment in using a commercial test means that if the UK NSC recommends any other conditions covered by this test for screening, then the cost of implementing will be very low. New conditions simply need to be selected from the list of options when running the mass spectrometer and as most of them use the same reagent. Commercial kits can measure over 50 different analytes and conditions.

114. Sensitivity analysis has been carried out to assess the impact of the cost being shared if new conditions are added to the screening programme in future, Table 10. Adding additional conditions reduces the screening costs per programme and therefore reduces the estimated lifetime ICER compared to Option 2. However, due to treatment costs for HT1, the cost per QALY is still higher than what NHSE typically pay.

115. The societal net present values (SNPV) for this sensitivity analysis are presented in Table 10. After accounting for the opportunity cost value of the financial costs to the NHS, it is estimated that the lifetime SNPV for one birth cohort is -£3.6m, -£3.3m and -£3.1m in the scenarios for adding one, two and three other conditions respectively. As mentioned, the modelling includes health benefits only, wider benefits are non-monetised.

*Table 10: Deterministic results based on costs and QALYs per birth cohort[54], where screening costs are shared between multiple conditions.*

| **Strategy** | **Expected total costs*** *2022/23 values* | **Incremental costs*** *2022/23 values* | **Incremental QALY*** | **ICER (£) per QALY gained** | **SNPV** *2022/23 values* |
|---|---|---|---|---|---|
| **No national screening for HT1** | £12.2m | - | - | - | - |
| **National screening for HT1:** | | | | | |
| HT1 + 1 other condition (cost shared 50/50) | £13.4m | £1.2m | 30 | 34,800** | -£3.6m |
| HT1 + 2 other conditions | £13.3m | £1.2m | 30 | 33,100** | -£3.3m |

[54] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

| | | | | | |
|---|---|---|---|---|---|
| (cost shared 33/33/33) | | | | | |
| HT1 + 3 other conditions<br>(cost shared 25/25/25/25) | £13.3m | £1.1m | 30 | 32,200** | -£3.1m |
| **Values have been multiplied by 569,000*<br>***Rounded to nearest 100*<br>*Exact results have been obtained from TreeAge.* | | | | | |

**Break-even analysis**

116. This analysis determines what additional monetised benefit would be needed per baby diagnosed with HT1 through screening, in order for the programme to have a net societal benefit.

*Table 9: Break even analysis outputs.*

| | Per birth cohort | Per additional positive screen result for HT1 |
|---|---|---|
| Cost of screening using commercial assay (Option 2) | [redacted] | [redacted] |
| Net costs of treatment (discounted at 3.5% per annum) | [redacted] | [redacted] |
| Net costs expressed as an opportunity cost | £6.5m* | £2.2m* |
| Lifetime QALYs (discounted at 1.5% per annum) | 30 | 10 |
| Total QALYs monetised at societal value (£70k) | £2.1m* | £0.7m* |
| Additional societal benefits to be cost effective | £4.4m* | £1.5m* |
| **Rounded to nearest £100,000* | | |

117. As shown in Table 11, an additional ~£1.5 million in monetised benefits per additional positive screen result is required for the programme to be a net societal benefit. Additional benefits could include:

    a. **Impact on parents** from caring for a sick child, including mental health detriment due to anxiety and stress, reduced economic productivity, and some direct costs of providing care such as travel costs, purchasing of over-the-counter medication, childcare costs.

    b. **Lifetime productivity** from missed education and sickness reducing employment rates.

c. **Reduction in uncertainty** both in the period of time spent waiting for a diagnosis through early diagnosis, and in relation to being on the transplant list through reduced likelihood of requiring transplant.

d. **Modernising the testing process** in England through enhanced harmonisation of results between labs and reduced lab to lab variation.

e. **Equity in treatments** available for very rare diseases – the value that society puts on providing greater parity in treatments for very rare diseases.

## Sensitivity analysis to differences in methodologies

### Assessing the cost effectiveness under NICE HTA methodology

118. As a further sensitivity analysis, the cost effectiveness of introducing national screening for HT1 was assessed under NICE methodology.

119. Methodologically the NICE HTA approach differs from the Green Book in some critical respects:

    a. It is a cost effectiveness analysis (so does not consider broader impacts beyond health and social care spend, and health impacts),

    b. It uses a higher discount rate for benefits (3.5% for versus 1.5% in the HMT Green Book),

    c. It has a cost per QALY threshold of £20,000-£30,000.

120. Below are results with and without a severity modifier.

*Without a severity modifier*

121. Table 12 below shows the incremental costs, QALYs without a severity modifier, and the estimated lifetime ICER for introducing a national screening for HT1 using commercial assays, Option 2. Costs and QALYs are both discounted at 3.5% per annum to align with NICE HTA methodology.

*Table 10: Deterministic results based on costs and QALYs per birth cohort[55], where costs and QALYs are discounted at 3.5%*

| **Strategy** | **Expected total costs*** *2022/23 values* | **Incremental costs*** *2022/23 values* | **Incremental QALY*** | **ICER (£) per QALY gained** | **SNPV** *2022/23 values* |
|---|---|---|---|---|---|
| **No national screening for HT1** | £12.2m | - | - | - | - |
| **National screening for HT1** | £13.6m | £1.4m | 20 | £60,900** | -£5.2M |

[55] Based on 2023 ONS population estimates at age 0 for England: 565,669 live births.

| | |
|---|---|
| **Values have been multiplied by 569,000*<br>***Rounded to nearest 100*<br>*Exact results have been obtained from TreeAge.* | |

122. The estimated lifetime ICER compared to the 'do nothing' option is ~£60,900 per QALY gained. As the ICER for the screening programme is above the £20,000 - £30,000 NICE HTA threshold, the programme is not cost effective under this methodology.

123. The societal net present value (SNPV) in this case is estimated to be -£5.2m, after accounting for the opportunity cost value of the financial costs to the NHS. As mentioned, the modelling includes health benefits only, wider benefits are non-monetised.

*With a severity modifier*

124. NICE HTA methodology includes allowances for a decision modifier for severity, Table 13[56]. Note that DHSC have so far not incorporated into their application of HMT Green Book for health evaluations.

*Table 11: NICE Severity decision modifier*

| **If one of the following apply:** | | **Resulting QALY Multiplier** | **Equivalent cost per QALY threshold** |
|---|---|---|---|
| **Proportional QALY shortfall** | **Absolute QALY shortfall** | | |
| Less than 0.85 | Less than 12 | 1 | £20,000-£30,000 |
| 0.85-0.95 | 12 to 18 | x 1.2 | £24,000-£36,000 |
| At least 0.95 | At least 18 | x 1.7 | £34,000-£51,000 |

125. Under the NICE HTA severity modifier, the committee will consider the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care). So, in the case of HT1 screening, it would consider the severity of HT1 in those who are not currently diagnosed through sibling or PKU screening, and hence currently have poorer outcomes due to delayed diagnosis without population level screening.

126. The committee would consider the associated absolute and proportional QALY shortfall. The absolute QALY shortfall is defined as future QALYs lost from living with a severe condition and receiving standard of care in the NHS compared to someone without the condition. The proportional QALY shortfall represents the proportion of future health, including quantity and length of life, that is lost by people living with the condition. The QALY weightings for severity are applied based on absolute and proportional shortfall, whichever implies the greater severity level.

[56] NICE health technology evaluations: the manual

127. HT1 universal screening is likely to attract the maximum severity modifier weighting of 1.7 as HT1 is a severe life-limiting condition in most cases when not diagnosed through existing screening. Applying this gives an ICER of ~£34,300.

128. The NICE health technology evaluations manual outlines that for diagnostics, a QALY weight for severity based on absolute and proportional QALY shortfall is unlikely to reflect the societal value and severity of disease in a way that is relevant to the diagnostics context. The Diagnostics Assessment Programme Manual discusses that there are methodological issues concerning how and in what circumstances to apply additional weights to QALY calculations and therefore the use of differential QALY weights is not currently recommended in diagnostics evaluations[57]. It does not reference screening, but the parallels between diagnostics and screening would suggest that the severity modifier is not necessarily applicable in screening evaluations either [58].

129. Under NICE's HTA approach, applying a severity modifier of 1.7, gives a lifetime ICER of ~£34,000 per QALY, which is above however closer to the £20,000 - £30,000 threshold.

**Assessing cost effectiveness under NICE HST methodology**

130. HT1 is a very rare disease and treatment includes the drug Nitisinone, which is available on the NHS to any person with HT1 via the highly specialised commissioning (HSC) route. Were it to be developed today, it is likely that it would be eligible for evaluation through the Highly Specialised Technologies Programme (HST).

131. The HST[59] programme evaluates technologies which meet its criteria for severe and very rare diseases to secure fairer and more equitable treatment access. It aims to encourage research and innovation for very rare conditions where there are challenges in generating a robust evidence base to bring the product to market, and to secure fairer and more equitable treatment access for small populations with rare diseases.

132. It is designed to be used in exceptional circumstances to evaluate technologies for very rare diseases that have small numbers of patients, limited or no treatment options or challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.

133. The HST programme evaluates technologies in a similar way to NICE's HTA, however applies a £100,000 per QALY threshold with an additional QALY weight which could bring the threshold up to £300,000 per unweighted QALY, Table 14.

*Table 12: NICE Highly Specialist Technologies decision modifier*

[57] Addendum to the Diagnostics Assessment Programme Manual, NICE Diagnostics-interim-addendum-access-proposals.pdf (nice.org.uk)

[58] There are several unresolved methodological issues concerning how and in what circumstances to apply additional weights to QALY calculations. Until such issues are resolved, the use of differential QALY weights is not recommended as part of the reference case. Section 15.6 *diagnostics-assessment-programme-manual.pdf (nice.org.uk)*.

[59] Highly specialised technologies guidance | NICE guidance | Our programmes | What we do | About | NICE

| Incremental QALYs gained (per patient using lifetime horizon) | Resulting QALY Multiplier | Equivalent cost per (unweighted) QALY threshold |
|---|---|---|
| Less than or equal to 10 | 1 | £100,000 |
| 11 to 29 | Between 1 and 3 | £100,000-£300,000 |
| Greater than or equal to 30 | 3 | £300,000 |

134. Given that screening is estimated to result in an additional 10 QALYs gained per additional HT1 case detected through screening, the appropriate QALY multiplier here is expected to be 1.

135. The stated purpose of the HST methodology relates to treating rare conditions, rather than screening programmes that identify rare conditions, and the rationale for evaluating against a higher threshold is in response to low volume of treatments for rare diseases and so a national, whole population, screening programme would not fall under this justification despite the treatment being assessed under this methodology.

136. However, screening results in a patient receiving a test result which then determines their patient pathway. There may be a small benefit to the patient from knowing their health status, but these benefits are generally treated as trivially small and unquantified, with the main health benefit coming from any treatment they receive afterwards rather than from the test itself. This makes evaluation of screening and diagnostics difficult, as they need to incorporate a care pathway that might involve different patient pathways and treatment outcomes. In the case of HT1, treatment costs are largely the costs of Nitisinone, which as discussed would likely be eligible under the HST approach.

137. One complication is that if screening increases how many people receive a HST it could in theory make it no longer highly specialised (the definition of which includes that it is a treatment for very rare diseases), however in the case of HT1 it does not increase how many people receive treatment only the duration of time they receive treatment.

138. Under NICE's HST approach, the estimated lifetime ICER is ~£60,900 per QALY as shown in Table 12. The HST approach factors in a value of equity of access for very rare diseases, and we find HT1 screening is likely to be cost effective under this methodology.

## Discussion

139. Assessing the cost effectiveness of HT1 screening is challenging because it would increase access, through earlier use, for this very rare genetic disease to Nitisinone, a very expensive drug that is already available via highly specialised commissioning. The additional use of Nitisinone treatment following earlier diagnosis through screening accounts for the majority of the cost of the screening programme. Were it to be developed today, nitisinone would be eligible for assessment under the Highly Specialised Technologies programme, which applies a far higher cost-effectiveness

threshold to service its aim of improving access to treatments for people with very rare diseases.

140. If screening is not provided, on the basis of the HMT Green Book analysis suggesting it to be unlikely to be a net positive benefit, it would mean that HT1 individuals will receive Nitisinone through the NHS's Highly Specialised Commissioning once symptomatically detected. However, they would not be able to benefit from earlier diagnosis and treatment via screening, which would lead to better health outcomes. Nitisinone is effectively made unavailable until after symptomatic detection for these patients, when though it is the recommended treatment for all HT1 patients and would improve their long-term health outcomes.

141. There is also value to providing greater parity in treatments for rare diseases, which could address inequality in the distribution of health. This is not because of rarity per se, but primarily because of disease severity and lack of therapeutic alternatives typically associated with rare diseases. More severe uncommon diseases are often inherited and disproportionately affect the very young, even when the cost per unit of health benefit is greater. The benefit of equity in treatments could be considered when determining whether to screen for HT1.

142. We have not been able to estimate the wider societal benefits of HT1 screening. Applying HMT Green Book methodology to the base case suggests that HT1 would be cost-effective if there are an additional £1.5m of unquantified benefits per diagnosed HT1 patient (i.e., of those newly identified through the screening programme.) The non-monetised benefits from implementing HT1 screening includes gains in productivity, reduced uncertainty for individuals and families, and modernisation of the testing process in England. Therefore, there is a risk that this analysis does not sufficiently reflect society's preferences for how health spend is allocated and reduce overall utility of the population.

    There is also uncertainty in the cost-effectiveness due to the nature of HT1 being a very rare disease and the resulting limitations in the available evidence. As shown in the Sensitivity analysis using liver transplant rates derived from Spiekerkoetter et al[60]., the incidence of liver transplants in symptomatically detected cases is one of the most significant contributing factors in the assessment of the cost-effectiveness of HT1 screening. The sensitivity analysis regarding liver transplant incidence rates, and the discussion of non-monetised benefits of screening, demonstrate that there are scenarios under which introducing HT1 screening could have a net positive benefit.

## Risks and assumptions

143. Risks with Option 1 include:

    a. **Patent law.** Use of a laboratory developed assay may be judged illegal in relation to patent law and subject to legal challenge if employed.

[60] 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.

b. **Uncertainty regarding future IVDR requirements.** Use of a laboratory developed test may not be consistent with future IVDR requirements and may prevent the use of laboratory developed tests for succinyl acetone needed to identity HT1.

c. **Operational risks.** A laboratory developed test, if devised, would be significantly more demanding than the current assays and/or commercial solutions and may result in significant operational issues for NBS screening laboratories seeking to use such an assay**.**

d. **Harmonisation of results.** As a lab developed test would be unlikely to harmonise results between laboratories, this may make the adoption of a consistent national approach and implementation problematic.

e. **Increased staff costs.** A laboratory developed test for succinyl acetone is likely to be difficult to operate in practice resulting in increased staff costs.

f. **Supply risks.** There is potential for difficulties with production, supply, and possible future withdrawal of products (these issues could also affect the components of commercial tests). However, this risk could be mitigated during the procurement process by seeking information on the supply chain.

144. Risks with Option 2 include:

a. **Harmonisation of results.** Three commercially available assays from different suppliers will be evaluated in early 2024. This could potentially lead to the use of differing commercial products in different laboratories across England and therefore may not realise the opportunity to harmonise results. This risk could be mitigated during the procurement process by arranging a single tender order.

b. **Supply risks.** There is potential for difficulties with production, supply, and possible future withdrawal of products (these issues could also affect the components of laboratory developed tests). However, this risk could be mitigated during the procurement process by seeking information on the supply chain.

c. There is a risk that companies raise the price of the assay in the future.

145. Risks with the modelling include:

a. **Cost to use a lab developed assay**. As presented in Table 3, average additional cost to include HT1 in the current NBS programme using a lab-developed assay is estimated as [redacted] per baby screened. However, there is uncertainty in this estimate as each lab developed test will depend on the source of the internal standards used which will vary across labs in each UK region. It is also important to note there is no lab developed test currently available to evaluate nor is there a laboratory currently exploring the development of such a method. The reasons for this are in the risks with Option 1.

b. **Utility values**. Modelling by Auguste et al.[61], assumed that the utility values were the same for clinically detected and screen detected new-borns due to no available evidence to support differences in utility values for these two groups. This could underestimate the cost effectiveness of national screening for HT1 if clinically detected babies have a worse health state which could be prevented through early detection.

c. **Long-term complications**. Modelling by Auguste et al.[61], incorporated long-term complications associated with HT1 or its treatment. The incidence of these were obtained from the literature. For some long-term complications, it was difficult to decipher the events that occurred in individuals who were detected through screening and those who presented with symptoms and were clinically diagnosed. Additionally, the modelling assumed a constant rate of events occurred over time which may have led to an over or underestimation of the cost effectiveness.

d. **Limited scope of cost effectiveness**. The scope of the economic analysis was limited due to excluding the costs borne by HT1 patients and their families such as, loss of productivity, carers costs and out-of-pocket expenditures such as travel costs, and equity of treatment which could underestimate the benefits and cost effectiveness of national screening for HT1.

e. **Liver transplants**. The costs of liver transplant in the model include the liver transplant surgery and lifetime transplant care including inpatient stay, x-rays and ultrasounds, drugs, blood tests, parental nutrition, and staff time, including surgical and anaesthetic team costs. It was assumed that all babies requiring a transplant received the procedure and that this was successful, resulting in no further need for treatment with Nitisinone and assuming no risk of transplant failure.

f. **Treatment compliance**. The model assumes individuals are 100% compliant with diet and Nitisinone treatment.

g. **Liver transplant incidence rates**. There are limitations in the evidence due to it being a very rare disease. In the base case scenario, incidence rates were derived from McKiernan et al.[62], and Bartlett et al.[63], which use a small sample of HT1 cases at Birmingham Children's hospital to compare the health outcomes of children treated with Nitisinone following selective screening with siblings who has presented symptomatically.

146. Risks of incurring additional costs:

a. Screening for HT1 is estimated to have an additional screening cost of around [redacted] per year using commercial assays. Compared to the

[61] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[62] Liver Transplantation for Hereditary Tyrosinaemia Type 1 in the United Kingdom. McKiernan, 2017, *Advances in Experimental Medicine & Biology*

[63] Early nitisinone treatment reduces the need for liver transplantation in children with tyrosinaemia type 1 and improves post-transplant renal function. Bartlett et al., 2014. *Journal of Inherited Metabolic Disease*

NHS budget, this is very small and should not have a significant impact on NHS funding available for other programmes.

b. By identifying an additional 3 HT1 patients per year earlier than otherwise, this increases the number receiving Nitisinone. The cost of this on highly specialised commissioning (HSC) has not been explicitly calculated, however it is a very expensive drug and if this is not appropriately planed for in finances, there is a risk that this impacts on the availability of this or other treatments from HSC.

147. Risks in the methodology:

a. The Green Book methodology is the default for DHSC Impact Assessments. This approach is a full cost benefit analysis; however, we have not been able to estimate the wider societal benefits of HT1 screening. More information on this is below.

b. For these reasons, there is a risk that the evaluation of HT1 screening will not sufficiently reflect society's preferences for how health spend is allocated, and therefore will reduce overall utility of the population.

c. There is also a risk that, if HT1 screening is not introduced following the UK NSC recommendation, that this is perceived to be caused by inconsistencies between NICE and HMT Green Book evaluations and could decrease confidence in Government evaluation approaches.

148. Risk of setting a precedent:

a. If the decision is made to proceed with HT1 national screening when there is uncertainty whether it is cost effective according to HM Treasury Green Book, this could set an expectation for proceeding with other screening programmes that face similar challenges in assessing the cost effectiveness.

b. It is anticipated that a there will be several UK NSC recommendations in the coming years which could include antenatal and new-born screening for rare genetic diseases. There will be important messages to manage over how this decision on HT1 is taken given it could set an expectation for the approach to assessing the cost effectiveness of future screening programmes.

## Impact on business

149. It is expected that national screening of HT1 could increase demand for Nitisinone and dietary products used to treat HT1 patients. Screening and early detection of HT1 in new-borns would allow patients to commence treatment earlier in life, compared to being detected symptomatically at a later stage. Screening could also reduce the likelihood of requiring liver transplant, and therefore a greater proportion of people are likely to remain taking Nitisinone for the duration of their lifetime.

## Wider, non-monetised costs and benefits

150. Implementing HT1 screening and adopting the commercial test kits needed to do this means that it also brings the benefit of modernising the testing process in England. The initial investment in using a commercial test means that if the UK NSC recommends any other conditions covered by this test for screening, then the cost of implementing will be very low and could be shared across the overall programme or related diagnostic tests that currently used lab developed assays that soon may not comply with IVDR. There is also scope for recouping the additional costs if the NHS chooses to redesign the NBS lab services in the future.

151. As discussed in the non-monetised costs and benefits section of this IA, only direct health benefits have been quantified within the model. The non-monetised benefits from implementing national HT1 screening include gains in future productivity and reducing uncertainty for families through asymptomatic diagnosis and reduced instance of liver transplants. Screening would also have the benefit of greater parity in treatments for HT1.

## Wider impacts

152. The Department of Health and Social Care (DHSC) published the UK Rare Diseases Framework[64] in January 2021. The framework outlines the vision for the how the UK plans to address health inequalities and improve the lives of individuals living with rare diseases.

153. While the UK Rare Diseases Framework is a UK-wide document[65], each UK nation has its own responsibility to implement and monitor nation-specific action plans and in February 2022, England developed the Rare Diseases Action Plan[65]. The Action Plan set out commitments, where one of the commitments was to improve how decisions are made on new-born screening for rare diseases[65] and HT1 is a rare disease of interest[66].

154. Proceeding with screening for HT1 would be consistent with the UK Rare Diseases Framework[67] and Rare Diseases Action Plan[68] which aim to ensure that the lives of people living with rare diseases continue to improve.

## Monitoring and Evaluation

155. DHSC will have a role in overseeing and accountability to arm's length bodies, and public health policy in general. If screening is introduced, a monitoring and evaluation plan will be required to go alongside this. Uptake will be monitored as part of the NBS programme.

[64] UK Rare Diseases Framework - GOV.UK (www.gov.uk)
[65] England Rare Diseases Action Plan 2022 - GOV.UK (www.gov.uk)
66 DHSC English rare diseases action plan 2022
67 The UK Rare Diseases Framework - GOV.UK (www.gov.uk)
[68] England Rare Diseases Action Plan 2022 - GOV.UK (www.gov.uk)

156. If UK NSC makes further advice DHSC and NHS England will be able to consider further policies to address this.

# Annex A

*Table 13: Description of the clinical pathways*[69]

| Pathway | Age screened | Proportion of new-borns | Test accuracy | Explanation |
|---|---|---|---|---|
| Current NBS screening programme | Day 5 | 96.5% | 25% (PKU screening) | There is no national screening for HT1 in this pathway. Incidental detection of HT1 may happen as a result of NBS screening for phenylketonuria (PKU). |
| Proposed expanded NBS screening programme | Day 5 | 96.5% | 100% | New-borns are screened for HT1 at day 5, where a diagnostic protocol to confirm diagnosis will be done soon after if there is an initial positive initial test result for HT1. The national protocol used to confirm and diagnose HT1 is assumed to be 100% accurate. New-borns with a confirmed diagnosis are asymptomatic but may develop long-term complications. |
| Symptomatic detection | Before 14 days of life | 0.000042% | 100% | New-borns who present with symptoms of HT1 before day 14 of life (and before release of NBS screening results) will receive a diagnostic protocol. |
| Cascade testing | 48-72 hours of age | 0.0018% | 100% | New-borns with older siblings with an HT1 diagnosis are assumed to be in an asymptomatic health state and will receive the diagnostic protocol at 48-72 hours of age. |
| Elude screening | After 14 days of life | 3.498158% | 100% | New-borns who are not screened at day 5 are assumed to be asymptomatic until they develop symptoms of HT1 after 14 days of life. |

*Table 14: Four-month and six-month transition probabilities by complication (central scenario estimates), assuming a constant rate of events*[69]

| Long-term complication | Screen detected | | Symptomatically detected | | Source |
|---|---|---|---|---|---|
| | 4-month transition probability | 6-month transition probability | 4-month transition probability | 6-month transition probability | |
| Liver disease | 0 | 0 | 0.118 | 0.172 | Larochelle et al.[70], "Post hoc 1" |

[69] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

[70] Larochelle J, Alvarez F, Bussieres JF et al. (2012) Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Molecular genetics and metabolism 107, 49-54.

| | | | | | |
|---|---|---|---|---|---|
| | | | | | analysis (Screen detection vs symptomatic detection, all with direct nitisinone initiation) as in Geppert et al.[71] |
| Liver transplant in cases with liver disease | 0 | 0 | 0.012 | 0.018 | McKiernan et al.[72]; information on follow-up time in screen-detected cases extrapolated from Bartlett et al.[73] |
| Renal dysfunction | 0.002 | 0.003 | 0.004 | 0.005 | Mayorandon et al.[74]; data for "Renal dysfunction". |
| Learning difficulties | 0.010 | 0.016 | 0.008 | 0.012 | Mayorandon et al. [75] (frequency/odds ratio for "psychomotor impairment") |
| Neurological crisis | 0 | 0 | 0.003 | 0.005 | Larochelle et al.[76]: "Post-hoc 3" analysis (Screen detection, direct nitisinone initiation vs screen detection, 1–12 months delayed nitisinone initiation) as in Geppert et al.[77] |
| Combination of learning difficulties and neurological crises | 0 | 0 | 0.003 | 0.005 | Assumed to be equal to the transition probability for neurological crises. |
| Combination of long-term complications | 0 | 0 | 0.003 | 0.005 | Assumption to be equal to the transition probability for neurological crises. |

[71] Geppert J, Stinton C, Freeman K et al. (2017) Evaluation of pre-symptomatic nitisinone treatment on long-term outcomes in Tyrosinemia type 1 patients: a systematic review. Orphanet J Rare Dis 12, 154.

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

[73] Bartlett DC, Lloyd C, McKiernan PJ et al. (2014) Early nitisinone treatment reduces the need for liver transplantation in children with tyrosinaemia type 1 and improves post-transplant renal function. Journal of Inherited Metabolic Disease 37, 745-752.

[74] Mayorandan S, Meyer U, Gokcay G et al. (2014) Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet Journal of Rare Diseases 9.

[75] Mayorandan S, Meyer U, Gokcay G et al. (2014) Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet Journal of Rare Diseases 9.

[76] Larochelle J, Alvarez F, Bussieres JF et al. (2012) Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Molecular genetics and metabolism 107, 49-54.

[77] Geppert J, Stinton C, Freeman K et al. (2017) Evaluation of pre-symptomatic nitisinone treatment on long-term outcomes in Tyrosinemia type 1 patients: a systematic review. Orphanet J Rare Dis 12, 154.

*Table 15: Utility values by health state*[78]

| Health state | Utility values | Range | Source |
|---|---|---|---|
| False positive screen result | 0.97 | 0.95-0.99 | Tiwana et al.[79] |
| Liver disease | 0.20 | 0.10-0.30 | |
| Liver transplant | 0.67 | 0.58-0.74 | |
| Renal dysfunction | 0.67 | 0.58-0.74 | |
| Learning difficulties | 0.70 | 0.60-0.80 | |
| Neurological crises | 0.84 | 0.70-0.85 | |
| Treatment without complications | 0.90 | 0.85-0.95 | |
| Neurological crises and learning difficulties | 0.70 | 0.60-0.80 | Assumptions in Auguste et al.[80] |
| Combination of sequelae | 0.30 | 0.10-0.50 | |
| Overdiagnosis | -0.09 | - | |

*Table 16: Annual costs for treating individuals with HT1 using Nitisinone*[81]

| Age | Weight (kg) | Daily dose (1mg/kg) | Formulation | Cost per year |
|---|---|---|---|---|
| Neonate | 3.5 | 3.5 mg (0.87ml) | 4mg/1ml Oral Suspension | £10,152 |
| 1 month | 4.3 | 4.3 mg (1.1ml) | 4mg/1ml Oral Suspension | £10,152 |
| 2 months | 5.4 | 5.4 mg (1.3ml) | 4mg/1ml Oral Suspension | £10,152 |
| 3 months | 6.1 | 6.1 mg (1.5ml) | 4mg/1ml Oral Suspension | £10,152 |
| 4 months | 6.7 | 6.7 mg (1.7ml) | 4mg/1ml Oral Suspension | £11,506 |
| 6 months | 7.6 | 7.6 mg (1.9ml) | 4mg/1ml Oral Suspension | £12,859 |
| 1 year | 9 | 9 mg (2.3ml) | 4mg/1ml Oral Suspension | £15,566 |
| 3 years | 14 | 14 mg (3.5ml) | 4mg/1ml Oral Suspension | £23,688 |
| 5 years | 18 | 18 mg (4.5ml) | 4mg/1ml Oral Suspension | £30,456 |
| 7 years | 23 | 23 mg (5.8ml) | 4mg/1ml Oral Suspension | £39,254 |
| 10 years | 32 | 32 mg (3x10mg & 1x2mg) | Capsules (Available as 2mg, 5mg and 10mg) | £24,141 |
| 12 years | 39 | 39 mg (3x10mg & 1x5mg & 2x2mg) | Capsules (Available as 2mg, 5mg and 10mg) | £29,456 |

[78] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download
[79] Tiwana SK, Rascati KL, Park H (2012) Cost-Effectiveness of Expanded New-born Screening in Texas. Value in Health 15, 613-621.
[80] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download
[81] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

| | | | | |
|---|---|---|---|---|
| 14 years | 50 | 50 mg (5x10mg) | Capsules (Available as 2mg, 5mg and 10mg) | £38,365 |
| Adult male | 68 | 68 mg (6x10mg & 4x2mg) | Capsules (Available as 2mg, 5mg and 10mg) | £50,526 |
| Adult female | 58 | 58 mg (5x10mg & 4x2mg) | Capsules (Available as 2mg, 5mg and 10mg) | £42,853 |

*Table 17: HT1 Resource use and unit costs*[82]

| Resource use | Cost |
|---|---|
| ***Neonatal admission (HRG code)*** | |
| • Inborn Errors of Metabolism with CC Score 0-2 (Elective inpatient stay) (KC04B) | £572.03 |
| • Neonatal Critical care, High dependency care (XA02Z) | £909.81 |
| • Neonatal Critical care, Normal care (XA05Z) | |
| ***Paediatric admission*** | £429.17 |
| • Average cost per stay | £2,880.00 |
| ***Outpatient visits*** | |
| • Paediatric consultant-led outpatient attendance | £201.00 |
| • Paediatric non-consultant-led outpatient attendance | £151.00 |
| • Adult outpatient attendance | £134.00 |
| ***Staff costs*** | |
| • Dietician | £86.00 |
| • Health visitor | £59.11 |
| ***Tests*** | |
| *Bloods* | |
| • Blood gases | £5.89 |
| • Full blood count | £10.33 |
| • Coagulation (PT, PTT, fibrinogen) | £8.36 |
| • Liver function tests (Bilirubin, AST, ALT, alkaline phosphatase, GGT, albumin) | £4.55 |
| • Urea and electrolytes, creatinine, calcium, phosphate | £3.79 |
| • Amino acids (quantitative, tyrosine, phenylalanine) | £118.00 |
| • Alpha-fetoprotein | £6.10 |

[82] Cost-effectiveness of New-born Blood Spot screening for Tyrosinaemia type 1 using tandem mass spectrometry - Final report, Auguste et al., July 2021 https://view-health-screening-recommendations.service.gov.uk/document/583/download

| | |
|---|---|
| • Glucose and ammonia | £0.82 |
| • Iron and ferritin, vitamins A, D, E, folate and vitamin B12, micronutrients (selenium, zinc, copper) | £75.44 |
| *Urine* | |
| • Glucose | £4.17 |
| • Amino acids | £36.00* |
| • Tubular re-absorption of phosphate | £0.76 |
| • Calcium/creatinine ratio | £0.73 |
| • Urine acidification | £4.17 |
| • Albumin, protein, β2-microglobulin | £0.74 |
| • Organic acids | £52.00* |
| *Imaging* | |
| • Liver imaging: ultrasound | £115.39 |
| • Renal imaging: ultrasound | £115.39 |
| • Liver imaging: MRI or CT | £515.14 |
| *Other tests* | |
| | £360.79 |
| • Developmental evaluation / neuropsychological assessment | £82.29 |
| • Bone mineral density | £29.19 |
| • Eye examination | £617.28* |
| • Molecular genetics | |
| ***Diet costs*** | |
| • Prescription charges | £8.80 |
| • Annual cost of diet | £8,887.99 |
| * *One-off tests* | |

# Annex B

### Environmental Principles Assessment One-page overview

*This template is designed to provide Ministers and decision makers a high-level overview of the consideration of the duty. It should be used alongside the Environmental Principles Assessment template provided above*.

You may wish to use it as part of the annex to when providing policy options for ministerial decision making.

| **Environmental Principles Assessment Overview**<br>*Duty to have due regard to the Environmental Principles Policy Statement* | |
|---|---|
| **Title** | *Decision to introduce a national screening programme for Hereditary Tyrosinaemia type 1 (HT1) in the New-born Blood Spot (NBS) screening programme.* |
| **Contact** | *Analytical: Zara Retallick, Economic Advisor, Zara.Retallick@dhsc.gov.uk, Christina Michael, Assistant Economist, Christina.Michael@dhsc.gov.uk* |
| **Clearance** | *Name, Title* |
| **Date** | *17/01/2024* |

1. The policy is in scope of the duty to have due regard to the Environmental Principles Policy Statement.

2. There are no environmental effects associated with this policy.

The environmental impact is expected to be negligible. HT1 screening will be added to the NBS programme, so there is no need to establish a bespoke service. The equipment that is currently used for the nine conditions screened will stay the same, even if a new condition (HT1) is added.

As HT1 screening will be included within the NBS programme, this could reduce resources used to separately test for HT1 following symptomatic detection.

The move to the use of commercial assays is expected to make it easier to assess test samples, and manufacturers can be asked directly about their environmental policies and impact as part of the procurement process.

Screening information is fully digital. Providers may need to provide a small number of printed information leaflets for accessibility requirements, but the process is ‘digital by default’. Therefore, there is a small potential environmental impact of updating information leaflets for distribution.