UK National Screening Committee

Newborn screening for adrenoleukodystrophy

An evidence map to outline the volume and type of evidence related to newborn screening for adrenoleukodystrophy for the UK National Screening Committee

Version: FINAL

Author: Solutions for Public Health

Date: February 2021

The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

UK NSC, Floor 5, Wellington House, 133-155 Waterloo Road, London, SE1 8UG
www.gov.uk/uknsc
Twitter: @PHE_Screening Blog: phescreening.blog.gov.uk

For queries relating to this document, please contact: phe.screeninghelpdesk@nhs.net

Published June 2021

Contents

Summary

This document discusses the findings of the evidence map on newborn screening for adrenoleukodystrophy (also known as X-linked adrenoleukodystrophy).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, no further work on newborn screening for adrenoleukodystrophy should be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to newborn screening for adrenoleukodystrophy in 3-years' time.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Newborn screening for adrenoleukodystrophy is a topic currently due for an external review update.

Adrenoleukodystrophy (also known as X-linked adrenoleukodystrophy) is a genetic disorder of peroxisomal fatty acid beta oxidation caused by mutations in the ABCD1 gene. This gene is usually passed by the mother to her offspring but can arise *de novo.* The X-linked inheritance pattern means that males are more severely affected as they only have a single X chromosome. Female carriers tend to avoid the more severe clinical manifestations but can become symptomatic later in life [1,2].

There are a range of different clinical phenotypes. Childhood cerebral adrenoleukodystrophy in affected males is associated with rapidly progressive demyelination in the brain and is the potential target of newborn screening. This typically presents during childhood with attention deficit and hyperactivity, visual and hearing impairment and co-ordination problems and can rapidly progress to severe disability and death without treatment. Other phenotypes include Addison's disease and adrenomyeloneuropathy. Addison's disease in affected males is characterised by unexplained vomiting, weakness, dehydration, dizziness and sweating which can lead to coma. Adrenomyeloneuropathy is characterised by neurodegeneration of the spinal cord and peripheral nerves resulting in progressive stiffness and weakness in the legs, sphincter dysfunction, impotence and sensory loss in the lower limbs in affected males as adults, with similar symptoms in adult female carriers. Adrenoleukodystrophy phenotypes develop over time and are often preceded by adrenal insufficiency in males [1,2].

The only currently available standard therapy for adrenoleukodystrophy includes cortisol for individuals with adrenal insufficiency and haematopoietic stem cell transplant in boys with childhood cerebral adrenoleukodystrophy which can be effective if performed early in the evolution of the disease [3]. There are currently no interventions that can slow or prevent the onset of adrenomyeloneuropathy for which only symptomatic support is available [4]. Though asymptomatic at birth, boys need to be routinely monitored with a combination of adrenal function, to detect incipient adrenal insufficiency, and brain MRI

to identify early evidence of cerebral demyelination with a view to referral for consideration of haematopoietic stem cell transplant [5].

Previous review on newborn screening for adrenoleukodystrophy

The UK NSC currently recommends against newborn screening for adrenoleukodystrophy. The Committee based this recommendation on the evidence provided by the 2017 assessment carried out by Solutions for Public Health [2].

The 2017 assessment of newborn screening for adrenoleukodystrophy was based on a combination of scoping review and early evidence map methodology. It found that there were significant gaps in the evidence base around newborn screening for adrenoleukodystrophy [2]. Specifically, the screening test in use at the time was still experimental and was subject to ongoing evaluation in the New York State screening programme. It was also noted that the test would identify boys with the genetic mutation who would not go on to develop cerebral adrenoleukodystrophy as well as infants with conditions other than adrenoleukodystrophy for which there were no interventions. There was also uncertainty about the balance of the long-term benefits and harms of haematopoietic stem cell transplant [1,2].

Current international landscape of newborn screening programmes

The aim of newborn screening for adrenoleukodystrophy is to identify all males with mutations of the ABCD1 gene before they become symptomatic. They can then be monitored for any initial signs of cerebral adrenoleukodystrophy and offered haematopoietic stem cell transplant as soon as possible [1].

New York State was the first to include adrenoleukodystrophy to its newborn screening programme in December 2013. This was followed by a second US state (Connecticut) in October 2015. Adrenoleukodystrophy was added to the US Recommended Uniform Screening Panel (RUSP) in February 2016 [6]. In 2020, screening for adrenoleukodystrophy is in place in 18 US states with pilot programmes in 2 further states [7].

Adrenoleukodystrophy was 1 of 14 new conditions added to the newborn screening panel in the Netherlands in 2015, with phased implementation. The recommendation of the Dutch Health Council was that the screening programme should be set up to only identify boys with adrenoleukodystrophy [8]. A prospective pilot study was set up in October 2019 (the screening for adrenoleukodystrophy in the Netherlands (SCAN) study) with the objectives of designing an algorithm that identifies males with adrenoleukodystrophy without unsolicited findings, integrating this algorithm into the structure of the Dutch newborn screening program, assessing the practical and ethical implications of only screening boys and setting up a comprehensive follow-up process.

The screening test for adrenoleukodystrophy is based on increased levels of lysophosphatidylcholine derivative of a very long-chain fatty acid marker in dried blood spots (C26:0). The details of the test may differ across laboratories. However, in the initial New York programme a 2-tier screening process was used consisting of flow-injection tandem mass spectrometry to measure C26:0 lysophosphatidylcholine followed by liquid chromatography tandem mass spectrometry to measure samples with elevated C26:0 lysophosphatidylcholines. Samples with elevated C26:0 lysophosphatidylcholines were subject to genotyping using the Sanger sequencing to test for the ABCD1 gene [1,7]. Other conditions may be confirmed at the genotyping stage. These include Zellweger syndrome deficiency, peroxisomal fatty acid oxidation disorders (caused by a defect in either the peroxisomal acyl-CoA oxidase 1 (ACOX1) or the multifunctional protein HSD17B4), the contiguous ABCD1 DXS1357E deletion syndrome, a protein deficiency (acyl-CoA binding domain containing protein 5 (ACBD5)) and Aicardi Goutières Syndrome [7]. These are rare conditions which are often associated with death in early infancy and for which no specific treatment exists [1].

Studies from 2 more recently implemented US screening programmes were identified by the search conducted for this evidence map. The screening process used in these programmes differs from the original New York screening process. For example, in North Carolina, negative ionization high-performance liquid chromatography tandem mass spectrometry is used as the first-tier screening test, followed by re-testing of samples above the specified cut-off level for either C24:0 lysophosphatidylcholines or C26:0 lysophosphatidylcholines. Positive samples are then sent for genotyping using Sanger sequencing to test for the ABCD1 gene [9]. In the Minnesota screening programme, negative ion-mode liquid chromatography tandem mass spectrometry is used to measure C26:0 lysophosphatidylcholines. Tests considered borderline are re-tested. ABCD1 gene and serum very long chain fatty acids analysis is applied to screen-positive specimens [10].

In the Netherlands, an additional test is added to the initial screening process to ensure that only boys are screened for adrenoleukodystrophy. This 3-tier screening process consists of flow-injection tandem mass spectrometry to measure C26:0 lysophosphatidylcholine, followed by a process to determine the number of X-chromosomes present and then liquid chromatography tandem mass spectrometry is used to measure samples with elevated C26:0 lysophosphatidylcholines. Genotyping for the ABCD1 gene is then performed [8].

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on newborn screening for adrenoleukodystrophy should be commissioned in 2020 and to evaluate the volume and type of evidence on key issues related to newborn screening for adrenoleukodystrophy.

The aim was to address the following questions:

1. What is the incidence of adrenoleukodystrophy in the UK?
2. Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?
3. What is the evidence on the accuracy of currently available screening tests using dried blood spots to detect adrenoleukodystrophy?
4. Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on adrenoleukodystrophy in 2020. The aim of this document is to present the information necessary for the UK NSC to decide this.

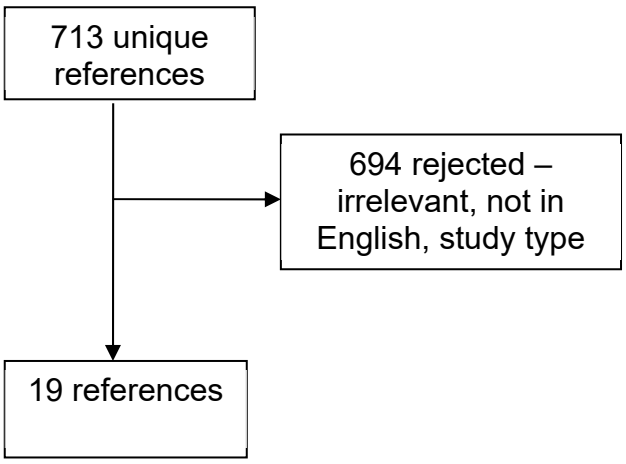
Search methods and results

The searches were conducted on 12 August 2020 on 3 databases: Medline, Embase and the Cochrane Library. The search period was restricted to January 2015 – August 2020. The date cut-off of January 2015 was informed by the searches carried out for the systematic review by Brosco et al [5] which advised the secretary of the US Department of Health and Human Services recommendation to add adrenoleukodystrophy to the RUSP. The detailed search strategies, including exclusion and inclusion criteria are available in Appendix 1. The search returned a total of 713 unique references which were initially sifted by an information scientist for potential relevance. One reviewer assessed 88 titles and abstracts for further appraisal and possible inclusion in the evidence map. Nineteen references were included in the final evidence map. These were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertainty. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2.

A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

Figure 1: Summary of included and excluded publications



Summary of findings

Question 1: What is the incidence of adrenoleukodystrophy in the UK?

Sub-questions:

- What is the proportion of people with a mutation of the ABCD1 gene who will develop symptoms associated with any form of adrenoleukodystrophy?
- What are the age of onset and clinical prognosis of each of these forms?

For question 1, 4 studies met the inclusion criteria and one further UK cost modelling study is briefly described for information. The inclusion and exclusion criteria are summarised in Appendix 1.

For this question we prioritised UK studies. However, as only one UK epidemiological study was identified [11] we have also included 2 studies about the incidence of adrenoleukodystrophy from US screening programmes [9,10] and one study on prevalence in different ethnic groups from a US database [13]. Further information about these 4 references is provided in the abstract reporting tables in Appendix 2.

One UK epidemiological study provided some information relating to this question. This study used data from the British Paediatric Surveillance Unit to describe children with brain white matter disorders and reported lifetime risk of adrenoleukodystrophy [11]. Between 1997 and 2014 this study identified 74 children with adrenoleukodystrophy in the UK, of which 19 were described as having asymptomatic adrenoleukodystrophy. The authors estimated a lifetime risk per million UK live births of 5.7 for adrenoleukodystrophy[*]. This study also reported median age at identification (72 months or 72.5 months for asymptomatic adrenoleukodystrophy) and described early signs and symptoms. The study did not report incidence, clinical prognosis or the proportion of people with a mutation of the ABCD1 gene who will develop symptoms.

The only other UK study identified was an economic modelling study. This study explored the economic impact of introducing newborn screening for adrenoleukodystrophy in the UK and included details of the incidence estimates used for the model [12]. The data sources used for the incidence estimates did not come from UK studies and all but one of the 5 references cited as sources were published prior to 2015. For information, the abstract of this study reported that screening 780,000 newborns annually would identify 18 (95% Confidence Intervals (CI) 12 to 27) boys and 17 (95%CI 12 to 25) girls with adrenoleukodystrophy, of which 10 (95%CI 6 to15) boys

[*] The original version of this paper gave an estimated lifetime risk per million UK live births of 6.6. However, a later correction was published due to an error in the choice of population figures used for the estimate

would develop cerebral childhood adrenoleukodystrophy. The authors also estimated that 7 (95%CI 3 to 12) children with other peroxisomal disorders may be detected. As this was not an epidemiological study, it is not counted within the references number and an abstract reporting table has not been completed.

The other references included for this question were all from the US. Two studies [9,10] reported outcomes from newborn screening programmes in 2 US states. Lee et al (2020) [9] reported the results of screening 52,301 newborns in North Carolina between January and June 2018. Following screening, 3 male infants were confirmed as having adrenoleukodystrophy and 3 female infants were confirmed as heterozygous for adrenoleukodystrophy. The authors stated that this represents an incidence of 1 in 8,717 births. Wiens et al (2019) [10] reported the results of screening 67,836 newborns in Minnesota in 2017. Following screening, 14 infants were confirmed as having adrenoleukodystrophy. The authors stated that this represents a birth prevalence of 1 in 4,845 for all newborns and 1 in 3,878 for males. The remaining reference was a case control study reporting the prevalence of adrenoleukodystrophy by ethnicity, based on data from October 2015 to September 2017 from the US Children's Hospital Association Pediatric Health Information System database [13]. The study reported on children diagnosed with 1 of 4 different leukodystrophies, but also included some separate figures for 111 patients with adrenoleukodystrophy. Prevalence per 100,000 ranged from 0.7 for people classified as 'Asian' to 2.4 for people classified as 'White non-Hispanic'. The highest prevalence reported (3.9 per 100,000) was for individuals described as being of 'multiple' ethnicity.

In summary, no studies reporting the incidence of adrenoleukodystrophy in the UK were returned by the search although an estimate of lifetime risk was identified. Some information on the number of cases detected through newborn screening programmes in the US is available. The studies identified do not address the sub-questions relating to the proportion of people with a mutation of the ABCD1 gene who will develop symptoms or the age of onset and clinical prognosis of different forms of adrenoleukodystrophy.

At present there is an insufficient volume of evidence to justify commissioning an evidence summary of this question.

Question 2: Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?

Two studies met the inclusion criteria for this question. The inclusion and exclusion criteria are summarised in Appendix 1.

No UK studies or cohort studies about predicting future phenotype in asymptomatic individuals were identified. In the absence of such studies, 2 case control studies from the US were included [14,15]. Further information about these 2 references is provided in the abstract reporting tables in Appendix 2.

One case control study analysed plasma samples for Profilin1 antibodies in 94 boys with cerebral adrenoleukodystrophy, 29 boys with adrenoleukodystrophy but no cerebral disease and 30 healthy controls (Orchard et al 2019) [14]. The other case control study explored monocytes and plasma blood samples for levels of antioxidant capacity and superoxide dismutase levels in patients with cerebral adrenoleukodystrophy (n=8) or adrenomyeloneuropathy (n=10), heterozygous female carriers (n=3) and age-matched healthy controls (n=9) (Turk et al 2017) [15]. In this study additional analysis was also conducted on 30 biobank samples from individuals with cerebral adrenoleukodystrophy (n=20) or adrenomyeloneuropathy (n=10).

Both studies found differences between patients and controls. In Orchard et al (2019) [14] anti-Profilin1 antibodies were present in 51% of boys with cerebral adrenoleukodystrophy, 7% of boys with adrenoleukodystrophy but no cerebral disease and 0% of healthy controls. In Turk et al (2017) [15] highest levels of antioxidant capacity and superoxide dismutase activity were shown in healthy controls, with progressively lower levels in heterozygous female carriers, patients with adrenomyeloneuropathy and patients with cerebral adrenoleukodystrophy. Turk et al (2017) [15] also reported analysis of 4 patients with cerebral adrenoleukodystrophy and showed an inverse correlation between superoxide dismutase levels and brain magnetic resonance imaging severity score and decreased superoxide dismutase activity prior to and at the time of cerebral diagnosis. The study authors concluded that anti-Profilin1 and superoxide dismutase respectively may be potential biomarkers for cerebral adrenoleukodystrophy.

The outcomes of these studies describe factors present in different groups of individuals rather than the proportion of individuals with these factors that will develop particular adrenoleukodystrophy phenotypes.

Three additional studies are described below for information.

An additional case control study explored the presence of molecular markers in blood samples from 6 pairs of brothers, where both had adrenoleukodystrophy but only one

had developed cerebral adrenoleukodystrophy [16]. As this small study was unable to identify any statistically significant candidate molecular markers, it has not been counted within the references number.

Although cohort studies describing the natural history of asymptomatic individuals with adrenoleukodystrophy were identified, these studies were not about factors that can predict future phenotype. For example, one retrospective cohort study [17] reviewed 291 magnetic resonance imaging scans taken from 47 asymptomatic boys over a median follow-up period of 18.4 months. These boys all had biochemically or genetically confirmed adrenoleukodystrophy and had a median age of 6.0 years at first scan. All were diagnosed due to a known family history or presence of adrenal insufficiency. The aim of the study was to provide a description of lesion development. Another retrospective cohort study identified was about describing natural disease progression in untreated ABCD1 heterozygous female carriers [18]. Patients (n=32) were either symptomatic (59%) or non-symptomatic (41%) at baseline and had a mean age of 42.8 years. None of the non-symptomatic patients developed symptoms during the study period. These studies are not counted within the references number and abstract reporting tables have not been completed.

In summary, limited evidence was identified on factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase. Two case control studies were identified proposing potential biomarkers for cerebral adrenoleukodystrophy.

The number and type of studies that met the criteria to address this question does not justify commissioning an evidence review at this time as the limited evidence available limits what could be expected from an evidence summary in this area.

Question 3: What is the evidence on the accuracy of currently available screening tests using dried blood spots to detect adrenoleukodystrophy?

Four studies met the inclusion criteria for this question. The inclusion and exclusion criteria are summarised in Appendix 1. Further information about the 4 references is provided in the abstract reporting tables in Appendix 2.

No UK studies on test performance were identified. In the absence of UK studies, we prioritised studies of randomly assigned or consecutively enrolled populations from comparable countries and included 2 studies based on the results of existing US newborn screening programmes [9,10]. As only 2 studies in consecutively enrolled populations were identified we also included 2 case control studies [19,20].

Two studies reported outcomes from newborn screening programmes in 2 US states. These studies were also included in question 1.

Lee et al (2020) [9] reported the results of screening 52,301 newborns in North Carolina between January and June 2018. The index test used was negative ionization high-performance liquid chromatography tandem mass spectrometry to measure C24:0- and C26:0-lysophosphatidylcholine concentrations with re-testing for results above initial cut-off levels. The reference standard was Sanger DNA sequencing to detect the mutation in the ABCD1 gene and was applied to 12 screen-positive specimens. Three males were confirmed to have adrenoleukodystrophy, 3 females were heterozygous for adrenoleukodystrophy, 2 females had other genetic disorders and there were 4 false-positive results. The positive predictive value for adrenoleukodystrophy or other genetic disorders was 67% with a false-positive rate of 0.0057%.

Wiens et al (2019) [10] reported the results of screening 67,836 newborns in Minnesota in 2017. The index test used was negative ion-mode liquid chromatography tandem mass spectrometry to measure C26:0 lysophosphatidylcholine with re-testing of borderline cases. The reference standard was genetic analysis to detect the mutation in the ABCD1 gene coupled with serum very long chain fatty acids analysis, and these were both applied to screen-positive specimens. There were 14 screen positive results (9 males and 5 females), all of which were confirmed to have adrenoleukodystrophy. There were no false positive results giving a positive predictive value of 100%.

Sensitivity, specificity and negative predictive value were not reported in either of these studies and the reference standard was only performed for screen-positive cases.

Two case control studies, both conducted by the same group of authors in India, are also included. Natarajan et al (2019) [19] investigated the sensitivity and specificity of a flow injection ionization-tandem mass spectrometry method using dried blood spots for estimating a panel of lysophosphatidylcholines (C20:0-C26:0), for use in newborn

screening for adrenoleukodystrophy. Natarajan et al (2018) [20] investigated the sensitivity and specificity of liquid chromatography-tandem mass spectrometry using dried blood spots for estimating a panel of lysophosphatidylcholines (C20:0-C26:0), for the identification of suspected cases of adrenoleukodystrophy.

Natarajan et al (2019) [20] included 28 patients with adrenoleukodystrophy and 282 healthy controls. The authors reported a sensitivity of 100% for both elevated C26:0 and C24:0 lysophosphatidylcholines with a specificity of 78.3% and 98.3% respectively for flow injection ionization-tandem mass spectrometry. Natarajan et al (2018) [19] included 21 patients with adrenoleukodystrophy and 375 healthy controls and reported a sensitivity and specificity of 100% for both elevated C26:0 and C24:0 lysophosphatidylcholines for liquid chromatography-tandem mass spectrometry. In both studies, detection of other lysophosphatidylcholines with the index test had lower sensitivity and specificity.

In summary, 2 studies from existing newborn screening programmes provided some information on false positives and positive predictive value of screening for adrenoleukodystrophy. A further 2 case control studies provided some information on sensitivity and specificity. The screening tests or approach reported by the different studies varied.

The number and type of studies that met the criteria to address this question does not justify commissioning an evidence review at this time as the limited evidence available limits what could be expected from an evidence summary in this area.

Question 4: Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?

Nine studies met the inclusion criteria for this question. The inclusion and exclusion criteria are summarised in Appendix 1.

No UK studies or comparative studies were identified that compared the early initiation of treatment in screen detected or asymptomatic populations to initiation of treatment following clinical detection.

In the absence of such studies, 9 case series or cohort studies from North America and Europe were included. The included studies were mainly retrospective and fell broadly into 3 types. Two studies included both patients detected due to a family history of adrenoleukodystrophy and patients detected due to clinical symptoms and explored potential factors associated with better treatment outcomes [21,22]. Four studies described treatment outcomes for patients described as having early stage disease [23,24,25,26]. Three studies described the management and treatment of individuals who were detected through newborn screening or at an asymptomatic stage [6,27,28]. However, the focus of these studies was on describing disease progression and management for these individuals with limited information about the outcome of treatment.

Most studies related to treatment with haematopoietic stem cell transplant, however 2 studies were about treatment with gene therapy and Lorenzo's oil respectively. Further information about these 9 references is provided in the abstract reporting tables in Appendix 2.

Two retrospective cohort studies described outcomes for patients who had received haematopoietic stem cell transplant for cerebral adrenoleukodystrophy and included patients detected due to a family history of adrenoleukodystrophy and patients detected due to clinical symptoms.

Raymond et al (2019) [21] included 65 patients treated at 5 centres in the US and France between 1997 and 2010. In this study, 43% of patients had been identified due to family history rather than due to clinical presentation with symptoms. The authors reported that early treatment was predictive of major functional disability-free survival. Kuhl et al (2018) [22] included 36 patients treated at one centre in Germany between 1997 and 2014. Eighteen (50%) of the included patients were described as being pre-symptomatic, of which 13 (36%) were diagnosed by family screening. Other reasons for diagnosis were given as symptoms or Addison's disease. The proportion of patients who were alive at a median follow-up of 108 months was reported separately for pre-symptomatic (89%) and symptomatic patients (61%), as was event-free survival (72%

and 6% respectively). Results were also reported separately for patients with lower or higher demyelination scores pre-transplant. The study authors described their analysis as explorative and did not conduct a statistical comparison between different sub-groups of patients.

In 4 studies, all included patients were described as having early stage disease at the time of treatment.

Two US retrospective cohort studies described outcomes for patients who had received haematopoietic stem cell transplant for cerebral adrenoleukodystrophy. Pierpont et al (2020) [23] included 33 patients who had received transplant at an early stage, prior to neurocognitive signs of disease at one centre between 1991 and 2017. Pierpont et al (2017) [24] included 62 patients who had received transplant at an early stage (a pre-transplant magnetic resonance imaging severity score of less than 10) at one centre between January 1991 and October 2014. In both studies it is not clear how patients were detected. Pierpont et al (2020) [23] reported that patients with more severe lesions pre-transplant had worse neurocognitive scores, neuropsychiatric symptoms and disease progression on magnetic resonance imaging than patients with less severe lesions. Pierpont et al (2017) [24] reported that higher pre-transplant magnetic resonance imaging severity scores were associated with a steeper decline in neurocognitive functioning during the 5-year follow-up.

One retrospective study from one centre in the Netherlands explored outcomes for 5 adults who had received a haematopoietic stem cell transplant as a child (van Geel et al 2015) [25]. All patients were diagnosed due to family history or due to adrenocortical insufficiency and in all cases cerebral adrenoleukodystrophy was detected at a clinically asymptomatic stage. The authors reported that 3 of the 5 patients developed signs of myelopathy in adulthood.

In addition, one multi-centre, international prospective cohort study described outcomes for 17 patients with early stage cerebral adrenoleukodystrophy who received gene therapy between October 2013 and July 2015 (Eichler et al 2017) [26]. It is not clear how these patients were detected. This study reports the results of interim analysis at a median follow-up of 29.4 months. The authors reported that 88% patients were alive and free of major functional disability with minimal clinical symptoms.

Three further studies described the management and treatment of individuals who were detected through newborn screening or at an asymptomatic stage, for example, due to family history. However, the focus of these studies was about describing disease progression and management for these individuals with limited information about the outcome of treatment.

One case series described the management of 2 infants with adrenoleukodystrophy detected by newborn screening in the US (Eng and Regelmann 2019) [6]. This study was published as a brief report and did not have a full abstract. The full text of the paper describes the monitoring and management of these infants up to the age of 20 months and 28 months respectively. Both infants received treatment with hydrocortisone.

One retrospective cohort study described the long-term follow-up of 48 patients at 2 centres in Canada (Tran et al 2017) [27]. All patients were diagnosed with adrenoleukodystrophy between 1989 and 2012. Seventeen patients were symptomatic at the time of diagnosis and 31 individuals, identified by positive family history of adrenoleukodystrophy, were asymptomatic. The history of individual patients is described including the number of asymptomatic patients that developed cerebral adrenoleukodystrophy, adrenomyeloneuropathy or Addison disease. Treatments received are also described including adrenal substitution, Lorenzo's oil, co-enzyme Q10 and haematopoietic stem cell transplant. A summary of outcomes for patients who received haematopoietic stem cell transplant (n=7) is described (number who remained stable or died due to haematopoietic stem cell transplant complications). However, treatment outcomes for individual patients are not described.

One cohort study described the effect of Lorenzo's oil on plasma C26:0 concentration on 104 asymptomatic patients with adrenoleukodystrophy (Ahmed et al 2016) [28]. Patients were identified through testing due to family history or due to a diagnosis of Addison's disease and were treated at one US centre between 2000 and 2014. The authors concluded that the administration of Lorenzo's oil reduces abnormally high plasma C20:0 concentrations.

In summary, a large number of new studies were identified about the treatment of adrenoleukodystrophy. However, no studies directly compared the effectiveness of treatments for individuals identified pre-symptomatically with those presenting with clinical symptoms.

The volume of evidence identified would be sufficient for more detailed consideration in an evidence summary. However, the conclusions that could be expected of an evidence summary would be limited by the type of evidence available.

Conclusions

New studies were identified for each of the 4 questions considered in this evidence map. The area with the largest volume of evidence available related to the treatment of adrenoleukodystrophy. However, the benefits of performing haematopoietic stem cell transplant for cerebral adrenoleukodystrophy at an early stage was acknowledged in the previous evidence map. It is therefore unlikely that a review of the available evidence in this area of treatment alone would lead to a change in the UK NSC's position. The evidence base relating to the other key questions about UK incidence, predicting adrenoleukodystrophy phenotype and the accuracy of screening tests was limited in relation to both the volume and type of evidence available.

With this in mind commissioning a full, more sustained review on newborn screening for adrenoleukodystrophy is not justified at the current time.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to newborn screening for adrenoleukodystrophy is currently insufficient to justify an update review at this stage and so should be re-considered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2015 to 12 August 2020

SEARCH STRATEGIES:

Medline search 1			**Embase search 1**		
1	Adrenoleukodystrophy/	1728	1	Adrenoleukodystrophy/	3535
2	(adrenoleukodystroph* or x-linked leukodystroph* or adrenomyeloneuropath* or xald or x-ald or c-cald or amn).ti,ab,kw.	2639	2	(adrenoleukodystroph* or x-linked leukodystroph* or adrenomyeloneuropath* or xald or x-ald or c-cald or amn).ti,ab,kw.	3552
3	((child* or cereb*) adj3 ald).ti,ab,kw.	204	3	((child* or cereb*) adj3 ald).ti,ab,kw.	336
4	(c26* adj5 (lpc or lysophosphatidylcholine or fatty acid*)).ti,ab,kw.	210	4	(c26* adj5 (lpc or lysophosphatidylcholine or fatty acid*)).ti,ab,kw.	272
5	(c26* adj3 (screen* or detect* or test* or level? or elevat*)).ti,ab,kw.	105	5	(c26* adj3 (screen* or detect* or test* or level? or elevat*)).ti,ab,kw.	168
6	1 or 2 or 3 or 4 or 5	3098	6	1 or 2 or 3 or 4 or 5	4783
7	(comment or letter or editorial).pt. or case report.ti,ab.	2180223	7	(editorial or letter or note or conference*).pt. or case report.ti,ab.	7540380
8	6 not 7	2882	8	6 not 7	3496
9	exp animals/ not humans/	4727421	9	(exp animals/ or nonhuman/) not human/	6548551
10	8 not 9	2659	10	8 not 9	3084
11	limit 10 to (english language and yr="2015 -Current")	465	11	limit 10 to (english language and yr="2015 -Current")	562
Medline search 2			**Embase search 2**		
1	adrenal insufficiency/	6926	1	adrenal insufficiency/	11756
2	(adrenal adj3 (insufficien* or hypofunction)).ti,ab,kw.	6555	2	(adrenal adj3 (insufficien* or hypofunction)).ti,ab,kw.	9361
3	1 or 2	10558	3	1 or 2	14595
4	Neonatal Screening/	10182	4	Newborn Screening/	19129
5	((neonat* or newborn?) adj2 (screen* or detect* or diagnos* or test*)).ti,ab,kw.	18992	5	((neonat* or newborn?) adj2 (screen* or detect* or diagnos* or test*)).ti,ab,kw.	28025
6	4 or 5	23117	6	4 or 5	33798
7	3 and 6	50	7	3 and 6	123
8	exp Infant, Newborn/	608058	8	exp newborn/ or newborn care/	534306
9	(neonat* or newborn?).ti,ab,kw.	385720	9	(neonat* or newborn?).ti,ab,kw.	478840
10	8 or 9	790560	10	8 or 9	740441
11	Mass Screening/	103552	11	Mass Screening/ or screening/ or screening test/	297088
12	Early Diagnosis/	26576	12	Early Diagnosis/	106954
13	Dried Blood Spot Testing/	1478	13	Dried Blood Spot Testing/	3922
14	exp Mass Spectrometry/	245717	14	exp Mass Spectrometry/	469133
15	Chromatography, Liquid/	51252	15	liquid chromatography/	84282

16	(screen* or test* or detect* or diagnos*).ti,ab,kw.	7193235	16	(screen* or test* or detect* or diagnos*).ti,ab,kw.	9506305
17	dried blood spot*.ti,ab,kw.	4275	17	dried blood spot*.ti,ab,kw.	6578
18	(mass spectromet* or lcms or lc-ms or ms).ti,ab,kw.	491213	18	(mass spectromet* or lcms or lc-ms or ms).ti,ab,kw.	658484
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	7555573	19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	10025620
20	3 and 10 and 19	374	20	3 and 10 and 19	575
21	7 or 20	374	21	7 or 20	589
22	limit 21 to (english language and yr="2015 -Current")	106	22	conference*.pt.	4616519
			23	21 not 22	389
			24	limit 23 to (english language and yr="2015 -Current")	136

Cochrane search 1	
#1	MeSH descriptor: [Adrenoleukodystrophy] explode all trees
#2	((adrenoleukodystroph* or "x-linked leukodystroph*" or adrenomyeloneuropath* or xald or x-ald or c-cald or amn)):ti,ab,kw OR (((child* or cereb*) NEAR/3 ald)):ti,ab,kw
#3	((c26* NEAR/5 (lpc or lysophosphatidylcholine or fatty acid*))):ti,ab,kw OR ((c26* NEAR/3 (screen* or detect* or test* or level* or elevat*))):ti,ab,kw
#4	#1 or #2 or #3
Cochrane search 2	
#1	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2	((adrenal NEAR/3 (insufficien* OR hypofunction))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Infant, Newborn] explode all trees
#5	MeSH descriptor: [Neonatal Screening] explode all trees
#6	(neonat* or newborn*):ti,ab,kw
#7	#4 or #5 or #6
#8	#3 and #7

Results by database

Medline	**571**
Embase	**657**
Cochrane Library	**25**
Total	**1,253**

After the exclusion of duplicates, 713 references remained.

Inclusions and exclusions

Publications not in the English language, case reports, conference abstracts, trial protocols and comment/editorials/letters were excluded.

Eligibility for inclusion in the map

Question 1

- population: individuals with adrenoleukodystrophy
- intervention: N/A
- comparator: N/A

- outcomes: any observable characteristic such as: incidence of adrenoleukodystrophy, timing of onset of symptoms, development of one of the adrenoleukodystrophy phenotypes and related health outcomes, mortality
- study design: cross-sectional studies, cohort studies, systematic reviews and reports from neonatal screening programmes should be prioritised for reporting

Question 2

- population: asymptomatic individuals with the ABCD1 mutation and/or diagnosis of adrenoleukodystrophy
- exposure: any clinical or laboratory parameter related to disease progression such as white matter lesions, synacthen test for adrenal insufficiency
- comparator: any or none
- outcomes: childhood cerebral adrenoleukodystrophy in affected males; adrenomyeloneuropathy in affected males; Addison disease in affected males; adrenomyeloneuropathy in female carriers
- study design: cohort studies and systematic reviews should be prioritised for reporting. Case control studies can also be reported

Question 3

- population: newborn babies
- index test: any standalone test or any series of sequential tests used to screen for adrenoleukodystrophy, such as flow injection analysis tandem mass spectrometry to detect the very long chain fatty acid marker C26:0 lysophosphatidylcholine, followed by tandem mass spectrometry coupled with High Performance Liquid Chromatography to quantify C26:0 lysophosphatidylcholine in all positive blood spots
- comparator: none or any
- reference standard: Sanger DNA sequencing to detect ABCD1 mutation or any other specific ‘gold standard’ as determined by the study itself
- target condition: adrenoleukodystrophy (with particular focus on childhood cerebral adrenoleukodystrophy)
- outcomes: sensitivity; specificity; positive and negative predictive values; likelihood ratios; area under the curve; incidental findings, for example, other peroxisomal conditions
- study design: a hierarchical approach should be taken: studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised in the reporting as more likely to justify the development of an evidence summary. If none or few of these designs are found, other study designs should be reported, for example, case-control studies

Question 4

- population: infants and children with adrenoleukodystrophy identified through screening should be prioritised but, in the absence of such studies or in the presence of a low volume of such studies, those in other early detected cases should be reported, for example siblings
- intervention: early haematopoietic stem cell transplant for childhood cerebral adrenoleukodystrophy; early steroid treatment for adrenal insufficiency; any other early treatments
- comparator: later treatment of children identified through clinical presentation/ usual diagnostic pathway with any of the interventions listed above; no comparator

- outcomes: delay or reduction in morbidity and mortality associated with adrenoleukodystrophy; harms of haematopoietic stem cell transplant and other treatments; overtreatment; improved quality of life; any other outcome
- study design: a hierarchical approach should be taken: studies in screen detected and asymptomatic populations should be prioritised as well as randomised controlled trials, cohort studies or systematic reviews of these. If none, or few or these designs are found, other study designs can be reported

Appendix 2 – Abstract reporting tables

Question 1 – What is the incidence of adrenoleukodystrophy in the UK?

UK studies

TITLE	
Citation	Stellitano et al (2016) [11]
BACKGROUND	
Study type	National epidemiological study
Objectives	To report the UK epidemiology of brain white matter disorders of children identified via a national prospective study
Components of the study	*Population* – Children with brain white matter disorders (including adrenoleukodystrophy) included in the British Paediatric Surveillance Unit system between May 1997 and November 2014 *Intervention* – N/A *Comparator* – N/A
OUTCOMES	
Outcomes reported	• number of children with a diagnosis of adrenoleukodystrophy • lifetime risk per million UK live births • median age at presentation • early signs and symptoms Outcomes specified by the commissioning document that are not reported include incidence, timing of onset of symptoms, development of one of the adrenoleukodystrophy phenotypes and related health outcomes and mortality [Full text checked]
Conclusions	This paper reports national data and estimates the lifetime risk/million live births for the commonest leukodystrophies, including adrenoleukodystrophy

Non-UK studies

TITLE	
Citation	Lee et al 2020 [9] *NB: This study is also relevant to question 3*
BACKGROUND	
Study type	Study reporting the results of newborn screening for adrenoleukodystrophy
Objectives	To evaluate the performance of a newborn screening assay for adrenoleukodystrophy in one US state (North Carolina)
Components of the study	*Population* – Newborns screened between January and June 2018 *Index test* – Negative ionization high-performance liquid chromatography tandem mass spectrometry to measure C24:0- and C26:0-lysophosphatidylcholine concentrations with re-testing for results above initial cut-off levels *Reference standard* – Sanger sequencing of the adenosine triphosphate-binding cassette subfamily D member 1 (ABCD1) gene [Full text checked]
OUTCOMES	
Outcomes reported	*Outcomes relevant to this question:* • number of cases detected by screening • prevalence of adrenoleukodystrophy in North Carolina • results of gene sequencing • description of results from follow-up assessment with the genetics, endocrinology and neurology departments Outcomes specified by the commissioning document that are not reported include timing of onset of symptoms, development of one of the adrenoleukodystrophy phenotypes and related health outcomes and mortality [Full text checked] *See question 3 for test accuracy outcomes*
Conclusions	The newborn screening programme identified infants with adrenoleukodystrophy and with other disorders

TITLE	
Citation	Wiens et al 2019 [10] *NB: This study is also relevant to question 3*
BACKGROUND	
Study type	Study reporting the results of newborn screening for adrenoleukodystrophy
Objectives	To evaluate the performance of a newborn screening assay for adrenoleukodystrophy in one US state (Minnesota)
Components of the study	*Population* – Newborns screened in the first year of a screening programme (2017) *Index test* – Negative ion-mode liquid chromatography tandem mass spectrometry to measure C26:0 lysophosphatidylcholine. Tests considered borderline are re-tested *Reference standard* – ABCD1 gene analysis and serum very long chain fatty acids analysis [Full text checked]
OUTCOMES	
Outcomes reported	*Outcomes relevant to this question:* • number of cases detected by screening • birth prevalence of adrenoleukodystrophy in infants screened in Minnesota • subsequent diagnosis and phenotypes of family members Outcomes specified by the commissioning document that are not reported (for newborns screened) include timing of onset of symptoms, development of one of the adrenoleukodystrophy phenotypes and related health outcomes and mortality *See question 3 for test accuracy outcomes*
Conclusions	The newborn screening programme identified infants with adrenoleukodystrophy and affected family members

TITLE	
Citation	Bonkowsky et al 2018 [13]
BACKGROUND	
Study type	Retrospective case-control study
Objectives	To explore leukodystrophy diagnosis in different racial backgrounds
Components of the study	*Population* – Children aged ≤18 years, diagnosed with one of 4 leukodystrophies (including adrenoleukodystrophy) included in the US Children's Hospital Association's Pediatric Health Information System Database from October 2015 to September 2017 *Intervention* – N/A *Comparator* – N/A
OUTCOMES	
Outcomes reported	• adrenoleukodystrophy prevalence by ethnicity • pathogenic leukodystrophy gene allele frequencies in different racial backgrounds (including ABCD1) Outcomes specified by the commissioning document that are not reported include incidence, timing of onset of symptoms, development of one of the adrenoleukodystrophy phenotypes and related health outcomes and mortality [Full text checked]
Conclusions	The authors concluded that leukodystrophy is underdiagnosed in patients from racial/ethnic minorities in the US

Question 2 – Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?

TITLE	
Citation	Orchard et al 2019 [14]
BACKGROUND	
Study type	Case control study
Objectives	To analyse plasma samples to identify a potential biomarker for cerebral adrenoleukodystrophy

Components of the study	*Population* – Boys with cerebral adrenoleukodystrophy, boys with adrenoleukodystrophy but no cerebral disease and healthy controls (US) *Exposure* – Anti-Profilin1 antibodies in plasma samples *Comparator* – N/A
OUTCOMES	
Outcomes reported	• presence of anti-Profilin1 antibodies • level of anti-Profilin1 antibodies • amount of gadolinium signal • levels of very long chain fatty acids (C26) • plasma B-cell activating factor (BAFF) The outcomes describe factors present in different groups of individuals rather than the proportion of individuals with these factors that will develop particular adrenoleukodystrophy phenotypes
Conclusions	The authors concluded that anti-Profilin1 may be a novel biomarker associated with the development of cerebral adrenoleukodystrophy in boys with adrenoleukodystrophy

TITLE	
Citation	Turk et al 2017 [15]
BACKGROUND	
Study type	Case control study
Objectives	To analyse monocyte and plasma blood samples to explore antioxidant capacity and superoxide dismutase levels as potential biomarkers for cerebral adrenoleukodystrophy
Components of the study	*Population* – Patients with cerebral adrenoleukodystrophy or adrenomyeloneuropathy, heterozygous female carriers and age-matched healthy controls (US) *Exposure* – Antioxidant capacity and superoxide dismutase in monocyte and plasma blood samples *Comparator* – N/A
OUTCOMES	
Outcomes reported	• levels of antioxidant capacity • levels of superoxide dismutase activity • longitudinal superoxide dismutase activity (over time) in patients with cerebral adrenoleukodystrophy

	• correlation between superoxide dismutase levels and brain magnetic resonance imaging severity score in patients with cerebral adrenoleukodystrophy The outcomes describe factors present in different groups of individuals rather than the proportion of individuals with these factors that will develop particular adrenoleukodystrophy phenotypes
Conclusions	The authors concluded that superoxide dismutase may be a potential biomarker for cerebral adrenoleukodystrophy

Question 3 – What is the evidence on the accuracy of currently available screening tests using dried blood spots to detect adrenoleukodystrophy?

Newborn screening studies

TITLE	
Citation	Lee et al 2020 [9] *NB: This study is also relevant to question 1*
BACKGROUND	
Study type	Study reporting the results of newborn screening for adrenoleukodystrophy
Objectives	To evaluate the performance of a newborn screening assay for adrenoleukodystrophy in one US state (North Carolina)
Components of the study	*Population* – Newborns screened between January and June 2018 *Index test* – Negative ionization high-performance liquid chromatography tandem mass spectrometry to measure C24:0- and C26:0-lysophosphatidylcholine concentrations with re-testing for results above initial cut-off levels *Reference standard* – Sanger sequencing of the adenosine triphosphate-binding cassette subfamily D member 1 (ABCD1) gene [Full text checked]
OUTCOMES	
Outcomes reported	*Outcomes relevant to this question:* • positive predictive value • false positive rate

	Outcomes specified by the commissioning document that are not reported include sensitivity, specificity and negative predictive value
Conclusions	The authors concluded that the newborn screening programme successfully identified infants with adrenoleukodystrophy and with other disorders

TITLE	
Citation	Wiens et al 2019 [10] *NB: This study is also relevant to question 1*
BACKGROUND	
Study type	Study reporting the results of newborn screening for adrenoleukodystrophy
Objectives	To evaluate the performance of a newborn screening assay for adrenoleukodystrophy in one US state (Minnesota)
Components of the study	*Population* – Newborns screened in the first year of a screening programme (2017) *Index test* – Negative ion-mode liquid chromatography tandem mass spectrometry to measure C26:0 lysophosphatidylcholines (C26:0-LPC). Tests considered borderline are re-tested *Reference standard* – ABCD1 gene analysis and serum very long chain fatty acids analysis [Full text checked]
OUTCOMES	
Outcomes reported	*Outcomes relevant to this question:* • positive predictive value • false positive rate Outcomes specified by the commissioning document that are not reported include sensitivity, specificity and negative predictive value
Conclusions	The authors concluded that the newborn screening programme successfully identified infants with adrenoleukodystrophy

Case control studies

TITLE	
Citation	Natarajan et al 2019 [19]
BACKGROUND	
Study type	Case control study
Objectives	To determine the sensitivity and specificity of a flow injection ionization-tandem mass spectrometry method for estimating a panel of lysophosphatidylcholines (C20:0-C26:0) in dried blood spots
Components of the study	*Population* – Samples from patients with adrenoleukodystrophy and healthy controls (India) *Index test* – Flow injection ionization-tandem mass spectrometry *Reference standard* – Diagnosis of adrenoleukodystrophy was confirmed by liquid chromatography-tandem mass spectrometry and gas chromatography mass spectrometry [Full text checked]
OUTCOMES	
Outcomes reported	• sensitivity • specificity Outcomes specified by the commissioning document that are not reported include positive and negative predictive value
Conclusions	The authors concluded that the flow injection ionization-tandem mass spectrometry method for estimating C26:0 and C24:0 lysophosphatidylcholines is suitable for screening newborns for adrenoleukodystrophy

TITLE	
Citation	Natarajan et al 2018 [20]
BACKGROUND	
Study type	Case control study
Objectives	To determine the sensitivity and specificity of liquid chromatography-tandem mass spectrometry for estimating a panel of lysophosphatidylcholines (C20:0-C26:0) in dried blood spots
Components of the study	*Population* – Samples from patients with adrenoleukodystrophy and healthy controls (India) *Index test* – Liquid chromatography-tandem mass spectrometry

	Reference standard – Diagnosis of adrenoleukodystrophy was confirmed by estimating plasma very long chain fatty acids [Full text checked]
OUTCOMES	
Outcomes reported	• sensitivity • specificity Outcomes specified by the commissioning document that are not reported include positive and negative predictive value
Conclusions	The authors concluded that liquid chromatography-tandem mass spectrometry for estimating C26:0 and C24:0 lysophosphatidylcholines can be used to detect adrenoleukodystrophy in suspected cases

Question 4 – Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?

TITLE	
Citation	Pierpont et al 2020 [23]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To report neurocognitive, neuropsychiatric and magnetic resonance imaging change for boys who received haematopoietic stem cell transplant for cerebral adrenoleukodystrophy to quantify benchmark treatment outcomes that may be enabled by newborn screening
Components of the study	*Population* – Patients who had received transplant at an early stage, prior to neurocognitive signs of disease, at one US centre between 1991 and 2017 *Intervention* – Haematopoietic stem cell transplant *Comparator* – None [Full text]
OUTCOMES	
Outcomes reported	• progression of radiologic disease on magnetic resonance imaging relative to the severity of the initial lesion

	• neurocognitive outcomes • neuropsychiatric outcomes As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that to realise the full benefits of newborn screening, clinicians must detect very small demyelinating lesions during surveillance and intervene quickly

TITLE	
Citation	Eng and Regelmann 2019 [6]
BACKGROUND	
Study type	Case series
Objectives	To present 2 patients with adrenoleukodystrophy detected by newborn screening with evidence of primary adrenal insufficiency during infancy [Full text checked]
Components of the study	*Population* – Infants with adrenoleukodystrophy detected by newborn screening in the US *Intervention* – Hydrocortisone *Comparator* – None [Full text checked]
OUTCOMES	
Outcomes reported	The study described symptoms and laboratory test results for the infants over time, before and after treatment was initiated including monitoring of: • adrenal insufficiency • growth • skin pigmentation • evidence for cerebral adrenoleukodystrophy As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in

	morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study [Full text checked]
Conclusions	The authors concluded that the natural history of these young patients with adrenoleukodystrophy and adrenal insufficiency supports the identification of newborns through screening for adrenoleukodystrophy

TITLE	
Citation	Raymond et al 2019 [21]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To characterise the natural history of cerebral adrenoleukodystrophy, to describe outcomes after haematopoietic stem cell transplant and identify predictors of treatment outcomes
Components of the study	*Population* – Patients treated at 5 centres in the US and France between 1997 and 2010. Patients were identified due to family history or through clinical presentation with symptoms *Intervention* – Haematopoietic stem cell transplant *Comparator* – None [Full text checked] This study also reported outcomes for patients who did not receive a haematopoietic stem cell transplant. However, a comparison of treatment versus no treatment is not within the scope of this evidence map
OUTCOMES	
Outcomes reported	• neurologic function score • Loes magnetic resonance imaging score • major functional disabilities • 2-year major functional disabilities survival • mortality rate at 100 days and 1 year post-transplant • 5-year overall survival • adverse events • predictors of overall survival • predictors of major functional disabilities survival

	As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that haematopoietic stem cell transplant is an effective treatment for cerebral adrenoleukodystrophy when performed early and proposed survival without major functional disabilities as a relevant indicator of treatment success

TITLE	
Citation	Kuhl et al (2018) [22]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To identify the risks to stable neurocognitive survival after haematopoietic stem cell transplant and to describe sub-groups of patients with distinct clinical long-term outcomes
Components of the study	*Population* – Patients treated at one centre in Germany between 1997 and 2014. Patients were described as pre-symptomatic or symptomatic *Intervention* – Haematopoietic stem cell transplant *Comparator* – None
OUTCOMES	
Outcomes reported	• overall survival • survival without major functional disabilities • event-free survival As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that all patients with favourable neuroimaging who received bone marrow remained stable after transplant while some other patients developed major functional disabilities

TITLE	
Citation	Eichler et al 2017 [26]
BACKGROUND	
Study type	Prospective cohort study
Objectives	To investigate the efficacy and safety of gene therapy for cerebral adrenoleukodystrophy
Components of the study	*Population* – Patients with early stage cerebral adrenoleukodystrophy who received gene therapy between October 2013 and July 2015 (multi-centre international study) *Intervention* – Gene therapy *Comparator* – None [Full text checked]
OUTCOMES	
Outcomes reported	• occurrence of graft-versus-host disease • death • major functional disability • change in neurologic function • extent of lesions on magnetic resonance imaging As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that gene therapy may be a safe and effective alternative to haematopoietic stem cell transplant in boys with early stage cerebral adrenoleukodystrophy

TITLE	
Citation	Pierpont et al 2017 [24]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To characterise neurocognitive outcomes of boys with cerebral adrenoleukodystrophy and early-stage cerebral disease who received haematopoietic stem cell transplant and to identify disease- and treatment-related factors associated with long-term functioning

Components of the study	*Population* – Patients who had received transplant at an early stage (a pre-transplant magnetic resonance imaging severity score of less than 10) at one US centre between January 1991 and October 2014 *Intervention* – Haematopoietic stem cell transplant *Comparator* – None
OUTCOMES	
Outcomes reported	• neurocognitive test performance in 4 domains (verbal comprehension, perceptual (visual) reasoning, working memory and processing speed) • measures of sustained attention, verbal memory, visual-motor integration and fine motor function As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that boys with cerebral adrenoleukodystrophy who have greater than minimal cerebral disease at the time of transplant are at risk of severe, persistent neurocognitive deficits

TITLE	
Citation	Tran et al 2017 [24]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To evaluate the long-term outcome of patients with adrenoleukodystrophy
Components of the study	*Population* – Individuals diagnosed with adrenoleukodystrophy between 1989 and 2012 and followed-up at 2 centres in Canada. Individuals were symptomatic or asymptomatic at diagnosis *Intervention* – Treatments described included adrenal substitution, Lorenzo's oil, co-enzyme Q10 and haematopoietic stem cell transplant. Some individuals did not receive treatment *Comparator* – None [Full text checked]

OUTCOMES	
Outcomes reported	The study described the disease progression and treatment history of individual patients. A summary description of treatment outcome (remained stable or died due to transplant complications) was provided for patients who received haematopoietic stem cell transplant. No other treatment outcomes were reported As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study [Full text checked]
Conclusions	The authors concluded that close monitoring of asymptomatic males resulted in early haematopoietic stem cell transplant and that identification of patients with adrenoleukodystrophy is important to improve neurodevelopmental outcome of asymptomatic males

TITLE	
Citation	Ahmed et al 2016 [28]
BACKGROUND	
Study type	Cohort study
Objectives	To characterise the effect of treatment with Lorenzo's oil on plasma C26:0 concentrations and to determine if there is an association between plasma concentrations of erucic acid or C26:0 and the likelihood for developing brain magnetic resonance imaging abnormalities on asymptomatic boys
Components of the study	*Population* – Asymptomatic patients with adrenoleukodystrophy treated at 1 US centre between 2000 and 2014 *Intervention* – Lorenzo's oil *Comparator* – None
OUTCOMES	
Outcomes reported	• plasma concentrations of erucic acid or C26:0 • risk of developing magnetic resonance imaging abnormalities

	As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that the administration of Lorenzo's oil reduces the abnormally high plasma C26:0 concentrations in patients with adrenoleukodystrophy

TITLE	
Citation	van Geel et al 2015 [25]
BACKGROUND	
Study type	Retrospective cohort study
Objectives	To explore whether adrenomyeloneuropathy still develops in patients with adrenoleukodystrophy who underwent haematopoietic stem cell transplant in childhood
Components of the study	*Population* – Adults treated at one centre in the Netherlands who had received a haematopoietic stem cell transplant as a child *Intervention* – Haematopoietic stem cell transplant. Some individuals did not receive treatment *Comparator* – None
OUTCOMES	
Outcomes reported	• signs of myelopathy in adulthood As this was not a comparative study, the outcomes specified in the commissioning document (delay or reduction in morbidity and mortality, harms of treatment, overtreatment and quality of life) in the context of when treatment is initiated are not addressed by this study
Conclusions	The authors concluded that haematopoietic stem cell transplant in for cerebral adrenoleukodystrophy childhood does not prevent the onset of adrenomyeloneuropathy in adulthood

References

Introduction

1. UK NSC. Commissioning document. Evidence map on newborn screening for x-linked adrenoleukodystrophy. 2020.
2. Solutions for Public Health. Newborn screening for adrenoleukodystrophy: pilot assessment of topic submission. January 2017.
3. Kemper AR, Brosco J, Comeau AM, Green NS, Grosse SD, Jones E, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. Genet Med. 2017, 19(1):121-6.
4. Turk BR, Moser AB, Fatemi A. Therapeutic strategies in adrenoleukodystrophy. Wiener Medizinische Wochenschrift. 2017, 167(9):219-26.
5. Brosco J, Comeau AM, Green NS, Grosse S, Kwon J, Prosser LA, et al. Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence Final Report (v5. 01). 2015.
6. Eng L, Regelmann MO. Early Onset Primary Adrenal Insufficiency in Males with Adrenoleukodystrophy: Case Series and Literature Review. Journal of Pediatrics. 2019, 211:211-4.
7. Salzman R, Kemp S. ALD info: Newborn screening. Last updated 17/7/20. Available from https://adrenoleukodystrophy.info/clinical-diagnosis/newborn-screening (Accessed September 2020).
8. Barendsen RW, Dijkstra IME, Visser WF, Alders M, Bliek J, Boelen A, et al. Adrenoleukodystrophy Newborn Screening in the Netherlands (SCAN Study): The X-Factor. Frontiers in Cell & Developmental Biology. 2020, 8:499.
9. Lee S, Clinard K, Young SP, Rehder CW, Fan Z, Calikoglu AS, et al. Evaluation of X-Linked Adrenoleukodystrophy Newborn Screening in North Carolina. JAMA Network Open. 2020, 3(1):e1920356.
10. Wiens K, Berry SA, Choi H, Gaviglio A, Gupta A, Hietala A, et al. A report on state-wide implementation of newborn screening for X-linked Adrenoleukodystrophy. American Journal of Medical Genetics Part A. 2019, 179(7):1205-13.

Question 1: Incidence (4 references)

11. Stellitano LA, Winstone AM, van der Knaap MS, Verity CM. Leukodystrophies and genetic leukoencephalopathies in childhood: a national epidemiological study. Developmental Medicine and Child Neurology. 2016, 58(7):680-9. [This article has a correction in Developmental Medicine and Child Neurology. 2017, 59(12):1315].
12. Bessey A, Chilcott JB, Leaviss J, Sutton A. Economic impact of screening for X-linked Adrenoleukodystrophy within a newborn blood spot screening programme. Orphanet Journal Of Rare Diseases. 2018, 13(1):179.

9. Lee S, Clinard K, Young SP, Rehder CW, Fan Z, Calikoglu AS, et al. Evaluation of X-Linked Adrenoleukodystrophy Newborn Screening in North Carolina. JAMA Network Open. 2020, 3(1):e1920356.
10. Wiens K, Berry SA, Choi H, Gaviglio A, Gupta A, Hietala A, et al. A report on state-wide implementation of newborn screening for X-linked Adrenoleukodystrophy. American Journal of Medical Genetics Part A. 2019, 179(7):1205-13.
13. Bonkowsky JL, Wilkes J, Bardsley T, Urbik VM, Stoddard G. Association of Diagnosis of Leukodystrophy With Race and Ethnicity Among Pediatric and Adolescent Patients. JAMA Network Open. 2018, 1(7):e185031.

Question 2: Predicting phenotype (2 references)

14. Orchard PJ, Nascene DR, Gupta A, Taisto ME, Higgins L, Markowski TW, et al. Cerebral adrenoleukodystrophy is associated with loss of tolerance to profilin. European Journal of Immunology. 2019, 49(6):947-53.
15. Turk BR, Theisen BE, Nemeth CL, Marx JS, Shi X, Rosen M, et al. Antioxidant Capacity and Superoxide Dismutase Activity in Adrenoleukodystrophy. JAMA Neurology. 2017, 74(5):519-24.
16. Richmond PA, van der Kloet F, Vaz FM, Lin D, Uzozie A, Graham E, et al. Multi-Omic Approach to Identify Phenotypic Modifiers Underlying Cerebral Demyelination in X-Linked Adrenoleukodystrophy. Frontiers in Cell & Developmental Biology. 2020, 8:520.
17. Liberato AP, Mallack EJ, Aziz-Bose R, Hayden D, Lauer A, Caruso PA, et al. MRI brain lesions in asymptomatic boys with X-linked adrenoleukodystrophy. Neurology. 2019, 92(15):e1698-e708.
18. Schirinzi T, Vasco G, Aiello C, Rizzo C, Sancesario A, Romano A, et al. Natural history of a cohort of ABCD1 variant female carriers. European Journal of Neurology. 2019, 26(2):326-32.

Question 3: Screening tests (4 references)

9. Lee S, Clinard K, Young SP, Rehder CW, Fan Z, Calikoglu AS, et al. Evaluation of X-Linked Adrenoleukodystrophy Newborn Screening in North Carolina. JAMA Network Open. 2020, 3(1):e1920356.
10. Wiens K, Berry SA, Choi H, Gaviglio A, Gupta A, Hietala A, et al. A report on state-wide implementation of newborn screening for X-linked Adrenoleukodystrophy. American Journal of Medical Genetics Part A. 2019, 179(7):1205-13.
19. Natarajan A, Christopher R, Netravathi M, Bhat MD, Chandra SR. Flow injection ionization-tandem mass spectrometry-based estimation of a panel of lysophosphatidylcholines in dried blood spots for screening of X-linked adrenoleukodystrophy. Clinica Chimica Acta. 2019, 495:167-73.
20. Natarajan A, Christopher R, Netravathi M, Bhat M, Chandra SR. Liquid chromatography-tandem mass spectrometry method for estimation of a panel of lysophosphatidylcholines in dried blood spots for screening of X-linked adrenoleukodystrophy. Clinica Chimica Acta. 2018, 485:305-10.

Question 4: Treatment (9 references)

21. Raymond GV, Aubourg P, Paker A, Escolar M, Fischer A, Blanche S, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biology of Blood & Marrow Transplantation. 2019, 25(3):538-48.
22. Kuhl JS, Kupper J, Baque H, Ebell W, Gartner J, Korenke C, et al. Potential Risks to Stable Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Children With Cerebral X-linked Adrenoleukodystrophy. JAMA Network Open. 2018, 1(3):e180769.
23. Pierpont EI, Nascene DR, Shanley R, Kenney-Jung DL, Ziegler RS, Miller WP, et al. Neurocognitive benchmarks following transplant for emerging cerebral adrenoleukodystrophy. Neurology. 2020, 95(5):e591-e600.
24. Pierpont EI, Eisengart JB, Shanley R, Nascene D, Raymond GV, Shapiro EG, et al. Neurocognitive Trajectory of Boys Who Received a Hematopoietic Stem Cell Transplant at an Early Stage of Childhood Cerebral Adrenoleukodystrophy. JAMA Neurology. 2017, 74(6):710-7.
25. van Geel BM, Poll-The BT, Verrips A, Boelens JJ, Kemp S, Engelen M. Hematopoietic cell transplantation does not prevent myelopathy in X-linked adrenoleukodystrophy: a retrospective study. Journal of Inherited Metabolic Disease. 2015, 38(2):359-61.
26. Eichler F, Duncan C, Musolino PL, Orchard PJ, De Oliveira S, Thrasher AJ, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. New England Journal of Medicine. 2017, 377(17):1630-8.
6. Eng L, Regelmann MO. Early Onset Primary Adrenal Insufficiency in Males with Adrenoleukodystrophy: Case Series and Literature Review. Journal of Pediatrics. 2019, 211:211-4.
27. Tran C, Patel J, Stacy H, Mamak EG, Faghfoury H, Raiman J, et al. Long-term outcome of patients with X-linked adrenoleukodystrophy: A retrospective cohort study. European Journal of Paediatric Neurology. 2017, 21(4):600-9.
28. Ahmed MA, Kartha RV, Brundage RC, Cloyd J, Basu C, Carlin BP, et al. A model-based approach to assess the exposure-response relationship of Lorenzo's oil in adrenoleukodystrophy. British Journal of Clinical Pharmacology. 2016, 81(6):1058-66.