UK National Screening Committee

UK National Screening Committee (UK NSC)

Newborn screening for adrenoleukodystrophy

Date: 05 March 2021

Contents

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for adrenoleukodystrophy (ALD) meets the UK NSC criteria for a systematic population screening programme.

Current Recommendation

2. The UK NSC currently does not recommend systematic population screening for ALD in newborns. The Committee based this recommendation on the evidence provided by the 2017 assessment of newborn screening for ALD which was carried out by Solutions for Public Health and was based on a combination of scoping review and early evidence map methodology.

Evidence Map

3. The 2020 evidence map was undertaken by Solutions for Public Health, in accordance with the triennial review process: https://www.gov.uk/government/publications/uk-NSC-evidence-review-process/uk-NSC-evidence-review-process

4. The aim of the 2020 evidence map was to address the gaps in the evidence from the 2017 report through the following questions:

a. What is the incidence of adrenoleukodystrophy in the UK?

    - 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?

b. Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?

c. What is the evidence on the accuracy of currently available screening tests using dried blood spots to detect adrenoleukodystrophy?

d. 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 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 ALD at the present time.

5. The conclusion of the 2020 evidence map is that the current recommendation should be retained and therefore whole population screening for ALD in newborns should not be introduced in the UK. This is for the following reasons:

    a. Nineteen references were included in the final evidence map

    b. For question 1 on incidence, only one UK epidemiological study was found that estimated a lifetime risk per million UK live births of 5.7 for adrenoleukodystrophy. Three further studies provided some information on the number of cases detected through newborn screening programmes in the US. None of the studies identified for question 1 addressed the sub-questions

    c. In relation to question 2, 2 case control studies were identified proposing that anti-Profilin1 and superoxide dismutase may be potential biomarkers for cerebral adrenoleukodystrophy

    d. For question 3, 4 studies were included: 2 studies from existing newborn screening programmes in the US provided some information

on false positives and positive predictive value of screening for ALD, and 2 case control studies from India provided some information on sensitivity and specificity. The screening tests or approach reported by the different studies varied

e. Nine studies (a mixture of case series and cohort studies) met the inclusion criteria for question 4 on treatment. The focus of these studies was on describing disease progression and management in individuals with limited information about the outcome of treatment. No studies were identified that directly compared the effectiveness of treatments for individuals identified pre-symptomatically with those presenting with clinical symptoms

f. In summary, although there might be sufficient evidence to commission an evidence summary on the treatment, it is unlikely that a review of the available evidence in this area alone would lead to a change in the UK NSC's position. The evidence relating to the other key questions about UK incidence, predicting ALD phenotype and the accuracy of screening tests was limited in relation to both volume and type and so an evidence summary is not currently justified

Consultation

6. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 11 stakeholders (See Annex A).

7. The public consultation closed on 5 January 2021. The total number of consultation responses received was 35.

8. Comments were received from the following stakeholders:

    a. Royal College of Paediatrics and Child Health

    b. Alex The Leukodystrophy Charity

    c. Zellweger UK

    d. Alex Hamilton – Syncona, SwanBio Therapeutics

    e. 31 members of the public with personal experience of ALD or Zellweger Spectrum Disorder

9. The consultation comments received are presented below in Annex B.

10. The Royal College of Paediatrics and Child Health indicated that it agrees with the comments and conclusions made by the evidence map.

11. Of the 35 responses received, 7 were from relatives of someone with Zellweger Spectrum Disorder (ZSD) and one response was from the charity Zellweger UK. They expressed their support for newborn screening for ALD as this would lead to the identification of patients with ZSD also. While there is no cure for ZSD, Zellweger UK and the families they support think that newborn screening would be beneficial because it would provide early knowledge of the condition, prevent a diagnostic odyssey and, for the worst affected children, it would allow families to spend quality time with their babies focusing on improving their wellbeing during the child's short life.

12. The remaining 27 responses referred to ALD.

13. All members of the public shared their own very personal experiences of ALD or ZSD. They all spoke of the devastating physical, mental and economic impact that the progressive neurodegenerative or lethal nature of these conditions has had and continues to have not only on the affected individual but on the broader family. These included depression and feelings of guilt for either passing on the faulty gene or for having a better outcome than their sibling. Responses were received from parents, siblings, relatives and carers of individuals affected by ALD, adrenomyeloneuropathy (AMN) or ZSD, as well as from people who are themselves carriers of the ALD mutation or who are affected by AMN.
    Response: the personal stories submitted by the members of the public are an important statement of the effect that a diagnosis of ALD and ZSD has on individuals and their families and friends. The UK NSC acknowledges this and is grateful for those many responses from such families and friends and their contribution to the consultation process.

14. The following themes were reflected across stakeholders' comments:

    a. Newborn screening would enable early diagnosis and allow monitoring and identification of the potential risks of developing Addison's disease and cerebral ALD soon after birth thereby avoiding a long diagnostic odyssey and enabling early treatment

    b. Screening is already happening in many states in the US and in the Netherlands. Newborn screening should therefore also be implemented in the UK

c. Screening to identify affected individuals and early knowledge of carrier status would be a comfort to families. It would also transform families' reproductive choices and enable pre-implantation genetic diagnosis

d. Better clinical management and awareness of the condition is needed because clinicians often lack awareness of the severity of this genetic condition. Newborn screening could be a "safety net" as it would be the ideal vehicle to alert endocrinologists about Addison's disease and ALD in general

e. Screening would enable more research on potential treatments. It would enable patients to participate in clinical trials to establish whether novel therapies are effective and safe, as well as better epidemiological data with a better understanding of the real burden of disease in the UK

f. Screening would benefit also family members other than the individual immediately affected, including women who are often misdiagnosed with multiple sclerosis and offered inappropriate treatments

Response: this evidence map concluded that, although there might be a sufficient volume of evidence to commission an evidence summary on the treatment, it is unlikely that a review of the available evidence in this area alone would lead to a change in the UK NSC's position. The evidence relating to the other key questions about UK incidence, predicting ALD phenotype and the accuracy of screening tests was limited in relation to both volume and type. Uncertainties remain more broadly about the impact of receiving an early diagnosis of ALD particularly for those who do not go on to develop childhood cerebral ALD (CCALD), but also for those diagnosed with other peroxisomal disorders. This is relevant because there are no established treatment options for non-CCALD patients and the same applies to many other peroxisomal disorders. Therefore, screening would be unlikely to improve clinical outcomes in these patients. Enabling reproductive choices and enabling pre-implantation genetic diagnosis is recognised as being important but again predicting the exact phenotype with the current state of knowledge means that further clarity and research in this area, is required to more fully understand the benefits when reproductive decisions are being made. Hence, the conclusion of the evidence map was that an evidence summary is not justified at the current time and so the topic should be re-considered in 3-years' time or sooner if significant evidence is published before this time.

Population screening is delivered in large populations of predominantly healthy people and one of the UK NSC's aim is to maintain oversight of the

evidence relating to the balance of good and harm of existing screening programmes, as well as possible new ones. Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. A systematic literature search is undertaken, and titles and abstracts are sifted to identify the relevant literature. For some references, the full-text may be reviewed for clarity but a formal quality appraisal of the evidence is outside the scope of an evidence map. This evidence map has been developed to assess whether a more sustained review of the evidence relating to newborn screening for ALD should be commissioned at the present time. The aim of this evidence map is to present the information necessary for the UK NSC to decide this. Evidence maps, as well as all the other evidence products commissioned by the UK NSC are produced in accordance to the UK NSC evidence review process published on the GOV.UK webpage and available to the public: https://www.gov.uk/government/publications/uk-NSC-evidence-review-process

The aim of the process is to ensure that each topic is addressed in a proportionate manner and to provide reassurance to stakeholders that decisions are grounded in, and informed by, up to date evidence.

15. Another point made by most consultees was that newborn screening for ALD would enable early initiation of bone marrow transplant which would offer significantly better outcomes than if ALD were diagnosed clinically due to detection of Addison's or other symptoms later in life. For example, Alex TLC noted that their database holds records for a number of boys who received transplants in an early stage of progression as well as for some boys who were transplanted at a late stage of cerebral ALD. Their records suggest that only 10/42 probands are alive and in good condition compared to all 28 siblings who were identified when asymptomatic. Gene therapy was also highlighted as very promising new treatment option, noting that a National Institute for Health and Care Excellence (NICE) highly specialised technologies (HST) appraisal would be held on 21 January 2021 to discuss fast tracking gene therapy for NHS commissioning.

Response: the UK NSC acknowledges that regular monitoring 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 bone marrow transplant constitutes usual clinical care for all boys known to have been diagnosed with ALD. The question on the benefits of early treatment compared to initiation of treatment following clinical detection is indeed an important one. The evidence map sought to address this by looking at evidence from infants and children with ALD identified through screening or from other early detected cases such as siblings, which

would constitute a good proxy for newborn screening. However, no studies directly compared the effectiveness of treatments for individuals identified pre-symptomatically with those presenting with clinical symptoms. This outlines a gap in the evidence base which would benefit from further research. The fact that the one of consultees (Alex TLC) outlined some data held in their database about treatment outcomes is a step in the right direction towards filling the evidence gaps. We would therefore urge stakeholders to publish this treatment outcome data in a peer reviewed journal, as well as any other additional data, so it might be taken into consideration and evaluated in the future.

Similarly, if significant peer-reviewed data should be published on gene therapy or any other new treatment option before the next review cycle in 3-years, it could be submitted via the UK NSC's early update process, so it might be taken into consideration and evaluated.

An analysis of published peer reviewed literature offers some reassurance about the quality of the evidence and is an essential element of the rapid review process. Different levels of evidence are considered for each review and evidence map, depending on the questions under consideration. The different types of evidence will follow the accepted hierarchy of evidence, that is systematic reviews, meta-analyses, randomised controlled trials, cohort studies, case-control studies, cross-sectional surveys, case reports. The UK NSC aims to ensure that screening does more good than harm at reasonable cost because screening is delivered in large populations of predominantly healthy people. This approach of evaluating evidence published in peer review journals is in line with the 2014 House of Commons Science and Technology Committee Report on health screening which recommended that the evidential barrier to the introduction of a screening programme should remain high (https://publications.parliament.uk/pa/cm201415/cmselect/cmsctech/244/24402.htm)

16. One stakeholder (Alex TLC) made the following pleas to the UK NSC, that:

    a. a named medical specialist with up-to-date and specific knowledge and experience of ALD will be present at further evidence reviews

    b. appropriate patient representation will be considered/permitted during the consultation/evidence review

    c. NSC will consider allowing representation for Zellweger's patients during further evidence reviews. We feel strongly that the views of

parents of Zellweger patients will be essential for comprehensive review of the perceived impact for this cohort of adding ALD to the newborn screening programme

Response: expert input is sought throughout the whole evidence review process, from the initial scoping stages all the way to prior to public consultation and afterwards. This applies to all the topics considered by the UK NSC and it has been the case for this evidence map on ALD also. The document was considered within the UK NSC's advisory structures and by the UK NSC membership. The expertise within these structures is broadly based and relevant to this condition. For example, the Fetal, Maternal and Child Health Reference Group which advises the UK NSC on all matters relating to antenatal, newborn and childhood conditions benefits from the expertise of a paediatrician and a consultant in metabolic medicine with knowledge and experience of ALD, as well as the broader expertise of neonatology, public health, ethics and screening experts, and patient and public voice representatives.

This is the first time that the UK NSC has publicly consulted on screening for ALD, since its addition in 2017 to the list of conditions that the UK NSC reviews on a regular basis. The UK NSC is pleased with the high level of patient and public involvement. This first public consultation has given the opportunity to individuals and organisations to register as stakeholders, which will ensure that they are notified whenever there is any UK NSC activity on this topic thereby enabling patient representation to be considered during the consultation process.

Zellweger patients are welcome to register as stakeholders interested in the topic of screening for ALD and they are welcome to participate as stakeholders to future consultations on ALD.

17. Two stakeholders noted that some of the terminology of the webpage relating to ALD is misleading and/or "does not reflect the progressive neurodegenerative or lethal nature of this condition adequately".

    Response: the wording on the webpage on ALD will be reviewed and rephrased appropriately as required to improve clarity.

18. One stakeholder (Alex TLC) flagged up various papers as further evidence for submission.

    Response: The reviewers considered the further evidence submitted by Alex TLC. The search dates for this evidence map were between January 2015 to 12 August 2020. The reviewers noted that many of the references submitted

by the stakeholder fall outside the scope of this evidence map due to being published prior to 2015 or because they are reports rather than peer reviewed articles. Three of the papers submitted were already included in the evidence map and others were detected by the search but excluded because they did not meet the inclusion criteria outlined in the evidence map. There are 2 papers relating to the question on the test (Tang et al 2020 and Hall et al 2020) that might have been included or at least mentioned in the map if they had been published sooner. However, one was published in October 2020. The other does have an online publication date from a number of days before the search but it was not listed in Medline until much later and was therefore not detectable by the search. Though these 2 papers were not included in this evidence map, they could be eligible for inclusion in subsequent update reviews.

Recommendation

19. The Committee is asked to approve the following recommendation:

A systematic population screening programme for adrenoleukodystrophy is not recommended

Annex A: List of organisations contacted

1. Genetic Alliance
2. Metabolic Support UK
3. British Inherited Metabolic Disease Group
4. UK Newborn Screening Laboratories Network
5. Alex - The Leukodystrophy Charity
6. Faculty of Public Health
7. Royal College of General Practitioners
8. Royal College of Physicians
9. Royal College of Physicians and Surgeons of Glasgow
10. Royal College of Physicians of Edinburgh
11. Royal College of Paediatrics and Child Health

UK National Screening Committee

Annex B: Consultation comments

1. Royal College of Paediatrics and Child Health

Name:	Comments received on behalf of Dr Ranveer Sanghera	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Paediatrics and Child Health		
Role:			
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required*.
General	**General**	**On review of the document, the reviewer agrees with the comments and conclusions made.**

UK National Screening Committee

2. Alex TLC

Name:	Sara Hunt	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Alex, The Leukodystrophy Charity (Alex TLC)		
Role:	**Chief Executive Officer of Alex TLC, patient voice representative**		

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

Yes

Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic?
Please see below for more information

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Consultation web page	More about ALD	The text in this section does not reflect the progressive neurodegenerative or lethal nature of this condition adequately. In our view this diminishes appreciation of the appalling emotional, educational and wider family impacts, and long-term health and social care costs of late, missed or mis-diagnoses. Alex TLC staff, and the

		patients and families we represent, are constantly affected by these deficiencies, made harder for us all by growing international experience of effective screening. We would therefore make the following pleas to the National Screening Committee, that: (a) a named medical specialist with up-to-date and specific knowledge and experience of ALD will be present at further evidence reviews. (b) appropriate patient representation will be considered/permitted during the consultation/evidence review. (c) NSC will consider allowing representation for Zellweger's patients during further evidence reviews. We feel strongly that the views of parents of Zellweger patients will be essential for comprehensive review of the perceived impact for this cohort of adding ALD to the newborn screening programme.
Page 5, para 4 Page 5, para 5 Page 6, para 3	Addison's Disease in affected males is characterised by…. Adrenoleukodystrophy phenotypes develop over time and are often preceded by adrenal insufficiency in males Available standard therapy	80% of males with ALD develop adrenal insufficiency (Addison's Disease, AD). Unfortunately, adrenal symptoms are often aspecific/misdiagnosed, especially in young children, and the path to a diagnosis can therefore be a lengthy odyssey. Multiple potentially life-threatening episodes/admissions often occur before diagnosis. It is documented that adrenal crisis results in preventable deaths in ALD patients (see Ronghe et al and case studies below), yet highly effective treatment can be instituted with timely diagnosis. Furthermore, failure to make rapid diagnosis of AD precludes timely diagnosis of ALD in such

Page 12 Page 16	Identification of boys who would not go on to develop cerebral ALD Q2 Factors to predict phenotype Q4 Early initiation of treatment vs treatment initiated with clinical detection	patients, who then often present with symptomatic cerebral ALD too advanced for further therapy. We also know from published and anecdotal evidence that an AD diagnosis does not always lead to a timely ALD diagnosis. This precludes definitive treatment of CALD at early stage which in turn impacts long term neurological function and survival deleteriously. Such delays have potentially grave implications for the patient and their family as illustrated by the patient case studies listed at the end of this section. To state that ALD phenotypes are often preceded by adrenal insufficiency in males implies that adrenal insufficiency is easy to diagnose and will lead to effective clinical diagnosis of ALD. However, the only comprehensive survey of this subject in the UK (Ronghe et al, reporting a decade's experience in South West England) found that diagnosis of Addison's Disease followed that of ALD in 50% of cases rather than preceding it. Alex TLC's experience and beneficiary reports further emphasise the difficulties of Addisonian diagnoses and relevant testing for ALD. **Further evidence for submission:** The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration

		Huffnagel et al https://pubmed.ncbi.nlm.nih.gov/30252065/ Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes Polgreen et al https://pubmed.ncbi.nlm.nih.gov/21279382/ Adrenoleukodystrophy in the Differential Diagnosis of Boys Presenting with Primary Adrenal Insufficiency without Adrenal Antibodies Ryalls et al https://pubmed.ncbi.nlm.nih.gov/32394691/ Adrenal Insufficiency In Asymptomatic Adrenoleukodystrophy Patients Identified By Very Long-Chain Fatty Acid Screening Dubey et al https://pubmed.ncbi.nlm.nih.gov/15812458/ Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death Erichsen et al https://pubmed.ncbi.nlm.nih.gov/19011006/ Premature mortality in patients with Addison's disease: a population-based study Bergthorsdottir et al https://pubmed.ncbi.nlm.nih.gov/16968806/

		The importance of testing for adrenoleucodystrophy in males with idiopathic Addison's disease Ronghe et al https://adc.bmj.com/content/86/3/185 **Highly informative case studies** from families represented by Alex TLC are as follows: 1. One family lost a young son, aged 7 years, in 2015 to an Addisonian crisis with ALD being diagnosed as the cause of his AD at post-mortem. From this her other son was also diagnosed and is now being treated for AD and monitored for CALD. 2. A mother was alerted to a diagnosis of AD in their family through her maternal brother. Two of her sons were then diagnosed with AD. After researching causes of AD on the internet she asked her GP to test for ALD and was initially refused, being told it was too unlikely as a diagnosis to be worthwhile pursuing. After a long fight for testing ALD was eventually confirmed. The initial MRI scan in her eldest son showed signs of active CALD. The mother herself took these scans urgently to a specialist and her son was admitted for urgent bone marrow transplantation. He is now a healthy adult working in xxxx xxxx for the xxxx xxxx. Her other son also developed CALD, received a bone marrow transplant in childhood and is now at university. NBS would have prevented enormous psychological trauma to this woman and her

		family; the outcome would have been disastrous for at least one of her sons without her pursuing prompt diagnosis. In our view no parent should be required to be the diagnostician and driving force for therapy for their child. 3. One family received an AD diagnosis after an Addisonian crisis in their younger son. The father worked as a xxxx xxxx and fortuitously a colleague alerted him to the various causes of Addison's and the family pushed for further testing for ALD. The initial MRI scan showed early signs of ALD and he was immediately admitted for bone marrow transplantation. He is now studying at university. 4. One family repeatedly took their son to the GP after bouts of illness symptomatic of AD. Despite noting his skin colour (it is common for Addisonian patients to have bronzed skin) he remained undiagnosed. He was later diagnosed with CALD, heartbreakingly at too advanced a stage for treatment. AD was still not diagnosed at this stage but three days after his ALD diagnosis he was admitted to A&E with an Addisonian crisis and then spent one week in ICU. During this period, he lost his sight and subsequently died of CALD. However, thanks to his diagnosis, his brother was diagnosed with ALD, monitored for AD (onset at 2 years old), had a successful bone marrow transplant aged 8 years, attended university and is now in work in his early 20s. 5. One family had a misdiagnosis of ACTH receptor defect instead of AD in their young son (age 5). Unfortunately, a correct Addisonian diagnosis was not received until he was 25, following a diagnosis of cerebral ALD, and he now has severe behavioural issues, and progressive mobility and cognitive issues. Had he been diagnosed

		correctly in childhood, he may have been able to receive a bone marrow transplant (his parents report that xxxx xxxx were prepared to proceed with an adult BMT, but unfortunately the MRI revealed that his ALD was too advanced). 6. Another family had a successful diagnosis of Addison's in their young son, but ALD was not identified despite a lengthy and traumatic diagnostic journey when behavioural symptoms began in his early teenage years. The family were often told that he was just a "bad lad". Subsequently he deteriorated and ended up in a care facility, where he died. ALD was identified at post-mortem. His brother, sister, mother, aunt and cousin have since been identified and have had further children who are waiting to be tested. 7. One man was diagnosed in his early 20s with Addison's after a lengthy diagnostic process. He then went on to develop progressive AMN symptoms over a number of years, although these symptoms failed to prompt an ALD diagnosis. During this period, he fathered two girls who are obligate carriers of ALD. The man states he would have accessed reproductive choice had he known the risks and suffers immense guilt at passing ALD to his daughters. This is just a sample of patient experience, demonstrating the far-reaching implications of undiagnosed AD as well as highlighting the benefits that an early diagnosis can bring.
Page 5, para 5 Page 6, para 3	Available standard therapy	**HAEMOPOIETIC STEM CELL TRANSPLANTATION (HSCT)**

Page 16	Balance of long-term benefits and harms of HSCT Q4 Early initiation of treatment vs treatment initiated with clinical detection	For decades HSCT has been the accepted worldwide standard of care for active childhood CALD. A major driver for pursuing NBS is so that all boys with ALD can undergo screening by regular cerebral MRI from 2-3 years of age with HSCT or gene therapy (as appropriate) performed before significant neurological handicap occurs. In our organisational experience, we have heard of many successful BMT stories, where patients have been diagnosed due to a diagnosis of another family member or have been lucky enough to have had a prior diagnosis of AD and a clinician or family member proactive enough to identify the cause. However, we are also aware of several unsuccessful transplants, purely due to late diagnosis and clinicians' sense of duty to give these families hope and a chance, however small, of saving their child. The Alex TLC database holds records for 18 boys who received HSCT in an early stage of progression. Of these boys, one died due to the transplant process (2005) and one developed an infection causing the transplant to fail. This latter boy was identified for transplant shortly after an Addison's related diagnosis in 2009. Sadly, due to progression of symptoms there was not an opportunity to repeat the transplant and he later died from CALD symptoms. All 16 remaining boys are now growing or have grown into healthy young men, able to access education and opportunities for future success. One important point to note is that those who were identified through brothers or other family members that were themselves unable

		to be treated, report significant issues around “survivor guilt” and depression. The Alex TLC database also holds records for 8 boys who received HSCT at late stage of CALD. For these 8 boys we know the decision to transplant was a difficult one for clinicians, giving families a glimmer of hope in an otherwise desperate situation. Of these 8 boys, two later died – one due to rejection of the transplant and the other due to rapid progression of ALD symptoms. The remaining 6 have had variable outcomes: • 3 have deteriorated to a semi-vegetative state, reliant on carers for all needs, blind, unable to communicate and tube fed • 1 is blind with significant behavioural and psychological difficulties, and some mobility issues, requiring 24-hour supervision • 1 is functioning reasonably well but has significant behavioural difficulties requiring specialist schooling • 1 is functioning reasonably well and attended but did not complete university and has significant physical defect on one side of the body. This particular patient only received bone marrow transplant once the mother contacted Alex TLC upon diagnosis, reporting that the child’s hospital saw no urgent need for treatment despite clinical signs of deterioration on an MRI scan. Alex TLC

		connected the family with a specialist and transplant was performed swiftly, however the delay has had an effect on the overall outcome for this patient. We are concerned that the NSC consider HSCT to be harmful due to the fact that transplants performed late, for the reasons outlined above, are included in the published clinical evidence. Since Alex TLC will not be aware of all transplanted children we can confirm that British Society for Bone Marrow Transplantation (BSBMT) data when last analysed in 2016 showed overall survival for all reported UK boys of 90% (personal communication, Professor xxxx xxxx). Survival was 100% following matched sibling transplants and 88% for unrelated donor transplants. A retrospective notes review study on UK HSCT experiences is in progress, but has been severely delayed by the Covid crisis and further evidence from this consultation is not yet available. However, Alex TLC do not consider it humane to deny patients the opportunity for this treatment at the earliest stage, which can only be accomplished via a newborn screening programme. Currently the UK does not treat adults (over 18s) who display onset of cerebral symptoms with HSCT. There is growing evidence from Europe and the US that this treatment can be successful and is therefore available to adult ALD patients in many parts of Europe and the US. Although we appreciate that not all adult patients will be suitable for

		transplant, and their physical condition will be a major factor, we would argue that it is not appropriate to deny access to this treatment. We appreciate that this is not an argument for consideration by the National Screening Committee, however it is clear from the evidence that this treatment can be successful, and therefore should be considered as a viable alternative for adult patients. **Further evidence for submission regarding HSCT:** Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation Raymond et al https://pubmed.ncbi.nlm.nih.gov/30292747/ Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy Waldhüter et al https://pubmed.ncbi.nlm.nih.gov/30746707/ Clinical efficacy of haematopoietic stem cell transplantation for adult adrenoleukodystrophy Matsukawa et al https://academic.oup.com/braincomms/article/2/1/fcz048/5701638 Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy

		Kuhl et al https://pubmed.ncbi.nlm.nih.gov/28375456/ **GENE THERAPY** Clearly the most exciting area of technological development in ALD therapy is gene therapy. Forty-two out of 45 patients now have highly promising results following gene therapy using modern viral vectors performed in treatment centres worldwide including Great Ormond Street Hospital. Detailed reports are given in the references below. Two UK families cared for by Alex TLC have proband sons who had devastating outcomes after HSCT performed for advanced cerebral disease but younger sons who remain completely neurologically asymptomatic after early identification (due to their affected sibling), serial MRI brain scanning and gene therapy at an early stage of cerebral disease development. These boys are now 8 and 4 years past gene therapy. As an organisation we believe that this speaks extremely eloquently to the power of this transformative therapy. We are aware that a NICE HST appraisal is being held on 21st January 2021 to discuss fast tracking gene therapy for NHS commissioning. Gene therapy will give opportunities for treatment to patients without matched sibling donors and also may prevent deaths from Graft versus

		Host Disease and engraftment and infectious complications associated with allogeneic HSCT. **One area of critical importance** that has not been addressed is the typical time taken from identification of need (ie progressive CALD) to definitive treatment. For sibling transplantation this would typically be around one month, for unrelated donor transplantation six to eight weeks, but for gene therapy considerably longer. If gene therapy is to become the accepted treatment, due to its low complication rates, this places immense importance on identification of cerebral disease at very early stage, as progression typically occurs so rapidly. This places huge emphasis on pre-symptomatic diagnosis and MRI screening, only achievable for all by implementation of newborn screening. **Further evidence for submission regarding gene therapy:** https://checkrare.com/gene-therapy-shows-promise-for-cerebral-adrenoleukodystrophy-cALD/ Hematopoietic stem-cell gene therapy for cerebral adrenoleukodystrophy Eichler et al https://www.nejm.org/doi/full/10.1056/NEJMoa1700554 The Landscape of Hematopoietic Stem Cell Transplant and Gene Therapy for X-Linked Adrenoleukodystrophy Mallack et al https://pubmed.ncbi.nlm.nih.gov/31768791/

		FUTURE DEVELOPMENTS In recent years, research into treatments for adults with ALD and AMN has increased significantly – we would argue that by the time babies screened in the UK reach their period of maximal risk (from 5 years old through into adulthood) it is highly likely that new treatment options will be available. We have substantial evidence, gathered from the informational research we conduct through annual surveys, focus groups and discussions, that adults would welcome an early diagnosis rather than endure lengthy diagnostic pathways, the guilt of unwittingly passing the gene to their children, or missed opportunities to identify other family members. This is despite having a (currently) untreatable phenotype of the condition themselves. Furthermore, the decision not to screen for ALD is also inhibiting research on potential new treatments that could reduce the need for transplant. An example is the currently open and recruiting study MT-2-02 (FRAMES) in boys with early cALD (https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-000654-59/ES) where the goal is to (ideally) prevent the very invasive and risky procedure of myeloablation and stem cell treatment. This study relies on early identification of boys with cerebral lesions. It is evident that early detection will increase the chance of success. It is known that boys very often lose valuable time during medical check-ups with physicians unaware of X-ALD and may be misdiagnosed for a long time. When they become symptomatic and the diagnosis is confirmed by MRI,

		it is often too late. Hence, boys must be identified at a very early stage. Developing this and other new treatments rely on identifying boys as early as possible, impossible without a newborn screening programme. **STEROID REPLACEMENT THERAPY** We would also reiterate that screening is vital for identifying patients at risk of developing Addison's Disease, for which the available standard therapy is widely used and highly effective. We do not feel it is justified to deny or limit access to this life-saving treatment by not recommending that ALD is added to the newborn screening programme. **THE EFFECT OF CURRENT THERAPIES ON OUTCOME IN INDEX CASES VS SIBLINGS IDENTIFIED WITH ALD** It seems to us that comparison between affected index males and their younger male siblings provides the ultimate "dry run" of what effects NBS could have if implemented. Diagnosis in newborns would allow (a) much earlier average diagnosis of Addison's Disease and instigation of steroid replacement therapy, preventing emergency Addisonian admissions and allied cerebral insult and (b) implementation of either HSCT or gene therapy at first onset of leukodystrophy - as it has in these younger siblings who were identified through their index brothers. The Alex TLC beneficiary database records 42 UK families where the diagnosis of an affected proband highlighted other male children affected by ALD. Forty nine affected male siblings were subsequently

identified. Their differences in long-term prognosis compared to their index siblings are extraordinary:

- 21 siblings were already symptomatic and could not undergo HSCT due either to lack of donors, absence of referral, family choice or because they already had leukodystrophy too advanced for HSCT. Seven of these siblings are dead and 14 are alive but neurologically symptomatic with a terminal prognosis for 11. Three have the rare variant of cerebral disease that spontaneously arrests but often reactivates at a later stage.
- 28 siblings were asymptomatic and candidates for screening, thereby having a status that should mimic completely future boys identified though NBS. Fourteen have undergone transplantation, all are alive and remain well, and 14 remain on MRI screening and are asymptomatic so far.
- Critically, only 10/42 probands are alive AND in good condition compared to all 28 siblings who were identified when asymptomatic.

These results are shown in table form below.

STATUS TO DATE	PROBAND	SIBLINGS
Asymptomatic	5	14
Good outcome BMT	5	14

		Poor outcome BMT: 2 / 0 Symptomatic and alive to date: 8 / 14 Symptomatic and dead: 22 / 7 **Total: 42 / 49**
Page 6, paras 2 & 3 Page 6, para 3 Page 14	International landscape Screening test still experimental Q3 Accuracy of screening test	NBS for ALD and associated peroxisomal conditions is being progressively implemented out across the USA and a pilot study is underway in the Netherlands. An important aspect of the latter will be that it will explore a method for analysing only males. Following a detailed consultative process X-ALD newborn screening was added to the USA Recommended Uniform Panel of Disorders Screened as Newborns (RUSP) and testing was implemented in the state of New York in December 2013. Connecticut followed in December 2015, California in September 2016 and Georgia and Minnesota in 2017. Twenty-two US states have now implemented testing. Strategies to ensure efficient and effective screening have been published. The single greatest experience reported is from New York State where a three tier algorithm is utilised (described in Moser et al). The first tier is standard MS/MS of C26:0 LPC, followed by measurement of C26:0 LPC using HPLC–MS/MS as the second-tier test (Hubbard et al, Turgeon et al below). All newborns are screened with the first tier and those with an out-of-range result are screened with the more specific

		second tier. If the C26:0 LPC remains elevated on the second tier, then third-tier sequencing of the ABCD1 gene is performed. Since service inception the New York team has screened 1.7 million individuals, detecting 46 males and 47 females with an elevated marker and a causative ABCD1 variant (email from Joseph Orsini PhD, Newborn Screening Lysosomal Storage Disease (LSD) and X-linked Adrenoleukodystrophy (X-ALD) Screening Laboratory). This represents a frequency of 1:18,280, in excellent agreement with the 1:17,000 estimate predicted from historical family studies. **Further evidence for submission:** Newborn Screening for X-Linked Adrenoleukodystrophy in Georgia: Experiences from a Pilot Study Screening of 51,081 Newborns Hall et al https://pubmed.ncbi.nlm.nih.gov/33239602/ The Clinical Impact of CLIR Tools toward Rapid Resolution of Post-Newborn Screening Confirmatory Testing for X-Linked Adrenoleukodystrophy in California Tang et al https://pubmed.ncbi.nlm.nih.gov/33239588/ Simultaneous Testing for 6 Lysosomal Storage Disorders and X-Adrenoleukodystrophy in Dried Blood Spots by Tandem Mass Spectrometry

		Tortorelli et al https://pubmed.ncbi.nlm.nih.gov/27440509/ Combined liquid chromatography-Tandem mass spectrometry as an analytical method for high throughput screening for X-linked adrenoleukodystrophy and other peroxisomal disorders: Preliminary findings Hubbard et al https://pubmed.ncbi.nlm.nih.gov/16828324/ Newborn screening for X-linked adrenoleukodystrophy (X-ALD): Validation of a combined liquid chromatography-tandem mass spectrometric (LC-MS/MS) method. Hubbard et al https://pubmed.ncbi.nlm.nih.gov/19423374/ Combined extraction of acyl carnitines and 26:0 lysophosphatidylcholine from dried blood spots: prospective newborn screening for X-linked adrenoleukodystrophy Sandlers et al https://pubmed.ncbi.nlm.nih.gov/22197596/ Improved analysis of C26:0-lysophosphatidylcholine in dried-blood spots via negative ion mode HPLC-ESI-MS/MS for X-linked adrenoleukodystrophy newborn screening Haynes et al https://pubmed.ncbi.nlm.nih.gov/22503909/

		Newborn screening for X-linked adrenoleukodystrophy: further evidence high throughput screening is feasible Theda et al https://pubmed.ncbi.nlm.nih.gov/24268529/ Streamlined determination of lysophosphatidylcholines in dried blood spots for newborn screening of X-linked adrenoleukodystrophy Turgeon et al https://pubmed.ncbi.nlm.nih.gov/25481105/ The stability of hexacosanoyl lysophosphatidylcholine in dried-blood spot quality control materials for X-linked adrenoleukodystrophy newborn screening Haynes et al https://pubmed.ncbi.nlm.nih.gov/25307302/ Newborn screening for X-linked adrenoleukodystrophy in New York State: Diagnostic protocol, surveillance protocol and treatment guidelines Vogel let al https://pubmed.ncbi.nlm.nih.gov/25724074/ Newborn Screening for X-Linked Adrenoleukodystrophy Moser et al https://pubmed.ncbi.nlm.nih.gov/31467997/

		The NSC already identifies additional conditions with existing newborn screening tests (see next comment). From our work with rare disease organisations across the UK we know that knowledge gives families the power to make comprehensive choices and improves outcomes as a whole. We feel strongly that an assumption that identification of untreatable conditions is not in the best interest of parents should be revisited and no longer applies in today's society and a rapidly evolving scientific landscape, where gaining knowledge of genetic makeup and disease prediction is increasingly sought out. Psychosocial impact on mothers receiving expanded newborn screening results https://pubmed.ncbi.nlm.nih.gov/29379194/ The Hidden Costs of Rare Disease, A Feasibility Study https://geneticalliance.org.uk/wp-content/uploads/2016/06/hidden-costs-full-report_21916-v2-1.pdf
Page 6, para 3	Identification of untreatable conditions other than ALD	The C26:0LPC testing developed in New York detects other conditions with aberrant peroxisomal fatty acid oxidation namely the Zellweger spectrum disorders (approximately one in 70,000 births) and less frequent peroxisomal fatty acid oxidation disorders, peroxisomal acyl-CoA oxidase 1 (ACOX1), the multifunctional protein (HSD1B4), and the "contiguous ABCD1 DXS1357E deletion syndrome" (CADDS). Babies with a second-tier positive screening test who prove negative for ABCD1

		mutation are referred to a geneticist where additional postnatal tests are done to elucidate the primary defect. We appreciate concerns around identification of these untreatable conditions other than ALD. However, through discussions with Zellweger UK (the support group for families affected by Zellweger) we know that this is also an important issue for them. Due to their work with affected families and in depth understanding of their views, the group positively advocates for newborn screening for Zellweger and therefore is very supportive of our efforts for ALD newborn screening. Furthermore, identification of Zellweger's at birth would also identify the child's high risk of adrenal insufficiency/Addison's Disease, an important early diagnosis for the reasons previously described. As previously stated, we would urge the NSC to actively seek out the views of families living with the additional conditions ALD newborn screening will identify. **Further evidence for submission:** High prevalence of primary adrenal insufficiency in Zellweger spectrum disorders Berendse et al https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4164755/ We know from our work with other rare disease charities and groups, such as Genetic Alliance, that parents are grateful for knowledge of

		these rare yet devastating diagnoses, even if there is no available treatment. Yes, it will initially be a shock and cause distress, but early diagnosis gives parents time to come to terms with what may come and prepare for the future, rather than receiving a sledgehammer diagnosis when symptoms begin and/or enduring a lengthy and traumatic diagnostic odyssey, distressing for the family and costly to the NHS. **Further evidence for submission:** Neonatal screening for treatable and untreatable disorders: prospective parents' opinions Plass et al https://pubmed.ncbi.nlm.nih.gov/20026497/ The Hidden Costs of Rare Disease, A Feasibility Study https://geneticalliance.org.uk/wp-content/uploads/2016/06/hidden-costs-full-report_21916-v2-1.pdf Reforming Rare Diseases https://rareexperience2020.geneticalliance.org.uk/wp-content/uploads/2020/12/Reforming-Rare-Diseases.pdf Rare Experience 2020 The Lived Experiences of people affected by genetic, rare and undiagnosed conditions https://rareexperience2020.geneticalliance.org.uk/wp-content/uploads/2020/12/Rare-Experience-2020-Report-.pdf

		Furthermore, the shift in the attitude and priorities in recent years in terms of genomic diagnoses has changed in the UK with the genomics healthcare strategic plan https://www.genomicsengland.co.uk/national-genomic-healthcare-strategy-launched/ We, as an organisation, when trying to explain health equality to those we support, are very mindful that some of the other conditions currently screened on the UK newborn screening programme identify carriers. This allows families access to expert genetic counselling and opportunities for informed reproductive choice. We would cite Cystic Fibrosis and Sickle Cell Disease as examples. We cannot understand why this should be true for one condition, and not another. This is particularly pertinent when revolutionary therapy (Kaftrio) to improve quality of life has recently been commissioned in July by the NHS for most patients with Cystic Fibrosis, whilst treatment is often denied or given too late to patients with cerebral ALD. https://www.gov.uk/government/publications/health-professional-handbook-newborn-blood-spot-screening/7-conditions
Page 6, para 3	Identification of boys who would not go on to develop cerebral ALD	It is a sad fact that, by not identifying ALD at birth, many families suffer a sacrificial lamb scenario, with one family member (usually a young boy), having to lose almost all quality of life or die in order to access

		treatment and reproductive options for other family members. We feel this is unacceptable. We know from our beneficiaries that this is a diagnosis that would be vital and welcomed from birth. Parents often express guilt that they have unwittingly passed the gene on to their children and that they would have accessed pre-implantation diagnosis or other methods to ensure they did not bring a child who may suffer due to ALD into the world, had they been aware that they were either affected males or female carriers. Furthermore, we know that even if an individual cannot be treated, the prospect of having choices around reproduction, being prepared for the future and the prospect of hope for upcoming treatments and research are incredibly important to them. Alex TLC is also commissioning a psychosocial study to explore the impact of an ALD diagnosis on families and individuals, from the perspective of both patient and carers. We know from the beneficiaries we have spoken to over the past 16 years, that they would value advanced knowledge of this condition and understand the implications of being denied that knowledge, whether or not individual cases can be treated successfully. Furthermore, there are options for parents wishing to have a child without ALD, with pre-implantation diagnosis available on the NHS for parents at risk of passing the ALD gene to children. Alex TLC has heard numerous success stories of using this procedure to have children free from ALD.

		• a man with AMN and his partner were able to have twin boys (only male embryos were reimplanted as the inheritance of ALD means fathers cannot pass the gene to their sons) • two sisters, identified as their father had died from progressive adult onset cerebral ALD, had PGD to have two sons and a daughter between them, all free of ALD • a woman whose mother was severely affected by AMN had PGD to have a daughter free of ALD • a woman who had lost her eldest son to ALD had PGD to have another child free of ALD • a woman whose father has AMN had PGD to have twins free from ALD. We have already discussed at length above the importance of identifying patients at risk of developing Addison's Disease, as well as improved and emerging treatment options for adults. It has long been acknowledged that HSCT achieves poor results in patients with advanced CALD (cerebral Loes score >9) and higher complication rates, emphasising the advantage of early diagnosis, MRI screening and timely transplantation. It is almost certain that similar qualifications will apply to gene therapy since so many aspects of this treatment are similar to HSCT. We would ask that NSC considers all of these aspects when considering this review of our original application.

		Further evidence for submission: X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Engelen et al https://pubmed.ncbi.nlm.nih.gov/22889154/ Evolution of phenotypes in adult male patients with X-linked adrenoleukodystrophy van Geel et al https://pubmed.ncbi.nlm.nih.gov/11220738/ Adrenoleukodystrophy: new approaches to a neurodegenerative disease Moser et al https://pubmed.ncbi.nlm.nih.gov/16380594/ https://adrenoleukodystrophy.info/clinical-diagnosis/facts-on-ALD
Page 10 Page 11	Q1 What is the incidence of ALD in the UK? Summary	**Further evidence for submission:** The incidence rate in the UK identified from the ScHARR study is reported at 1:22,286, in very good agreement with the incidence data widely reported by Moser et al in the US of 1:17,000. This would imply a UK population of 3,100 individuals with ALD. However, the Alex TLC database since 2011 holds records for just 448 UK individuals with an A

		LD diagnosis as at 5th January 2021. Of these 365 are alive and 83 (mostly young boys) are dead. Although we appreciate not everyone with ALD will seek our services, nevertheless this indicates there is a worrying number of currently unidentified individuals living with ALD in the UK. We also fear that our database statistics cast grave doubt on the reliability of the estimate of incidence rates used in the previous NSC evidence review. The *PIND study*, Leukodystrophies and Genetic Leukoencephalopathies in Childhood: A National Epidemiological Study https://pubmed.ncbi.nlm.nih.gov/26866636/, states that 74 children were identified as having leukodystrophy in the period 1997 to 2014. The Alex TLC database, by contrast, records 106 male children in the UK diagnosed between those dates, implying significant under-ascertainment in this pivotal study. In the period 2011 to 2020 alone, the Alex TLC database reports 31 UK deaths of boys. Where could missing cases be hiding? We have already addressed the highly variable nature of presentation and the existing diagnostic difficulties of both Addison's Disease and ALD. Additionally, in adults we fear many are not diagnosed as they present with features which mimic psychiatric disease, for example relationship breakdown, homelessness, inability and/or unwillingness to access medical services and isolation.

	Overall conclusion	We live in a time of increasingly sophisticated and safe HSCT technology and with the exciting recent advent of gene therapy. In this document, and through the testimonies of our affected beneficiaries, we are providing compelling new evidence that ALD still causes preventable illness and death. This is primarily due to late diagnosis. HSCT in the UK (in keeping with decades of published international experience) has been associated with excellent outcomes which are starkly better when transplant has been performed in the earlier stages of CALD than that at advanced stage. The data that we have presented above, demonstrates that, when transplant is performed in advanced CALD, compromised neurological outcome and/or death is certain. Furthermore, severe disease at diagnosis contraindicates transplantation in many boys, consigning them to a devastating neurological death. NBS would allow identification of the potential risks of developing AD and CALD soon after birth as well as identifying families at risk and transforming their reproductive choices and the risk of bearing multiple affected children. Not only would screening therefore prove lifesaving but – arguably more importantly – it will prevent many boys developing moderate to severe, disabling neurological handicap with devastating implications for the affected person, their wider family and healthcare, educational and social welfare budgets. It is widely acknowledged that lack of awareness and access to specialist services for rare conditions such as adrenoleukodystrophy

		results in widespread health inequalities. In order to reduce these health inequalities and ensure opportunities for timely and effective treatment for both new patients, and any additional family members identified, newborn screening is essential. **Further evidence for submission:** Rare diseases social epidemiology: analysis of inequalities Kole et al https://pubmed.ncbi.nlm.nih.gov/20824449/ We should also consider the hidden costs of living with these conditions if untreated or where transplant is performed too late: job loss, psychological trauma, education choices, effect on siblings (we receive many reports of survivor guilt, school problems, isolation and suicidal thoughts amongst successfully transplanted, unaffected or asymptomatic siblings), housing (many families are forced to move home or fund extensive disability adaptations). An NHS England commissioned Inherited White Matter Disorder Registry is due to commence in April 2021, which will help to confirm

		BMT outcomes against diagnostic circumstance, as well as giving robust incidence and phenotype data. An accompanying IWMD Service has also been commissioned for roll out in late 2021. This will ensure accessible, timely and appropriate treatment for ALD and AMN patients, further reducing health inequalities. Alex TLC has great hopes for this centralisation and coordination of care in our modern NHS. However, truly great improvements for these patients can only come by identifying all of those affected and at a stage early enough in their disease to make a real difference to their lives. Alex TLC believes there is a compelling case from the evidence we have presented that screening for ALD will do phenomenally more good than harm, thereby meeting the overarching objective of the National Screening Committee.

3. Alex Hamilton, Syncona; SwanBio Therapeutics

Name:	Alex Hamilton	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Syncona; SwanBio Therapeutics		
Role:	Partner (Syncona); Board Director (SwanBio Therapeutics). Syncona is a venture capital investment company that founded SwanBio, which is developing a gene therapy for adrenomyeloneuropathy, the adult phenotype of adrenoleukodystrophy		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **~~No~~**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **~~No~~**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Online	"Newborn screening for ALD is not recommended. This is because…the test will	This terminology is highly problematic in the context of ALD. It is fair to describe ccALD as the 'most lethal' form of

	identify boys who will not develop the severe form (childhood cerebral ALD)"	disease. It is not fair to imply that the other phenotypes are not severe. For example, Addison's disease can lead to death from Addisonian crisis, which is indisputably a 'severe' outcome; the availability of therapy for this phenotype (once diagnosed) does not render it 'not severe'. In particular, for many ALD patients, their first experience of disease is Addisonian crisis resulting in hospitalisation – a situation which could be easily prevented with routine monitoring of patients identified through newborn screening. This phenotype places a heavy burden on young men in their teenage years and early twenties, who find they cannot socialise or play sports with others and have no explanation for this until they are lying in a hospital room, having vomited and lost coNSCiousness on a night out with friends, who fail to realise the seriousness of the situation, thinking it's a normal case of acute alcohol poisoning. Going on a night out and ending up in hospital is not a good way to find out that you have a debilitating genetic disease that may kill you and will probably put you in a wheelchair within 30 years, and that if you have a daughter, she will also carry the gene and probably develop adrenomyeloneuropathy herself. If we can diagnose better, we must do so.

		Furthermore, the adrenomyeloneuropathy phenotype is also severe: it has 100% penetrance amongst men, is extremely debilitating (bladder and bowel dysfunction; erectile dysfunction; severe gait impediments; painful neuropathy) and is relentlessly progressive. I have spoken with a number of patients and their families with ALD; while all are relieved not to have cerebral ALD, both the Addison's and adrenomyeloneuropathy phenotypes are a very real burden on patients that materially affect their daily lives, their personal relationships, and their families, and no patient fails to consider their situation 'severe'. So, at the very least, please change the terminology of this statement.
Page 5	"Available standard therapy"	There are no approved therapies for ccALD aside from bone marrow transplantation, and there are no approved therapies for adrenomyeloneuropathy at all. However, earlier diagnosis will enable patients to participate in clinical trials to establish whether novel therapies are effective and safe, in particular in ccALD patients who are unable to find a suitable donor. It does seem that the Lenti-D gene therapy is safe and effective and may receive marketing authorisation in due course; it is important not to understate the role that newborn

		screening played in supporting the development of this breakthrough.
Page 6	“It was also noted that the test would identify boys with the genetic mutation who would not go on to develop cerebral adrenoleukodystrophy”	Biochemical screening cannot prognose the path of ALD, but it can set patients on a monitoring path that enables earlier intervention during the at-risk period(s). ALD is, to the best of our knowledge, an entirely penetrant disease. Identifying boys at birth who will go on to develop Addison’s disease and adrenomyeloneuropathy will be additive to diagnosis of these clinical phenotypes. Further, the substantially later onset of Addison’s and adrenomyeloneuropathy means that by the time patients identified through newborn screening become symptomatic, there may in fact be therapies available and therefore they would be able to access treatment earlier in the course of disease, which is generally expected to lead to superior clinical outcomes. It is also important to consider the clinical benefits of screening not just on the identified boy but also potentially on family members. For example, women suffering adrenomyeloneuropathy are fairly frequently misdiagnosed with multiple sclerosis – this results in patients being given highly potent therapies (e.g. CD20 depletion) that are not only not approved for AMN, but are in fact wholly inappropriate on a mechanistic basis,

		exposing such patients to severe and undue risks for absolutely no clinical benefit. Identification of such women would enhance their treatment, inform their family planning, and save money for the NHS by removing their inappropriate pharmaceutical therapy. The opportunity to enhance diagnosis of other ALD phenotypes should not be excluded from the consideration of the benefits of newborn screening purely for ccALD. Finally, parents commonly have children within the space of a few years – a timeframe that may be shorter than clinical manifestation of ccALD (particularly, shorter than time to diagnosis). This can result in a single family having multiple children with ALD, unwittingly and entirely avoidably: a confirmation of ALD in the first child could enable pre-implantation genetic diagnosis to ensure subsequent children do not suffer the disease. This would also help to alleviate the overall healthcare burden over time as the faulty gene is removed from the gene pool. Unwittingly passing on the gene to their children is a major source of guilt for parents.
Page 6	"It was also noted that the test would identify…infants with conditions other than	The argument made here appears to be that 'ignorance is bliss': that families of children with (potentially fatal) diseases would prefer to have diagnosis delayed until the

	adrenoleukodystrophy for which there were no interventions”	disease manifests clinically. In many such cases, this is too late for the family to explore therapeutic options by participating in exploratory clinical trials, or to assist in the detailed provision of natural history data. Such an approach is extremely limiting to the progress in understanding of such disorders; in many cases, the poor understanding of the course of disease is exactly why therapeutics are not developed. Notably, most of these diseases are, as the consultation points out, ‘often associated with death in early infancy’ (page 7), so it is not the case that the screening test is likely to identify a number of patients with an unexplained phenotype lacking a realistic forecast of the likely clinical outcome for the patient, even if we may be powerless to prevent such an outcome at this time. While it is true that the test will identify babies with conditions other than ALD for which there are no treatments, the evidence from other countries indicates that the substantial majority of positive tests will result in a confirmed diagnosis of ALD and therefore the decision to make must be based upon the expected relative ratio of ALD to non-ALD patients detected.

		The identification of conditions other than ALD may provide an opportunity to gain earlier, more detailed insight into the pathology and clinical course of such diseases; this knowledge is usually a comfort to families rather than a burden. It may also enable non-ALD families to make decisions around family planning, where to live, and how to arrange finances to enable the best possible care for their child – decisions that are currently taken away from them due to their lack of knowledge of their child's disease. However, even if you wish to avoid the enhanced knowledge of other disorders, there is little justification for failing at the least to implement the screening test and provide a diagnosis only for those who are confirmed as ALD patients.
Page 6	"There was also uncertainty about the balance of the long-term benefits and harms of haematopoietic stem cell transplant"	On the individual basis this may be true, but it is not correct at the level of the patient population. While the decision to treat rightly rests with the managing clinician, and bone marrow transplant is indisputably a costly and risky procedure, the failure to provide the procedure to a patient with progressing lesions as assessed by MRI is thought likely to result in death about 90% of the time. Risks of bone marrow transplant are not unique in this patient population and therefore an understanding of the risk profile can be gleaned from its other clinical applications (e.g. in the oncology setting), where it is

		widely accepted that children are better at recovering from transplant than adults, with lower risk of graft-versus-host disease, improved grafting, and better tolerance of myeloablative conditioning. It is also widely accepted amongst the clinical community that earlier intervention in ccALD will usually lead to superior outcomes, and that there are no alternative treatments available that may delay or prevent clinical decline.
Page 10	"Question 1: What is the incidence of adrenoleukodystrophy in the UK?"	The analysis here is disappointing and a more thoughtful approach is required. The epidemiology of ALD is substantially underestimated in the literature; this is well-established. There is no reason to believe prevalence is materially different from the results of the Dutch or American newborn screening programmes, which indicate a birth prevalence of around one in seventeen thousand. Part of the reason the epidemiological data in the UK is so weak is because of poor diagnosis. Implementing the newborn screen is a way to break this vicious circle and get a much better understanding of the real burden of disease in the UK, which is likely substantially higher than current estimates available in the literature. Many patients are likely 'lost in the system': relationship breakdown, homelessness, care homes, that prevent them accessing proper medical care.

Page 19	Conclusions	The conclusion not to implement screening is rather circular in that it asserts there is insufficient evidence to support a review. It is difficult to find good epidemiological studies of ALD in the absence of newborn screening activities. The late diagnosis contributes to poor prognostication, poor outcomes data, and a lack of therapies, all of which are in turn cited as reasons not to implement screening in the first place. In a similar vein, the document implicitly criticises screening results for failing to report sensitivity, specificity, and negative predictive value (page 14). However, in contrast to positive predictive value (where test performance is indisputably impressive), all these diagnostic metrics require an orthogonal way of diagnosing patients (or excluding the diagnosis). This is impossible in the screening context as these patients are pre-symptomatic and therefore cannot be clinically diagnosed. Indeed, clinical diagnosis of the adrenomyeloneuropathy phenotype may require more than half a century to confirm the performance metrics of the diagnostic test. If this is the considered conclusion of the UK National Screening Committee, it is very difficult to see how this can ever be overcome. Is it the intention

		of the Committee to set an impossible bar to implementation, and if so, why run a consultation at all? Further, newborn screening is, as the consultation points out, now established under the Recommended Uniform Screening Panel in the US, and is also occurring in the Netherlands. UK patients and families are aware of this and feel this injustice acutely. Why should Americans and Dutch people get this, and not Britons?

4. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	xxxx xxxx **carrier of Adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	*We want to demonstrate the importance of identifying Addison's Disease through newborn screening and how life-threatening undiagnosed Addison's can be.*

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*Please insert here your stories about why having an early Addison's diagnosis was important for you/your family. Stories should highlight the impact of:* • *a previously undiagnosed Addisonian crisis that caused death* • *a lengthy Addison's diagnostic odyssey (how long it took to get an Addison's diagnosis and the problems faced before diagnosis)* • *identifying Addison's/ALD for other family members* • *an Addison's diagnosis which led to a successful BMT* • *a late Addison's diagnosis which led to an unsuccessful BMT* • *a late Addison's diagnosis which led to untreatable ALD*
Page 5, para 5;	Available standard therapy	*We want to demonstrate the successes of treatments other than BMT for children.* *Please insert here your stories about:* • *Adult BMT* • *MIN-102 trial* • *Gene therapy – was your son unable to access a BMT as there wasn't a suitable donor and gene therapy was not available at the time*

		• *Any other treatment you have received for your condition that has been successful or helped*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*We want to demonstrate how beneficial early diagnosis of ALD is to you and/or other family members, even if you/your loved one can't be treated at the moment.* *Please insert here your stories about:* *Knowing prior to conceiving that* xxxx xxxx *was a carrier of a rare genetic disorder allowed my* xxxx xxxx *and* xxxx xxxx *to make very important decisions for our family. Knowing the devastation ALD causes I neither wanted to pass the gene on to any daughters or risk having an affected son. It was therefore vital to me that* xxxx xxxx *was able to access pre-implantation genetic diagnosis (PGD) which allowed* xxxx xxxx *to have a non-affected son.* xxxx xxxx *now know that this terrible disease has not been passed on to the next generation and that my family will not be affected by its awful consequences. These decisions were only available to* xxxx xxxx *because* xxxx xxxx *had the knowledge of carrying the disease. It is vitally important that newborn screening tests for ALD in order to give families the best chance of treatment for their children in*

		situations where they have no prior knowledge that they carry this genetic condition. .
page 10, Q1	What is the incidence of ALD in the UK?	*We want to demonstrate that the incidence of ALD reported in clinical papers, is far higher than the number of patients that have been identified and that this is an unacceptable situation.* *We want to get across our worries that there are many adults that are "lost" in the system as the condition initially causes behavioural changes that can mean relationship breakdown, isolation, homelessness, inability to access medical help.* *We also want to highlight the risks of not allowing reproductive choice for adults who do not know they have ALD.* *Please insert here your stories about:* • *How the behavioural problems caused by adult onset ALD caused relationship breakdown/isolation* • *Issues in accessing medical help* • *Issues in accessing a diagnosis* • *Your feelings about unidentified adults with ALD passing on the gene to their children*

Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*We want to demonstrate that knowledge of an ALD diagnosis from birth offers significantly different outcomes than if ALD is diagnosed due to detection of Addison's or other symptoms.* *Please insert here your stories about:* • *Transplants that have been successful because of early diagnosis identified through another family member* • *Transplants that were "just in time" due to clinical detection eg through an Addison's diagnosis, your own persistence, any other reasons* • *Successful transplants where the patient is now an adult and how they are doing eg. in work, married, no further issues* • *Successful transplants where the patient has gone on to develop AMN– we would like to demonstrate that the development of AMN is secondary to the fear of cerebral ALD* • *Transplants that have been unsuccessful as they were performed too late* • *A diagnosis that was too late for transplant and the consequences for you/your family*
Page 19	Conclusion	*The NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage.*

		Please insert here your thoughts on this decision – you might want to think about the following: • *Newborn screening for ALD would add enormous benefit to children and their parents right now and for generations to come. Being able to accurately assess the prevalence of ALD in the UK will give families in the future so many positives. The ability to initiate early treatment in symptomatic boys which may lessen or delay the disease's terrible effects, but also the power of information. Generations to come will be able to make informed decisions about their pregnancies based on an accurate assessment of their ALD status. This can only have positive benefits for the children, their families and ultimately the NHS in* xxxx xxxx *opinion.*

5. Member of the public

Name:	Aaron Corr	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**relative of someone with adrenoleukodystrophy**		

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

Yes

Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic?
Please see below for more information

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	xxxx xxxx sons were diagnosed with Addison's disease at age four and five, following many hospital admissions with undiagnosed Addisonian crises. Family life was upside down at the time

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	with no or incorrect diagnoses, including salmonella. The fact that Addison's is not genetic led to an eventual diagnosis of ALD. The youngest boy now leads a normal life with only Addison's disease but the oldest has a very expensive package of care and has a long list of disabilities that that affect his quality of life in an enormous way.
Page 5, para 5;	Available standard therapy	*n/a*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	Both xxxx xxxx boys are in their twenties and live at home. We have the consequences of early diagnosis rubbed in our faces every day. We see what xxxx xxxx eldest boy's life could have been by looking at xxxx xxxx youngest. Family life has been turned upside down for the last twenty years. xxxx xxxx, a xxxx xxxx, has not been able to return to work as xxxx xxxx expertise has been needed at home. xxxx xxxx has also spent, literally, hours every day arranging care and liaising with various agencies for xxxx xxxx eldest boys needs. xxxx xxxx have had to work part time and xxxx xxxx career progression stopped dead. xxxx xxxx are very aware of the lack of attention xxxx xxxx xxxx xxxx daughters have received over that time as well. This late diagnosis has

		profoundly affected the lives of xxxx xxxx people. Had xxxx xxxx had a diagnosis at birth xxxx xxxx would have been a much happier family as well as having everyone economically active rather than being a burden on society.
page 10, Q1	What is the incidence of ALD in the UK?	xxxx xxxx son will have an expensive package of care for the rest of his life. The life of xxxx xxxx xxxx xxxx and xxxx xxxx will never be the same again. If this disease was identified at birth it would save enormous amounts of money and unmeasurable heartache for so many families.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	xxxx xxxx have two sons with ALD. One is fifteen months older than the other. They were diagnosed with ALD at the same time and received lifesaving BMTs fourteen weeks apart, meaning the younger boy was one year younger when he was treated. The outcome of this disparity in diagnosis is that the older boy needs, very expensive, 24/7 care and supervision. He is deafblind, Addisonian, epileptic, dyspraxic, speech impaired, along with a string of other disabilities. His younger brother, who was treated at an earlier age, is a graduate and a productive member of society.

Page 19	Conclusion	With an early diagnosis of ALD xxxx xxxx xxxx xxxx would have returned to work once xxxx xxxx children were a little older, relieving the pressure on xxxx xxxx in the xxxx xxxx (a little bit). xxxx xxxx would have been working full time which would have had a beneficial impact on the children xxxx xxxx have xxxx xxxx over the past twenty years. xxxx xxxx eldest boy would be working and contributing to society. The lives of the xxxx xxxx members of xxxx xxxx would have been so much easier, with so many more opportunities for xxxx xxxx children and a much happier upbringing. Instead our son has a package of care that costs the taxpayer approximately £150,000 every year and is set to increase dramatically when he leaves home.

UK National Screening Committee

6. Member of the public

Name:	Deirdre Corr	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	xxxx xxxx 2 sons had frequent undiagnosed Addisonian crises for several years. If xxxx xxxx hadn't been a xxxx xxxx, I suspect we might have lost them both, as they

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	both had severe Adrenal Insufficiency. They would typically start vomiting and lose consciousness over a period of hours. We used to syringe fluids into their mouths every 10 minutes, as any more fluid would trigger more vomiting and more dehydration. At hospital they would be put on IV antibiotics and fluids and baffled Doctors would investigate diagnoses such as Meningitis and Salmonella. Usually, xxxx xxxx think it was a dramatic Addisonian reaction to a simple throat virus. A tragic mistake was made of checking our older son's Cortisol levels during an Addisonian Crisis and they fell within normal limits. The medical staff should have realised that during an acute illness, Cortisol levels are always elevated. An earlier Addison's diagnosis would have led to an earlier ALD diagnosis and our older son would have been spared all his disabilities and the distress that comes with them.
Page 5, para 5;	Available standard therapy	Both our boys were BMT'd. the elder son with a sibling donor and the younger son an unrelated donor.
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	If we had been able to have newborn screening, our boys would have been monitored from birth, offered timely BMTs and our lives would be completely different. Our older son's care package costs the NHS nearly £3000 per week, which would make newborn screening well worth what it costs financially as well as morally. We

		received the diagnosis when they were 5 & 6 years old, which was devastating. In Ireland it was presented as a terminal diagnosis. If xxxx xxxx had been screened at birth and aware that I carried the gene defect, xxxx xxxx would have pre-implantation genetic diagnosis.
page 10, Q1	What is the incidence of ALD in the UK?	xxxx xxxx was originally diagnosed with MS. If xxxx xxxx had been offered a test (even if I had needed to pay privately), xxxx xxxx would have been glad to take it, rather than unknowingly bear sons unaware of their illness. xxxx xxxx started having subtle symptoms from the age of 27 years and used to feel like people suspected that xxxx xxxx was attention seeking, so learnt to not talk about them. xxxx xxxx wish so much that our sons had been diagnosed earlier, so that our older boy did not suffer so much. Doctors should be better informed. Even when both sons were diagnosed with Adrenal failure, it was a battle to get their Consultant to agree to test for ALD. Newborn screening would eradicate this situation.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	Newborn screening would psychologically prepare parents for the rollercoaster of caring for a child with ALD. By the time that our boys were diagnosed with Addison's disease, we had been through so many distressing life-threatening episodes. Despite the Addison's diagnoses, we had to push medical staff to test for ALD. We were

		told that the boys were too well to have such a serious disease, but that they would (reluctantly) test for ALD to put our minds at rest. When the ALD diagnosis was confirmed, we were advised to enjoy our boys for what time we would have with them and had a Children's hospice nurse allocated to us. We followed every lead we could until we found Dr xxxx xxxx in xxxx xxxx, who took over their care. Our younger son, now 24 years old, had a timely BMT and has been to university and has a very normal life, apart from taking medication for Adrenal Insufficiency. If our older son, now 25 years old, had been diagnosed even a year earlier, he would most likely also be a happy young man living a fulfilled life. Instead he requires 24/7 1:1 support and struggles to function with blindness, hearing & speech impairment, epilepsy and slow cognitive functioning. He is painfully aware of how different his outcome is to his brothers and suffers from depression, anxiety and jealousy. This could all have been avoided by newborn screening.
Page 19	Conclusion	xxxx xxxx wish, with all my heart, that newborn screening had been available for us. It would have been a shock, but nothing like the devastation of discovering that our normal healthy, happy boys had such a serious disease later. xxxx xxxx would have adjusted to the fact that BMT or some other treatment might be necessary at some

		point, rather than receiving a terminal diagnosis followed by the turmoil of two BMTs three months apart. Our younger son had quite severe behavioural problems for years at school, which we suspect was survivors' guilt and anger at me for passing the faulty gene to him. He now understands that xxxx xxxx did not know about it and is more able to relate to his brother. Our xxxx xxxx daughters have struggled with so much attention being diverted to their brothers and the xxxx xxxx daughter needed support from the CAMH service. The emotional and financial cost of not having newborn screening is enormous.

7. Member of the public

Name:	Emily Penrose	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of two boys with Adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **~~No~~**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **~~No~~**			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*

Page 6, para 3	Test would identify boys with the genetic mutation who would not go on to develop cerebral ALD…	It may well identify boys who would not go on to develop cerebral ALD, but if the genetic mutation is picked up it would also flag up possible adrenal insufficiency - Addison's Disease. This occurs in 93-140 per million people. A previously undiagnosed Addisonian crisis can be fatal. My oldest son has a rare phenotype of arrested ALD with Addison's disease: https://adc.bmj.com/content/102/Suppl_1/A151.1 This would not have been picked up had I not had a second boy who developed childhood cerebral ALD. Had the newborn screening test been available when my oldest son was born, it would have flagged up Addison's disease. We were extremely fortunate that he didn't have any crises prior to his diagnosis. We would have seriously considered pre-implantation genetic diagnosis for a second child to ensure that I was not passing on the defective gene. The effect on us having two children with ALD has been life-changing. I have given up my career in xxxx xxxx to stay at home and become a full-time carer for my youngest son. He was a fit and healthy 9 year old who

		loved drumming, swimming, and karate. This disease has completely taken everything away from him. He can no longer walk, talk and swallow. He is tube fed via a gastrostomy and is doubly incontinent. We didn't get a diagnosis until symptoms started to show, at which point the disease had progressed too far in his brain for any treatment. Had we have known (with newborn screening) that the disease had started progressing, we could have then considered a haematopoietic stem cell transplant, whist with great risks it also gives hope to halt this horrific disease. Early initiation of treatment following screening would most definitely have provided better outcomes compared to initiation of treatment following clinical detection. We never had that chance and we are watching our son slowly die in front of our eyes. I want no other parent to go through what we have, and a simple blood test will do this. Imagine if it was your child. You would want to fight too.
Page 6, para 3	"as well as infants with other conditions…for which there were no interventions"	Any blood test can identify conditions for which there are no treatments i.e. the current heel prick test looks for

		sickle cell, but also finds carriers and other red cell diseases
Page 10, Q1	What is the incidence of ALD in the UK?	X-Linked Adrenoleukodystrophy is the most common peroxisomal disorder affecting both males and females with an estimated birth incidence of about 1 In 14,700 (Bezman et al. 2001; Moser et al. 2016) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7041623/ There are many unidentified adults in the UK unknowingly passing on this gene to their children. Newborn screening would then mean other family members could be identified, which in turn could be life-saving for them too.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for Adrenoleukodystrophy compared to initiation of treatment following clinical detection?	I believe it most certainly does. My son was diagnosed following an MRI scan, after symptoms of the disease started to show. Lesions had grown too far in his brain for him to receive any treatment. Had they been monitored from birth, the growth would have been picked up and treated as soon as possible to have given him the best opportunity to halt the disease. There is no cure, he will die because we didn't know he was affected before it was too late. Our whole house has had to be adapted to accommodate his needs. We require hoists in most rooms, a specially adapted wet room, medical

		equipment, not mentioning the ongoing carers who help with all his personal care both during the day at home, school, and overnight.
Page 19	Conclusion	1 in 17,000 individuals are affected by Adrenoleukodystrophy worldwide, regardless of race, ethnicity and geography. It affects males more severely and is more common in males because it is an X-linked condition. Other inherited metabolic diseases are tested for, such as IVA, GA1, MSUD and HCU, all of which have lower incidence rates. Without treatment for these metabolic diseases babies and young children can become suddenly and seriously ill The conditions can be life threatening or cause severe developmental problems. This is the same for Adrenoleukodystrophy, but the only outcome for the child if the disease is not picked up is death.

UK National Screening Committee

8. Member of the public

Name:	Mary McNicol	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Support worker and friend. of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3 Page 12, Q2	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	I work and am friends with a family with 2 boys who have ALD and Addisons disease. The younger boy was diagnosed at 5 and had a bone marrow transplant and although he has health needs and takes regular medication he has been to university and is a fit capable lad. His older brother who I work with was given a BMT a year later and barely survived, he is deaf/blind has epilepsy and addisons disease. He takes vast quantities of

Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	medication and his life has been severely curtailed. He needs 1 to 1 support all the time. This would have been avoidable if he had been tested at birth.
Page 5, para 5;	Available standard therapy	
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	The elder boy would not have had such severe deterioration if he had been diagnosed at birth. He would not have developed the cerebral ALD.
page 10, Q1	What is the incidence of ALD in the UK?	The family I work for fight for everything they need. It is a full time job.The mother also has the condition. It is very hard and so unjust to not go ahead with the screening like other countries are doing.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	As above
Page 19	Conclusion	I feel the NSC should come and meet the 2 lads in the family I work for. The difference is huge on one hand a lad who can live

		a full life with the help of medication and on the other hand a lad who is dependent on others for so much help and who will never reach his full potential. They may change their minds.

9. Member of the public

Dear Sir/Madam

Please find attached my family's journey with Addison's, and later adult cerebral adrenoleukodystrophy and adrenomyloneuropathy. My 8 pages of evidence outline the way this genetic disease has affected my son - xxxx xxxx xxxx xxxx years of age.

It is my belief you have received insufficient evidence up until now. We are a developed country, and no family should be left 'out in the cold' to 'go it alone', when this could have been avoided.

Please make 2021 when this important genetic condition receives the top priority it deserves. Without screening we will never know how many boys are affected. My son is certainly 'lost in the system', and without government newborn screening this situation will happen to other boys.

Thank you, and please keep me informed how this situation is developing.

Best regards

UK National Screening Committee

Name:	Jane Watson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of son with adult cerebral adrenoleukodystrophy, then later developing adrenomyeloneuropathy**		

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Yes

Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic?

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Section and / or page number	Text or issue to which comments relate	Comment
Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of	I want to demonstrate the importance of identifying Addison's Disease through newborn screening and how life-threatening undiagnosed Addison's can be. My son was wrongly diagnosed - in 1995 - with ACTH receptor defect. This, in fact, was early Addison's following an adrenal crises. The consultant endocrinologist was wrong in not identifying Addison's disease.

	treatment following clinical detection? (referring to treatment of Addison's)	**The impact this has been:** A lengthy odyssey (20 years!) of treating my son with oral hydrocortisone, and lulling him, and his parents, into a false sense of security, that he could expect to lead a normal life span. The medical profession assured us, that the condition could be easily treated with lifelong oral steroids. The Addison's diagnosis was only diagnosed in 2015 when he developed cerebral ALD at 25 years of age. An early Addison's diagnosis could have led to a successful BMT, when my son was a teenager. I now know he could, and should, have had MRI scans as a teenager. This late Addison's diagnosis has led to untreatable adult cerebral ALD, and AMN. His life has been ruined unnecessarily in the last 5 years. He is now 30 years of age. He is a successful graduate with an honours xxxx xxxx degree, which he has been robbed of using. A waste of talent. Newborn screening would have identified Addison's, which can develop into ALD in later life. His symptoms manifested as sight loss at 25 years of age. An MRI scan, in 2015, showed demyelination in his brain. This was DEVASTATING, and TOO LATE for any treatment. Medical awareness of the severity of this genetic condition is lacking, and newborn screening would create the necessary alert.
Page 5, para 5;	Available standard therapy	I want to demonstrate the successes of treatments other than BMT

		My son's story about treatment in the last 5 years is: NHS xxxx xxxx were quite prepared to proceed with Adult BMT at xxxx xxxx Hospital in xxxx xxxx. This is a centre of excellence in BMT, because of their progress in treating leukaemia. The expertise was all there – xxxx xxxx miles from home! My son's Loes score had reached 13 by then, and too late to intervene, and stop the inflammation in his brain. His cognition and mobility were affected at this time. Further evidence BMT would be unsuccessful. Two bone marrow donors had been identified in USA. We went to France to consult a professor there. They would have acted faster than the UK. They are alert to the implications of defects in the ABCD1 gene. My son was approached by the MIN-102 clinical trial in Amsterdam. His condition was too severe to meet their inclusion criteria. Another devastating setback. Gene therapy – this is another development of science, but it is a very distant dream for an adult with the severe form of this genetic condition. We live in hope now, that CRISPR will come to his rescue. These are the hopes for our son, and the government cannot dismiss our plea to screen newborns to prevent another desperate situation like ours. There are consequences to the lack of screening, and a lack of awareness to the severity of how Addison's can develop. My 30 year old son is proof of this.

		My son's only help and treatment is from the Physically Disabled Rehabilitation Unit at xxxx xxxx. Their help is exceptional. But this is all too late and too little. Why does this heart-breaking scenario have to happen to an exceptional young man? The expertise and money is there to prevent this happening in a developed country like the UK. Our family, and NHS xxxx xxxx, are in the situation where we are 'trying to shut the stable door, but the horse has bolted'!
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	Early diagnosis of ALD would have meant my 30 year old son could have benefited from the BMT expertise and facilities that exist in NHS xxxx xxxx. Diagnosing ACTH receptor defect – wrongly in 1995 – has led to a young man leading a lie. He has assumed he would lead a normal adult life. To receive a diagnosis of adrenoleukodystrophy in 2015 has been DEVASTATING. Our family cannot recover from. A diagnosis from birth would have made a world of difference to our family. My son could have expected to lead his life. He has been robbed of his future, and it is a waste of talent. The xxxx xxxx have paid – in good faith - for his University of xxxx xxxx. He cannot use his honours degree, and pay back to society. He loved his xxxx xxxx degree, and thought he would have had the opportunity to use it. As a country we are boasting about

		our expertise in coronavirus, why not use this laboratory expertise to analyse these genetic diseases early? I have unwittingly passed on ALD to my son and I feel quilt and shame, that I have not used my own skills more to prevent ALD being diagnosed in him at 25 years of age. But where were the experts, when I needed them? A system of newborn screening could have been our 'safety net'. My son is living with the consequences of a government not waking up to the devastation caused by a lack of genetic screening for Addison's. The medical profession's lack of training in adrenal insufficiency is also insufficient. Newborn screening would be the ideal vehicle to alert endocrinologists more to this condition. Some in the medical profession are 'sleeping on the job' without a nationwide initiative like newborn screening to alert them to how adrenal insufficiency can develop 25 years later. This scandal can be prevented in future. Pre-implantation genetic diagnosis (PGD) was not a route I could have used in 1990, and I am in the unusual situation, where this genetic condition of Addison's and ALD, has not affected anyone in my extended family. To know ALD is in my DNA has been a 'bolt from the blue' for me.
page 10, Q1	What is the incidence of ALD in the UK?	The incidence of ALD, reported in clinical papers, must be far higher than the number of patients that have been

		identified. My son has genotyping of the ABCD1 gene c.1634+1G>A known to be pathogenic. This genotyping appears in a scientific paper by an ALD expert, xxxx xxxx, who also compiles the ALD Connect database. xxxx xxxx paper does not refer to my son. So there is one ALD sufferer, who is not recorded in scientific papers. He is "lost" in the system. How many more? **Our story is:** My 30 year old son has behavioural problems caused by adult onset ALD. He cannot have the relationships he craves. He is isolated from his peers, and he cannot access medical help without his parents' help. There is sympathy in abundance, and the question everyone asks is 'Do you get help?' Yes, we do access carers, who are brilliant, but it is NEVER enough. Accessing general practitioner help is a problem. Help at consultant level is first class. In May 2015 the neurologist suspected he had adrenoleukodystrophy, but it was not till November 2015, that we were to receive definitive analysis of the ABCD1 gene. This was a result of enlisting the expertise of the genetics department at xxxx xxxx, and their help was not actioned until AUGUST 2015. This demonstrates – once again – how abundant the expertise is, but is NOT USED swiftly enough, because of a lack of knowledge of how this genetic condition affects a real live person. The

		genetics department were very efficient in outlining the implications of passing on the ABCD1 gene to the next generation, and the need to alert our extended family about any member, who could have been affected by this x-linked gene. We did this. My son was made aware – by the neurologist and geneticist - that any son he may have would not carry the ALD gene, but a daughter would be a carrier. The geneticist and the neurologist, were efficient in conveying this information. The geneticist and neurologist, should, however, have speeded up their confirmation of my son's situation, and concentrated less on who else could be affected. My son was their patient, and he should have been of the most concern to them. Our family fulfilled our obligation to alert any family member who could have been affected. No-one else is. Speed of diagnosis was not their top priority. The NHS was of the opinion that my son would just have to live with the consequences of an adult cerebral adrenoleukodystrophy diagnosis. They were right about that!!!
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	A genetic test from birth would have offered a significantly different outcome for my son if Addison's, and potentially later cALD, had been diagnosed at 5 years of age. **Our story is:**

		A successful BMT transplant could have resulted in my son using his honours xxxx xxxx degree usefully in society. He could have been married, and have no further issues. He would still have had to live with the potential of AMN developing in later life. He could have been wheelchair bound, but would not have the devastating cognition problems he has now. As things stand, at 30 years old, he is wheelchair bound, but with vision and learning difficulties. These are impossible difficulties to live with. My son's diagnosis was too late for transplant and the consequences for our family are that we live a very restricted life. It isolates us from society, because everyone asks about our son, but no-one has any real idea of what it is like to live our life. It takes 12 hours a day attending to an adult with physical and mental disabilities – even with 'help' from a 'caring' society.
Page 19	Conclusion	It is my understanding that NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage. **My thoughts on this decision are:**

		Screening is already happening in many states in the US and Netherlands. This leaves me dismayed. I have outlined the impact the UK government and devolved Scottish government's lack of initiative on this issue has made on my family's life, because there was no screening when my son was born. Please take heed. This adult cALD and AMN diagnosis has affected my physical and mental health too, but more so my son. I've had my life. He has lost the ability to lead a social life and the ability to work and live outside his parents' home. The condition did not manifest itself until 25 years old, with the result he received a full primary, secondary and university education. This has been cruel in itself, because he thought he was like his peers all along, only to have his future plans and career dashed unexpectedly. This has been devastating. He has no other siblings. This may be a good thing, because they may have enjoyed the health he lacks, and that would have been hard to bear. As parents, our life, and our boy's life, could have been so much different, if the UK government was as forward thinking as the Netherlands, and many states in the USA . Please, please put screening for Addison's, and ALD, on your agenda for 2021. It will save future boys' lives, and create a 'red alert' in the medical profession about

		adrenal insufficiency. This 'red alert' was missing for our son.

UK National Screening Committee

10. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy**		

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

~~**Yes**~~ **No**

Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic?
Please see below for more information

Yes ~~**No**~~

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	*We want to demonstrate the importance of identifying Addison's Disease through newborn screening and how life-threatening undiagnosed Addison's can be.*

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*Please insert here your stories about why having an early Addison's diagnosis was important for you/your family. Stories should highlight the impact of:* • *a lengthy Addison's diagnostic odyssey (how long it took to get an Addison's diagnosis and the problems faced before diagnosis) –* xxxx xxxx *son did not show symptoms until he was around 5-6 years old, his fine motor skills and academic ability was slow which was identified by his teacher.* • *identifying Addison's/ALD for other family members – it is important for early detection so an appropriate treatment can be provide to prevent life time disabilities.* • *a late Addison's diagnosis which led to an unsuccessful BMT-* xxxx xxxx *son was too late to receive BMT as his condition had progressed too far by the time he was diagnosed. Hence he now has to live with this illness which result in severe disabilities and poor quality of life.* • *a late Addison's diagnosis which led to untreatable ALD- no treatment was available at the time of diagnosis so he was only given management plans, as a result his condition have deteriorated significantly.*

Page 5, para 5;	Available standard therapy	*We want to demonstrate the successes of treatments other than BMT for children.* *N/A*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*We want to demonstrate how beneficial early diagnosis of ALD is to you and/or other family members, even if you/your loved one can't be treated at the moment.* *Please insert here your stories about:* • *How a lengthy diagnostic odyssey has affected you/ your family –* xxxx xxxx *had no idea about his condition until his diagnosis* • *How you felt when you received a diagnosis, was your anxiety lessened? –* xxxx xxxx *were given unclear prognosis and also was not explained how his condition would progress.* xxxx xxxx *had no idea what* xxxx xxxx *were going to go through,* xxxx xxxx *were devastated.* • *If you would have wanted to have your diagnosis from birth – what difference would this have made to you/your family? –* xxxx xxxx *son would have received a suitable treatment and he would have lived a normal, also out whole family would had a normal lives.* • *Unwittingly passing on ALD to your children and how this makes you feel – As a* xxxx xxxx*, I*

		• xxxx xxxx *feel extremely guilty and sad* • *Your experiences of pre-implantation genetic diagnosis (PGD) and the reasons why you chose this route – to prevent other family going through what* xxxx xxxx *are going through. This is very cruel situation and* xxxx xxxx *do not wish to anyone to go through.*
page 10, Q1	What is the incidence of ALD in the UK?	*We want to demonstrate that the incidence of ALD reported in clinical papers, is far higher than the number of patients that have been identified and that this is an unacceptable situation.* *We want to get across our worries that there are many adults that are "lost" in the system as the condition initially causes behavioural changes that can mean relationship breakdown, isolation, homelessness, inability to access medical help.* *We also want to highlight the risks of not allowing reproductive choice for adults who do not know they have ALD.* *Please insert here your stories about:* • *Issues in accessing medical help- once he was diagnosed it was easy to access medical help* • *Issues in accessing a diagnosis – GP was not able to detect early signs when I thinking back.*

		• *Your feelings about unidentified adults with ALD passing on the gene to their children – Had xxxx xxxx known about xxxx xxxx gene xxxx xxxx would not had children of my own.*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*We want to demonstrate that knowledge of an ALD diagnosis from birth offers significantly different outcomes than if ALD is diagnosed due to detection of Addison's or other symptoms.* *Please insert here your stories about:* • *A diagnosis that was too late for transplant and the consequences for you/your family- my son was diagnosed in 2015 when he was six, he was a healthy boy until then. When he was diagnosed his condition was progressed as a result he was not qualified for BMT. He lost his abilities fast, affected mobility, eating and drinking, speech and learning. He lost his mobility very soon after diagnosis, and then speech, then eating and drinking. He has to move to a special school for physical disabilities. He lost all his friends. The whole family have to move to a new accommodation. He is now none verbal, tube feed, not able to express nor eat or drink. He is transferred and has to be on a special chair or wheelchair. He needs 24 hours care. This whole situation has affected our family. Not mentioning*

		other associated symptoms he has developed since he became ill.
Page 19	Conclusion	*The NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage.* *Please insert here your thoughts on this decision – you might want to think about the following:* • *Benefits of early diagnosis- you just need to see what i have written above. If* xxxx xxxx *son was diagnosed early enough our lives would have been a normal. But we are living in a hell. He has no life.* • *Screening is already happening in the US and Netherlands – how does this make you feel? – it makes* xxxx xxxx *feel sick. If* xxxx xxxx *had a choice* xxxx xxxx *would definitely went for the screening.* xxxx xxxx *was given screening for other things, like Downs and so on. Why not AL D????* • *The impact it has made on your/your family's life because there was no screening when you/your loved one was born – has an ALD or AMN diagnosis affected your physical or mental health, ability to work, live in your home, education choices. How has the diagnosis affected siblings - have they experienced mental health issues such*

		as survivor guilt, depression, has their education or personal life been affected? – xxxx xxxx had to give up xxxx xxxx work to care for xxxx xxxx son full time, xxxx xxxx suffer with anxiety, also diagnosed with diabetes lately, moved to a different job. Our xxxx xxxx involves with xxxx xxxx brother's care, xxxx xxxx is only 14. We don't have family outings anymore. xxxx xxxx xxxx xxxx missed xxxx xxxx childhood due to xxxx xxxx brother's illness. • *The impact it would have made on your life if screening had been in place when you/your loved one was born – xxxx xxxx son would have received a suitable treatment like BMT and live a normal life, it would not have affected to all xxxx xxxx family like now.*

11. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy [delete as appropriate]**		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	
Page 5, para 5;	Available standard therapy	
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*I AM SISTER OF A BOY DIAGNOSED IN 1966 WITH SCHILDER'S DISEASE, WHO DIED IN 1969. 30 YEARS LATER A GENETICIST CONFIRMED THAT IT WAS LIKELY TO HAVE BEEN ALD. AS A YOUNG PERSON I DISCOVERED THAT THE DISEASE COULD BE PASSED ON BY FEMALE RELATIVES WHO MAY BE CARRIERS. THIS AFFECTED MY DECISIONS ABOUT HAVING MY OWN FAMILY. I WAS FEARFUL OF PASSING ON THE GENE AND DID NOT HAVE CHILDREN. MY PARENTS' RELATIONSHIP BROKE DOWN IN 1968 AS A RESULT OF MY BROTHER'S ILLNESS AND MY* xxxx xxxx *SUFFERED A BREAKDOWN. THERE WERE NO SUPPORT NETWORKS THEN AND LIMITED KNOWLEDGE OF THE ILLNESS. I HAVE REMAINED SINGLE WITH NO CHILDREN AND I BELIEVE THIS TO BE AT LEAST IN PART BECAUSE I CAME TO SEE FAMILY LIFE IN*

		TERMS OF TRAGEDY AND TRAUMA. I HAVE HAD TO DEAL WITH THE SADNESS OF THIS. I WORRY FOR MY xxxx xxxx *AND* xxxx xxxx xxxx xxxx *YEAR OLD* xxxx xxxx*.*
page 10, Q1	What is the incidence of ALD in the UK?	
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	
Page 19	Conclusion	• *AS SCREENING IS ALREADY HAPPENING IN THE US AND NETHERLANDS – THIS IS UNACCEPTABLE, IN THE UK. IT AMOUNTS TO A LOTTERY THAT DEPENDS ON WHERE YOU WERE BORN.* • *SEE MY STORY ABOVE AS TO HOW THIS HAS AFFECTED MY FAMILY.* • *IF THERE WERE TREATMENTS AVAILABLE IT WOULD HAVE MADE A HUGE DIFFERENCE . SADLY THERE WERE NONE AT THAT TIME SO IT WAS PERHAPS BETTER NOT TO KNOW IN ADVANCE. IF IT WAS HAPPENING TO US NOW, WITH THE CHANCE OF TRATMENT I WOULD WANT SCREENING TO BE AVAILABLE.*

UK National Screening Committee

12. Member of the public

Name:	Mrs Martina Wilson	**Email address:**	xxxx xxxx
Organisation (if appropriate):	private		
Role:	**Relative of someone with adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	Our family is lucky and not affected by childhood onset ALD, nor Addison's Disease.

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	
Page 5, para 5;	Available standard therapy	*I do not have enough medical knowledge to comment*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	• *Knowledge that* xxxx xxxx xxxx xxxx *has the gene and therefore the potential for ALD and AMN, would have informed decisions about career choices, where to live and financial planning.* • *We would have done certain things, while* xxxx xxxx *could walk easily, rather than putting them off to our retirement. Those mountain and beach walks will now never be taken by* xxxx xxxx. • *As a family, our conversation with our children about the disease and its implications for their* xxxx xxxx *and them would have been different, if we had early knowledge. When you are in shock, talking to your children and other relatives is even more stressful. Facts are post hoc and it is*

		impossible to prevent an overwhelming sense of panic taking over in all concerned.
page 10, Q1	What is the incidence of ALD in the UK?	*Based on* xxxx xxxx *family, probably higher than the statistics suggest:* • *After suffering several years with back spasms, unexplained sudden tripping and fatigue after longer walks (in a walking family),* xxxx xxxx *diagnosis from the initial visit to our GP took 10 months, which* xxxx xxxx *understand to have been unusually fast. It involved an initial referral to an orthopaedic specialist as the GP assumed that the awkward gate, occasional stumble and permanent backache was skeletal rather than nerve related. Fortunately, the orthopaedic surgeon recognised within 5 minutes that* xxxx xxxx *needed to be referred to a neurologist. The neurologist in turn then looked for the most common ailments that might have those symptoms. We had about six appointment at each of which* xxxx xxxx *told us what it wasn't. Having done the usual thing and googled the symptoms ourselves, we did actually go home and opened a bottle of bubbly to celebrate the diagnosis that it isn't Motoneuron Disease. This was followed by a three day stay in hospital involving lumbar puncture and a fleet of*

		other tests, and a six week wait before the diagnosis of 'adult onset ALD' was sent. The effect on us as a family was very stressful until some month later, after the referral and further tests at the xxxx xxxx *the diagnosis was amended to AMN. Taking into account the time investment by NHS specialists and the numerous tests, MRI scans etc, having an early, pre-symptomatic alert about the genetic mutation that a newborn screening would enable, there would have been financial savings for the healthcare system and better decision making by us, when the first symptoms appeared.* • xxxx xxxx *had a cousin on his mother's side, who died following an adult onset ALD diagnosis, following an infection after a BMT. The decision to go to BMT was taken after unmanageable headaches and other pains made life unbearable. Diagnosis was very late and things progressed so fast that the wider family only learned of the illness after his death.* • xxxx xxxx *grandfather suffered chronic backpain, which was explained by his physical work on the railways. However, as his daughter must have been the carrier, the question remains if it was undiagnosed AMN.* • xxxx xxxx xxxx xxxx *also suffers with backpain and more recently falls.* xxxx xxxx *GP in* xxxx xxxx

		ignores the information that xxxx xxxx son has an AMN diagnosis and blames xxxx xxxx age. • *Three of xxxx xxxx xxxx xxxx sisters suffer with chronic backpain that eludes successful treatment.* • *Knowing that the genetic defect runs in the family, one of xxxx xxxx xxxx xxxx wanted to be tested before starting a family and was told by xxxx xxxx GP that the test would not be carried out, unless xxxx xxxx mother (the potential carrier) requested a test first. She did and fortunately was in the lucky 50%. However, the fact that the GP could refuse to initiate the test was a surprise, as was the fact that xxxx xxxx could place the onus on xxxx xxxx patient to 'make her mother' agree to be tested. I had stupidly assumed that within the NHS there was a code of conduct that enabled patients to access information (i.e. have pertinent tests), especially if the outcome enables preventative measures to be decided.* • *When xxxx xxxx got his diagnosis, xxxx xxxx xxxx xxxx was an older teenager, just ready to become sexually active. It was a difficult conversation to not only explain xxxx xxxx father's diagnosis, but also the implications of it for xxxx xxxx future children. In the context of xxxx xxxx decision making it was fortunate timing. We know of a*

		number of families through the Alex TLC support network, where that knowledge was not available, when unwitting carriers started families. It is a doubly cruel twist, when a parent needs all the physical and emotional support a family can muster and at the same time, children/grandchildren are watched with paranoia each time a boy stumbles or throws a tantrum, let alone actually develops the disease. It is not only the patient who experiences pain, fear and loss of quality of life. Siblings and all carers experience the losses. Forewarned is forearmed and allows rational risk taking, preventative planning, and also timely medical decision making, should the need arise.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	• *Again through the Alex TLC network, we have observed that many boys who had an early BMT thrive, often in awful contrast to their older brother, who had a relatively late diagnosis in a family who had no early warning of the possibility that their boys could develop ALD.*
Page 19	Conclusion	• *I gather that "The NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage."*

		• *I do not understand the reasoning in the UK, knowing that it happens in other countries systematically and that it can be requested by families in others. I do understand that the decision is probably cost-based against the rarity of this gene mutation. However, newborn screening does happen for other conditions. It cannot be that difficult, or expensive to add another line in the genetic analysis. The opportunity pre-symptomatic diagnosis offers to individual's chances of a healthier, longer and more comfortable life must be worth the investment, even if the cost savings across medical treatment and management of ALD and AMN combined with social care costs, loss of household earnings (patient and carers) do not equal those needed to invest in the newborn screening process.* • *I especially do not understand the refusal to include the ALD/AMN in newborn screening at this time, when more and more very effective treatment seems to be coming on stream. If this was the US, failure to conduct such testing routinely would sooner or later result in a lawsuit about medical neglect bring about actual harm. Inaction = lack of test = lack of opportunities for*

		early treatment = harm with potential for early death • *I would like to think that the decision makers have spent a day in the company of an ALD patient in the latter stage of the disease before reviewing the earlier rejection of the application to be included in the testing regime.*

UK National Screening Committee

13. Member of the public

Name:	Shane Nelson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**1st and foremost – Parent of a son with X linked adrenoleukodystrophy ALD, parent of a daughter with adrenomyeloneuropathy AMN – ALD gene) and a husband to my wife who has adrenomyeloneuropathy AMN – ALD gene.**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

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Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*My immediate family consists of me, Shane 45,* xxxx xxxx xxxx xxxx xxxx xxxx xxxx xxxx xxxx xxxx, xxxx xxxx xxxx xxxx xxxx xxxx , xxxx xxxx xxxx xxxx xxxx xxxx, xxxx xxxx xxxx xxxx xxxx xxxx *and* xxxx xxxx xxxx xxxx xxxx xxxx . *In December 2017 we went to India as a family to celebrate Christmas 2017 and see in the new year 2018. We had the best time and hoped 2018 would continue to be a happy one. However that wasn't to be……..* *A few months into the new year* xxxx xxxx *who was* xxxx xxxx *then started to very gradually become* *withdrawn – he would not want to play with cousins and would just sit and watch (this was very unlike* xxxx xxxx*)* xxxx xxxx *was always very kind, playful and social.* xxxx xxxx *started to not want to go to school. This was very unusual as he always liked school, teachers and being with his friends. Always a clever, popular and friendly boy who achieved all his key milestones and beyond.* *confused and disorientated – he would not realise which way was the school exit. He would walk in the opposite direction to where he was supposed to go? He suddenly*

		stopped being able to read simple words which he was previously able to. *Sight –* xxxx xxxx *developed a squint. Which we pursued this to be looked into. Saw an ophthalmologist and was advised all ok despite us explaining that* xxxx xxxx *seems to lose concentration now which is unusual. The ophthalmologist just said – he is probably bored reading back the visual test ques. Come back in a few months if the squint is still a problem. We were not happy with this response.* *Hearing: Literally suddenly it seems that* xxxx xxxx *hearing would intermittently stop? He could hear at times and other times he couldn't – why was this happening?* *Sight:* xxxx xxxx *would walk into glass doors, have difficulty with his peripheral vision. He would trip over easy, he would walk into doorways / door frames and seem to misjudge distance? He even told me us he could not see properly sometimes.* *Speech:* xxxx xxxx *speech became slower and slurred. This was what prompted our GP to send* xxxx xxxx *for M RI.*

		xxxx xxxx *MRI showed* xxxx xxxx *had extensive damage caused to his brain.* xxxx xxxx *was referred for a blood test to determine the damage. On* xxxx xxxx *(our* xxxx xxxx xxxx xxxx *birthday), we went to the* xxxx xxxx *to be told the most horrific news imaginable.* *Our son* xxxx xxxx *has X- linked adrenoleukodystrophy. As* xxxx xxxx *was symptomatic, there is no cure.* xxxx xxxx *life expectancy is on average 4 years from diagnosis. If this had been picked up at newborn screening then* xxxx xxxx *would have had a chance with bone marrow transplant and be carefully monitored for life. Instead, we were told to take him home and love him.* *3 months later* xxxx xxxx *stopped being able to walk, talk or eat. From October 2018, severe excruciating painful all over body dystonia attacked our son and has been doing so every single day since……. EVERY SINGLE DAY! He is unable to move any part of his body and is forced to live out the rest of his life in this state. How can this be quality of life? How can this be justified by not screening for at birth?*

Page 5, para 5;	Available standard therapy	*Gene therapy – our son at 5 years old was too late to have treatment let alone BMT because he had started to show symptoms albeit for just a few months!* xxxx xxxx *was given a death sentence instead of help! How can a healthy child of 5 years old suddenly be told he will not be able to grow up and he will have his life cruelly cut so short because he has this disease that was not screened for when he was born.* xxxx xxxx *has had absolutely everything taken away from him.*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*We wish to God* xxxx xxxx *was given a chance of life by having ALD included in his newborn screening test. He would have a very very good chance of leading a normal healthy life. Given the opportunity to have BMT and given a chance. Instead it seems we have all been given the death sentence as that is how we feel since* xxxx xxxx *was diagnosed.* *Our family has been torn apart since* xxxx xxxx *diagnosis, in July 2018. We have to stand by a watch* xxxx xxxx *deteriorate in front of our eyes.* *Diagnosis has given us no comfort whatsoever – how can it ? What can they the doctors say when they are unable to offer any help, hope or future for your child*

		…… you will lose your child. xxxx xxxx *has to live with knowing the fact that* xxxx xxxx *has passed this gene mutation which has caused this horrific disease to take place in* xxxx xxxx*. Also knowing* xxxx xxxx *has passed the ALD gene to* xxxx xxxx xxxx xxxx xxxx xxxx *who now has been confirmed as having AMN (from the ALD gene). The future will tell if* xxxx xxxx *has passed the same ALD gene on to* xxxx xxxx xxxx xxxx xxxx xxxx xxxx xxxx*.* xxxx xxxx *and I jointly care for our son.* xxxx xxxx *has not been able to go to work since diagnosis and have been diagnosed as having* xxxx xxxx xxxx xxxx *as a result of what is happening to* xxxx xxxx*. This is a huge strain on family 'normal' life and of course has a huge emotional effect and financial strain and worry.* xxxx xxxx *siblings have been robbed of a brother who has the biggest heart and has so much love to give. Despite being showered with continuous love* xxxx xxxx *is unable to communicate, move, interact with his siblings. He is locked inside his own self- destructing body and his siblings watch this everyday.* *Imagine thinking about planning your own child's funeral*

		– unimaginable and this SHOULD NOT BE HAPPENING! *We as parents would have wanted to know that* xxxx xxxx *has this gene at birth so he would have been given a chance of life and not the unfair death sentence.* *As mentioned, I have* xxxx xxxx xxxx xxxx*. From the* xxxx xxxx xxxx xxxx *that have been tested since* xxxx xxxx *diagnosis. Our* xxxx xxxx xxxx xxxx *has also been diagnosed with AMN as* xxxx xxxx xxxx xxxx *unbeknown passed the ALD gene to* xxxx xxxx*. This has a huge impact on* xxxx xxxx xxxx xxxx *as this gene mutation and dictates* xxxx xxxx *family planning and equally could go on and have the same devastating effects. We have the continuous dark "killer" cloud over us as we wait for our other* xxxx xxxx xxxx xxxx *to be tested when they are off an appropriate age.*
page 10, Q1	What is the incidence of ALD in the UK?	*ALD is supposed to be rare. 1 in 20,000. However, as soon as* xxxx xxxx *was diagnosed, I met another* xxxx xxxx *who had a child diagnosed with ALD from the same town 'xxxx xxxx . xxxx xxxx has since lost* xxxx xxxx *own* xxxx xxxx *to ALD and* xxxx xxxx *son.* xxxx xxxx *nephew*

		also lives locally and he too has ALD. *Not testing at newborn stage is playing deathly Russian roulette with so many lives. There are thousands of boys running around healthy now but yet little to do they will start to display symptoms of ALD and then it is too late. So many people are lost in the system.* *As a dad who have xxxx xxxx children and told each time during newborn testing – your child is fine. xxxx xxxx xxxx xxxx had been left unidentified as having AMN and have then passed this killer disease onto our son and have also passed AMN to one of my xxxx xxxx (that I currently know off).*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*Newborn screening would have given early diagnosis of this gene before it had chance to damage my son's brain. xxxx xxxx could have gone on to have BMT and live a normal healthy life now. He would have been given chance!*
Page 19	Conclusion	*The NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage.* *Early diagnosis would have shown xxxx xxxx had ALD and before any damage was caused by the gene*

		mutation – xxxx xxxx would be clinical monitored regularly and offered BMT which would have saved his life. • *Screening is already happening in the US and Netherlands – it is saving lives?? How can this be ignored by UK screening? It makes me beyond upset and devastated to know this – it's as if ALD has been ignored because its rare.* *The damage and impact xxxx xxxx diagnosis has had on our family will never be repaired. The continuous pain will never go away. We are grieving for the xxxx xxxx that was but yet know we will have to grieve again when xxxx xxxx reached the end of his life due to ALD.* *We are a very close family who are physically exhausted providing 24 hour care for our Son with this evil demanding condition. We are all emotionally exhausted and I have to support xxxx xxxx xxxx xxxx as xxxx xxxx battles xxxx xxxx xxxx xxxx due to what is happening to my son, unable to work (which xxxx xxxx a has always done in the past). Not only do I have to give emotional support, I have been left as the only person to bring an income into our household - which is financially straining as I have to work all*

		hours to try and make money. When I should be at home caring for my family. *The damage is there in each and every one of us family members. Tell tale signs are there already but the life long scars and damage this has caused our family will no doubt come to view and haunt us in the future and will stay with us forever. Why – because ALD was not included in the UK's newborn screening programme.*

UK National Screening Committee

14. Member of the public

Name:	Ashley Nelson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenomyeloneuropathy and relative of someone with adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	• *My xxxx xxxx was born with ALD, this progressive disease was diagnosed at the age of 5 years old* • *This late diagnosis means that BMT was no longer an option*

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	• *However, if this genetic condition was detected via new-born screening, BMT would have been an option for my* xxxx xxxx • *Since his diagnosis, he has disease has progressed rapidly, he is now in a completely vegetative state at the age of 7 years old.* • *He lost the ability to walk, talk and eat just a few months after diagnosis.* • *Overall, the late diagnosis and undetected ALD in early years has led to untreatable ALD which is inevitably terminal.*
Page 5, para 5;	Available standard therapy	• *There have been no successful treatments for my brother as his undetected ALD led to the unavailability of BMT or any other standard therapy.*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	• *An early diagnosis could have saved my* xxxx xxxx *life, his late diagnosis has been devastating for him and* xxxx xxxx *family.* • *My anxiety initially increased when I found out I had the ALD gene, purely because of my* xxxx xxxx *experience in the condition of ALD. However, this diagnosis has been life changing for myself and my future. The detection of the ALD gene allows me to plan for my future and to make informed decisions when family planning. My future children will be free from the ALD gene, this*

		is an immense relief for myself and xxxx xxxx family, as we have experienced the first hand effects of such a cruel disease. • *As I am the xxxx xxxx xxxx xxxx carrying ALD gene, if this was detected at birth, my xxxx xxxx would have been able to receive treatment for his ALD from birth, a much higher success rate.* • *The detection of my ALD gene condition due to my xxxx xxxx late diagnosis of ALD has meant that my future children can be protected from this devastating disease. My children will not have to endure such a cruel, life limiting illness.*
page 10, Q1	What is the incidence of ALD in the UK?	• *My xxxx xxxx had unidentified ALD gene who then passed on this genetic condition to my xxxx xxxx, who has ALD. My xxxx xxxx has to deal with the guilt xxxx xxxx feels for passing on a deadly undetected gene.* • *Being able to identify carriers of this gene will be lifechanging for future generations. No child should have to endure such an illness to detect others in the family with the same gene.* • *My xxxx xxxx life could have been saved with early detection. It is heart-breaking that such a devastating condition often goes undetected until it is too late.*

		• *As a young adult with the ALD gene, I feel completely reassured that I will be able to ensure I do not pass this genetic condition to my children through alternative family planning options. Detection saves lives.*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	• *The diagnosis was too late for my* xxxx xxxx xxxx xxxx*, meaning a transplant was no longer an option.* • *This has had devastating effects on* xxxx xxxx *family. My* xxxx xxxx *has had to live with no quality of life due to a condition that could have been detected at birth.* • *We live each day in fear for my* xxxx xxxx*. His life has been tragically destroyed at the age of just 5 years old.* • *A little boy who was once a very happy child has been completely taken from us by this condition.*
Page 19	Conclusion	• *There is no doubt that if there was an early diagnosis in my* xxxx xxxx*, there would have been more options for preventative measures to delay or inhibit the progression of this disease* • *Screening is already happening in the US and Netherlands – I feel utterly betrayed that our country cannot acknowledge a condition that has so much more treatment potential with an early diagnosis.*

		• *The impact has been completely devastating for* xxxx xxxx *family. Being the* xxxx xxxx *sibling of* xxxx xxxx *makes it incredibly heart breaking to watch my* xxxx xxxx xxxx xxxx *life be taken away from him in just a matter of months after diagnosis. He would ask questions like "what was happening to me", questions we could not answer as a family.* • xxxx xxxx *family life would be completely different if new-born screening for ALD was in place.* xxxx xxxx *would have had a chance to survive and fight this cruel disease, instead, it has caused utter heartbreak in* xxxx xxxx *family, watching my* xxxx xxxx xxxx xxxx *transition from a bubbly, fun, energetic 5-year-old to a helpless, lifeless 7-year-old boy. I cannot stress enough the importance of new born screening.*

UK National Screening Committee

15. Member of the public

Name:	Tim French	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

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	Our son was tested for ALD before birth (as AMN was diagnosed in the Grandmother).	Due to a diagnosis of AMN with the xxxx xxxx, xxxx xxxx xxxx xxxx was tested when pregnant with our son. The test result came back showing that the ABCD1 gene was

		faulty. We decided to continue with the pregnancy and now have a very active 3.5 year old called xxxx xxxx. While I am English, my wife is xxxx xxxx and we are currently with xxxx xxxx in the xxxx xxxx medical system. xxxx xxxx has now been to the xxxx xxxx hospital which specialises in this condition in xxxx xxxx on 4 occasions now for a 6 monthly check-up. Thankfully to date the results have been clear, however Addisons was diagnosed and xxxx xxxx takes a 3x daily supplement. The first two occasions at the hospital xxxx xxxx was very young and it was difficult to explain to him that the doctors needed to take blood and he must participate in tests. Though from the 3rd visit on he is now great. He tells the doctors he doesn't like them taking blood, but complies perfectly and then asks when done, "where are my sweets – I was very good like you asked – I have earnt the sweets". Which is wonderful to see as parents, as the first two times were admittedly tough. In day to day life (apart from including xxxx xxxx Addison supplement into mealtimes) we live as if nothing is wrong with xxxx xxxx. When we are at the hospital and waiting

		for the final day confirmation of the test results we have of course some anguish. Though we also see the positive in this. Every six months xxxx xxxx is checked by experts and we have the knowledge that all is well with our little boy. It was the knowledge that ALD can be managed when diagnosed early that helped with the decision to have xxxx xxxx. It is the best decision we have made as he is a most wonderful little boy.

UK National Screening Committee

16. Member of the public

Name:	Tom Wilson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*Even though I had an AMN diagnosis late in 2005 I have no Addison's disease links whatsoever my specialist at* xxxx xxxx *considers this will be the case for the rest of my life*
Page 5, para 5;	Available standard therapy	*N A*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*After many years working in* xxxx xxxx *in* xxxx xxxx *with a 30 mins walk most lunchtimes I noticed on moving by 2003 to a similar job in* xxxx xxxx *that my walking was slowly deteriorating there was no scope nearby for that lunchtime stroll and also I developed considerable back pain with a 2-3 mins effort needed to go from a lying to a standing position once up I was broadly OK for hours on end around this time* xxxx xxxx *and I also gave up the one hour's gentle tennis at a local park we had enjoyed for 6-7 years on a brief trip to Rome May 2005 I found it tricky to quicken my pace to run for buses etc so we agreed on*

		return to London we would see my GP to see if an explanation could be sought by then I had slight tightness in the front of each foot and I was taking longer to do the 700 steps each morning on a 3 leg Tube and bus trip to each day the consultant checked all my leg/ foot muscles and tendons and said all was fine he then asked me to hold out my hand to see if any tiny tremor or shake was viewable his immediate recommendation to the neurology team at xxxx xxxx *Hospital was a good one after tests by Dr* xxxx xxxx *months of tests and MRI cans and lumbar puncture test in a 2-3 day hospital stay led to a diagnosis of ALD On going back to the office and checking online what this was we were alarmed to read it could have a remaining life span for me of 2-7 years we alerted our* xxxx xxxx *year old son and especially our* xxxx xxxx *year old daughter (as she could have carrier implications and much to consider later if starting a family) there was much family chat about later perceived wider family consequences for me my movement my job any anxiety and re perceived earning limitations pressure on* xxxx xxxx *as a carer and maybe house improvements to assist me well within 3 months the diagnosis was changed after blood tests at a specialist centre in* xxxx xxxx *from ALD to AMN There was huge relief among the whole family it was not a disease with outrageous negative consequences like Motor Neurone Disease I also notified my* xxxx xxxx xxxx xxxx *in* xxxx

		xxxx *as they had children then aged2 to 27 11 years later our* xxxx xxxx *after much research and the finest NHS specialist advice on PIGD did give birth to* xxxx xxxx *lovely healthy* xxxx xxxx *who daily are a constant joy to her and of course to us as devoted grandparents*
page 10, Q1	What is the incidence of ALD in the UK?	*My neurologist Dr* xxxx xxxx *- by now I was under the care/ guidance of* xxxx xxxx *told us 1 in 28,000 had this condition in the UK Such was its rarity it has been until the mid 70s quite often been misdiagnosed as MS around this time my* xxxx xxxx *then aged 71 and a sufferer from back pain advised me a cousin of* xxxx xxxx *(male aged 35) in* xxxx xxxx *had died 2 years back he had a ALD diagnosis terrible headaches in his garage work and he foolishly against* xxxx xxxx *advice chose to have an Adult Bone Marrow Transplant within a few weeks he lost his sight and sadly died* *With what many of us now know it's a real shame that parents of ALD diagnosed boys do not have more information early on to guide later choices more new born pin prick heel tests surely need to encompass many more neurological conditions as is happening in some US states and in Holland too I gather my* xxxx xxxx *good story above could widely have been shared by many others UK and worldwide had the knowledge been more commonly been*

		accessible with all the advantages (and some down sides too) been in the public realm of accessible knowledge
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*I have no close or anecdotal knowledge of any transplant information to share*
Page 19	Conclusion	*My day to day handling of what I call my AMN condition not my disease is I hope a kind of useful way to those around me in my very close and wider family neighbours and former work colleagues of showing it affects me but doesn't as such trouble me most weeks I have special devoted and caring* xxxx xxxx *who assists ne greatly in so many ways this alone means I can handle any negativity associated with AMN and celebrate the positive things in life still open to us both next month and in the years ahead I have a little monthly contact with the UK ALD community but eagerly look forward to the annual get togethers* *This broadly keeps me informed of developments regarding my condition and ongoing tests being undertaken by those diagnosed with AMN/ALD some of which may lead to future benefits to us all and more importantly to those yet undiagnosed. Hearing of those stories where missed opportunities meant delayed treatment is always distressing and you feel for those involved. As we move ahead we can*

		but hope that there will be fewer such instances. The inclusion of this condition in the future new born screening will be hugely advantageous and bring about early knowledge which is critical for planning a path ahead.

UK National Screening Committee

17. Member of the public

Name:	Ellie Nelson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Sister of someone with adrenoleukodystrophy**		

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Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	*My brother's teachers reported a lack of focus and inability to communicate effectively in his lessons. Our family also recognised unusual behaviours that my*

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*brother would not normally display for example, not wanting to socially play. Following these signs my brother was taken to several neurospecialists until he was finally diagnosed with ALD. Of course, once symptoms show, the chances of any recovery is almost eliminated as potential treatments such as bone marrow transplants are required at early stages of life. This is why, if detected early enough, young boys will be given more opportunities to live their life as a healthy, youthful individual. This privilege was taken away from my brother as his diagnosis was discovered after his symptoms. Therefore it is important that more of the general population are aware of and educated in the consequences of ALDin order to predict the phenotype of their children for example through genetic screening and as a result have access to treatments that could be life-saving.*
Page 5, para 5;	Available standard therapy	*Alongside general medication to help minimise his pain, my brother has received no other form of treatment. There was hope when an American drug industry was carrying out a trial with ALDpatients however an investor pulled out and there was no longer any option to decelerate the deterioration he experienced from this neurological disease.*

		In boys yet to experience symptoms, there are current therapies that aim to tackle this condition before it has the chance to affect the individual for example, by preventing their conscious ability to move.
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*When my brother was diagnosed with ALD, I remember my family having to educate ourselves of what the condition involved and how this would affect our day to day lives. As ALD has different effects on different boys for example, different symptoms can arise at various ages, we were unsure of exactly what my brother would experience and when. I think it is therefore important that research into this critical field is continued so that families like mine can be knowledgeable of the disease and what it entails.* *If my brother received his diagnosis from birth, our family would have had more hope – hope that my brother could continue his life in a regular manner due to the possible treatments available. We would have been more prepared as a family to tackle this devastating disease.*
page 10, Q1	What is the incidence of ALD in the UK?	*We want to demonstrate that the incidence of ALD reported in clinical papers, is far higher than the number of patients that have been identified and that this is an unacceptable situation.* *Because ALD is a condition that is not well-known or screened for at birth many boys have to wait long periods*

		of time for their diagnosis. Many boys have to travel across the country to be seen by a specialist doctor, also slowing diagnosis, which is awful considering how quickly ALD deteriorates the individual. *It is worrying that adults, like my xxxx xxxx, who was unaware of carrying the gene for ALD are passing these genes onto their children and only discovering this when it is too late – when their son shows ALD symptoms. If more parents were aware of tis condition, they can also be educated of the reproductive choices' adults have to eliminate the trauma families with ALD boys experience*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*Unfortunately, my brother's diagnosis was too late for a successful transplant. This has imposed heart-breaking consequences for my family. My brother is continually deteriorating and in a completely vegetative state, relying on us as a family. He is unable to consciously move, communicate and self-feed. A transplant may have eliminated or decelerated these effects of ALD and allowed my brother to live more years of his life in an enjoyable and healthier way. Our usual family activities such as going on family holidays are no longer able to take place. ALD initiates different types of trauma within a family such as depression of family members who cannot carry out usual activities like going to the supermarket.*

		With an early initiation of treatment following screening, better outcomes for adrenoleukodystrophy patients are possible. It gives them opportunities to live their lives into adulthood, doing usual activities such as going to school or getting married. Without early treatment, these opportunities are almost completely eradicated for an individual with ALD due to the rapid decline of conscious control.
Page 19	Conclusion	*The fact that screening has been introduced in other countries such as the US and the Netherlands is extremely upsetting. Since introducing this programme, it has saved multiple lives of young boys with ALD. It is only fair that each and every boy has the same opportunity to live their lives. It is shocking to discover that if my family were situated elsewhere in a country like the Netherlands my brother's condition could have been detected at birth. This would have led to an early diagnosis and offered routes of treatment that would have allowed him to be an active young boy and man.*

UK National Screening Committee

18. Member of the public

Name:	Chris Ogden	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Alex TLC		
Role:	**Person with adrenomyeloneuropathy**		

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

Yes **~~No~~**

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Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	*I have AMN adrenomyeloneuropathy.* *I have no adrenal dysfunction*

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*I was diagnosed at age 42. I am now 77 years old.* *If I had been diagnosed through new born screening my parents would have been able to be aware of the likelihood of the disease developing.* *I was told at diagnosis that progress would be slow but it was likely I would be wheelchair bound when I reached older age. This has come true.* ***Although I have no children, if I had, then a female child would automatically have been affected. If newborn screening was available I would absolutely wish to have known this at birth so any disease symptoms could be monitored and treated**.*

page 10, Q1	What is the incidence of ALD in the UK?	*I was made aware some years ago that AMN is often misdiagnosed as MS, although this may occur less now.* *There are cases of men with AMN who have **no** symptoms. I have met at least one individual in this situation. This is bad because such individuals could have children and unwittingly pass of the disease to another generation**. New born screening would alert the health authorities to the true prevalence of the disease.***
Page 19	Conclusion	*There is a great need for ALD to be on the new born screening list. We know of many cases of misdiagnosis, or no diagnosis even in adults and hence our understanding of the prevalence of the disease is incomplete.* ***The absence of newborn screening means that individuals pass into adulthood with a strong likelihood of draining the resources of the NHS for year to come.***

UK National Screening Committee

19. Member of the public

Name:	Lilly Nelson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Sister of a person with adrenoleukodystrophy and adrenomyeloneuropathy. Daughter of a mother with adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **No**			

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		about adrenoleukodystrophy at xxxx xxxx birth, new born ALD screening could of took place and the effects of this brain damage would not have been nowhere near as powerful.
EPage 5, para 5;	Available standard therapy	• *As previously mentioned, due to the late diagnosis, Bone marrow transplant was no longer an option for us. xxxx xxxx has not received any other form of treatment as the adrenoleukodystrophy was too far developed when we reached the diagnosis stage.*
Ces page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	• *When receiving the diagnosis as a family we were all heartbroken and still are two years down the line. Before xxxx xxxx was diagnosed, I knew something was incorrect due to his behavioural changes as previously mentioned, but I had absolutely no idea of how dramatic the diagnosis would be. ALD is even more heart-breaking as boys like my brother only start to deteriorate in later years of their lives, xxxx xxxx was diagnosed at 5 years old, for 5 years xxxx xxxx was a healthy young intelligent boy who did not suffer from any harmless diseases, until his diagnosis of ALD since then xxxx xxxx has lost his ability to walk, talk and use his face to express emotions. He has become completely dependent of everything!*

		• *If xxxx xxxx was diagnosed at birth it would have been a completely different story for my family, as we would not have seen xxxx xxxx true characteristics and funny sense of humour. I am glad that we had those 5 healthy years with our brother, but it makes if even more heart breaking to see my brother dramatically change, due to the brain damage of ALD.*
page 10, Q1	What is the incidence of ALD in the UK?	• *I find it very unfair how anyone can carry the ALD gene but have no clue that they are doing so. People who pass on the gene to their children are also filled with an overload of guilt. My xxxx xxxx was the carrier of the ALD gene, which was passed onto my brother, my xxxx xxxx had no idea that xxxx xxxx was carrying this gene and had no idea that ALD had even existed! Therefore, more awareness needs to be raised on this matter.* • *When I turn xxxx xxxx xxxx xxxx xxxx xxxx in xxxx xxxx, I will be able to be tested to identify if I am a carrier of ALD just like my xxxx xxxx, this is a relief as I will be fully aware of the outcomes of ALD in the foreseeable future.*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for	• *My brother had a late diagnosis therefor it was too late for any transplants to take place, or any medical/clinical help toward the brain disorder.*

	adrenoleukodystrophy compared to initiation of treatment following clinical detection?	
Page 19	Conclusion	• I personally believe that an early diagnosis of ALD is extremely beneficial to young male individuals, as treatment can then take place to prevent or slow down further symptoms. • Screening is already happening in the US and the Neverlands, this excites me to know that other boys across the world will not have to suffer the traumatic disease of ALD, in the future I hope that screening talks place in our local hospitals in England so other boys like my brother xxxx xxxx will be prevented from dramatic brain damage. • If we as a family would've been aware of ALD when xxxx xxxx was first born, xxxx xxxx story would have been completely different to tell today.

20. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenoleukodystrophy/adrenomyeloneuropathy and Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
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		The inability of several gps to diagnose Addison's despite characteristic symptoms indicates to me that screening for Addison's alone is vital for these children's health and to avoid costly treatment (and even death) from adrenal crises.
Page 5, para 5;	Available standard therapy	xxxx xxxx my sons are/were on regular treatment for their Addison's Disease. Apart from the pre-diagnostic crisis with my xxxx xxxx, neither have suffered further crises. This treatment is standard, very available and very effective. My xxxx xxxx son had a successful bone marrow transplant at the age of 8. I see no issues with either of these treatments that would suggest newborn screening should not be recommended.
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	If my xxxx xxxx had been screened he would most likely still be alive. If my eldest had not gone on to develop ALD symptoms, we would not have had a timely diagnosis for my xxxx xxxx son, later saved by BMT. If I had known I was a carrier of ALD I would have explored the reproductive choices available to me before having children. As a female, I do not feel this diagnosis would have aversely affected my life, rather empowered me with vital information for my and my children's future.

		If neither of xxxx xxxx sons had developed cerebral ALD in childhood, I appreciate they may have faced issues growing up with the knowledge they may get symptoms at some point. I asked my xxxx xxxx son, now 21, if he would have wanted to know about his ALD from birth, even if he didn't get symptoms in childhood and could be facing untreatable ALD in adulthood. He stated "Yes, absolutely. I'd rather know than be hit by something out of the blue. And there's no way I'd want to be passing it on, the guilt would kill me. No-brainer." Humans, especially children, are resilient and learn to come to terms with their situations – a lesson I learnt at great expense when we received our devastating diagnosis of ALD. Having this diagnosis once it was too late to do anything for my xxxx xxxx has irreparably damaged all our lives and caused irreplaceable loss to our family.
page 10, Q1	What is the incidence of ALD in the UK?	It worries me greatly that there are many people in the UK yet to receive this life-changing and life-taking diagnosis. I often wonder how many adults drop out of society and become isolated from those that could care for them due to cerebral ALD, ending up on the streets or in care institutions with no recourse to proper diagnosis. Knowing how difficult it is to diagnose the condition, even with symptoms, I feel there are too many people living

		with this ticking time bomb, waiting for it to explode into their families, either through themselves or their children.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	I find it incredibly concerning that this is even a consideration. It is so widely documented that early BMT delivers the best outcomes and I have heard so many tragic stories of late BMTs due to late diagnosis, how can this not be obvious? My xxxx xxxx son was identified due to his brother's diagnosis at the age of 1, monitored for Addison's (onset age 2) and ALD symptoms regularly. His BMT was initiated within two weeks of seeing early signs on an MRI scan and I cannot begin to impress on you how very grateful I am that this was the case for him. To even think that he might have had an equitable outcome without his early diagnosis is unfathomable.
Page 19	Conclusion	I feel that it is clear that screening for ALD will benefit those that will be affected in childhood and those that won't. The guilt I feel at having passed this disorder to my children, albeit unknowingly, will never leave me. It is disappointing that the UK is so far behind the US and Netherlands in this matter, and I cannot understand why the UK does not feel it is as important a diagnosis as these countries. The result of this diagnosis for my family is:

		• Loss of my xxxx xxxx son at age 7 (age at diagnosis) and 19 (age at death) – yes it was like losing him twice, an aspiring fireman, top of his class at school, orange belt in Jiu Jitsu, goal scorer and tree climber extraordinaire • Loss of a brother to my xxxx xxxx son, who never knew his brother when healthy (he was 1 when his brother's symptoms started and only remembers him as severely disabled and unable to communicate). He states he finds it difficult to feel anything for his brother, which is deeply traumatic for him. • Loss of my career (I'd just accepted a xxxx xxxx training place at university and resigned from my job when we got the diagnosis) • Relationship breakdown with my partner, my mother and her family – they couldn't cope/bear to be around • Inability to give my xxxx xxxx son the attention he deserved/needed growing up due to caring responsibilities (his brother always had to come first) and the long-term consequences of this • My long term (12 year) use of anti-depressants • Need for an early (in my 40s) hip replacement brought on by wear and tear of caring for a young man with complex disabilities for 12 years

		• Reduced job prospects (who wants to employ someone with a 12 year gap in their CV, particularly a bereaved parent?) • My xxxx xxxx son's struggles with depression and "survivor guilt" – when told he needed to have a bone marrow transplant at age 8 he stated "It's not fair, [my brother] didn't get one. I don't want it, it would be better to be like him.". His feelings culminated in suicidal thoughts in his teens, counselling and then dropping out of university. Screening will save lives, prevent families going through devastation, reduce traumatic diagnostic odysseys, empower those identified, giving them choice and a sense of control, and ultimately reduce the incidence of this horrific disorder.

UK National Screening Committee

21. Member of the public

Name:	Sona mitra	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of someone with adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	
Page 5, para 5;	Available standard therapy	•
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	• *Today I should be playing board games with my beautiful family but instead I am writing about how ALD stole my sons life and tore our family's future into a million pieces. Prior to* xxxx xxxx *may 2019, we were living a blessed life. We had 2 sons aged 10 and 12 who were apparently healthy.* xxxx xxxx*,aged 10, was a super keen sportsman, playing cricket and tennis with children 2 years ahead and football with children 1 year older. He was in year 5 and predicted greater depth in all areas(highest achievement) and was studying for the local Grammar school entrance exam. He couldn't talk or walk without smiling. People always commented on his beautiful big brown button eyes. He was the kindest, most popular friendly boy you could imagine.*

		• *We skied yearly and he was accomplished on black runs.* • *I am a GP and apart from watching the film Lorenzo's oil 30 years ago had never read or really heard about ALD. Most GP's never see a case in their lifetime.* • *As A Mum and a GP, I think it was impossible, in retrospect to pick up on any symptoms in time prior to the squint, by which time, treatment is deemed ineffective* • *We have a family history of longevity, with good health on both sides of our extended family.* • *There is no history of ALD or ALD like disease.* • *At the end of march 2019,* xxxx xxxx *developed a squint. I was concerned and had him seen by his regular Optometrist within the week- she was unconcerned but on my persistence referred him urgently to Opthalmology at the local hospital. There we were reassured and told he would need further visial field tests in 6 weeks. In those6 weeks, I continued to worry but was reassured by this advice. ^ weeks later we were seen by the Consultant Opthalmologist who wasn't concerned and suggested reviewing him again in 6 months. At this stage, I insisted on an MRI as he was also showing signs of disorientation and confusion.*

		• *The MRI results the next day confirmed cerebral ALD, Loe's score 16 and along with the diagnosis we were discharged to hospice care.* • *At this advanced stage, xxxx xxxx was still functioning on a very high level- being able to recall every flag in the world with ease.He was still scoring wickets in cricket.* • *Our lives fell apart.* • *I have since found out that I am a carrier, my parents tested negative.* • *Thankfully my xxxx xxxx son tested negative, he will be left an only child by this cruel disease.* • *I was working as a part time GP,being a doctor for the past 25 years.*
page 10, Q1	What is the incidence of ALD in the UK?	*We want to demonstrate that the incidence of ALD reported in clinical papers, is far higher than the number of patients that have been identified and that this is an unacceptable situation.* *We want to get across our worries that there are many adults that are "lost" in the system as the condition initially causes behavioural changes that can mean relationship breakdown, isolation, homelessness, inability to access medical help.*

		We also want to highlight the risks of not allowing reproductive choice for adults who do not know they have ALD. *Please insert here your stories about:* • *How the behavioural problems caused by adult onset ALD caused relationship breakdown/isolation* • *Issues in accessing medical help* • *Issues in accessing a diagnosis* • *Your feelings about unidentified adults with ALD passing on the gene to their children*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*We want to demonstrate that knowledge of an ALD diagnosis from birth offers significantly different outcomes than if ALD is diagnosed due to detection of Addison's or other symptoms.* *Please insert here your stories about:* • *Transplants that have been successful because of early diagnosis identified through another family member* • *Transplants that were "just in time" due to clinical detection eg through an Addison's diagnosis, your own persistence, any other reasons* • *Successful transplants where the patient is now an adult and how they are doing eg. in work, married, no further issues*

		• *Successful transplants where the patient has gone on to develop AMN– we would like to demonstrate that the development of AMN is secondary to the fear of cerebral ALD* • *Transplants that have been unsuccessful as they were performed too late* • *A diagnosis that was too late for transplant and the consequences for you/your family*
Page 19	Conclusion	*As a doctor, I couldn't imagine a more cruel and devastating disease to affect a person, especially a child.* *To watch* xxxx xxxx *deteriorate every week has been the most painful experience of my life, one I'm unsure I will ever recover from* *If* xxxx xxxx *had newborn screening, yes we would have had an anxious wait until he showed MRI changes but there is a large likelihood that he would have had LIFE SAVING treatment.* *Instead, over the past 18 months, our beautiful son has lost his continence, ability to see through those beautiful big brown button eyes, walk, talk, feed himself and smile. He is too unwell to attend school.* *12 months after his diagnosis, I resigned from my role as a GP* xxxx xxxx *as* xxxx xxxx *needed full time care.*

		I have worked extremely hard to get to that point in my professional career. xxxx xxxx *now needs 2 to 1 care.* *Using the term 'criminal 'may seem harsh but when there is life saving treatment available in the presymptomatic stages, I feel it is NEGLIGENT that the UK do not include screening for ALD in newborn testing, allowing our beautiful boys to die a painful cruel death.* *I am very angry that he would still be healthy if he was born in parts of USA where newborn screening is available.* • *I always felt priviliged living in the UK with its world renound healthcare system but this system has taken* xxxx xxxx *life.* • *I now struggle to function on a daily basis both physically and mentally.* • *If newborn screening was in place,* xxxx xxxx*,most likely would be living a full and healthy life*

UK National Screening Committee

22. Member of the public

Dear sir/madam,

This is a form outlining my comments regarding the effect ALD has had on mine and my family's life, whilst also stating why I believe ALD should be added to newborn screening in the UK.

I am 21 and feel like I have not lived a normal or care-free life at any point so far due to this disease. You will be able to read more in the forms attached. Please understand that the disease could be almost eradicated through newborn screening, saving so many lives.

Yours faithfully

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Alex TLC		
Role:	Carrier of Adrenoleukodystrophy		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic?			

Please see below for more information **Yes**		
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	My father suffered several Addisonian Crises before he received an actual diagnosis. These were very traumatic for him and also for the family to see. During one particularly bad incident the GP refused to come out to the house and said he would only see him if he came to the surgery. My Dad had to be supported by 2 people to get into the surgery but we had no idea what was wrong & in hindsight (and with the diagnosis) would have treated it with more seriousness if we had known it was Addisons. Addisons was not even diagnosed after this episode. In fact, it wasn't correctly diagnosed until approximately 5 years later when we had to call an ambulance. The doctor then prescribed a steroid injection that we had to keep in the house if he had another episode. He did suffer multiple Addisonian crises in the following years, but these were dealt with by giving the steroid injection which brought the condition under control. Without diagnosis and thus quicker response, my Dad's body would not have been able to

		cope with the crisis alongside AMN/ALD, which would have been life-threatening. Early Addison's diagnosis aids many families in detecting a worse diagnosis of ALD or AMN, and if found early a person can undertake bone marrow transplant, saving their life. Unfortunately, as Addison's was only detected when my Dad was an adult, he was unable to get bone marrow transplant and later died with cerebral ALD when I was 17. This has caused many problems within my family and has completely derailed my life. As a carrier of ALD, I am able to watch out for Addison's symptoms myself (despite research so far showing no link between Addison's and carriers, I am still cautious).
Page 5, para 5;	Available standard therapy	As I am aware that my Dad had ALD and that I am thus a carrier of ALD, I am able to prepare for adequate conceiving and pregnancy options. I am planning to undergo IVF in order to eradicate the ALD gene from my child before giving birth. This will ensure that ALD does not continue into further generations. In addition, I am able to explore different treatments available for me when I develop symptoms. As I am able to detect my symptoms early, I have booked an appointment at a specialist neurology hospital in order to explore

		treatments for my possible walking difficulty. For example, I know that my Dad tried using some kind of electric stimulator to help his walking - I hope to try this in the future. By the time that adult BMT became available, my Dad's body was too weak to cope with the operation and after-effects of a weakened immune system.
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	We as a family have been devastated by the loss of my Dad. If this outcome can be avoided by anyone else in the future due to early diagnosis, then extreme heartache and continued mental health illnesses of a wider group (families) can be avoided. Early diagnosis from newborn screening is absolutely necessary so that no one else has to suffer in the way that we do. Personally, I have spent my whole childhood and young adulthood under extreme stress, anxiety and grief due to my Dad's illness, and I feel it has derailed the rest of my life. Early ALD diagnosis for my Dad would have meant that we would have lived so many years not being confused by his illness and the consequences. He could have found the best options/therapies straight away to help his condition. Without diagnosis, my Dad struggled a lot

		knowing there was something wrong with him (but not knowing what). I have suffered immensely knowing that I might pass on ALD to my children, with the only hope being that I can catch it before giving it to them so that we can get treatment or I can avoid giving it altogether through IVF.
page 10, Q1	What is the incidence of ALD in the UK?	My xxxx xxxx noticed a complete change in my Dad's character and personality from the age of 20 to 30. After this, it got progressively worse. My Dad became impatient, argumentative, intransigent and ignored social boundaries in public (crossing the line often). This was especially towards the latter part of his life. My Dad wouldn't listen to anyone else's point of view, and became unable to differentiate between trustworthy and untrustworthy characters. This resulted in him "investing" £66,000 in a man he had spoken to in a cafe, against the advice of all his family and friends (this was unlike his character). He became quickly irate when questioned about this. He also became aggressive further into his diagnosis of cerebral ALD. He went from an amenable, happy-go-lucky, friendly character to sullen, brooding, argumentative and negative. His relationship with xxxx xxxx xxxx xxxx (after 25 years) broke down, causing separation, heartbreak and mental

		and financial difficulties for the family thereon. After separation and some distance, the relationship repaired slightly however my Dad was confused about the roles of "xxxx xxxx" and "separated" and continued to break social etiquette by acting inappropriately. During this, my relationship with my Dad also struggled for the latter years, a contrast to our always close relationship that many commented on, which caused me extreme heartache, confusion and stress throughout key years of my life. Watching his illness coupled with his change of character caused me to go to various counsellors, however he refused to believe that his illness would have an effect on me. Throughout the early years, my family were aware that this wasn't him, however we were unaware that these were symptoms of ALD. It was only because his family and friends were so forgiving that he was still surrounded by loved ones. Even after all our trials and tribulations, my Dad was still an amazing man and my xxxx xxxx and I were both with him when he died. Once we better understood the diagnosis, we were able to take step forwards and improve the relationships.

		This is all incredibly hard to describe accurately as no-one really understands the impact to the family unless you have lived through it. From the age of 20 (around 1986), my Dad suffered with walking problems. He was in the xxxx xxxx at this time and saw many doctors who put it down to 'knee dislocations'. He had many arthroscopies on his knees, which did not solve the problem as of course this wasn't the real issue. Around 1998, he was referred to a consultant who diagnosed ALD in December 1999 (a few days after I was born). This was the wrong diagnosis at the time, as my Dad actually had AMN. My Dad was also told he had cerebral (terminal) ALD in 2015, but this was wrong (again). He was eventually correctly diagnosed with cerebral ALD in late 2016. Of course, this has meant much unnecessary confusion and panic throughout the years for our family. Doctor's and consultants couldn't provide much information as not much was known about the disease. It's only when we came across the ALD Life (now Alex TLC) website that we began to understand the disease.

		For anyone else to experience what our family has experienced would be an unnecessary heartbreak. A young carrier that I know in the US is publicly thankful everyday that her son was diagnosed through newborn screening as it means he can access the treatment he needs as early as possible and avoid these issues. The earlier the diagnosis, the more chance there is for young boys to receive treatment, giving them a better chance for survival. There is no question that this should be introduced to newborn screening. My Dad lived with enormous guilt, sadness and devastation knowing that he had passed the ALD gene to me. My Mum also feels this way and it has added extra worry to her everyday life as we notice my symptoms come on. It feels there is no end to ALD as it affects each generation (even women, a fact only recently found). Newborn screening can stop it devastating family after family. I feel like I have a “disability” sentence hanging over my head, and cannot look forward to the future as a result. This has had a detrimental impact to my mental wellbeing.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for	As said before, my Dad was unable to receive BMT or other therapies to combat his ALD, resulting in his death.

	adrenoleukodystrophy compared to initiation of treatment following clinical detection?	This has devastated my family, and in my view it has stopped my life in its tracks as I have found it hard to move past grief for the last 3 years. I am doing what I can, but still feel that I am fighting a silent battle every day, and am unable to perform tasks as well as my friends without it feeling like an incredible challenge.
Page 19	Conclusion	My whole life has been affected by this disease. From watching my Dad suffer and get progressively more ill for 16 years, to experiencing his last few years after his terminal diagnosis, to grieving for the next 4 years. There are so many consequences that are unthought of. Due to this disease, I believe that I can never get anywhere in life as a problem or disability is constantly looming. I have had so many relationship breakdowns due to my family problems affecting my mental health. I have suffered from depression for the last 3 years knowing that no matter what I do, this disease will always affect me (as a carrier and a child that has suffered trauma due to my Dad's illness). It is hard to describe the effect my Dad's and my diagnosis has had on our physical and mental health, however I can only speak very negatively. I would never wish the pain I have experienced from grief on anybody, and frankly I don't know how people who have lost children have survived this long, as I struggled (and still struggle) immensely.

		The fact newborn screening for ALD has been made available in the US and the Netherlands shows its importance. My Dad was one of the people that made newborn screening happen in the US as he set up an ALD global alliance to join forces and combat this. It is so upsetting that despite all his previous work, the UK is still not recognising the need for ALD to be screened at birth.

UK National Screening Committee

23. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenoleukodystrophy/adrenomyeloneuropathy or Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy [delete as appropriate]**		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*

Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	*Our introduction to ALD was following a lengthy, three years, investigation of my late* xxxx xxxx *condition which baffled a string of doctors. Had* xxxx xxxx *condition been promptly identified as a result of my father having been screened as a newborn* xxxx xxxx *would not have been ignorant of* xxxx xxxx *carrier status, nor would I, and our respective children could all have been screened and treated as necessary from birth. Recognition of* xxxx xxxx *condition was delayed to a time when our children were on the point of themselves having children while ignorant of the potential illness they would be passing on.*
Page 5, para 5;	Available standard therapy	*No member of my family has received any treatment confirmed as effective. My son is on a trial but the results are unknown.*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*My late* xxxx xxxx *was angered that* xxxx xxxx *condition was not diagnosed promptly.* xxxx xxxx *and* xxxx xxxx *family knew something was wrong and when at last the diagnosis was received it created great uncertainty amongst* xxxx xxxx *children and mine.* *With another line of cousins sharing the same descent from the earliest carrier identified, there are about 20 individuals who are or may be*

		carriers, asymptomatic or not, and affected sufferers. If you then consider that the average family is some 2.5 people, it can be seen that some 50 members of my own wider family are affected, directly.
page 10, Q1	What is the incidence of ALD in the UK?	*I understand that the incidence of ALD is far higher than reported, a situation that can result in unacceptably late diagnosis and treatment which may be too late to be effective.* *Delayed diagnosis of my late* xxxx xxxx *condition caused enormous distress to* xxxx xxxx *and* xxxx xxxx *family who were bewildered by* xxxx xxxx *physical and mental degeneration. This would not have arisen if the condition was known about more widely in the medical profession and practitioners were encouraged to consider it a possibility when patients presented with symptoms.*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*I understand BMT to be particularly effective if undertaken early. I should certainly have liked the opportunity to consider early treatment for my son, and I am sure others in the family feel the same.*

Page 19	Conclusion	***I consider the NSC conclusion, that review should be postponed, should be reconsidered urgently.*** ***It is simply unacceptable that our NHS should lag health systems in other developed countries. Through the Covid response we have shown that our scientists are world class: this expertise should be released to address ALD: this is dependent on gathering data as a start, by screening.*** ***I think that as a family we have managed my son's diagnosis quite well in the circumstances but there is no doubt that early diagnosis and the possibility of BMT, had he required it, would have improved his prospects, possibly out of all recognition.*** ***My late*** xxxx xxxx ***distress and the effect it had on*** xxxx xxxx xxxx xxxx ***would have been lessened and more easily contained if early diagnosis had been possible.***

UK National Screening Committee

24. Member of the public

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Submission on behalf of a parent of two sons with ALD**		
Do you consent to your name being published on the UK NSC website alongside your response? **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

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Page 5, para 5 Page 6, para 3 Page 16	Available standard therapy Balance of long-term benefits and harms of HSCT	The following patient story reflects the experience of one family, from the diagnosis and subsequent death of their younger son, to their battle to access treatment for his older brother, then a 27-year-old adult. This story clearly highlights the benefits of adult treatment as well as the

	Q4 Early initiation of treatment vs treatment initiated with clinical detection	implications of an untreatable ALD diagnosis for the family as a whole. It sadly also highlights the health inequalities involved in access to this treatment in the UK. The story is told verbatim from the father's perspective, who asked us to submit his story on his behalf. "We sat in a small office with xxxx xxxx neurologist. On the wall was an MRI scan of our sons brain. The white arch was clearly visible . Being told your son is going to die , in hindsight was the easy part. Imagine , Watching your son trying to walk along a path, or jump over a hurdle , but he is struggling because the optic nerve is being destroyed, first the peripheral vision and then slowly but surely total loss of vision. if you were with your child and you were told he was going to loose the use of his right arm. Devastating news to any parent. But you cope , and with time things get easier. Then you go back to the doctor who tells you that he is sorry but your son will loose the use of his right leg. Seeing xxxx xxxx, dragging himself across the floor was heart rendering. Strike three A lost use of his left arm and left leg.

		If it was to stop there, as parents , you would cope. We had to find and buy a wheelchair which would allow xxxx xxxx to still be mobile and to continue to socialise. Obviously he needed 24 hour care, which puts an immense pressure on all the family. Not just financially but mentally. Antidepressants were frequently used. Our eldest son, who was then 14 could not watch his brother continue to deteriorate, so spent most nights staying over at friends. His school work deteriorated, so much so that he was taken out . So we are 18 months in and it is noticeable that xxxx xxxx is not hearing very well and he is struggling to speak. By this time we have a daily procession of delivery's . Special bed Hoist to be able to put xxxx xxxx on a trolley so we can shower him in the newly built downstairs wet room. Large size nappies, ah yes xxxx xxxx can no longer control his bowels or bladder. Laughing , which he is prone to has consequences.

		Now we are off to have splints fitted to try and keep his legs straight , as the nerves are being destroyed, features like facial expressions change as muscles relax or tense. Including hands clenching, legs and spine curving. But xxxx xxxx is happy as he can not remember, I forgot to mention dementia is part of the package. Inhibitions have all gone . Trying to explain that to the lady who has just been called a ******* ****! Can at times be challenging. Thankfully xxxx xxxx can no longer use his hands to undo his zip so the girls at his special school are spared . We took him to the school in an adapted car which took his wheelchair. We are two and a half years in and xxxx xxxx has been back to hospital to have a tube inserted in his stomach so he can be fed and take his medication. We are at the hospital that much we had to buy a monthly parking pass to save money. xxxx xxxx is now blind and cannot talk. He cannot control his swallowing, so his oxygen level monitor is often going off as this is the only way we know he is choking. The ambulance service know our house now , which makes it quicker when he needs oxygen.

		We have now been given our own supply, and trained how to use morphine and how to inject him when he has a seizure. We are nearly three years in. xxxx xxxx is being kept alive by four machines pumping oxygen into him. We have a nurse who stays at night , they know it is only a few days before the oxygen is turned off and the monitors stop their incessant bleeping. xxxx xxxx our eldest is 16 and does not come home much. It was 3.00am when the nurse called me . I went downstairs, turned the machines off and the dreadful monitors. I went to fetch xxxx xxxx our eldest from a friends house, and watched the sun rise. I felt relief . xxxx xxxx never suffered as far as I know. The rest of the family are no longer living together. If that was the end of a family's story with ALD it would have been more than enough for any parent to have to bear. But in our case no. In 2017 our son xxxx xxxx who was 27, was diagnosed with cerebral ALD. Fortunately we knew he had the gene , so he had an MRI every year.

		The treatment for a child is a bone marrow transplant. The treatment for an adult in the UK for cerebral ALD is “nothing”. Yes , I am not joking . The NHS were prepared to do the transplant in return for £60k. Which compared to the United States is very reasonable. I went to appeal and with the help of my friends around the world , our appeal was recognised and xxxx xxxx had his transplant in December 2017. He married in August 2019. The moral of this story. New born screening will save lives. Save money and resources. Save families.”

UK National Screening Committee

25. Member of the public

Name:	Rosie Aldridge	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of someone with adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
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Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	
Page 5, para 5;	Available standard therapy	*My son has not been able to access any treatment due to his late diagnosis; he only has supportive symptom management.*
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	*My son xxxx xxxx was born deaf and had to have cochlear implants, we thought that this would be the biggest hurdle we would have to face. The process and operation to have his implants was long, difficult and stressful but we knew that this was the very best option for him, and once he had the implants his life was transformed.* *Everything was going well, and we were a normal happy family, then when xxxx xxxx was 7, we started to notice changes in his behaviour these were very uncharacteristic of him as he had always been a happy little boy. We also noticed that his writing was deteriorating, he had been doing very well at school and was developing normally, we thought that this might just*

		be a phase. Things deteriorated further and I took him to our GP as I was extremely concerned. After a number of appointments xxxx xxxx was referred for an MRI, we had to wait as his cochlear implants had to be removed before the MRI could be carried out. It was now July 2018 and after the MRI we were given the devastating and life changing diagnosis of ALD. I had never heard of this condition, and when the doctor told us that there was no cure or treatment my world came crashing down. I just simply couldn't believe that my beautiful, funny happy son was going to lose all of his abilities. You really can't imagine or believe that this can happen. *We had to wait again for xxxx xxxx implants to be put back in again and during this period we noticed that he was going downhill quickly, he didn't seem to be understanding us and seemed very disorientated, I thought that this was due to the fact that he couldn't hear but devastatingly even once his implants were back in and working the deterioration did not improve. During the following months xxxx xxxx continued to deteriorate and by September 2018 he could no longer walk, talk or eat. He is now fed through a gastrostomy. xxxx xxxx has had several hospital inpatient stays; he was in intensive care last year. We have had to learn so many things such as gastrostomy feeding, how to give numerous medications. xxxx xxxx also has seizures, so we have to know what to*

		do when these happen. He suffers from extremely painful muscle spasms which are heart-breaking to watch, and I feel useless when I can't help him to be ore comfortable, no one wants to see their child in that sort of pain. xxxx xxxx *can do nothing for himself and needs 24/7 care, we do have carers who help but that is another thing we have to get used to having strangers in your home, but we just simply couldn't cope without them.* *This has absolutely devastated our family, we should be enjoying life and looking forward to the future, but I now dread very day.* *I was tested and am a carrier of ALD, the guilt I feel every single day that I passed this horrendously cruel disease to my son is something I will never get over. I also have a* xxxx xxxx xxxx xxxx *and know that* xxxx xxxx *will have to be tested when* xxxx xxxx *is older. If* xxxx xxxx *is a carrier although this will also be a huge blow at least we know that* xxxx xxxx *will be able to have children who don't have ALD and this disease will stop in our family.* *If newborn screening had been available when* xxxx xxxx *was born, I would definitely have agreed to the test, as he was tested for all of the other conditions which are currently screened for. And yes it would have been devastating at the time of his birth but we would have learned to live with the fact that he would have had to*

		have regular MRI scans and it would have become part of life because we would have known that we were having to do this to make sure that if the disease started xxxx xxxx *could have treatment, a Bone Marrow Transplant which would have stopped the disease and* xxxx xxxx *would have grown up and had a normal life.*
page 10, Q1	What is the incidence of ALD in the UK?	*Due to my son being diagnosed my* xxxx xxxx xxxx xxxx *has also been diagnosed with Adult onset Cerebral ALD and* xxxx xxxx xxxx xxxx *is a carrier.* *My* xxxx xxxx *had been struggling for a few years and could no longer work, he had been a successful* xxxx xxxx*. When* xxxx xxxx *behaviour started to change, and* xxxx xxxx *started to not seem to understand things no one knew what was wrong and* xxxx xxxx *was diagnosed with depression. After* xxxx xxxx *genetic test came back positive for ALD he had a consultation with a Specialist in London who carried out an MRI and we were give a second devastating diagnosis of cerebral ALD.* xxxx xxxx *has severe walking and cognitive difficulties and is looked after by* xxxx xxxx xxxx xxxx *and* xxxx xxxx xxxx xxxx*;* xxxx xxxx *can no longer work.* xxxx xxxx *has had a serious prolonged seizure and is currently in intensive care.*

		xxxx xxxx xxxx xxxx *has a heavy burden I that* xxxx xxxx *feels an overwhelming sense of guilt that* xxxx xxxx *not only passed the gene on to* xxxx xxxx xxxx xxxx *and* xxxx xxxx*, but also* xxxx xxxx *grandson. The impact of diagnosis is s far reaching and affects every area of life.*
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	*Neither my son nor* xxxx xxxx xxxx xxxx *had a chance of a bone marrow transplant as they were both diagnosed too late, this is so difficult to know that there is a treatment that works and has been used for many years but yet due to not knowing that we have ALD in our family that treatment has been denied to us. Of course, if screening had been in place both of them would have had the chance to have transplants and save their lives.*
Page 19	Conclusion	I know that screening is being carried out in the Us and in the Netherlands, and I think it is just so very unfair that we are being denied the chance of knowing that even although our boys have this disease there is hope. All of that hope has been stolen from us. I know that this won't help my son but I hate to think of other families having to face what xxxx xxxx, myself and my whole family have to face every day knowing that there is a test which can be easily done at birth but isn't being carried out. This condition has absolutely crushed my family and we will never be the same again, we try to make every day count and I also try to give xxxx xxxx xxxx xxxx as

		normal a life as possible but it is hard to juggle caring 24 hours a day and finding time and energy to give xxxx xxxx the attention xxxx xxxx deserves. So, I am asking you to put yourself in my family's position and imagine if it was your child, would you want to know that without this test at birth your son would die.

UK National Screening Committee

26. Member of the public

Name:	Karen Harrison	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with Adrenomyeloneuropathy and Parent of someone with Adrenoleukodystrophy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD	My father was diagnosed with Addison's disease many years ago, the doctors were uncertain of the cause and put it down to Tuberculosis as at the

Page 12, Q2 Page 16, Q4	Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	time that was the biggest cause of Addison's even though my father had no symptoms or signs of TB. In the following years he started having walking difficulties, again they were dismissed he was only in his late 30's at the time. He then started having behavioural changes becoming aggressive, inpatient and just very different t how he used to be, as a child I remember being 'careful' around dad so as not to upset him. He was investigated for a brain tumour, in the absence of MRI scans etc the doctors had to physically operate to investigate and the outcome was that he didn't have a tumour but that there was damage to his brain, ALD was mentioned at any time. His behaviour went rapidly downhill and he had to leave his job as a xxxx xxxx as he could not function properly. This cause the breakdown of my parents' marriage and my xxxx xxxx and I couldn't see our dad unless we were accompanied at all times. My dad died from an Addisonian crisis when he was 48 years old. We had no idea what was to come… My xxxx xxxx xxxx xxxx sons were born in 1996, all was well until they were 5, when xxxx xxxx

		developed a squint we were reassured by an ophthalmologist that there was nothing to worry about, he was given corrective glasses and we paid for 2 courses of specialist eye exercises, the squint improved, then we noticed that he appeared to not be hearing what we were saying and was disorientated not being able to find his bedroom. I took him to see out GP and was told that 6-year-old boys often ignore their parents, I knew it was more than that but felt that I was being paranoid. However, I took him to see a different GP in our practice and he agreed to refer xxxx xxxx to a Paediatrician at our local hospital, when I chased this appointment after several weeks I was told that there were 15 children ahead of him in the queue and he couldn't be seen until January, this was now September 2002. In the end we paid privately to see the same consultant at our local private hospital, he knew there was something wrong but didn't know what. He was sent to have an EEG to test for epilepsy which we also had to pay for. The result came back as abnormal brainwaves so xxxx xxxx needed to have an MRI, which we were told would be done on the NHS but that this was in fact

		queue jumping!! We were referred to a neurologist at xxxx xxxx hospital, and after seeing xxxx xxxx for around 20 minutes he said that he thought he knew what was wrong with our son, we thought the doctor was going to say that he had a brain tumour, but what he actually said was that he had a leukodystrophy and more than likely adrenoleukodystrophy. We had never heard this word and the doctor started to explain the disease…suddenly I asked if it was anything to do with Addison's and he said yes, I explained about my dad and the doctor said it was all connected. Now what about xxxx xxxx if they were xxxx xxxx (we had never had xxxx xxxx formally tested but xxxx xxxx only had xxxx xxxx xxxx xxxx and xxxx xxxx xxxx xxxx) then he too would be affected at this point xxxx xxxx was completely asymptomatic, and to add to the situation I was 40 weeks pregnant with our xxxx xxxx child. xxxx xxxx was formally diagnosed on xxxx xxxx 10/2002 and xxxx xxxx xxxx xxxx /2002 and I gave birth to our xxxx xxxx son xxxx xxxx on xxxx xxxx 10/2002, were we going to lose xxxx xxxx xxxx xxxx of our sons, we couldn't bear to even think about that.

Page 5, para 5;	Available standard therapy	As xxxx xxxx was asymptomatic, he had a chance, his M RI scan showed demyelination and he had a Loe' s score of 8 which is in the upper limit for BMT. Our Consultant at xxxx xxxx Hospital decided that there was much to gain for xxxx xxxx and that we should press ahead with transplant as soon as possible. It was decided that for speed my husband would be xxxx xxxx donor. He went into transplant just 4 weeks after diagnosis. During this time we learnt everything about ALD. xxxx xxxx had two transplants, as he rejected the first, we found an unrelated donor who after having donated the initial blood for further HLA matching decided to not go ahead with donating so we had to use xxxx xxxx xxxx xxxx cells for a second time, the transplant worked but xxxx xxxx had a prolonged period of time immunosuppressed, he was in isolation for 8 weeks. xxxx xxxx could not have any treatment and the only treatment available was supportive symptom management.
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	If only we had known from birth our xxxx xxxx beautiful perfect and xxxx xxxx xxxx xxxx xxxx xxxx would have had a full life. Yes, it would have been devastating at the time of xxxx xxxx birth to have been told but once we had been put in contact with Specialists, I believe those fears would have been allayed. Being pregnant with xxxx xxxx

		xxxx xxxx who were perfectly healthy throughout my pregnancy we were taken to visit the SCBU just in case xxxx xxxx xxxx xxxx xxxx xxxx were to need special care as is often the case with identical twins. Believe me that visit was extremely difficult to see all those tiny little babies fighting for their lives, luckily xxxx xxxx of the boys need any special care but at least we were prepared. If only we had had that chance with NBS for ALD. xxxx xxxx our xxxx xxxx son was tested when he was 3 months old as we all felt that we needed to know, thankfully he does not have the gene and is now a healthy 18 year old, why we needed to know was because we knew that if he had ALD he would have had the monitoring needed to save his life, which is the same as NBS, I am heartbroken that my other sons did not get this chance and it has devastated us as a family.
page 10, Q1	What is the incidence of ALD in the UK?	As mentioned above my father clearly had Adult onset CALD, and this caused the breakdown of my parents' marriage, it also meant that my xxxx xxxx and I were estranged from our dad for a number of years due to the fact that no one understood what was causing his behaviours, he was in fact sectioned twice. I lost my dad when I was 10. Due to my sons being diagnosed my xxxx xxxx cousins from my father's sister have also been diagnosed. One male adult cousin who was about to

		undergo invasive tests including lumber puncture and urinary investigations to find the cause of his walking difficulties and sensory deficit in his legs also his ongoing urinary problems, these tests did not need t be carried out as they were put on hold until he had his genetic results, he has xxxx xxxx daughters who are obligate carriers. My female cousin is also a carrier and she has a xxxx xxxx whose status is unknown as xxxx xxxx is under 16. My Aunt had extremely bad walking difficulties from her early 60's having to use a wheelchair, she also tested positive for the gene. So, the implications for families can be far reaching. I know for a fact that my cousins are very glad that they know the risks that their xxxx xxxx face when they have children and it will enable them to make reproductive choices.
Page 16, Q4	Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	As mentioned above my son xxxx xxxx was diagnosed too late for transplant and he suffered in the most horrific way for a year and a half until his death at the age of 8. No parent should ever have to watch their beautiful perfect son deteriorate from a fun loving, cheeky 6-year-old to a vegetative state in a matter of months. The pain he suffered both physically and mentally will be with me always, and I will always feel such enormous guilt that I passed this gene onto my sons.

		xxxx xxxx did have a transplant but devastatingly it was just too ate to halt the disease in his brain, he is still with us today and he is 24, but he is very severely disabled, blind, no speech, tube fed, wheelchair bound and can do nothing for himself. I am heartbroken that my sons were not given the chance of life simply because the test was not available at the time of their birth. xxxx xxxx, my other son has had to watch his brothers die in-front of his eyes, he has seen things that adults would not cope with. We always try and protect him but inevitably when you have to call an ambulance because xxxx xxxx is having a huge clonic/tonic seizure which you can't get under control he is going to see it. This has affected xxxx xxxx in many ways, he has mental health problems and is very anxious about his brothers' health. We are a very strong close family, but this has tested us to the limit, and there have been many times when my marriage could have ended but we are committed to each other and providing the best care for our sons. xxxx xxxx should have his xxxx xxxx xxxx xxxx brothers but instead he is like an only child. We were very fortunate that my xxxx xxxx works for a large company and he was able to take 18 months of on compassionate grounds and the company continued to pay him, otherwise I have no idea how we would have paid our mortgage etc, as there is no support for the first

		six months if you own your own home unlike if you are in rented accommodation where your rent is paid straight away. We had taken the decision that I would stay at home to look after the children, I had always wanted to be a mum, and due to my dad dying at such a young age my mum had to work full time so I was looked after by my grandmother, I didn't want that for my children, I am so glad that I had that time with my wonderful sons but it just isn't right at all that we were only allowed 6 years with them.
Page 19	Conclusion	So, in conclusion ALD has devasted my family's life, we were a happy normal family looking forward to the future with our sons, and this was taken away from us in the most cruel and horrific way. It has affected every part of our lives. I can't comprehend why families are still having to face the exact same difficulties in getting a correct and timely diagnosis which we faced 18 years ago, and that there are still boys who are given the same death sentence when there is a test which can be carried out at birth, which would save the lives of these boys and enable families to live a normal happy life. There are many states un the Us who carry out screening and our near neighbours in the Netherlands are also giving families the opportunity at life. The NHS is

		a world leading healthcare system and yet you are letting families down when they need it most. So please just think for a minute that if this was your family you would want to know so that you could save your sons' life.

UK National Screening Committee

27. Member of the public (Zellweger)

Name:	Carly Brown	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenoleukodystrophy/adrenomyeloneuropathy or Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy [delete as appropriate]**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	*I am a parent to* xxxx xxxx *boys who have Zellweger syndrome. Nothing was picked up with my* xxxx xxxx *son*

		at birth as he was healthy but had hearing loss. So not knowing about Zellweger syndrome his brother was born. xxxx xxxx *was very poorly at birth, we stayed in hospital for a few days to have Down syndrome testing which was negative so we was sent on our way.* xxxx xxxx *failed to thrive, he couldn't gain weight and he had low muscle tone. New born screening was clear and it was only after a outpatient check up that more tests was done that pointed to a peroxisomal biogenesis disorder.* *After* xxxx xxxx *s diagnosis of Zellweger syndrome it was only right to test his* xxxx xxxx *brother* xxxx xxxx*. If* xxxx xxxx *hadn't been conceived then his* xxxx xxxx *brother still to this day would not have a diagnosis because there is nothing that picks it up at newborn screening. To not know that* xxxx xxxx *had a life limiting condition for a few years and then be hit with the results at the same time as his brother was heartbreaking. Also the fact we could still not know 9 years later and this could be something that is happening to a lot of families with children on the mild spectrum.* *If I had known that* xxxx xxxx *had this condition from birth then it would of helped to make further decisions about more children. Testing could have been done whilst pregnant and we could of prepared for the future. It was*

		mentally hard to think for months that xxxx xxxx was struggling with his health and no one had any answers. *The boys have regular tests to check for Adrenal Insufficiency, xxxx xxxx now requires steroid dosing for illness management.* *These have been crucial in keeping xxxx xxxx well when he has been ill. If he didn't have his Zellweger's diagnosis then they would of never tested him for adrenal Insufficiency. This has also been crucial for when xxxx xxxx has had operations as they stop his body going into crisis and aid his recovery.*
Page 19	Conclusion	*I think the benefits of early diagnosis is crucial to getting the right care, the medicines, vitamins and early intervention for hearing & vision loss.* *xxxx xxxx went 2 years being undiagnosed with hearing loss due to their being no background problems. It has affected my mental health because I now my xxxx xxxx only children have life limiting conditions that I have passed down to them, I feel guilty that they have to suffer on a*

		daily basis because there was no testing in pregnancy or in new born. I can't work because my sons have too many hospital appointments that trying to hold down a job is impossible and employers find it difficult to have time off without loosing money.

UK National Screening Committee

28. Member of the public (Zellweger)

Name:	Chloe Hobson	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of someone with Peroxsimosal biogenesis disorder on the Zellweger spectrum**		

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Yes ✔ **No**

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Yes ✔ **No**

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	• *It took a year and a half for* xxxx xxxx *diagnosis which is a long time to wait, lots of unnecessary tests and expense at the NHS and lots of time to*

		cause anxiety. xxxx xxxx was 3 when they started testing him and 4 and a half on diagnosis. • *I would have preferred to know his diagnosis at birth* • *Having his mutation identified helped with further family planning decisions. I am very scared it could happen again, xxxx xxxx was diagnosed at 4 and a half years old. Other siblings have been born.* •
Page 19	Conclusion	• I feel screening should be available in the UK as it is currently available in parts of the USA. • Once diagnosis was given, my partner became his full time carer, I went part time at work and xxxx xxxx was able to go from mainstream school to a SEN school and get the support he needed. Up until diagnosis, we were not able to offer this type of support for him. The actual support he needed. • We suffer with survivors guilt and it has affected xxxx xxxx siblings badly as xxxx xxxx has passed away. One brother is very angry, my partner and I are heartbroken. • If we had known from birth then better options could have made and lots more memories with him to cherish. Like most parents, when he was little , we thought he would grow into an adult but

		this was not case. Please consider screening so future families have this opportunity to know what they and their child is facing.

UK National Screening Committee

29. Member of the public (Zellweger)

Name:	Kerry Hughes	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent of someone with adrenoleukodystrophy/adrenomyeloneuropathy [delete as appropriate] Zellwegers**		

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

Yes

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Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	*We want to demonstrate here the value of diagnosis at birth.*

	My xxxx xxxx at the age of 3 months old, went through a month of being in hospital to try and discover what was wrong with xxxx xxxx, xxxx xxxx liver, and failure to thrive. xxxx xxxx only lived till 9 months old so this month of xxxx xxxx technically being tortured with several blood tests a day, different formulas, nil by mouth for scans, tests, more blood tests, etc was a large portion of xxxx xxxx life that if xxxx xxxx had been diagnosed at birth, xxxx xxxx could have spent this month at home being cuddled and sensory play to improve the quality of xxxx xxxx short life. During this time, I blamed myself, I convinced myself that I had caught hepatis somehow and had given it to my xxxx xxxx and partner and that we were all going to die (not true). I couldn't sleep or eat, I was petrified and my partner and I started to feel immense pressure in our relationship. As soon as xxxx xxxx was diagnosed, we were able to find support from a charity dealing with Zellweger Syndrome, referred to xxxx xxxx xxxx xxxx for respite and bereavement support, connect with other parents dealing with the same disease, talk about treatments and give xxxx xxxx the best	*We want to demonstrate how beneficial early diagnosis of your condition could be even if the condition can't be treated at the moment.* *Please insert here your stories about:* • *How a lengthy diagnostic odyssey has affected you/ your family* • *How you felt when you received a diagnosis, was your anxiety lessened?* • *If you would have wanted to have the diagnosis from birth – what difference would this have made to you/your family?* • *Unwittingly passing on your condition to your children and how this makes you feel* • *Any experiences of reproductive choice following a diagnosis* *For families affected by Zellweger's, we're particularly interested in highlighting the importance of identifying those at risk of adrenal insufficiency or Addison's Disease and how life-threatening undiagnosed Addison's can be.* *Please insert here your stories about why having an early Addison's diagnosis was important for you/your family. Stories should highlight the impact of:* • *a previously undiagnosed Addisonian crisis that caused death*

	treatments for xxxx xxxx condition, call in portage for sensory play, know she terminal and quality of life was important as was time with xxxx xxxx. Also stop blaming ourselves for something that was genetics, it wasn't something we had done wrong for xxxx xxxx. Diagnoses at birth would have saved xxxx xxxx and us a month of hell. We also knew that if we had another child together the chances were 1 in 4 of having another affected child that would die very young and be severely disabled. Luckily, I didn't fall pregnant during that time. It would have saved the NHS money in us not being in hospital during this period and on possibly caring for future children together. Some families are not diagnosed until more children are born with the same condition, thus too late to save their children (as other options had not been considered). My xxxx xxxx was severe so her diagnoses was at 4 months old, however this would have been much better at birth.	• *a lengthy Addison's diagnostic odyssey (how long it took to get an Addison's diagnosis and the problems faced before diagnosis)* • *identifying Addison's/ALD for other family members*
Page 19	Conclusion Benefits of early diagnosis, save money for the NHS, it will save more children being born with A	*The NSC concluded that the volume and type of evidence related to newborn screening for ALD is currently insufficient to justify an update review at this stage.*

	LD, treatments can be introduced before regression sets in saving lives, improves quality of life, helps with statistics for grants for scientists working on treatments and cures, impedes research, better support can be given to the family on diagnoses, saves parents from being falsely accused of abuse or neglect, helps with family planning, etc Do we want the US and Netherlands providing a better treatment for patients than the children in the UK? Noooooooooo If New Born Screening was available to my little xxxx xxxx, we could have spent her short life providing a much better quality of life for xxxx xxxx. It has made a massive influence on my and xxxx xxxx dads mental health, spending so much time in hospital searching for answers, survivors guilt, depression, we actually split up after xxxx xxxx passed away.	*Please insert here your thoughts on this decision – you might want to think about the following:* • *Benefits of early diagnosis* • *Screening is already happening in the US and Netherlands – how does this make you feel?* • *The impact it has made on your/your family's life because there was no screening when you/your loved one was born – has a diagnosis affected your physical or mental health, ability to work, live in your home, education choices. How has the diagnosis affected siblings - have they experienced mental health issues such as survivor guilt, depression, has their education or personal life been affected?* • *The impact it would have made on your life if screening had been in place when you/your loved one was born*

UK National Screening Committee

30. Member of the public (Zellweger)

Name:	Melanie Pugh	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy/ [delete as appropriate]**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	Back in 2011, I had a miscarriage at 19 weeks. I was told by doctors at xxxx xxxx Hospital that it was not common to have a late miscarriage, given my circumstances. After

		all, I had a nuchal translucency test a few weeks before and the chances of my baby having Down's syndrome was 1 in 100,000. I had no symptoms – no infection, no bleeding – nothing that would indicate anything was wrong. Unfortunately my husband and I never found out what caused it and I blamed myself for years. I suffered from depression for a long time afterwards. Two years later, I gave birth to my xxxx xxxx. It was an incredibly stressful pregnancy because at the 20 week scan, my baby's femur measured very small (less than 3%). I was seen by an obstetrician every two weeks until xxxx xxxx was born. At the time it was thought xxxx xxxx had IUGR but in the back of my mind I knew something was very wrong, given my previous case history. I was right. Something was terribly wrong – my xxxx xxxx was born blue in the face, unable to breathe well on xxxx xxxx own. xxxx xxxx was swiftly taken up to NICU where xxxx xxxx spent the rest of xxxx xxxx short life. The first time I saw xxxx xxxx, I took a good, long look at xxxx xxxx and of course xxxx xxxx was perfect to me but xxxx xxxx appeared to have a genetic or chromosomal disorder. xxxx xxxx karyotype came back fine almost immediately so we knew it had to be genetic. The

		doctors told us given the rarity of what xxxx xxxx had (given no one could diagnose xxxx xxxx at the time), that we may never have a diagnosis. I was absolutely floored – we had no prognosis, therefore no cure, no idea of what lay ahead of xxxx xxxx, what suffering xxxx xxxx may have had to go through. Then came the barrage of tests – xxxx xxxx had MRIs to check xxxx xxxx brain function (xxxx xxxx had dilated ventricles), ultrasounds to check xxxx xxxx kidneys (hers were enlarged), x-rays to check xxxx xxxx long bones (xxxx xxxx had stippling), ECG (xxxx xxxx had seizures), eye tests to examine xxxx xxxx cataracts and myopia and copious blood tests which eventually had to stop as xxxx xxxx veins were collapsing. No baby should ever go through that much trauma. And for us, xxxx xxxx parents, with each test result it felt as if it was like death by a thousand cuts. We could handle the first bit of news regarding xxxx xxxx limited sight and hearing. The results that came after? Devastating to hear. Dilated ventricles potentially meant brain damage. A small VSD meant a wait and see approach, but possible heart surgery. Talipes meant an operation plus

		braces. Enlarged kidneys meant medication. I had no idea what an enlarged liver meant, apart from jaundice. Those were just the test results. What we saw was even worse. Our xxxx xxxx was hooked up to all sorts of machines, most of which seemed to beep ominously everyday we were there, necessitating panicky checkups from paediatric nurses. xxxx xxxx oxygen levels were well below 90% numerous times a day. xxxx xxxx couldn't feed as xxxx xxxx sucking reflex was poor. xxxx xxxx had a NG tube which needed to be checked every so often for stomach acidity levels. xxxx xxxx had bad acid reflux – I'm convinced a particularly bad bout set off an epileptic seizure which stopped xxxx xxxx breathing for 90 seconds and saw a flurry of doctors rush to xxxx xxxx side to resuscitate xxxx xxxx. Thinking back on all this years later, it wasn't any of this which broke me. No, what did it was not knowing what xxxx xxxx condition was. Not knowing what else there was to come. Not knowing whether xxxx xxxx was coming home with us. Not knowing how long xxxx xxxx had to live. Not knowing if xxxx xxxx did live, what xxxx xxxx quality of life would be like. Not knowing what kind of care xxxx xxxx needed. My husband and I were completely distraught. No words can describe the sheer hell we went through. We were

		one of the lucky ones though, because we had a very good geneticist who identified Zellweger syndrome almost right away (this was kept from us until actual confirmation) - I know of other parents whose geneticists are not as knowledgeable about ZSD and therefore, didn't get a diagnosis until much later. We were told they strongly suspected ZSD when xxxx xxxx was about six weeks old and we got a confirmation two weeks later. xxxx xxxx died a few days afterwards, having never left xxxx xxxx xxxx xxxx hospital.
Page 19	Conclusion	I understand that ALD and ZSD may be added to newborn screening. Please consider it. No parent, no extended family members should go through what we did. I mentioned my miscarriage at the start because the most distressing part was not knowing what caused it, the two years between pregnancies where I constantly wondered what I'd done wrong and what that meant in terms of our fertility. I know that newborn screening wouldn't have made a difference with our miscarriage. I just want to highlight the repercussions of not having known the cause. I took loads of tests afterwards via private doctors to come up with reasons for what happened. I got made redundant shortly after and couldn't face going back on

		the job market for quite some time. I'm now quite confident that my first miscarriage was as a result of Zellweger syndrome (each pregnancy to both carriers has a 25% chance of having the condition). After my xxxx xxxx much needed diagnosis, awful as it was knowing my xxxx xxxx would not survive xxxx xxxx first birthday, I felt a strange sense of relief. I no longer blamed myself for the miscarriage, nor for xxxx xxxx condition. In a very strange sense I felt more at peace knowing this. If we never got a diagnosis I would still be torturing myself to this day. Given I was 40 at the time and facing involuntary childlessness, we were given very practical, prosaic advice from our consultants at the fertility clinic. We knew that "normal" IVF was not viable for us. By restricting our choices, we knew we had to opt for either PGD-IVF or go straight to sperm/egg donor. How much more heartbreak would we have had if we didn't know that xxxx xxxx and I are carriers of a mutation in a particular gene? We may very well have gone on to have more children with ZSD. Other family members carrying the same mutation may well have gone on to have ZSD children. Given some of

		my family are Dutch and that that particular population has a higher incidence of ZSD, it is quite likely. Lastly, having met other ZSD parents has helped me tremendously with my grief. I feel the annual ZUK (Zellweger UK) conferences I've attended have kept our children's memories alive. It's wonderful to know that much progress has been made in a wider context with restoring hearing and eyesight which may help ZSD sufferers. It gives me hope to hear that leading ZSD researchers around the world are tackling this horrendous disease. I can't imagine not knowing any of this or not meeting such a wonderful support group. It has made such a difference to my life after xxxx xxxx.

31. Member of the public (Zellweger)

Hi, I hope this isn't too late, we joined this campaign late in the day, but I have attached my comments form and I hope that you will be able to see that my own son's life was made exponentially better for a diagnosis, but could have been made even better had it come so much earlier.

Many thanks for taking the time to read it

Best wishes

Name:	Natasha Anderson-Hunt	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Zellweger UK		
Role:	Parent of a child who was affected by Zellweger Spectrum Disorder Chairperson to Zellweger UK		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			

UK National Screening Committee

Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**		
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	12. My son xxxx xxxx was born in 1997 and lived for an incredible 21 years. I credit his long life with the fact that he was diagnosed with Zellweger Spectrum Disorder in time to diagnose his adrenal insufficiency just before he suffered an adrenal crisis. His diagnosis came just after his first birthday and at that point he was already getting tired and weaker. It wasn't until he was diagnosed with ZSD that on the advice of the UK's specialist, tested for adrenal insufficiency. His original prognosis was very poor due to his lethargy and hypotonia, however on starting him on steroid replacement therapy we realised just how much of this was simply due to extremely poor adrenal function, and we saw a remarkable improvement in his general health and

		wellbeing. Since his adrenal function was so poor, and disease progression is so often triggered and hastened by an acute illness, I am certain that had his ZSD diagnosis not come when it did, he would have suffered an adrenal crisis and not only died many years before he did, but lost the life quality that he enjoyed for so many years. I am grateful that he received this diagnosis in time, however I wish he could have been diagnosed so much sooner and I'd have given my right arm for a diagnosis shortly after birth. He spent the first year of his life being put through test after test including constant blood tests, a CT scan, MRI scan, a skin and muscle biopsy that left an open wound that got infected and left him with a scar on his leg that was still there when he died. All of this came at a cost to the NHS and was incredibly stressful on us as a family. We celebrated xxxx xxxx first birthday not knowing that he was going to have limited birthdays. I often look back

		at this and wonder why this does not feel like a gift to me now, but the truth is that I spent his first birthday scared for his future and convinced that I was responsible for his failure to thrive; that I'd let him down in some way. This wasn't helped healthcare professionals who thought his failure to thrive was caused by failure to cope and neglect on my part. I was accused of not feeding him when I dedicated my life to feeding him in the short bursts throughout the whole day that he needed. Even the quality of my breastmilk was called into question and I was put on a diet of high fats to try to put more fat into my milk. As children on the Zellweger Spectrum can't metabolise long chain fatty acids this was in fact extremely detrimental to him and the opposite of what his diet needed to be. Had he have been diagnosed at a much younger age, this would have been dealt with correctly and perhaps may have given him better health and even more years.
Page 19	Conclusion	I was slightly shocked that the identification of patients with Zellweger Spectrum Disorder came up detrimental aspect of newborn screening for Adrenoleukodystrophy, as I and every family impacted by ZSD that I have spoken with about this can only see this as a benefit.

		xxxx xxxx diagnosis was devastating of course, but it led to better care for him, a better quality of life and a better outlook for us as parents. I only wish I could go back in time, get his diagnosis a year sooner and erase the distress the barrage of tests caused him for that year, and the stress, anguish and self-blame that came with the unknown for us. I'd desperately love to see newborn screening for ALD rolled out in the UK as it has been in the US and the Netherlands and I urge you to please consider the benefits not only to patients with easily treatable forms of leukodystrophy, but also the positive impact on the quality of life for children on the Zellweger spectrum.

UK National Screening Committee

32. Zellweger UK

Name:	Natasha Anderson-Hunt	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Zellweger UK		
Role:	**Chairperson to Zellweger UK**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	As a charity focused on supporting families impacted by Zellweger Spectrum Disorder (ZSD), it is of high interest to us that patients with ZSD would be identified in newborn screening for adrenoleukodystrophy, and for this reason we fully support this campaign.

		It is incredibly important that it is understood that while it's true that there is no cure for Zellweger Spectrum Disorder, this does not mean that there are no treatments. Several severe illnesses associated with ZSD are treatable and even avoidable but only if diagnosed, something that often only happens after a diagnosis of ZSD. A recently published study by Dr. Mousumi Bose of Montclair State University https://www.sciencedirect.com/science/article/pii/S2214426920301403?fbclid=IwAR0ZQWs6cgVGKCQCxhTTUS7zNQBaVVj-uaUo23iXbnjJqXpmPSMGW3deK4Q#! has identified that 45% of patients out of the 76 patients in the study suffered from adrenal insufficiency (Addison's Disease). This suggests that nearly half of all patients on the zellweger spectrum could potentially have impaired adrenal function. It is well documented that untreated adrenal insufficiency can have a devastating effect and even lead to death. A serious adrenal crisis, even when survived can significantly shorten the life of a child on the zellweger spectrum, yet if diagnosed it is so easily treatable and avoided. Therefore, early monitoring of adrenal function is essential to keep children with Zellweger Spectrum Disorder suffering premature disease progression. According to the Office for National Statistics, there were 640,370 live births in England and Wales in 2019. Using this statistic, given that

		approximately 1 child in every 50,000 babies born this leaves the potential for at least 12 babies affected by ZSD to be born every year, all heavily relying on regular early adrenal monitoring given the high rates of adrenal insufficiency in children on the zellweger spectrum. However, Addison's disease is simply one treatable condition associated with ZSD. Children are at a high risk of renal stones, which cause absolutely debilitating pain. These are avoidable by regular monitoring the oxalic acid levels in the urine. If these levels prove to be high, oral citrate can keep stones from forming, avoiding extreme pain and distress. Quality of life is a hugely important factor in getting a diagnosis as early as possible. A diagnosis usually comes for our children after a lengthy, stressful process. A month of diagnostic tests for a child who will only live a few short months is a huge proportion of their lives. Milder children can wait over a year for a diagnosis or in extremely rare cases children can deal with years of tests and uncertainty. Sedation, general anaesthetics, countless blood tests, skin and muscle biopsies, sweat tests, scans, x rays; these are not only extremely stressful for families, but extremely costly to the NHS. Newborn screening to cut costs to the NHS and improve the quality of life for a child and their families. An early diagnosis is beneficial to families for so many reasons, not least that they can get a diagnosis before their child is severely symptomatic, which means the shock of the diagnosis does not come on top of the

		emotional trauma of disease progression. It also means that support can start early; something that is crucial for our children for the several treatable or even avoidable symptoms of ZSD. Many families have experienced extreme dismissive responses from healthcare professionals when they bring up their concerns for their child's health and development. There have even been cases where families have been accused of neglect or even abuse due to their child's failure to thrive, or for something like a spontaneous pathological fracture, common in children on the Zellweger Spectrum due to the prevalence of severely low bone density in ZSD. With the right support, bisphosphonate infusions can avoid pathological fractures. Low bone density is also a cause of chronic pain in children with ZSD, along with renal stones, neuropathic pain, muscle spasms, hip dislocation, all things that a diagnosis can alert to and therefore lead to the proper diagnosis and treatment of any of the above issues, even if it's more appropriate pain relief (morphine, for example will do nothing to help a child who is suffering from neuropathic pain or something as acute as renal stones or hip dislocation). An early diagnosis not only opens a door for earlier and more appropriate healthcare, but support in terms of early education, and even support from our charity. Our charity name will come up if a family googles the condition and therefore, we are able to offer our support early on. We offer information, practical advice, emotional support for families; we can offer hope.

		Something that simply can't be underestimated is peer to peer family support; there is no person who understand what it's like to live with this condition. The comfort, experience and understanding that comes from another family affected by the same condition is invaluable and often holds families together during the most devastating times. Tragically for children on the most severe end of the spectrum who can die within days or even hours of birth, it is entirely possible for the diagnosis to be missed entirely and for parents to suffer the death of their baby without ever knowing the cause. Given that ZSD is an autosomal recessive disorder and that there is a 1 in 4 chance of further children being affected, this can and has led to further affected children being born and also dying at a very young age. A diagnosis can lead to the identification of the gene variants responsible for the disease and therefore families can be offered PGD to ensure a further child not be affected by ZSD, and families can be fully aware of all options available to them when planning to add to their family. On the opposite end of the spectrum, there are children so mild that this disease goes undetected until disease progression down the line. If disease progression is sudden and death comes quickly these patients may also never be given a diagnosis leaving a family with the anguish of the loss of their child with no known cause. There are several children who got a diagnosis only after the diagnosis of their younger and more severely affected sibling, who are now being monitored carefully and stand a good

		chance of keeping ahead of many treatable clinical disorders caused by ZSD, something that could be offered by detection shortly after birth. The inclusion on ZSD in the newborn screening for Adrenoleukodystrophy would allow for more cases being detected here in the UK, more accurate statistics for this disease which is crucial for impending research, especially for studies and roll outs of trials for any potential treatments. Something that can benefit children and their families for years to come, and even one day even lead to a cure for Zellweger Spectrum Disorder.
Page 19	Conclusion	Here at Zellweger UK we feel that it is extremely detrimental to presume families' perspectives on early diagnosis. Within our families the overwhelming census is that families wish they had known sooner. We would urge you to please speak to our communities and we feel it's extremely important that we receive representation in any further reviews into Newborn screening for Adrenoleukodystrophy. It is clear that while there is not a cure for Zellweger Spectrum Disorder, there are obvious and crucial benefits of an early diagnosis in terms of the health, wellbeing and life quality of patients, for the early care and support they and their families receive, and in terms of further medical and scientific research into future treatments and symptom management. Screening for Adrenoleukodystrophy in newborns has already successfully rolled out in the US and in the Netherlands and we have every reason to believe that it would be a great success here in the UK too. We would urge

		you to seriously consider this and certainly not dismiss it based on a misconception that the families would not want to know about the detection of Zellweger Spectrum Disorder, because speaking to the families we support, and as families of affected children ourselves, we can say that this simply couldn't be further from the truth.

UK National Screening Committee

33. Member of the public (Zellweger)

Name:	Sarah Cowley	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Person with adrenoleukodystrophy/adrenomyeloneuropathy or Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy [delete as appropriate]**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes** **No**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes** **No**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	*Our* xxxx xxxx *(*xxxx xxxx*) was diagnosed with Zellweger Spectrum Disorder at 3 months old. We were told* xxxx

		xxxx was at the severe end of the spectrum and unlikely to live until xxxx xxxx first birthday. As you can imagine when we received this diagnosis we were absolutely devastated however it also ended a 3 month battle of not knowing why our xxxx xxxx would not feed properly or could not maintain xxxx xxxx temperature. *The diagnosis came after we walked into A&E with xxxx xxxx as we were completely exhausted and had no where else to turn. After 2 weeks of tests in hospital we were finally given a diagnosis. Newborn screening would have saved xxxx xxxx and ourselves from this ordeal.* *If we had been given xxxx xxxx diagnosis at birth we could of enjoyed the first 3 months of xxxx xxxx life instead of being out of our minds with worry.* *I understand that the health visitors, GP's, dieticians etc. are not qualified to diagnose these sorts of conditions but me and xxxx xxxx felt very unsupported by these professionals. Newborn screening would have saved us a lot of time and frustration.* *As parents you cannot help but feel responsible for passing on a genetic condition to your child. Early*

		diagnosis would have made our experience less traumatic. As it was we were left feeling angry and frustrated with the health professionals and guilty that we had not done something sooner. xxxx xxxx *was born through IVF as we have other fertility issues. We have now been offered PGT if we would like to try for another child in the future. This has given us confidence to try again.*
Page 19	Conclusion	*If we had received* xxxx xxxx *diagnosis sooner we could have started putting things in place to make* xxxx xxxx *life as comfortable as possible. For example, once diagnosed* xxxx xxxx *had an NG tube.* xxxx xxxx *spent the first three months of* xxxx xxxx *life constantly feeling hungry and unsettled. Early diagnosis would also have saved* xxxx xxxx *from a lengthy stay in hospital and many tests. This was traumatic for both* xxxx xxxx *and us.* *I am glad that screening is now happening in the US and the Netherlands but it angers me that it is not in the UK. Screening should be available for everyone. Everyone has the right to know a diagnosis.*

		Before diagnosis I was accused of struggling to cope as a new mum and as a person who has suffered from anxiety before I began to wonder if It was just me being over anxious. It took a huge amount of courage to take xxxx xxxx *into A&E but I honestly believe if we hadn't then* xxxx xxxx *would have not lived as long as* xxxx xxxx *did.* xxxx xxxx *would have passed away without us knowing why and we would have blamed ourselves.*

UK National Screening Committee

34. Member of the public (Zellweger)

Name:	Stephanie Curry	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 6, para 3	Identification of untreatable conditions other than ALD	My son xxxx xxxx was diagnosed with Zellweger Spectrum Disorder when he was just under 8 months old in 2018. Until this time, what should have been the

		dreamy new parent phase was filled with dread, a minimum of once weekly hospital visits and endless traumatic investigatory procedures for xxxx xxxx .During this 8 month period things were pretty tough for xxxx xxxx while he was wracking up a long list of health conditions. It was a stressful time, not only for him, but xxxx xxxx and myself. After a 10 week stint in hospital, xxxx xxxx received his diagnosis of a peroxisomal biogenesis disorder, and a whole host of other life threatening conditions associated to it, for example adrenal insufficiency. When we left hospital with a long list of medications, hospital machinery, strict care plan…. And I life sentence. However, now that he was under the care of the right doctors with the treatment, our boy was the happiest he had ever been. This happiness was short lived though. 2019 was tough for xxxx xxxx and for us as a family. As his condition regressed it felt like we were watching our boy slip away from us. We made what memories we could with xxxx xxxx and clung onto those few months we had when xxxx xxxx was at his best.

		Having experienced this now, and felt the anxiety of waiting for a diagnosis, wondering what would come of all of these problems; the prospect of finding a way to get an earlier diagnosis would be amazing. Watching your child suffer if torture. If things could have been identified earlier (introduction of hydrocortisone) and managed, we could have had longer with a happier, healthier child.
Page 19	Conclusion	Knowing that newborn screening for ALD is available in other countries but not here is a tough pill to swallow. To know that xxxx xxxx suffering could have been lessened if we would have got an earlier diagnosis makes me feel like a failure as a parent- knowing that something was out there that may have helped. Those memories made with 'well' xxxx xxxx are invaluable- if we had an earlier diagnosis we could have had more if these so that he could enjoy the world for the short time he was in it.

35. Member of the public

Name:	Virginia Prifti	**Email address:**	xxxx xxxx
Organisation (if appropriate):			
Role:	**Parent/relative of someone with adrenoleukodystrophy/adrenomyeloneuropathy**		
Do you consent to your name being published on the UK NSC website alongside your response? **Yes**			
Would you like to register to receive email alerts whenever there is any UK NSC activity on this topic? Please see below for more information **Yes**			

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 5, para 4; Page 6, para 3 Page 12, Q2 Page 16, Q4	Addison's Disease phenotype Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase? Does early initiation of treatment following screening provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection? (referring to treatment of Addison's)	We were completely unaware of Addison's Disease and just thought that the strange pigmentation on my son's skin was nothing to be worried about. He was already seeing GP and consultants for the fact that his behaviour was changing but nobody picked up on the fact that he had a large area of dark pigmentation on his skin.
Page 5, para 5;	Available standard therapy	By the time we received the diagnosis for my son's ALD it was too late for any treatment – the quality of his life had he

		survived would have been awful and the treatment may well have killed him as it did a friend's son
page 6, para 3 Page 12, Q2	Identification of boys who would not go to develop cerebral ALD Are there any factors that can predict the future adrenoleukodystrophy phenotype in the pre-symptomatic phase?	Our family has been completely devastated by the loss of our son. Although his diagnosis in October and death the following July was a short length of time it was a very traumatic experience which haunts me frequently. Watching your child lose all his faculties is just undescribably awful. I feel guilty that I unwittingly passed the gene on to him, and also feel a sense of unfairness that my daughter does not have the gene but would not have died if she had had the condition (though she might have passed it on to any sons she may have in the future). Whilst we would not have had the seven years of our son's life without any anxiety about his health, if he had been screened and diagnosed at birth we would at least have been given the opportunity to look for early signs, and attempt to do something to save his life.
page 10, Q1	What is the incidence of ALD in the UK?	It has been suggested that the incidence of ALD in the UK is higher than the number of people identified as having the condition, particularly amongst adults for whom symptoms may mirror other conditions. This is not acceptable. Screening at birth would give accurate data from which to allow people to make decisions about trying not to pass the condition on to children, and in time to eradicate this awful condition.
Page 16, Q4	Does early initiation of treatment following screening	Because diagnosis of ALD is difficult, and the medical

	provide better outcomes for adrenoleukodystrophy compared to initiation of treatment following clinical detection?	profession by and large have not encountered the condition, currently diagnosis can only be made once a child has demonstrated a change in behaviour by which time it is really too late to do anything about it. Having to rely on the death of any older male sibling to be able to save younger siblings is horrible
Page 19	Conclusion	The fact that the US and Netherlands are forward thinking enough to screen for ALD, and yet here in the UK there is no screening is very frustrating. If my son had been born in one of those countries would have have lived? Nobody who has lost a child can imagine what it is like. Those who decide on who to screen might feel more sympathetic if they had gone through the experience.