Alex TLC Newborn screening study

Summary Report August 2022

prepared by Genetic Alliance UK

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Recommendations

- More research is needed with the population affected by ALD / AMN as there is limited literature focussing on their lived experiences. This should include:
    - investigations about reproductive choices which have been made / could have been made.
    - the experiences of those who were diagnosed early (and their parents / family members) with both those that have received intervention and those that have experienced a long time before becoming symptomatic.
    - the experience of receiving a false positive result and any long-term impacts of this
    - how individuals balance benefits and risks of newborn screening
    - how individuals balance 'knowing' and 'not knowing'
- Study with a bigger sample including more diverse perspectives such as those of:
    - women who are carriers
    - family members of those diagnosed including those who have chosen not to be screened once they are aware that a relative has been diagnosed
    - people diagnosed early (and their parents / carers / family members) including those receiving treatment and those waiting for symptoms and being monitored
    - people not currently associated with support groups

Literature Review *(see also Alex TLC Literature doc)*

Currently screening for X-ALD is only available in the Netherlands and selected states in the US (Dangouloff et al., 2021, Kemper et al., 2017, Moser et al., 2022, Zhu et al., 2020, Eng and Regelmann, 2020). In the Netherlands a boys-only screening algorithm has been developed which the authors hoped would lead to more uptake of screening programmes worldwide to include X-ALD (Barendsen et al., 2020). Several studies have assessed the impact of inclusion of X-ALD in the newborn screening programme in terms of averting both death and disability (Brosco et al., 2015). Individual States have also reported on the findings from including X-ALD within their own newborn screening programmes and highlight some achievements and challenges: Minnesota (Wiens et al., 2019), California (Schwan et al., 2019), Nebraska (Baker et al., 2022) and Pennsylvania (Priestley et al., 2022). In the States the current underdiagnosis of ALD amongst some ethnic minority groups is also believed to have implications for the newborn screening programme (Bonkowsky et al., 2018).

Benefits of newborn screening for X-ALD have tended to focus on the opportunity to save life or prevent severe disability by early intervention (Tran et al., 2017, Turk et al., 2017, Turk et al., 2020, Raymond et al., 2007). Studies of boys receiving therapy have shown the best outcomes for those with the most favourable Loes scores pre-hematopoietic stem cell transplant (Beckmann et al., 2018, Engelen, 2017, Miller et al., 2011, Mallack et al., 2019). Surveillance and

monitoring after identification through newborn screening are therefore considered crucial to fully realise the benefit (Pierpont et al., 2020). However, treatment for CCALD in childhood does not necessarily protect against the development of adrenomyeloneuropathy (AMN) in adulthood (van Geel et al., 2015). Another benefit is being able to identify adrenal insufficiency which is experienced by a large proportion of boys with adrenoleukodystrophy (ALD) (Eng and Regelmann, 2019). A potential cost benefit has also been identified through the "*estimated reductions in the social care and education costs.*" (Bessey et al., 2018).

Other benefits have been identified from newborn screening studies for other conditions such as being able to prepare for a child with additional needs (Christie et al., 2013, Qian et al., 2015), earlier access to care (Qian et al., 2015), being able to shorten the journey to diagnosis if the person is identified symptomatically (Qian et al., 2015) and reproductive planning (Christie et al., 2013). Genetic screening has been identified as being able to go beyond the traditional aim of screening, which is to identify disease early in order to give preventive therapy, to be able to give people knowledge to be able to make reproductive decisions (Burke et al., 2011, Botkin, 2016).

The aforementioned studies have also identified some potential risks or harms associated with a newborn screening programme, these include fear that the parents' attitude towards their newborn may change if a condition is identified at birth putting a strain on parent-child bonding (Christie et al., 2013, Qian et al., 2015, Frankel et al., 2016). Early identification of someone with a condition has also led to the concept of a "*patient-in-waiting*" which may lead to fear and anxiety about the uncertainty of their health before any symptoms arise (Pruniski et al., 2018, Timmermans and Buchbinder, 2010). Other risks which have been identified include "perceived child vulnerability" and the possibility of self and partner blame when a genetic condition is identified (Frankel et al., 2016). A study in California where newborn screening for X-ALD is available identified some concerns raised by parents which included "*stress at initial phone call, difficulty living with uncertainty, concerns regarding mental health support, and desire for more information on disease progression, treatments and clinical trials*" (Schwan et al., 2019).

False-positives, when an initial identification of someone with a condition is shown to be incorrect, is one of the major risks of any screening programme and the impact of false-positives has been investigated for newborn screening (Morrison and Clayton, 2011, Schmidt et al., 2012, Tu et al., 2012, Vernooij-van Langen et al., 2014). The impacts include both short and long term anxiety for some parents (though long term worry was not identified in all studies) and risk for the parent-child relationship.

The rate of false-positives for newborn screening of X-ALD has been investigated for some states in America where screening for X-ALD has been included in the newborn screening programme. In North Carolina, of 12 infants with screen positive results, 4 were found to be false positive (3 females found to be unaffected and 1 male with indeterminant results after further testing) (Lee et al., 2020). Overall, this gave "*The positive predictive value for X-ALD or other genetic disorders for the first-tier assay was 67%, with a false-positive rate of 0.0057%.*" In

Illinois for 16 cases where follow up was received, one was found to be false positive, the authors described this as 'low' (Burton et al., 2022). Another earlier study which took place in Maryland found no false positives amongst their results (Theda et al., 2014).

Some studies from the States where newborn screening for X-ALD is available has shown that babies are identified with variants of uncertain significance (Wiens et al., 2019, Baker et al., 2022). Other studies showed that there was little concern amongst parents about identification of carrier status or adult-onset disorders (Christie et al., 2013). It has been suggested that longer follow up studies are needed to understand some of the issues and ethical concerns with identifying people with adult-onset or untreatable conditions through newborn screening (Gaspar et al., 2014, Wasserstein et al., 2021) as well as considering the implications around the knowledge to be able to make reproductive decisions (Burke et al., 2011, Botkin, 2016).

Public perceptions of decisions around newborn screening programmes have been investigated with some mixed results prompting calls for further research (Tarini et al., 2018, Green et al., 2004, Taylor-Phillips et al., 2014, Taylor-Phillips et al., 2018, Vass et al., 2019, Wright et al., 2015). For example, some studies found that people supported screening for conditions where there was no treatment but did not support screening for conditions which were late childhood or adult-onset (Hasegawa et al., 2011). Other studies including public dialogue found support only for screening conditions where a known treatment was available (Hopkins et al., 2021). While a study considering being able to identify those who were at greater risk of developing diabetes found that parents wanted "*to know if their child has increased risk of getting diabetes even if there is no preventive measure available*" (Stolt et al., 2003).

Study methodology

Interviews *(see qual ppt slide 3)*

The topic guide for the interviews was developed based on a review of the literature (*see topic guide*). Four interviews took place between April and May 2022 with men based in the UK diagnosed with AMN. All the interviews took place over the phone after receiving informed consent. The audio recordings were transcribed verbatim by a professional transcription company. The transcripts were uploaded into NVivo to manage the data and create a coding frame; the data were analysed thematically.

All men had been diagnosed symptomatically experiencing a range of tests to establish diagnosis, with misdiagnoses along the way for some of the men. Three of the four had children; two of these had had the diagnosis after having children. Not all the respondents' mothers had been tested but those who had were found to be carriers. The respondents experienced some variation in quality of life with use of a variety of mobility aids and different levels of problems with fatigue, concentration and memory loss. Some respondents had been able to continue working (in different roles) whilst others had had to stop working.

Table 1: Survey demographics

Demographic		Number
Sex	Female	18
	Male	11
Age	16-24	4
	25-34	2
	35-44	4
	45-54	8
	55-64	5
	65-74	5
	75+	1
Ethnicity	White English / Welsh / Scottish / Northern Irish / British	24
	Irish	1
	Indian	2
	Caribbean	1
	White and black Caribbean	1
Region of residence	East of England	5
	East Midlands	0
	London	4
	North East and Cumbria	0
	North West of England	1
	South East of England	4
	South West of England	7
	West Midlands	1
	Yorkshire	1
	Scotland	5
	Wales	1
	Northern Ireland	0
Living situation (multiple answers possible)	Alone	4
	With spouse / partner	15
	With children (16+)	12
	With children (under 16)	4
	Other family members	4
Work / study status (multiple answers possible)	Working full time	12
	Working part time	6
	Voluntary work	2
	Care for someone (full time or part time)	4
	Not working / unemployed	1
	Retired	6
	In education	1
Eligibility (multiple answers possible)	Living with ALD diagnosis	9
	Living with AMN diagnosis	9
	Family member of male (16+) with ALD / AMN diagnosis	16
	Current carer of male (16+) with ALD / AMN diagnosis	5
	Previous carer of male (16+) with ALD / AMN diagnosis	5

Survey *(see quant ppt slides 2-11)*

The survey was designed based on the literature and the interviews which had taken place. The survey was available online via SmartSurvey from 9 June to 25 July 2022. Overall, 29 respondents were included (21 complete responses and 8 partial responses). Eligible respondents had to be aged 16 plus, based in the UK and someone with an ALD / AMN diagnosis, the carer / family member of an adult (16+) male with an ALD / AMN diagnosis or a previous carer. See Table 1 for a detailed demographic breakdown.

Of the nine men who answered the survey who had a diagnosis, six had been diagnosed symptomatically and three had been diagnosed as a result of a family member being diagnosed. Of the fifteen people who answered as family members / current carers, six men had been diagnosed symptomatically, six as a result of a family member being diagnosed and three gave other answers. For the five people responding as previous carers, one man had experienced symptoms and four gave other responses as to how the diagnosis came about (*see quant ppt slide 7*). Across the sample, 12 of the men had not experienced any misdiagnoses, 13 had experienced one or more misdiagnoses, for the remaining four men there was uncertainty if they had had any misdiagnosis or other answers were given (*see quant ppt slide 8*).

Age at diagnosis varied from birth to age 50 and the length of time to diagnosis varied from months to years (*see quant ppt slide 9*). There was a variety in the level of experiences of fatigue, memory loss and problems with concentration (*see quant ppt slide 10*). Some used a variety of mobility aids - walking sticks / wheelchairs / other aids (*see quant ppt slide 11*) and there were varying levels of symptom severity from mild to moderate to severe.

Findings

Balancing 'knowing' and 'not knowing'

On the whole the survey respondents indicated that they would have preferred to know about their diagnosis earlier, with only one previous carer saying that they would not have wanted the person they cared for to have known about their condition through newborn screening (*see quant ppt slides 12 & 13*). The interviews showed that men took a balanced view of the advantages and disadvantages of knowing about the condition sooner with three of the four men stating that they would have wanted to know whilst one man said he was glad that he did not know sooner (*see qual ppt slides 13-15*). Open text comments from the survey also mainly favoured knowing about the condition through newborn screening (*see qual ppt slide 16*).

> "[Did not want person to know about condition through newborn screening] Because he was able to live a mostly happy life and I wonder how it would have felt for him to live with the knowledge that his life was going to be cut short." (resp 28)

"I think if I'd known about it I would have had things in place, you know? … 100%, it would have been totally different, yeah." (Int 02)

"… it's a really difficult one isn't it because if you're going to be fine until you're in your 20s or 30s, do you want to live with that hanging over you? Again, it's knowledge is power in terms of knowing what to expect. I think I'd probably come down on the side of I would want to know" (Int 03)

Availability of screening in the UK

All the interviewees felt that screening for X-ALD should be available in the UK. All the survey respondents felt it should be available for boys whilst 25 of the 29 said it should be available for girls, 3 were not sure and 1 preferred not to answer (*see quant ppt slide 14*). There were strong feelings that screening should be available and that it was not fair that it was available in some countries but not in others. (*see qual ppt slides 56-60*).

"It makes me feel quite annoyed. I mean, you know, the NHS and the UK are under pressure like every other country at the moment, but it does make me annoyed that if one country so close to us can do it, why can't we?" (int 04)

"But I think in general, if I could help my children find out with the 9 conditions that they can test for, I think I would need to say I would prefer to know about it early." (int 01)

"New born screening is a right, nobody should have to suffer like this when it can be avoided." (resp 10)

Of the survey respondents who had had children, 14 of the 15 said they would definitely have screened their children if it had been available. Of the 6 respondents who had not had children they all said they would want to screen children if they had them (*see quant slide 15* – note only 21 respondents answered the question about screening children).

Balancing benefits versus the risks

During the interviews the benefits and risks of newborn screening for X-ALD where discussed. All the interviewees felt that the benefits outweighed the risks but they were able to give balanced views and acknowledged that there were risks involved (*see qual ppt slides 5-8*). The 21 survey respondents who answered the question about the balance of risks and benefits all felt that the benefits outweighed the risks a lot (*see quant ppt slide 21*), this was supported by comments given in the free text parts of the survey (*see qual ppt slides 9-12*).

"So yeah, it [false positives] is a risk but I think for the – I don't know the stats but I think for the small percentage of times that happens, it's probably worth that risk. " (int 03)

"for the sake of preparedness the family has to know about the conditions of their child pretty early in life. And the risks just can't beat that, that is what I think." (resp 1)

"Long term conditions are part of an individual's genetic makeup and cannot change, however the individual may be affected later in life. Having this knowledge from birth would be empowering, the benefits outweighing the risks significantly, not only for the individual but also for their wider family." (resp 15)

"The benefits are avoiding at worst a premature death. Whereas a lot of the risks can be managed." (resp 6)

Benefits and risks of including X-ALD in the newborn screening progamme

The benefits and risks of newborn screening, as discussed during the interviews and comments made by the survey respondents, have been categorised under the following themes (see table 2):

- **Disease course**
  - ***Individual / family***
  - ***Medical Intervention***
- **Knowledge – parents / child / wider family**
- **Societal**
  - ***Healthcare system***
  - ***Costs***

Disease Course

Individual /family experience *(see qual ppt slides 18-22)*

Under this sub-theme there were only benefits identified which were to do with the chance of survival, someone reaching their potential, an improved quality of life, a reduced diagnostic odyssey both in terms of length of time to reach diagnosis and the ease with which the diagnosis is obtained, also better access to support and education.

Medical intervention *(see qual ppt slides 23-28)*

The main benefit in this sub-theme was the opportunity to get timely treatment and the potential to diagnosis adrenal insufficiency earlier. The risks were that a child could be over medicalised in the early years of their life if they are under constant surveillance and monitoring and the risk of receiving a false-positive result.

Knowledge *(see qual ppt slides 29-41)*

The benefits of having knowledge included being able to prepare mentally for a child with a diagnosis, parents being able to make the most of the time they have with a child, parents being able to make further reproductive choices, the child themselves being able to make future reproductive choices, being able to share the information with other family members who could then act on that information, able to make suitable lifestyle choices and not having to live with finding out too late that a treatment opportunity has been missed.

There were also several risks associated with having knowledge that a child has a condition without the certainty of when that condition would appear. The risks included having to inform others about the condition which could lead to tensions, perceived child vulnerability before symptoms arise leading the child to be treated differently and putting pressure on child-parent bonding. The burden of knowledge was being continually alert for symptoms (“patient in

waiting") and the anxiety and grief which could be experienced anticipating that the child will not reach their potential.

Societal

Healthcare system *(see qual ppt slides 42-44)*

The benefits identified under this sub-theme were that overall the healthcare system would experience less of a burden over the diagnosed person's lifetime if they had been successfully treated early on. There was also the benefit that there would be raised awareness amongst healthcare professionals and the public about ALD if it was part of the screening programme. Through having an earlier diagnosis it was also felt that there would be increased knowledge about the condition and more opportunities to do research.

Risks in this sub-theme concerned potential reduced trust in the medical system if the parents experienced inaccurate or inconclusive results from the screening programme. Also, some may consider it a risk to have medical information stored about someone for a long period of time.

Costs *(see qual ppt slides 45-47)*

Benefits put forward were that there would be reduced costs incurred if someone was treated early on – this would not just be in the healthcare system but also for education, social support and so on. Another potential benefit if someone was treated early was that parents may not have to give up paid employment to care for their child full-time and would therefore be able to contribute more to the economy. Risks were that the screening programme would cost money which could then not be spent on other healthcare needs.

Scoring benefits and risks

In the survey the respondents were asked to score benefits and risks out of 10 based on how important they considered them to be, see tables 3 and 4 *(see also quant ppt slides 16-20)*. An overall average score has been calculated for each benefit / risk based on the total of the individual scores given divided by the number of respondents who provided a score for each element.

All the benefits had an average score between 9 and 10, with the highest rated score being for *'Increased chances of an individual who is treated early to be able to fulfil work / family / life potential'* which scored 10, the lowest benefit score of 9.36 was for *'Potentially lower levels of treatment required if diagnosed before symptoms arise'*.

The average scores for the risks were between 3.27 and 6.26, reflecting how the respondents considered the benefits to outweigh the risks. The most important risk was *'Patient in waiting (potential anxiety caused by continually being on the alert for the condition arising)'* and the least important risk was *'Having medical information about the individual stored somewhere'*.

Table 2: Benefits vs risks of Newborn Screening for X-ALD – interviews and survey respondents

Category		
DISEASE COURSE	**Benefits**	**Risks**
Individual / family experience	• increased chances for someone treated early to fulfil potential / survive • improved quality of life if treated early • access to benefits and support sooner / access to an education • reduced length of time of the diagnostic odyssey - reduced impact on whole family • avoidance of being told that 'there is nothing wrong' • avoidance of being blamed for "bad" behaviour • potential avoidance of survivor guilt	
Medical intervention	• able to monitor and receive timely treatment before symptoms arise (symptomatic stage may be too late for effective intervention) • potential early diagnosis of adrenal insufficiency • potential lower levels of treatment required/ less inappropriate treatment / testing	• false positives - long term anxiety about the result, potential overtreatment of infant without the condition • potential overmedicalisation of infant / child early on
KNOWLEDGE	**Benefits**	**Risks**
Parent / parent & child / wider family	• knowledge to prepare for child's condition • make the most of time which they have with the child • parents able to make reproductive decisions • knowledge to share with other family members (so can be acted upon) • knowledge for future child to be able to make reproductive decisions • knowledge to influence lifestyle choices • avoidance of knowing that have a condition which could have been treated if diagnosed sooner	• unresolved / inconclusive result - causing potential anxiety • having to inform others (family / friends) of condition • carrier status knowledge - anxiety, potential stigma • perceived 'child vulnerability' before symptoms arise • "patient in waiting" (continually being alert for symptoms) – burden of knowledge • anxiety / grief for the child and anticipation of not reaching potential • impact on child's mental and physical well-being • child-parent bonding potentially put at risk • self /partner blame / feelings of guilt from the parent once diagnosis is known • potential to reveal non-paternity
SOCIETAL	**Benefits**	**Risks**
Healthcare system	• encourages health service improvement and better healthcare frameworks • less burden on the healthcare system • raises awareness amongst healthcare professionals and public • increased medical knowledge about the natural history of the condition • more opportunities for research from birth	• inaccurate screening results – potential lowered trust in medical system • storage of medical information about an individual
Costs	• societal benefits if reduced costs incurred through life-course if able to treat early • carers may have to give up jobs to care for someone (if diagnosed late), this can impact the economy through reduced taxes	• financial cost of the screening programme which could have been put into other areas of the healthcare system

Table 3: Importance of benefit - scores out of 10

	Benefit	Benefit Score of importance out of 10
B1	Increased chances of an individual who is treated early to be able to fulfil work / family / life potential	10.00
B2	Potential early diagnosis of adrenal insufficiency	9.96
B3	Able to monitor child so that they can receive timely treatment before symptoms arise	9.85
B4	Avoidance of delay in diagnosis after experiencing symptoms	9.85
B5	Knowledge for the parents to be able to make reproductive decisions about having more children	9.81
B6	Less inappropriate treatment / testing before diagnosis	9.76
B7	Increased medical knowledge about how the condition progresses, if people are identified before symptoms develop	9.73
B8	Knowledge for the child to be able to make future decisions about having their own children	9.69
B9	Reduce costs of healthcare and other support services by treating people earlier	9.69
B10	Knowledge to prepare for child's condition which may start in childhood	9.64
B11	Knowledge to share with other family members which may help identify someone who is pre-symptomatic	9.54
B12	Raises awareness for the public and healthcare professionals about X-ALD if it is included in the newborn screening programme	9.54
B13	Encourage health service improvement by diagnosing more people early with X-ALD	9.46
B14	More opportunities to undertake research with those who are diagnosed from birth	9.41
B15	Potentially lower levels of treatment required if diagnosed before symptoms arise	9.36

Table 4: Importance of risk - scores out of 10

	Risk	Risk Score of importance out of 10
R1	"Patient in waiting" (potential anxiety caused by continually being on the alert for the condition arising)	6.26
R2	Self / partner blame if child is diagnosed with an inherited condition	5.91
R3	Perceived 'child vulnerability' before symptoms arise (leading to child being treated differently compared with not knowing about the condition)	5.65
R4	False positive results – this is where someone is given a diagnosis which turns out to be incorrect; this can lead to short and long-term anxiety about the result and / or potential medicalisation of an infant without the condition	5.36
R5	Reduced trust in the medical system through receiving an incorrect or inconclusive result	5.35
R6	Carrier status knowledge (leading to anxiety and potential stigma)	5.30
R7	Unresolved / inconclusive result (leading to anxiety)	4.91
R8	Having to inform other family members of the possibility of an inherited condition (possibly leading to anxiety and potential conflicts within the immediate and wider family)	4.87
R9	Child-parent bonding put at risk	4.27
R10	Potential of test result to reveal issues around non-paternity (the person who thought they were the father is shown not to be the biological father)	4.13
R11	Financial cost of the screening program	3.41
R12	Having medical information about the individual stored somewhere	3.27

Other findings

Interviewees had informed other members of their family once they had their own diagnosis, but not all family members had gone on to be tested. On the whole the interviewee wanted others to be tested so that they could take any necessary action – *see qual ppt slides 48-52*. Interviewees also talked about other considerations to do with screening such as consent, ethics, who should decide which conditions are included and how should parents be informed about the results. There was also some discussion around the support which is needed for those who have been diagnosed and their families. Many of the interviewees had been engaged in awareness raising amongst the general public and work colleagues.

Conclusion

The interviewees and the survey respondents all held strong views that newborn screening for X-ALD should be available in the UK. They were aware that there were risks as well as benefits but the benefits were believed to considerably outweigh the risks; all the benefits scored on average between 9.36 and 10 out of 10 (risks scored between 3.27 and 6.26). Many of the benefits and risks identified in the academic literature were mentioned by the interviewees and the survey respondents in the open text comments. Interviewees also took a balanced approach to whether they would have wanted to know about their condition sooner; here the balance between knowing and not knowing was more difficult to judge for the interviewees diagnosed with AMN.

Limitations

Small sample size with strongly held views that screening should be available in the UK. A larger sample with a broader range of perspectives would be beneficial to get a greater understanding of the benefits and risks of introducing X-ALD into the UK newborn screening programme. However, the sample was diverse with a range of perspectives (those with the condition and carers – current and previous). The quality of life for the men affected also varied with different levels of severity experienced and different usage of mobility aids.

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