National Institute for Health and Care Excellence

Highly specialised technologies

Elivaldogene autotemcel for treating cerebral adrenoleukodystrophy [ID1284]

Response to consultee and commentator comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Bluebird bio	CALD is a devastating but ultra-rare disease. Based on insight from treating physicians in Great Ormond Street Hospital London and from available literature, we estimate that approximately one boy per year may be treated with eli-cel in England and Wales **(see Attachment: How many children may receive eli-cel in England and Wales?)**. We believe direct national specialist commissioning by NHS England could be the most time and resource efficient route to secure timely patient access to the treatment.	Comment noted. This topic will be scheduled into the highly specialised technology programme.
	Association of British Neurologists	Very appropriate: Lenti-D (brand name unknown, Bluebird bio) is a viral vector which is used in gene therapy. Haematopoietic stem cells with the CD 34 marker are taken from the patient's bone marrow. The lenti-D vector is used to insert a healthy version of the disease-causing gene (ABCD1) into the stem cells which are then grown in culture. They are administered back to the body after myeloablative treatment (radio or chemotherapy).	Comment noted. This topic will be scheduled into the highly specialised technology programme.

Section	Consultee/ Commentator	Comments [sic]	Action
	Alex, The Leukodystrophy Charity	Yes The proposed treatment is essential for patients who are unable to have a more traditional HSCT. Without an alternative treatment they will unfortunately deteriorate from cerebral ALD symptoms and usually die. The overall impact this horrific disorder has for the patient and also their family is wide-reaching and must be appreciated. Therefore we would urge that Lenti-D is evaluated and commissioned via the fastest possible route.	Comment noted. This topic will be scheduled into the highly specialised technology programme.
	Great Ormond Street NHSFT	Appropriate for referral to NICE	Comment noted. This topic will be scheduled into the highly specialised technology programme.
	NHS England	It is appropriate to refer this topic to NICE for evaluation	Comment noted. This topic will be scheduled into the highly specialised technology programme.
Wording	Association of British Neurologists	The background and overall wording reflect the remit. There should be a little more background on why Lenti-D is chosen and the benefits above other therapies.	Comment noted. The background section of the scope is intended to give a brief overview of the condition and description of the technology. The committee will consider all relevant evidence in relation to the

Section	Consultee/ Commentator	Comments [sic]	Action
			technology. No changes to the scope required.
	Alex, The Leukodystrophy Charity	Yes [appropriate]	Comment noted. no changes to scope required.
	Great Ormond Street NHSFT	Appropriate	Comment noted. no changes to scope required.
	NHS England	Yes, the wording of the remit reflects the issue(s) of clinical and cost effectiveness	Comment noted. no changes to scope required.
Timing Issues	Bluebird bio	CALD progresses rapidly without treatment. If approved for use, eli-cel may be deemed as the preferred (or, in some cases, the only) treatment option for boys with early CALD and for whom a closely matched donor is not available. Early access to the treatment may make a significant difference in outcomes for any patients diagnosed with this ultra-rare disease in the immediate future.	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic will be scheduled into the highly specialised technology programme.
	Association of British Neurologists	Important but given the risks of stem cell transplant, the risk of Covid-19 related mortality will currently be high	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic will be

Section	Consultee/ Commentator	Comments [sic]	Action
			scheduled into the highly specialised technology programme.
	Alex, The Leukodystrophy Charity	We are aware that the trial for this vital treatment closes during 2021. It is imperative that there is not a period whereby this treatment might become unavailable for those unfortunate enough to need it. We would therefore consider it is of the utmost urgency that this treatment remains available for patients as soon as the trial closes.	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic will be scheduled into the highly specialised technology programme.
	Great Ormond Street NHSFT	Urgent	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic will be scheduled into the highly specialised technology programme.
	NHS England	Not urgent.	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic will be scheduled into the

Section	Consultee/ Commentator	Comments [sic]	Action
			highly specialised technology programme.
Additional comments on the draft remit	Great Ormond Street NHSFT	Should the use of HSCT as a comparator be mentioned here?	Comment noted. No changes to the scope required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bluebird bio	1. The background does not reflect the broad range of clinical manifestations of ALD at onset. CALD may develop in boys already diagnosed with ALD, or it may be the first clinical manifestation of the condition. In boys not known to have ALD, early symptoms of CALD are often misdiagnosed as attention deficit hyperactivity disorder, and diagnosis may be delayed. Delayed diagnosis has historically been common. For example, in the cohort of 60 patients undergoing allo-HSCT for CALD reported by Miller in 2011, 50% had radiologically advanced disease at baseline and 62% had some clinical neurologic impairment. These patients had less favorable outcomes. A further proportion of boys are diagnosed too late to be eligible for allo-HSCT 2. Lorenzo's oil is indicated as part of current treatment, however this is an experimental therapy and in trials it failed to improve neurologic function and does not arrest the progression of cerebral disease (van Geel BM, J Neurol Neurosurg Psychiatry, 1999; Aubourg P, N Engl J Med, 1993)	Comments noted. The background section of the scope is intended to give a brief background of the condition. The company may refer to the relevant manifestations, diagnosis and baseline characteristics of the condition in its evidence submission. Based on consultation comments and discussion at the scoping workshop, Lorenzo's oil has been removed from the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologists	The background and overall wording reflect the remit. There should be a little more background on why Lenti-D is chosen and the benefits above other therapies.	Comment noted. The background section of the scope is intended to give a brief overview of the condition and description of the technology. The committee will consider all relevant evidence in relation to the technology. No changes to the scope required.
	Alex, The Leukodystrophy Charity	We would consider that more up to date incidence rates could be found at https://adrenoleukodystrophy.info/clinical-diagnosis/facts-on-ald. We would consider that identifying Lorenzo's Oil as a treatment for CALD is no longer correct. There is much disagreement on its effectiveness and specialists in the UK no longer prescribe this routinely. It is not made clear that transplant is not considered unless there are indications that cerebral symptoms have started, usually through six monthly MRI scanning, alongside additional regular monitoring for other potential signs.	Comments noted. The background section of the scope is intended to give a brief background of the condition. Committee will consider the relevant manifestations, diagnosis and baseline characteristics of the condition in its evidence submission. Based on consultation comments and discussion at the scoping workshop, Lorenzo's oil has been

Section	Consultee/ Commentator	Comments [sic]	Action
			removed from the background section.
	Great Ormond Street NHSFT	Para 2: “As the disorder is caused by a faulty gene from the X-chromosome it almost exclusively impacts upon males, as they only have one X-chromosome.” This statement relates only to Cerebral ALD, as females can develop adrenomyeloneuropathy. Para 4: Stem cell transplant is considered in boys who have been diagnosed with the condition but in whom symptoms have not yet appeared. HSCT can also be considered in boys with very early symptoms (Neurological function score up to 1 ref Moser et al 2000). The MRI appearances (Loes score +/- Gadolinium enhancement) are also very important in decision-making	Comments noted. The background also refers to the possibility of females developing ALD. The background section of the scope has been changed to reflect the comments made in relation to stem cell transplantation.
	NHS England	The information is accurate and complete.	Comments noted. No changes to scope required.
The technology/ intervention	Bluebird bio	Please note that we are seeking marketing authorisation for the technology with the international non-proprietary name of Elivaldogene autotemcel (eli-cel). Could you please replace the former Lenti-D with eli-cel here and throughout the document?	Comments noted. The scope has been amended to reflect these comments.
	Association of British Neurologists	Yes but more detail needed	Comments noted. The technology section of the scope is intended to give a summary. No

Section	Consultee/ Commentator	Comments [sic]	Action
			changes to the scope required.
	Alex, The Leukodystrophy Charity	As far as we are aware [appropriate]	Comments noted. No changes to the scope required.
	Great Ormond Street NHSFT	Yes [appropriate]	Comments noted. No changes to the scope required.
	NHS England	The description of the technology is accurate.	Comments noted. No changes to the scope required.
Population	Bluebird bio	The population should reflect that the treatment would be restricted to patients with early CALD: "Treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy for whom a human leukocyte antigen matched sibling haematopoietic stem cell donor is not available".	Comments noted. Following discussion at the scoping workshop the population has been changed to reflect this comment.
	Association of British Neurologists	Yes [appropriate]	Comments noted. No changes to the scope required.
	Alex, The Leukodystrophy Charity	Yes [appropriate], however we would like to ask for consideration of those who would choose gene therapy over HSCT.	Comment noted. The committee will consider all relevant evidence when appraising the

Section	Consultee/ Commentator	Comments [sic]	Action
			technology. No changes to the scope required.
	Great Ormond Street NHSFT	Although rare, it would be appropriate to also include Adult Cerebral ALD.	Comments noted. NICE will appraise the technology within its marketing authorisation. No changes to the scope required.
	NHS England	There is no information about the number of individuals who might be eligible for the treatment, noting that this is one of the questions in the scope. We had understood this number to be very small, of the order of 1-5 per annum.	Comments noted. Consultation comments and workshop discussion confirmed that the number likely to receive treatment is considered small. No changes to the scope required.
Comparators	Bluebird bio	Patients with early CALD and with an available matched sibling donor would not be eligible for eli-cel. Among those patients without a matched sibling donor the comparators would be: • patients for whom a matched unrelated donor is not available • patients for whom a matched unrelated donor is available Based on insights collected from treating physicians at Great Ormond Street Hospital, one of the centres of excellence in the country, the first comparator would be extremely uncommon in the UK, although not completely unlikely. For these patients eli-cel could represent a preferred alternative to a poorly matched HSCT or to palliative/supportive care. In the second comparator group, eli-cel could represent an alternative for the treating physician and the patients to consider on a case-by-case basis.	Comments noted. The comparator section has been updated to state that stem cell transplant and best supportive care are relevant comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
	Association of British Neurologists	Ideally more detail	Comments noted. The comparator section has been updated to state that stem cell transplant and best supportive care are relevant comparators. No changes to the scope required.
	Alex, The Leukodystrophy Charity	Yes [appropriate]	Comments noted. No changes to the scope required.
	Great Ormond Street NHSFT	- HSCT is the established clinical management, and can be described as the best alternative treatment. - Symptomatic and palliative management is appropriate for patients with advanced disease at diagnosis.	Comments noted. The comparator section has been updated to state that stem cell transplant and best supportive care are relevant comparators. No changes to the scope required.
	NHS England	The comparators are correct.	Comments noted. No changes to the scope required.
Outcomes	Bluebird bio	Based on insights collected from ALEX TLC, the leading patient support group focusing on ALD, the psychological impact of the disease on patients	Comments noted. The scope currently outlines health-related quality of

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		and carers is a neglected but critical element in the overall assessment of quality of life.	life for both patients and where relevant carers. No changes to the scope required.
	Association of British Neurologists	Generally given but not specific	Comments noted. No changes to the scope required.
	Alex, The Leukodystrophy Charity	We would urge that the psychosocial quality of life for the patient, carers and wider family (siblings) should also be considered. We would also urge that the outcomes for not having Lenti-D gene therapy as an alternative to HSCT are taken into consideration. The following are examples of the transplant experiences (where gene therapy was not available) of ALD patients and their families as told to Alex TLC: • one family had a child that had no match due to his mixed race heritage; they had to watch the child deteriorate and die, closely followed by his two brothers who also had no match • another family with the same issue lost one son, and helplessly watched his brother's disease progression. Although this thankfully stabilised, he has been left as an adult with significant behavioural and mobility problems requiring 24 hour care • one family had an ALD diagnosis in their twin sons. One twin was untreatable and sadly died. The other twin was matched to an unrelated donor, who unfortunately pulled out. He then received two haplo-identical donations from his father (the first did not work) and his symptoms progressed rapidly post transplant. He is now in his 20s, wheelchair bound, completely dependent and unable to communicate. • One boy has had long-lasting GvHD effects on his liver • One boy lost his life to GvHD during transplant. • One family had to repeat their son's transplant due to GvHD.	Comments noted. The scope currently outlines health-related quality of life for both patients and where relevant carers. The comments relating to potential equality issues have been noted and committee will consider these in their decision-making where relevant. The committee will consider all relevant evidence relating to the technology in its decision-making. No changes to the scope required.

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		• Another family had a similar experience, and the boy has been left with significant behavioural issues including ADHD and Tourette's. Additionally, one family chose to have Lenti-D gene therapy for psychological reasons. The boy's older brother had had HSCT with a poor outcome and they were understandably anxious that there might be a similar outcome for the younger boy. We would also therefore urge that consideration is given to allowing families a choice when considering treatment options.	
	Great Ormond Street NHSFT	1. Time from decision to treat to definitive treatment is also an important outcome measure. Some patients can progress and become too advanced in the disease course whilst awaiting HSCT or Lenti-D, potentially rendering them unsuitable for transplantation. 2. The Neurological function score (Moser et al 2000) is also an important outcome measure and should be included.	Comments noted. The outcomes section of the scope is not an exhaustive list. Discussion at the scoping working concluded that time from decision to treat to definitive treatment would be captured in other outcomes, but that this information can be considered by the committee if relevant. Neurological function has been added to the scope.
	NHS England	Yes, the outcomes are correct.	Comments noted. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Equality and Diversity	Bluebird bio	No comment	Comments noted. No changes to the scope required.
	Association of British Neurologists	N/A, this is an inherited disorder	Comments noted. No changes to the scope required.
	Alex, The Leukodystrophy Charity	As a whole, patients with rare conditions often experience health inequalities, particularly those who live in remoter areas and do not have access to specialist centres. Availability of this treatment to all UK patients will be integral to reducing these health inequalities.	Comments noted. The committee will consider relevant issues relating to equalities. No changes to the scope required.
	Great Ormond Street NHSFT	Inclusion of patients with Adult CALD as above.	Comments noted. NICE will appraise the technology within its marketing authorisation. No changes to the scope required.
	NHS England	No equality considerations as the scope already notes that the condition is almost exclusively found in males.	Comments noted. No changes to the scope required.
Other considerations	Alex, The Leukodystrophy Charity	Under the section: Nature of the condition, you detail impact of the disease on carer's quality of life. This should include the patient: if HSCT does not go well or is delayed, these boys are often left with difficulties ranging from behavioural problems to complete dependency as detailed above.	Comments noted. The committee will consider all relevant outcomes in relation to those experienced by the

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		Impact should also encompass the wider family, in particular the impact on siblings. Unsuccessful or unavailable treatment has longstanding impact on families. In Alex TLC's 16-year experience we have seen this impact demonstrated through: • loss of parental jobs due to new caring commitments • inability to pursue career paths • inability to contribute to society • issues with sibling education, behaviour and familial relationships • financial worries • mental health issues • physical health issues brought on by caring responsibilities We believe there is significant cost benefit to the NHS from this treatment: the costs incurred treating patients with complex and multiple disabilities, not to mention the associated costs of care, equipment and special education will far outweigh the one-off costs of this treatment. This has already been considered in an economic impact study for ALD newborn screening https://pubmed.ncbi.nlm.nih.gov/30309370	patient and where relevant carers. The scope also outlines that committee will consider whether there are significant benefits other than health and whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services. No changes to the scope required.
	NHS England	No comments	Comments noted. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Innovation	Bluebird bio	Clinical data to date suggest that early treatment with eli-cel can halt the progression of CALD, eliminating the risk of GVHD, graft failure and graft rejection in the small population of CALD patients. Under current standard of care, these patients have very limited treatment options and often poor outcomes.	Comments noted. The committee will consider if the technology is innovative. No changes to the scope required.
	Association of British Neurologists	Yes, the area of genomic medicine is emerging as very important	Comments noted. The committee will consider if the technology is innovative. No changes to the scope required.
	Alex, The Leukodystrophy Charity	Yes, it provides options for patients that are unable to access 10/10 matched donors. Without this option they will face potentially unsuccessful treatment or no treatment at all, relentless deterioration and usually death.	Comments noted. The committee will consider if the technology is innovative. No changes to the scope required.
	Great Ormond Street NHSFT	Yes Autologous Lenti-D transplant carries a lower mortality risk, decreases the time to definitive treatment, reduces the risk of disease progression whilst awaiting donor search for HSCT, and avoids the need for complex transplants (such as mismatched transplants), and is associated with much reduced transplant-related complications such as GVHD and transplant rejection. The outcome of Lenti-D treatment in terms of survival, major functional disability, and neurological progression (Neurological Fuction Score), also represents a step change from conventional management with HSCT.	Comments noted. The committee will consider if the technology is innovative. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	The product is innovative and potentially reflects a 'step-change' in the management of the condition in individuals whose disease has not progressed.	Comments noted. The committee will consider if the technology is innovative. No changes to the scope required.
Questions for consultation	Bluebird bio	**How many children are diagnosed with ALD, how many with CALD every year in England/Wales?** There are no reliable published numbers: based on some partial data and on expert opinion, a reasonable estimate is around **35-40 children a year with an ALD diagnosis.** Of these, we can estimate 17-20 to be boys and approximately **5-6 children a year to develop CALD**. **Sources**: Global epidemiology: ALD incidence at birth has estimated at around 1:17,000-1:20,000 live births[1], and approximately 1:3 boys with ALD are believed to develop CALD[2]. Based on this estimate, and considering a birth cohort in England and Wales of just under 680,000[3], there will be an estimated 35 children born each year with ALD. Of these, 17-18 will be boys and approximately 5-6 will develop CALD.	Comments noted. No changes to the scope required.

[1] Bezman L, Moser HW: Incidence of X-linked adrenoleukodystrophy and the relative frequency of its phenotypes. Am J Med Genet. 1998, 76: 415-419. 10.1002/(SICI)1096-8628(19980413)76:5<415::AID-AJMG9>3.0.CO;2-L.

[2] Engelen et al. Orphanet Journal of Rare Diseases 2012, 7:51 http://www.ojrd.com/content/7/1/51

[3] Infant mortality (birth cohort) tables in England and Wales, Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/infantmortalitybirthcohorttablesinenglandandwales (last accessed, 17/09/2020)

Section	Consultee/ Commentator	Comments [sic]	Action
		Published data from Great Ormond Street Hospital (Keshavan, poster presentation at BIMDG 2019): GOSH was referred 29 boys with ALD in the past 20 years (approximately 2-3 children per year in recent years, 1-2 children per year in the past decade). There are seven metabolic centres in England and Wales: - GOSH - Evelina - Manchester - Bristol - Birmingham - Sheffield - Cardiff The centres may differ somewhat in size and catchment area, but if we assume every centre to be referred the same number of children as GOSH, then the estimate is 14-21 boys overall with an ALD diagnosis each year. **How many children with CALD receive a haematopoietic stem cell transplant?** Not all children with a CALD diagnosis are eligible for haematopoietic stem cell transplant (HSCT), as HSCT has been shown to be associated with poor outcomes in children with advanced CALD. Data available and expert opinion ([redacted]) suggests that **approximately 2-3 children per year** receive HSCT in England and Wales. **Sources:** British Society Bone Marrow Transplant (BSBMT): The BSBMT registry reported an average of two HSCTs per year performed in the UK in 2007-	

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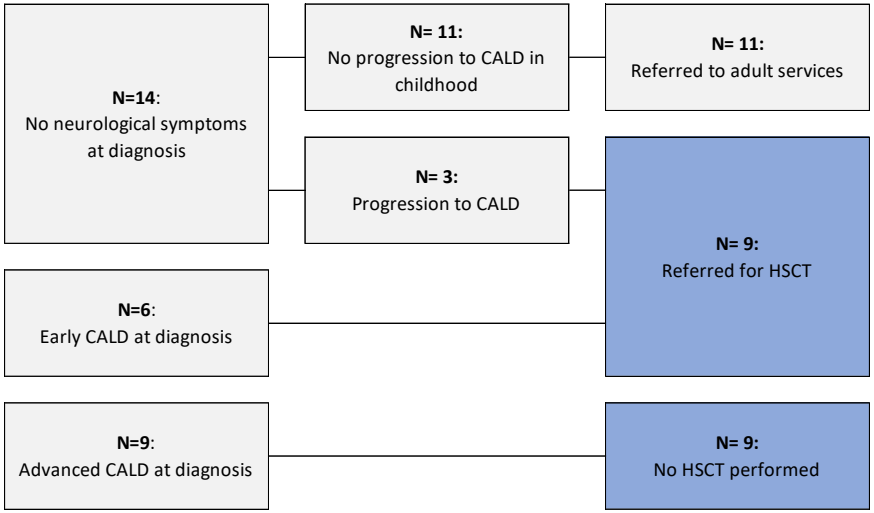
2017 (unpublished data, table 1). In the last five reported years, the average number of HSCT has been 2.6 per year.

Table 1: number of paediatric CALD HSCTs performed in the UK in 2007-2017 by year.
<table>
<tr><th>Year</th><th>HSCTs performed</th><th></th><th>Year</th><th>HSCTs perforr</th></tr>
<tr><td>2007</td><td>1</td><td></td><td>2013</td><td>4</td></tr>
<tr><td>2008</td><td>2</td><td></td><td>2014</td><td>3</td></tr>
<tr><td>2009</td><td>4</td><td></td><td>2015</td><td>2</td></tr>
<tr><td>2010</td><td>0</td><td></td><td>2016</td><td>2</td></tr>
<tr><td>2011</td><td>3</td><td></td><td>2017</td><td>2</td></tr>
<tr><td>2012</td><td>0</td><td></td><td>Total (2007-2017)</td><td>23</td></tr>
</table>

According to the BSBMT registry, out of the 23 HSCTs performed in 2007-2017, 6 (26%) were performed using a matched sibling donor (MSD) source and 17 (74%) using an matched unrelated donor (MUD) source.

<u>Audit performed recently at Great Ormond Street Hospital (GOSH)</u>:
GOSH was referred 29 British boys with ALD in the past 20 years. Of these, 18 had or developed a CALD diagnosis in childhood and 9 were referred for HSCT (figure 1). Although these figures present historical data, and it is likely that the more children with a CALD diagnosis would have access to HSCT than in the past, it is reasonable to assume that a significant proportion of them are still diagnosed too late to be eligible for HSCT
</td><td></td></tr>
</table>

Figure 1: clinical presentation at diagnosis and referral to HSCT for children with ALD referred to GOSH in 2000-2019 (N=29). The squares in purple (N=18) represent the children with CALD.



Based on clinical efficacy/safety data for eli-cel, where (if at all) would eli-cel fit into the current care pathway, and for which patients?
According to [redacted], based on clinical data for eli-cel (ALD-102 and ALD-104), and within the current proposed indication (children with early CALD, for whom HSCT is indicated but MSD is not available), eli-cel:

- Would fit into the standards of care to treat patients with CALD in the very unlikely situation that neither an MSD nor an MUD are available

Section	Consultee/ Commentator	Comments [sic]	Action
		1. - Where a MUD is available, the treating physician could be more inclined to perform an allo-HSCT given the lack of long-term efficacy and safety data of eli-cel. On the other hand, clinical data currently available suggest that efficacy is comparable to HSCT with MSD and there are no events of GvHD related to treatment with eli-cel. The choice of using eli-cel instead of MUD HSCT would depend on an assessment of the treating physician. In particular, the physician would need to weigh: (1) the degree of matching of the donor source available and the likelihood of GvHD; and (2) the potential unknown risks of using a new treatment with no long-term safety and efficacy endpoints. This would not be a clear-cut decision but a case-by-case assessment. Eli-cel may be chosen as an option in those situations where only a less closely matched MUD is available, whereas the treating physician may be more likely to choose allo-HSCT when a closely matched MUD is available. 2. - Based on the estimate of 3-4 children with CALD receiving allo-HSCT each year, and within the proposed indication for eli-cel, a reasonable estimate is that no more than 1-2 children per year would effectively receive eli-cel.	
	Association of British Neurologists	1. More detail on the technology 2. Why Lenti-D is superior 3. Any difference in initial mortality risk	Comments noted. The committee will consider the relevant evidence for the technology. No

Section	Consultee/ Commentator	Comments [sic]	Action
			changes to the scope required.
	Alex, The Leukodystrophy Charity	We have a concern that the NICE route may be too slow and that therefore there may be a significant risk to life.	Comment noted. NICE aims to provide guidance within 6 months of a technology receiving its license. This topic has been scheduled into the highly specialised technology programme.
	Great Ormond Street NHSFT	***How is CALD diagnosed in NHS practice?*** The majority of patients present with neurological symptoms. A small number present with adrenal insufficiency, without neurological symptoms. Some patients can also be diagnosed through family screening when asymptomatic. ***Is CALD typically diagnosed before symptoms develop?*** A majority of CALD patients are diagnosed after the onset of neurological symptoms. ***Would Lenti-D be a treatment option for asymptomatic and/or symptomatic CALD?*** Similar to HSCT, Lenti-D can be a treatment option for - asymptomatic, and - early symptomatic patients (Neurological Function score < or = 1) with minimal changes on MRI (Loes score >0.5 to 9)	Comments noted. The background and comparator sections of scope have been updated to reflect these comments.

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Which treatments are considered to be established clinical practice in the NHS for people aged under 18 years with CALD?
- HSCT for those with early symptoms and early MRI changes as above.
- Symptomatic and palliative care for those with more advanced neurological and MRI features on MRI.

Do these treatment options differ depending on the availability of a willing 10/10 HLA-matched sibling donor?
No, but the likelihood of transplant related complications and mortality are higher with non 10/10 HLA matched transplants.
The longer-term neurological outcome and overall survival are also worse with non 10/10 HLA matched transplants.

Are stem cell transplants considered as a treatment option for those with a less than 10/10 HLA-matched sibling, an unrelated matched donor or an unrelated mismatched donor?
Yes, whilst recognising the higher risk and poorer outcome as above.

If so, are outcomes expected to vary with these options?
Yes, as per reference 6, table 3, simplified below (Raymond et al 2019)
<table>
<tr><td>Parameter</td><td>HLA Matched</td><td>HLA Mismatched</td></tr>
<tr><td>Overall Survival</td><td>92%</td><td>72-80%</td></tr>
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Section	Consultee/ Commentator	Comments [sic]	Action

2y Post HSCT		
Major Functional Disability-free survival 2y Post HSCT	69-82%	38-40%

Are the outcomes listed appropriate? Are there any other important outcomes that should be included?

1. Time from decision to treat to definitive treatment is also an important outcome measure. Some patients can progress and become too advanced in the disease course whilst awaiting HSCT or Lenti-D, potentially rendering them unsuitable for transplant.

2. The Neurological function score (Moser et al 2000) is also an important outcome measure and should be included.

Section	Consultee/ Commentator	Comments [sic]	Action
		What services exist for the diagnosis and management of CALD in people aged under 18 years in the NHS? General Paediatrics Community Paediatrics Neurology Neurodisability Metabolic Disorders services Paediatric Endocrinology HSCT services Palliative care and supportive services (dietetics, specialist nursing, physiotherapy, feeding services, Speech and Language therapy, etc) ***How many treatment centres in the NHS would provide treatment with Lenti-D?*** 1-2 ***What is the size of the population that would be eligible for treatment with Lenti-D in England?*** 5-8 patients per year ***Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?*** Asymptomatic patients who are prospectively monitored for early clinical and radiological signs of CALD would be expected to do much better than those diagnosed with early symptoms of CALD. If newborn	

Section	Consultee/ Commentator	Comments [sic]	Action
		screening for X-ALD is introduced, this group would form a significant proportion of the treated patients.	
	NHS England	No comments	Comment noted. No changes to scope required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Neonatal and Paediatric Pharmacists Group (NPPG**)**