Highly Specialised Technologies (HST) criteria checklist

Maralixibat for treating cholestatic pruritus in Alagille Syndrome [ID3941]

**Introduction:** The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. [section 7 of NICE health technology evaluation topic selection: the manual](https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies)

### Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met | There is clear and strong evidence that this criterion is met |
| Not met | There is no evidence or limited evidence that the criterion is met. |

### Confirmed MA wording: Treatment of cholestatic pruritus in patients with Alagille syndrome 2 months of age and older

| **Number** | **Criterion** | **Description of how the technology meets the criteria** | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The condition is very rare defined by 1:50,000 in England | **Incidence of live birth/birth prevalence estimate:**  The underlying condition of this topic is Alagille syndrome. It is mostly caused by mutations in *JAG1* gene, and in a minority by mutations in *NOTCH2* gene1. It is a rare disease, and its diagnostic criteria have evolved over the years with the understanding of the condition increasing and advances of genetic testing.  Early incidence estimate:   * When the condition was first recognised in the 1970s, it was defined as bile duct paucity associated with at least 3 of 5 major criteria (cholestasis, heart disease, vertebral anomalies, eye problems) and treated as a liver condition1. An early population screening study of the incidence at birth (birth prevalence) estimated that Alagille syndrome occurred in 1 in 70,000 live births2. * For this early estimate, diagnosis was mainly based on a clinical finding in the neonatal period of intrahepatic biliary atresia (later renamed as Alagille syndrome).   Revised diagnostic criteria:   * In 1997, the association of Alagille syndrome with mutations in JAG1 gene was published, and later the NOTCH2 gene was also found to be associated with Alagille syndrome. The availability of genetic testing for these mutations led to its incorporation into the revised diagnostic criteria of Alagille syndrome in 20073. * These revised criteria differed from the classical criteria because other diagnostic clinical parameters, such as renal disease and a family history of Alagille syndrome were added. The revised diagnostic criteria allow diagnosis of Alagille syndrome to be made based on a compatible genetic abnormality with either 1 syndromic feature or a family history of Alagille syndrome4.   Diagnosis in practice:   * A clinical expert noted that *“genetic diagnosis is increasing the total number by including asymptomatic and paucity-syndromic patients.”* The expert also explained that for the past 5 to 7 years, their practice was to *“perform genetic testing in patients who either have unexplained neonatal cholestasis or having any features to suggest Alagille syndrome. This means in practice all who either do not have absolute clear biliary atresia or who do have other clear reasons for cholestasis get genetic testing.”* * Whilst genetic analysis is often undertaken looking for *JAG1* and *NOTCH2* mutations, a small minority of patients meeting the clinical diagnostic criteria for Alagille syndrome will have neither5. Also, a significant number of people with *JAG1* mutations will not have sufficient clinical findings to meet the classical criteria (liver disease with 3 of 5 major criteria) but will have some features of Alagille syndrome6. The diagnosis must therefore be primarily based on a broad understanding of the clinical features of the syndrome.   Updated incidence estimate:   * Today Alagille syndrome is treated as a multi-system disorder. With an understanding that not all patients with the disorder will have hepatic abnormalities in the neonatal period, and with the revision of the diagnostic criteria requiring fewer positive findings from an expanded range of characteristics, especially in those patients with a positive family history4,7, it is well acknowledged that the early 1:70,000 live birth estimate is a significant underestimate1.   When researchers re-examined the early estimate in view of the revised diagnostic criteria, the live birth incidence of Alagille syndrome was estimated between 1:30,000 and 1:50,0005, and most recently it was reported the true incidence (or birth prevalence) is likely to be 1:30,000 live births7-9.  **Prevalence estimate:**   * Estimates of prevalence vary between 1 in 30,000 and 1 in 100,00010.This leads to a prevalence of 565 to 1,885 in England ([using 2021 mid-year England population estimate](https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates#timeseries), 56,550,000)11.   So criterion 1 is “not met”. | Not met |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications | **Live birth incidence:**   * There were 595,948 live births in England in 202112, so the incidence equates to about 20 (595,948/30,000) live births each year in England using 1:30,000 live birth estimate.   **Population eligible for treatment:**  The technology aims specifically to treat cholestatic pruritus which can occur in Alagille syndrome. The exact number of people in England with Alagille syndrome who may be eligible for treatment is not known but the NICE technical team considered that, where appropriate, this may be estimated using real world evidence.  The Global Alagille Alliance (GALA) study is an international cohort of more than 1,500 children with Alagille syndrome, which included clinically and/or genetically confirmed cases.9 It is the largest cohort of paediatric patients to date and aims to explore the natural history of Alagille syndrome13. The NICE technical team considered that it may be reasonable to use some findings of this study to inform the estimation of population eligible for treatment, specifically:   * Proportion of population with cholestatic pruritus: include only people with cholestatic pruritus, about 74% as reported in the GALA study9. Cholestatic pruritus is what the technology aims to treat. * Proportion of liver transplantation: exclude people who are likely to have had a liver transplant, 36% had a transplant due to persistent cholestasis (with intractable pruritus the most common complication of persistent cholestasis) in the GALA study,9 because it is expected that they would not need treatment with the technology. * Mortality: exclude mortality, about 9%, which is the risk of mortality among people who had not had a liver transplant by age 18 years, as reported in the GALA study9. * Age: exclude people who are too young to receive the technology based on the licensed indication.   Taking account of these adjustments, the estimated population of people with Alagille syndrome who would be eligible for the technology exceeds 300. So criterion 2 is ‘not met’.  There are uncertainties in the estimation of population eligible for treatment. But there is not sufficient or robust evidence clearly indicating that criterion 2 is met. | Not met |
|  | The very rare condition significantly shortens life or severely impairs its quality | Pruritus associated with cholestasis in Alagille syndrome severely impairs the quality of life, impacting on all aspects of the child’s life, including sleep, appetite, education, relationships, and ability to take part in everyday activities. This has an impact on the caregivers and the wider family. Severe and unremitting pruritus is present in about 80% of cases at 2 years14.  The disease can stabilise and symptoms may improve, but between 15% and 50% of children with Alagille Syndrome will have a liver transplant before 18 years of age9,14 including 50% of those with neonatal cholestasis9. Currently there is no way to predict whether liver symptoms in infancy will resolve or progress15.  The overall survival rate in Alagille Syndrome is 88% at 18 years9. The 20-year life expectancy was higher (80%) for patients who did not require a liver transplant, and lower (60%) for patients who did require a liver transplant.16 | Met |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | Current treatment for Alagille Syndrome focuses on alleviating symptoms. Treatments to reduce itching may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone, ondansetron, SSRIs and antihistamines such as chlorphenamine17. Nutritional supplements and high-calorie diets are important for many people with Alagille Syndrome, because of the difficulties cholestasis causes with absorbing fats and nutrients15. If Alagille Syndrome does not respond to drug and dietary therapies, a partial biliary diversion may be carried out18 although this is rare in the UK. Between 15% and 50% of children with Alagille Syndrome will have a liver transplant before 18 years of age9,14 including 50% of those with neonatal cholestasis9. | Met |

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Highly specialised technologies vision and routing criteria

The Highly Specialised Technologies Programme is designed to be used in exceptional circumstances. Its purpose is to evaluate technologies for very rare diseases that have:

* small numbers of patients
* limited or no treatment options
* challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.

The Highly Specialised Technologies Programme aims to:

* encourage research on, and innovation for, very rare conditions when there are challenges in generating an evidence base that is robust enough to bring the product to market
* secure fairer and more equitable treatment access for very small populations with very rare diseases
* recognise that an approach that maximises health gain for the NHS may not always be acceptable: it could deliver results that are not equitable.

The Highly Specialised Technologies Programme acknowledges that:

* It is important for NICE to apply appropriate limits on the very rare populations that can potentially be routed to the programme. This is because the Highly Specialised Technologies Programme is a deliberate departure from the standard technology appraisal process (valuing the benefits from these technologies more highly by having a much higher [incremental cost-effectiveness ratio [ICER]](https://www.nice.org.uk/Glossary/incremental-cost-effectiveness-ratio) threshold) for the reasons outlined above.
* Each time NICE routes a topic to the Highly Specialised Technologies Programme it is deciding that, if the technology is recommended, the NHS must commit to allocate resources that would have otherwise been used on activities that would be expected to generate greater health benefits.
* NICE has sought to strike a balance between the desirability of supporting access to treatments for very rare diseases against the inevitable reduction in overall health gain across the NHS that this will cause. Both considerations are valid and important, and neither can be given absolute priority over the other. Therefore, the Highly Specialised Technologies Programme criteria and their anticipated application intentionally do not seek to capture every case when there are challenges in generating an evidence base or when there is a small population with a rare disease.
* This approach ensures that technologies routed to the Highly Specialised Technologies Programme fulfil the vision of the programme and manages the displacement in the wider NHS.

However, it can be difficult to identify the exceptional circumstances when the highly specialised technologies methods and processes should be used because of the difficulty in getting the information needed. Proxy information is often relied on and used to make subjective judgements. The routing criteria identify which technologies should be routed for highly specialised technologies guidance. These criteria help make subjective judgements as informed, justifiable, consistent and predictable as possible. NICE’s capacity to develop highly specialised technologies guidance can react to need and there is no limit on the number of technologies that can be routed.

The final routing criteria for the Highly Specialised Technologies Programme are:

* The disease is very rare – defined as 1:50,000 population in England.
* Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications.
* The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life.
* There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.