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European strategies in the screening of biliary atresia: a scoping review

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ABSTRACT

Background Biliary atresia (BA) is a rare condition that meets the criteria for neonatal screening. Taiwan province of China led the way in BA screening during the 1990s by introducing a neonatal stool color card (SCC), which proved effective in facilitating early BA diagnosis and improving outcomes. Another commonly studied BA screening approach is serum bilirubin measurement. Several European countries have also begun implementing BA screening initiatives, although slowly. In this study, we evaluate BA screening strategies across Europe.

Methods Published data, after having performed a scoping review, as well as internet searches were analyzed. Screening approaches proposed in Europe are described, including SCC, serum bilirubin measurements, and other biochemical markers such as bile acids or amino acid profiles.

Results In Europe, national BA screening programs have been established solely in Switzerland, France, and Germany, all using the SCC. Other European countries, such as the Netherlands, Portugal, and Italy, have made efforts, but have yet to achieve broad implementation beyond localized initiatives. Skepticism among healthcare professionals and logistical challenges seem to hinder broader adoption. Emerging technologies, such as artificial intelligence-enhanced SCC applications, may show promise in overcoming these barriers. Serum bilirubin measurement is another widely deliberated method, particularly in the UK, where it has been shown to be sensitive and specific for BA detection. However, logistical and financial limitations remain key obstacles to its widespread use. Other biochemical methods, such as bile acid and amino acid profiling, have shown potential in research settings, but lack clinical translation in Europe.

Conclusions This review highlights Europe's limited role in global BA screening efforts and emphasizes the need for advocacy, collaboration, and integration of screening strategies tailored to regional healthcare systems. Combining the SCC with bilirubin measurements could optimize cost-effectiveness and efficiency. Expanding BA screening programs requires strengthening advocacy efforts to improve outcomes for affected infants.

INTRODUCTION

Biliary atresia (BA) is a rare neonatal condition of unknown cause that involves obstruction of the biliary tree, leading to severe cholestasis, biliary cirrhosis, and, ultimately if untreated, to death within the first years of life. It is the most common surgical cause of cholestatic jaundice in neonates and the leading indication for pediatric liver transplantation globally. BA is typically suspected in jaundiced neonates with pale stools and firm hepatomegaly. Diagnostic steps include a panel of investigations such as blood tests, ultrasound and/or cholangiography or endoscopic retrograde cholangiopancreatography, to rule out other causes of neonatal cholestasis. Treatment follows a two-step approach: first, a hepatoportoenterostomy (Kasai procedure) performed during the neonatal period with the goal to restore bile flow; and second, liver transplantation for cases where the Kasai procedure fails or complications from biliary cirrhosis arise. It is widely recognized that early intervention significantly improves outcomes.[1]

The incidence of BA is similar to other congenital conditions for which neonatal screening is standard, such as phenylketonuria or galactosemia. The criteria for an effective newborn screening program - (1) an important health problem, (2) an early intervention window, (3) a reliable screening test, and (4) available treatments—undoubtedly apply to BA.[2 3] Various screening methods, including serum or urinary markers or stool color monitoring, have been proposed worldwide. This paper explores BA screening strategies across Europe, offering a historical perspective and an overview of the current European landscape.

MATERIALS AND METHODS

To maximize the inclusion of reports and papers, a scoping review was conducted instead of a systematic review. Scoping reviews offer a broader framework for analysis, help identify knowledge gaps and allow for more inclusive criteria compared with systematic reviews. The scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews methodology for scoping reviews, and the methods were established a priori.[4]

The search strategy aimed to identify published and unpublished studies and was developed with support from a senior library assistant at the University of Geneva. A Peer Review of Electronic Search Strategies (PRESS) checklist was used to ensure its comprehensiveness and precision.[5]

The search followed two steps: (1) search development and optimization, during which relevant studies were identified through an initial search of two databases: National Library of Medicine (PubMed) and Excerpta Medica Database (Embase). The titles, abstracts and index terms of eligible studies were extracted; (2) electronic search, during which the optimized search terms identified in step 1 were used to perform an electronic search across two databases.

Databases were searched from inception until December 20, 2024. Each database was searched separately with search terms relevant to that database. We used the search terms: '((‘bile duct atresia’/exp OR ‘bile duct atresia*’:ab,ti,kw OR ‘biliary atresia*’:ab,ti,kw OR ‘intrahepatic bile duct malformation*’:ab,ti,kw) AND (‘newborn screening’/exp OR ‘screen’:ab,ti,kw OR ‘screened’:ab,ti,kw OR ‘screening*’:ab,ti,kw OR ‘serum bile acid*’:ab,ti,kw OR ‘stool color card*’:ab,ti,kw OR ‘testing polic*’:ab,ti,kw OR ((urin*) NEAR/3 (‘sulfated bile acid*’)):ab,ti,kw OR ((direct OR conjugated) NEAR/2 (bilirubin)):ab,ti,kw)) for Embase and ‘((“Biliary Atresia”[Mesh] OR “bile duct atresia*”[tiab] OR “biliary atresia*”[tiab]) AND (“Neonatal Screening”[Mesh] OR “screen”[tiab] OR “screened”[tiab] OR “screening*”[tiab] OR “serum bile acid”[tiab] OR “stool color card*”[tiab] OR “testing polic*”[tiab] OR “urine sulfated bile acid”[tiab:~3] OR “urinary sulfated bile acid*”[tiab] OR “direct bilirubin”[tiab:~2] OR “conjugated bilirubin”[tiab:~2])) for PubMed.

Publications were considered if they met the following criteria, based on population, intervention, context or outcomes: (1) patients with BA (population) and (2) described or investigated an intervention for BA screening; (3) in any setting (context); (4) if they reported outcomes (to be included in the list of quantitative/analytic publications) such as sensitivity and specificity in BA detection, or age at Kasai, or age at liver transplantation, or efficacy of screening method. There were no limits on language to ensure the inclusion of all potentially relevant studies and to reduce the risk of language bias. Google Translate, recognized as a reliable tool for translating studies in systematic reviews, was used to screen and extract data from non-English language studies.[6]

Studies were excluded if: (1) they focused on BA screening outside the European continent; or (2) they were abstracts later expanded into full articles.

All identified citations were uploaded into Rayyan review software, and duplicates were automatically removed. Data were extracted from eligible studies using a predefined data extraction form. The extracted data included details on participants, methods, and key findings. The PRISMA 2020 flow diagram is shown in figure 1. Data are presented both as a narrative summary and in tabular form, highlighting the main findings of the studies.

In addition to available publications, this paper incorporates data carefully searched on the internet, using the same search terms as above, and personal experience of the authors, to further enrich the report.

GLOBAL HISTORY AND OVERVIEW OF BILIARY ATRESIA SCREENING

The history of BA screening reflects a range of strategies that have been conceived and explored both globally and across Europe.

Globally, Taiwan province of China pioneered BA screening in the 1990s with the introduction of a stool color card (SCC).[7–9] This simple yet effective tool enables parents and caregivers to identify pale, acholic stools in their newborns, the hallmark of cholestasis and BA in particular. In Taiwan province of China, the introduction of the SCC led to a notable decrease in the age at which the Kasai operation was performed, with the proportion of infants undergoing surgery before 60 days of age increasing from 49% before the screening program to 66% afterwards.[8] Moreover, the hospitalization and mortality rates of BA cases in Taiwan province of China significantly declined following the introduction of the SCC screening program.[10] The program's success set a benchmark for other countries to later also introduce the SCC nationwide, such as Switzerland,[11] France,[12] Germany[13] and Brazil,[14] or regionally, such as Japan,[9] China,[15 16] Canada,[17 18] and Egypt.[19] The SCC is available either in paper format, often integrated into the child's personal health booklet, or more recently, as part of mobile smartphone applications. These applications, such as PoopMD,[20] Baby Poop,[21] or PopòApp,[22] feature a touch screen interface, use the smartphone camera, and employ specially designed color analysis software to evaluate the baby's stool color.

Other means such as quantification of stool color saturation have been shown to prove its principle by Japanese[23] and Chinese[24] authors, but so far has never gained acceptance in its wider use.

Countries or areas, North America, but also Taiwan province of China[25] and the UK,[3] has focused on raising awareness among healthcare providers and parents regarding the importance of early cholestasis detection using serum conjugated bilirubin,[26 27] which is highly sensitive and specific: a recent study by Harpavat *et al.* showed a sensitivity of 100.0% and a specificity of 99.9% of this screening method, and the age at which infants underwent Kasai portoenterostomy was significantly lower after the implementation of the screening program using bilirubin measurements.[26] Yet, evidently, this method is also costlier and more resource intensive than the SCC. For this approach and around the globe, nationwide screening programs do not exist.

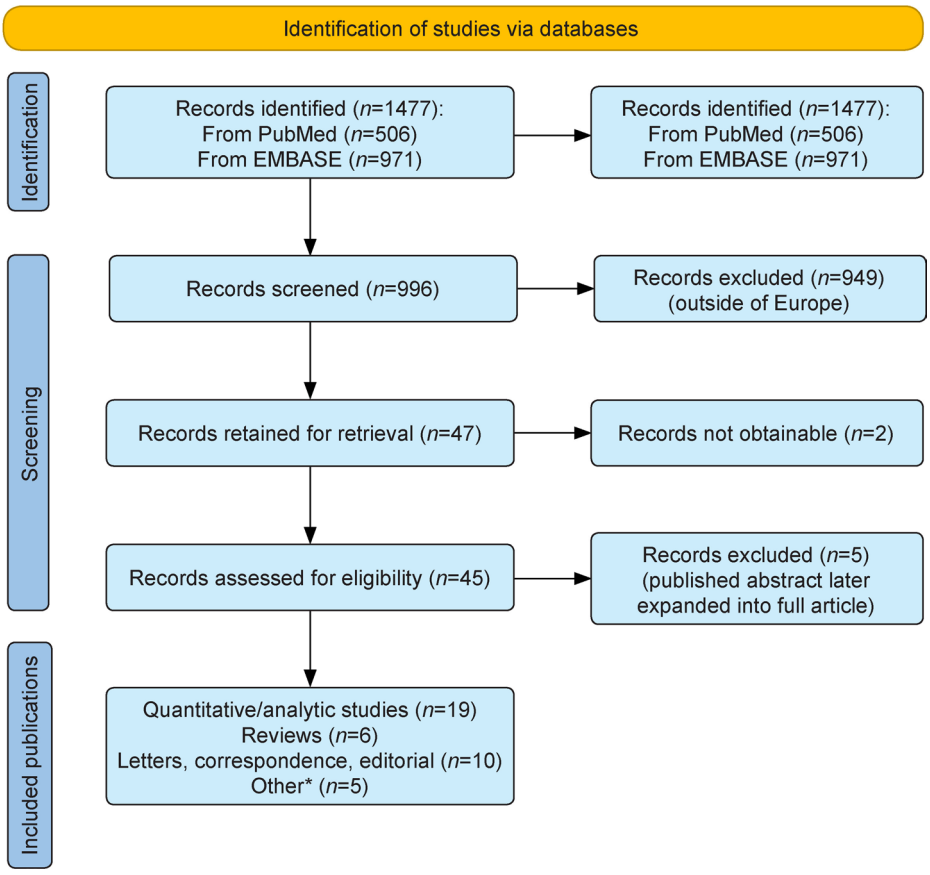

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the scoping review of publications. *Outcome is different from what was defined for quantitative/analytic studies.

Further, other methods have shown to be potentially suitable for BA screening, such as the measurement of blood bile acids, first suggested by Japanese authors,[28] or the assessment of blood carnitine levels,[29] as well as blood amino acid profiles[30] by Chinese colleagues. In 2011 in Japan, researchers explored urinary sulfated bile acid testing as an alternative screening method.[31] While this approach demonstrated high sensitivity and specificity, its complexity and logistical challenges likely hindered widespread adoption.

The global review of BA screening reflects the medical community's shared commitment to improving early BA detection. From This pioneering SCC program in Taiwan province of China to Europe's standardized national SCC campaigns, and North America and the UK's awareness efforts in bilirubin measurement, it has become clear that BA screening has been acknowledged as being important, potentially life-saving and seemingly cost-saving. In the following sections, we delve deeper into the European efforts in BA screening.

OVERVIEW OF BILIARY ATRESIA SCREENING IN EUROPE

In Europe, the most extensively studied and used BA screening methods are the SCC and serum bilirubin measurements, while bile acid measurements and amino acid profiling have received limited attention.

Stool color assessment

Several studies across Europe have quantitatively evaluated stool color recognition and its effectiveness in early BA detection (table 1). However, the implementation of the SCC in Europe has been a slow process: the first European feasibility study using an SCC was published by a Swiss group only in 2011,[11] two decades after its initial introduction. Indeed, Switzerland, inspired by the success in Taiwan province of China, had initiated a nationwide campaign in 2005 to observe stool colors in newborns, using a custom-made Swiss form of the SCC. The program's success proved to be evident in the clinical setting: during the period 1994–2004, age at the Kasai procedure was a median of 68 days (30–126 days), whereas from 2005 to 2021 it decreased to 57 days (range 18–107 days) (p=0.020, unpublished data). In 2019, the Swiss SCC achieved a new level of integration when it was incorporated into the Swiss national child health booklet, making it a standard part of neonatal care. By 2022, an updated version of the paper-based SCC was reintroduced in parallel, available in multiple languages (English version, Supplement Figure 1). It is provided by the Swiss Pediatric Liver Center, free of charge, and continued to be ordered by many European countries due to the absence of alternative SCC options.

Table 1 BA screening using stool color assessment

Article	Participants	Age	Design	Method	Aims	Key findings
Wildhaber, 2011, Switzerland[11]	–	–	Pilot study	Abnormal stool color triggers immediate further evaluation.	To evaluate the feasibility and acceptance of the screening program.	Open study.
Witt, 2016, Netherlands[36]	183	–	Survey	Classification of stool photographs into normal and abnormal, without and with an SCC, 2014.	Analyze if parents or physicians recognize discolored stools; whether they seek medical help or refer the patient for further investigations and if using the SCC could improve discolored stool recognition.	None reliably recognized discolored stool. The SCC is effective but should be accompanied by unequivocal advice regarding referral on recognition.
Santos Silva, 2017, Portugal[38]	266	–	Survey	Cross-sectional study conducted with physicians and nurses evaluating clinical practices concerning jaundiced newborns and a panel of stool photographs, 2014.	Evaluate clinical practices concerning jaundiced newborns and their ability to recognize pale stools.	A significant number of healthcare professionals follow clinical practices that hinder the timely recognition of cholestasis and pale stools, highlighting the need for further education.
Borgeat, 2018, Switzerland[39]	107	–	Survey	Semistructured questionnaire to assess the SCC's handiness of use and its psychological impact, 2013–2016.	Analyze and clarify parental reaction to the card in Switzerland.	The vast majority of parents appreciate the SCC. The card creates uneasiness in a minority of patients.
Gaio, 2017, Italy[37]	165	–	Survey	Iconographic stool test.	To investigate the ability of parents in identifying acholic stools and the degree of awareness within a population of general pediatricians.	Parents are not able to correctly identify pathological stools, and general pediatricians rarely evaluate stool color at scheduled visits within the first months of life.

Continued

Table 1 Continued

Article	Participants	Age	Design	Method	Aims	Key findings
Madadi-Sanjani, 2021, Germany[40]	57	–	Survey	Questionnaire on usefulness and referral after the SCC use.	Evaluation by pediatricians and parents of the SCC 3 years after implementation.	The SCC has low acceptability among attending pediatricians who feel more the burden and less the benefits of such a policy.
Angelico, 2021, Italy[22]	160	2.7 months (15 days–6 months)	Diagnostic study	Classification of stool photographs by PopòApp and four independent doctors.	Develop and validate a mobile phone application to identify acholic stools.	PopòApp is an accurate and easy tool for acholic stool recognition.
Lacaille, 2024, Europe/ France[60]	785	53 days (48–60 days)	Survey	Europe: age at referral and age at Kasai. France: awareness and compliance with the SCC.	Awareness, referral and age at Kasai for BA.	Referral of infants for Kasai remains late, indicating low adherence to cholestasis in icteric infants by ages 2–3 weeks. SCC has high visibility, routine use and adequate resulting management, but there is a low level of knowledge about cholestatic diseases in infancy.
Griessmair, 2023, Germany[41]	1201	–	Cohort study	Photos selected from multicenter stool image collection were classified by a neural network, and the results were compared to expert assessments using an analog stool color chart.	To test the accuracy of a deep learning-based algorithm to classify pictures of BA and healthy stools.	Detection of acholic stools by neural networks shows a high level of sensitivity and specificity. Performances were comparable to or better than assessment by trained pediatric gastroenterologists. Technical requirements for smartphone implementation are met, thus integration of a deep learning-based stool color analysis into a user-friendly smartphone application within federal newborn screening programs might support timely BA diagnosis.

Overview of quantitative/analytic studies performed in Europe.
BA, biliary atresia; SCC, stool color card.

Following Switzerland's pioneering efforts in Europe, Germany also launched, in 2017, a regional screening program in Lower Saxony, emphasizing home-based screening, empowering parents to monitor their infants' stool color and seek timely medical attention if abnormalities were detected.[13 32] After prolonged debates, Germany ultimately followed Switzerland's example, making the SCC mandatory in 2023. It was thus integrated into the national 'Gelben Heft', the baby's health booklet, alongside awareness-raising publications aimed at educating healthcare professionals and parents.[33]

Of note, in France, the implementation of a nationwide BA screening program was not driven by clinicians but by a parent-led initiative. In 2009, a group of parents founded the Association Maladies du Foie depuis l'Enfance (AMFE), advocating for better early detection of BA. After nearly a decade of persistent efforts and appeals to French health authorities, their advocacy succeeded, and in 2017, the SCC was officially integrated into the French individual health booklet provided to every family at birth.

Several other European countries are working on implementing the SCC: in 2016, the Netherlands initiated a pilot study in the Amstelland region, incorporating an SCC also into the child health booklet, with positive reception and the goal of expanding to nationwide screening.[34] Also, Italy has made efforts to implement neonatal stool color assessment. The development of Bambino Gesù's PopòApp has enabled digital screening in the Italian language.[22] Also, Portugal aims to include the SCC into the Portuguese 'child and youth health booklet'. Further, in a recent publication from 2021, Portuguese authors advocate for a digital version of the SCC to be accessible to both parents and caregivers, such as via a web link or a mobile app.[35] However, to our knowledge, neither the paper nor the electronic version has been implemented to date.

Challenges with the SCC

Challenges with stool color assessment should not be underestimated. Research has emphasized difficulties in recognizing pale stools: Dutch and Italian studies showed that both parents and physicians could not reliably identify discolored stools, although SCCs improved recognition when paired with clear referral guidelines.[36 37] Further, Santos Silva *et al.* from Portugal highlighted that a significant proportion of healthcare professionals followed clinical practices, including stool color assessment, that delayed the recognition of cholestasis, underscoring the need for further education.[38] For example, the decision to refer patients for medical evaluation was largely influenced by the severity of jaundice among nurses; regarding jaundiced, breastfed, and otherwise healthy newborns, only 43% of physicians would request a conjugated bilirubin assay after 14 days of age; and in cases where newborns presented with additional signs or symptoms of disease, again only two-thirds of physicians indicated they would request a conjugated bilirubin assay immediately.[38]

Further, the implementation of a screening initiative can encounter substantial challenges. Designing an effective SCC is more complex than it may initially seem. In Switzerland, the design process in 2005 first focused on collecting and selecting accurate stool color samples to be photographed, and special attention was given to paper quality for the SCC print. Indeed, the choice of paper material can affect the printed stool samples, causing them to appear in shades that differ from what is perceived by observing the same natural stools. By 2009, a feasibility study had refined the card after having it used in the local cultural setting, finally featuring seven stool images that depicted both normal (four) and abnormal (three) colors. As the country is multilingual, the card was made available in German, French, Italian, and English, ensuring accessibility across Switzerland's linguistic regions. Midwives and pediatricians distributed the SCC free of charge, and it was discussed with parents during their child's first pediatric appointment, typically around 1 month of age. Consequently, in 2011, Swiss health authorities expressed concerns about the SCC, fearing it might provoke parental anxiety, require too much time for healthcare providers, and thus incur additional costs. To address these objections, a national study was conducted to evaluate parental reactions to the SCC. This study demonstrated that the vast majority of parents valued the SCC, with only a small minority expressing unease, highlighting the SCC's benefits.[39] This lastly contributed to reducing resistance to its use and allowed for intensified advocacy.

Indeed, pediatrician skepticism can hinder the adoption of the SCC and its effectiveness as a screening tool. This was particularly evident in Germany, where, in 2020, the SCC had low acceptance among physicians, who viewed it as more of a burden than a benefit.[40]

Technological advancements in stool color assessment have emerged as potential solutions. Angelico *et al.* from Italy developed and validated in the early 2020s the PopòApp, a mobile phone application that accurately recognized acholic stools, demonstrating its potential for clinical use.[22] In 2023, a further preliminary innovation in automated stool assessment came from Germany, which developed a deep learning-based neural network to classify stool images from a multicenter collection.[41] The findings showed that using neural network detection of acholic stools had high sensitivity and specificity, performing comparably or better than trained pediatric gastroenterologists using an analog SCC. The study concluded that integrating artificial intelligence-based stool color analysis into smartphone applications within newborn screening programs may enhance the timely diagnosis of BA.

Bilirubin measurement

UK is one of the earliest European countries that recognized the importance of BA screening in the 1990s. The

campaign known as 'Yellow Alert' was launched with the goal of promoting direct or conjugated bilirubin testing in infants with persistent jaundice beyond 2 weeks of age.[42] Again in 2021, the Lancet Commission's review on liver disease in the UK emphasized the critical importance of early detection, particularly for BA, to improve survival rates.

Indeed, studies on bilirubin measurement confirm its significant value and recognition in the landscape of European BA screening (table 2). Already in 2003, Powell *et al.* from Birmingham, UK, showed that measuring conjugated bilirubin in neonatal screening specimens between 6 and 10 days of age is a reliable marker for cholestatic liver disease.[3] Already before this publication, from December 2000, a community-based midwife-led selective screening program for identifying cases of pathological prolonged jaundice had been implemented in Leeds, UK: all infants with conjugated hyperbilirubinemia (conjugated >20% of total bilirubin and >18 µmol/L) were supposed to be referred for investigation of liver disease. An intervention-related audit, published in 2012, 8 years after implementation of this screening program, revealed that indeed, no neonate with conjugated bilirubin below the threshold developed liver disease.[43] However, some infants diagnosed with liver disease were not identified through this protocol. Furthermore, and given the authors' conclusion emphasizing the need for better education among healthcare professionals, it can be inferred that only a subset of infants underwent testing.

The UK approaches were based on a 2-week age limit for testing, which seemingly resulted in a significant number of unnecessary blood tests. Thus, the discussion arose when these babies were meant to receive their blood tests: between 2005 and 2007, two studies in England evaluated prolonged jaundice screening protocols, concluding that delaying assessment from the age of 2 weeks to 3 weeks reduced unnecessary investigations without overlooking significant pathologies.[44 45] This rationalized approach would also enhance cost-effectiveness by reducing workload and minimizing unnecessary laboratory tests.

As for the high number of laboratory tests to evaluate prolonged jaundice in neonates, another alarm of public health specialists, a group from Glasgow explored in 2012, in a non-randomized controlled trial, a more rationalized approach for assessment of referred babies and concluded that the number of laboratory investigations could be safely reduced to a small number, after thorough clinical evaluation, again improving both safety and cost-effectiveness.[46]

The UK studies always used split bilirubin measurements. This was challenged in 2015 by a Danish group, when Madsen *et al.* examined the necessity of both absolute and relative conjugated bilirubin values in BA screening.[47] Their findings suggested that an absolute conjugated bilirubin threshold alone was sufficient for further evaluation. Indeed, as a follow-up in 2018, a London group retrospectively analyzed split bilirubin levels, concluding that absolute direct bilirubin was more informative than the direct/total bilirubin ratio.[48] This led to the proposition of a threshold of 25 µmol/L for direct bilirubin to incentivize further investigation. Indeed, recently, Danish investigators evaluated the efficacy of their national screening recommendations, which had changed in 2017: based on recommendations from North American and European societies, the Danish Pediatric Society had abandoned the conjugated fraction of total bilirubin of ≥20% and had introduced a lower conjugated bilirubin threshold of 17 µmol/L. They found that this threshold detected all BA cases but resulted in overdiagnosis and unnecessary investigations.[49]

Unfortunately, the UK has so far failed to implement a screening program beyond localized initiatives using bilirubin measurements or to establish a nationwide approach, despite extensive national research supporting this method. The same holds true for all other European countries. The 2003 recommendation by Powell *et al.*, advocating for the adaptation of bilirubin measurement to the dried Guthrie blood spots for practical implementation, could serve as a potential path forward for future advancements in BA screening.

Bile acid measurements and amino acid profiles

Elevated bile acid levels in the blood of neonates with cholestatic hepatobiliary disorders seemed to present a potential avenue for conditions like BA.[50] Already in 1998, Mills *et al.* from the UK described the potential of chromatography-mass spectrometry for detecting bile acids isolated from dried blood samples.[51] In addition, in 2006, Gustafsson *et al.* from Sweden quantified lithocholic acid or chenodeoxycholic acid and suggested that they play a role in BA pathogenesis and could potentially be used as a screening method.[50] And already in 1999, a study group from London evidenced that indeed, the majority of neonates who later were diagnosed with BA, but also other cholestatic hepatobiliary diseases, exhibit markedly elevated conjugated bile acid levels when measured by tandem mass spectrometry at the time of Guthrie test sampling.[52] This remains the only quantitative study conducted in Europe using this screening method (table 3), and none of these bench results have seen a translation into clinical practice.

Since the early 1990s, it has been known that there are significant differences in amino acid profiles between patients with BA and healthy controls.[53] Yet, the possibility of its use as a screening method was equally scarcely explored. In Europe, only one study reports quantitative results for amino acid profiles from Guthrie dried blood spots and suggests that this method might be used as a BA screening approach.[54] Once again, these research efforts have not been translated into clinical use.

DISCUSSION

Already in 2020, Chung *et al.* emphasized that many Eastern countries have successfully established national

Table 2 BA screening using bilirubin measurement

Article	Participants	Age	Design	Method	Aims	Key findings
Powell, 2003, UK[3]	23 214	8 days (7–9 days)	Cohort study	Concentration of conjugated bilirubin in spare plasma from routinely collected liquid neonatal screening specimens, 1995–1997.	To evaluate a community-based screening program for detecting neonatal liver disease.	Conjugated bilirubin in plasma measured at 6–10 days is a reliable marker for neonatal liver disease, also BA.
Banakar, 2008, UK[44]	58	–	Cohort study	Investigation of prolonged jaundice (>2 weeks) in babies as per unit protocol (including serum bilirubin) between 2005 and 2006.	Evaluate clinical practice and usefulness of unit protocol for prolonged jaundice screening.	Negative prolonged jaundice screening is reassuring, and further investigations are unwarranted.
Tyrell, 2009, UK[45]	183	–	Cohort study	Investigation of prolonged jaundice in babies as per unit protocol (including serum bilirubin) between 2006 and 2007.	Evaluate practice to delay screening tests for 1 week after referral.	Delayed assessment of babies with prolonged (>3 weeks) jaundice significantly reduced the number of babies who required screening investigations without missing important pathologies.
Cartledge, 2012, UK[43]	882	21 days (0–51 days)	Cohort study	Infants with jaundice >2 weeks who had a split bilirubin test by their midwife and who showed conjugated hyperbilirubinemia were referred for investigation for liver disease, 2000–2008.	Protocol assessment.	None of the infants with conjugated bilirubin <18 µmol/L or <20% of conjugated fraction of total bilirubin developed liver disease.
Rodie, 2012, UK[46]	92	18 days (13–49 days)	Non-randomized controlled trial	Prospective evaluation of the assessment of prolonged jaundice, 2006–2008.	Identify the safety and cost-effectiveness of a rationalized approach.	While neonates with prolonged jaundice may have detectable problems, the number of investigations could be safely reduced after a thorough examination.
Madsen, 2015, Denmark[47]	73	–	Cohort study	Retrospective evaluation of patients with BA (1993–2012) to assess if both criteria for conjugated bilirubin are necessary (>20% and/or 20 µmol/L).	Evaluate if relative percentage with total bilirubin should be further used versus only absolute value.	The absolute conjugated bilirubin value is sufficient to require further evaluation for BA.
Hodgson, 2018, UK[48]	420	10–70 days	Cohort study	Retrospective analysis of split bilirubin levels and subsequent follow-up for neonates with prolonged neonatal jaundice, 2012–2014.	Establish the spread of direct bilirubin levels and inform national guidance for the investigation of prolonged neonatal jaundice.	In disease-free neonates with prolonged jaundice, both total and direct bilirubin decreased with age. The absolute direct bilirubin is more useful than the direct/total bilirubin ratio. Conjugated bilirubin >25 µmol/L constitutes an appropriate threshold for further investigation.
Pedersen, 2022, Denmark[49]	693	14–35 days	Cohort study	Conjugated bilirubin measurements in infants developing prolonged (>2 weeks) jaundice and final outcome between 2016 and 2021.	Assess the efficacy of the national recommendations in identifying infants with BA.	The 17 µmol/L threshold limit detected all patients with BA, but its use leads to overinvestigation and overdiagnosing.

Overview of quantitative/analytic studies performed in Europe.
BA, biliary atresia.

Table 3 BA screening using bile acid measurement or amino acid profile

Article	Participants	Age	Design	Method	Aims	Key findings
Screening type: bile acid measurement						
Mushtaq, 1999, UK[52]	177	47 days (14–248 days)	Cohort study	Concentration of conjugated bile acids on Guthrie test (dried blood spot) for cholestatic versus non-cholestatic children.	Feasibility to detect cholestatic disease, particularly BA, by measuring conjugated bile acids in the dried blood spots.	Most children with BA and other cholestatic hepatobiliary diseases have significant raised concentrations of conjugated bile acids on the Guthrie test. There was too much overlap with control, normal infants.
Screening type: amino acid profile						
Uecker, 2024, Germany[54]	81	–	Non-randomized controlled trial	Retrospective targeted metabolomic measurements of amino acid profile of dried blood from the Guthrie test of patients with BA and a non-diseased control cohort.	To analyze amino acid profiles in dried blood spots of infants with BA.	Patients with BA exhibited an altered amino acid profile within 72 hours after birth.

Overview of quantitative/analytic studies performed in Europe.
BA, biliary atresia.

BA screening programs, whereas Western countries, including Europe and North America, have lagged behind.[55] The disparity is likely driven by debates over cost-effectiveness, especially in regions with lower BA incidence, such as European countries. Indeed, our review confirms that access to BA screening in Europe is limited (figure 2). Moreover, Europe appears to play a minimal role in the global landscape of BA screening. In our scoping review, 996 publications on BA screening were retrieved, but 949 were excluded as they did not originate from Europe, highlighting the limited involvement of European research in this area.

Despite various screening methods demonstrating their impact on the early diagnosis of BA, as highlighted in 2021 by Schreiber *et al.* in their review on BA epidemiology, screening, and public policy, the SCC remains a cornerstone of BA screening worldwide.[56] Indeed, and of now common knowledge, over 95% of infants with BA exhibit pale stools in early infancy, making stool color monitoring an accessible and reliable tool for early detection. Countries or areas that have adopted SCC screening have seen significant improvements, including lower age at referral with earlier surgical intervention, such as Taiwan procinve of China, and in Europe.[8]

While SCCs have improved BA recognition in some settings, low adherence, physician skepticism, and a

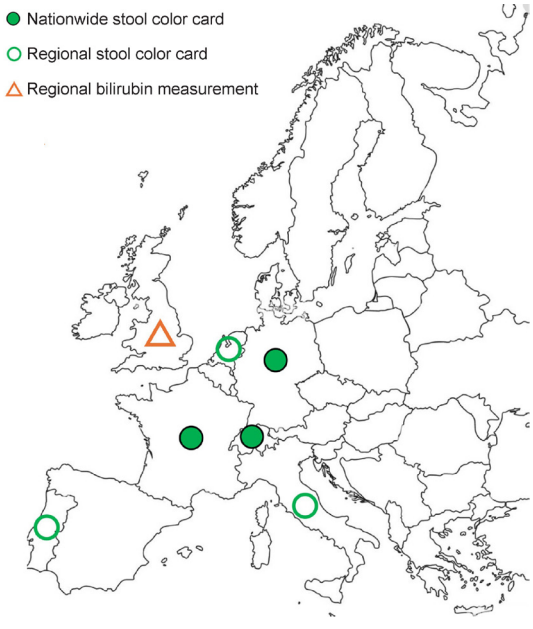

Figure 2 European map illustrating the different types of biliary atresia (BA) screening programs, distinguishing between regional and nationwide implementations. Of note, although 'regional bilirubin measurement' has been widely studied in the UK, there is no current *established* screening program based on this method.

lack of awareness about cholestatic diseases continue to hinder early detection. Emerging technologies, particularly artificial intelligence-driven tools, may offer a promising path forward for more effective and widespread screening strategies. But despite being paper based, Switzerland has shown the potential of SCC as an essential screening tool, even within the cultural context of Europe, significantly improving age at referral—but also showcasing the importance of collaboration between researchers, healthcare providers and policymakers, as explored in the section below.

Alongside SCC, bilirubin measurement remains one of the most studied screening methods, as confirmed by Arshad *et al*. in their 2020 meta-analysis on BA screening, demonstrating its enhanced sensitivity and specificity in BA detection, and thus also widely studied in Europe, mostly the UK.[57] In contrast, challenges appear too significant with alternative biochemical screening approaches, such as bile acid measurements or amino acid profiling in dried blood spots, collected during Guthrie tests. Those approaches face significant limitations that hinder their feasibility for mass screening. Further, the overlap between elevated bile acid levels in affected infants and those in the general population, as well as the similarity in biochemical profiles among neonates with other cholestatic liver diseases that do not require early surgery, limits the practicality of this method for widespread BA screening.[52] As a result, these approaches have not been further pursued in Europe or globally.

It seems that the SCC and bilirubin measurements compete on the European ranking list for BA screening. Indeed, Gopal *et al*. concluded in their 2024 global review on BA screening that bilirubin measurement—and still specifically the ratio of direct over conjugated bilirubin—within the first few days of life offers the highest diagnostic accuracy for BA newborn screening when compared with SCC.[58] However, financial and logistical considerations must not be overlooked and are likely the greatest obstacle in the implementation of bilirubin screening. Indeed, in comparison, the SCC remains a simple, non-invasive, and cost-effective tool and makes a more accessible alternative to blood tests. But, as emphasized by McKiernan and in the text above, in countries where the first physician examination occurs after the first month of life—the targeted age for BA diagnosis—SCC screening may be less attractive, making recent advancements in direct bilirubin measurement in dried blood spots a promising alternative.[59] Given this, the future of BA screening may lie in a combination of strategies. But last but not least, when conducting a cost-effectiveness analysis of BA screening for the healthcare system as a whole, it is important to consider the screening targets. These could focus solely on BA, could be extended to congenital cholestasis, or even include all cases of pathological neonatal jaundice. Indeed, serum bilirubin screening can detect a broader range of conditions, including pathological jaundice, such as jaundice with elevated indirect bilirubin, and cholestasis. Therefore, the value of bilirubin screening cannot be judged solely by the early detection rate of BA, since in contrast, the SCC mainly detects BA and severe cholestasis.

Future research should focus on developing integrated screening algorithms that combine stool color assessment with bilirubin measurements, optimizing cost-effectiveness and efficiency for any jaundiced neonate.

Advocacy efforts

Even when a country is logistically prepared, as is the case for many, if not most European nations, significant hurdles persist, preventing the successful implementation of BA screening, both in Europe and worldwide. As, for example, for the UK, McKiernan insists in a compelling 2022 editorial that, given the UK's structured healthcare system and expertise in BA management, the country appears well positioned to develop a national screening strategy to improve BA outcomes—yet it is disappointing to observe that no nationwide screening has been implemented so far.

Indeed, as mentioned earlier, research and evidence-based findings alone are not enough to drive change, and the value of screening can vary between healthcare systems. Screening is only one part of early diagnosis and treatment of BA. Its necessity and effectiveness largely depend on how well the healthcare system is developed. The surgical age for BA is usually around 45–60 days: most newborns have their first routine follow-up within 1 month after birth, and in some countries, raising awareness among parents and primary care doctors may be enough for early diagnosis. In fact, this could even avoid the need for strict SCC or serum bilirubin screening. Yet, in other countries, strict screening programs are necessary, and these countries also need clear referral and treatment pathways to ensure early diagnosis. Clinicians and researchers must actively engage and collaborate with parents, communities, politicians, and policymakers to ensure meaningful progress and lasting impact.

A powerful example of meaningful clinician–parent collaboration in advocacy is France. As mentioned earlier, in 2009, the 'Alerte Jaune' campaign was launched as a national initiative to raise awareness among parents and healthcare professionals about neonatal cholestasis, with a particular focus on BA. Initiated by the AMFE, in collaboration with the National Reference Center for Rare Diseases of Biliary Atresia and Genetic Cholestasis at Kremlin-Bicêtre University Hospital of Paris, the campaign operates under the auspices of the French Society of Pediatrics and receives support from the Ministry of Health and the Alliance Maladies Rares. The initiative includes informational leaflets, a downloadable SCC, and educational, sometimes comical, videos to help parents recognize pale stools in newborns (https://alertejaune.com/la-minute-blonde/). This campaign underlines the importance of collaborative efforts among medical institutions, professional organizations, and advocacy groups to improve BA awareness and outcomes. And indeed, in France, it culminated in the nationwide

integration of the SCC into the child's health booklet 8 years after its launch.

CONCLUSION

Despite all our efforts, significant challenges remain. A 2022 European survey by the ESPGHAN Quality of Care Task Force revealed that while SCC screening in France is widely recognized and routinely used, delays in referrals for the Kasai procedure persist, stressing continued gaps in European's healthcare professionals' awareness of cholestatic diseases.[60] The implementation of BA screening in Europe remains limited, faces significant challenges, and has shown little progress toward seamless advancement. Tailoring screening strategies to regional healthcare systems, integrating global best practices, and, probably of greatest importance, strengthening local and national advocacy efforts appear crucial to expanding BA screening programs and thus improving outcomes for affected infants and their families.

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REFERENCES

1 Serinet MO, Wildhaber BE, Broué P, *et al*. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. *Pediatrics* 2009;123:1280–6.
2 Therrell BL Jr. U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab* 2001;74:64–74.
3 Powell JE, Keffler S, Kelly DA, *et al*. Population screening for neonatal liver disease: potential for a community-based programme. *J Med Screen* 2003;10:112–6.
4 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467–73.
5 McGowan J, Sampson M, Salzwedel DM, *et al*. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40–6.
6 Jackson JL, Kuriyama A, Anton A, *et al*. The Accuracy of Google Translate for Abstracting Data From Non-English-Language Trials for Systematic Reviews. *Ann Intern Med* 2019;171:677–9.
7 Hsiao CH, Chang MH, Chen HL, *et al*. Universal screening for biliary atresia using an infant stool color card in Taiwan. *Hepatology* 2008;47:1233–40.
8 Lien TH, Chang MH, Wu JF, *et al*. Effects of the infant stool color card screening program on 5-year outcome of biliary atresia in Taiwan. *Hepatology* 2011;53:202–8.
9 Gu YH, Yokoyama K, Mizuta K, *et al*. Stool color card screening for early detection of biliary atresia and long-term native liver survival: a 19-year cohort study in Japan. *J Pediatr* 2015;166:897–902.
10 Lee M, Chen SCC, Yang HY, *et al*. Infant Stool Color Card Screening Helps Reduce the Hospitalization Rate and Mortality of Biliary Atresia. *Medicine (Baltimore)* 2016;95:e3166.
11 Wildhaber BE. Screening for biliary atresia: Swiss stool color card. *Hepatology* 2011;54:367–8.
12 Fanna M, Masson G, Capito C, *et al*. Management of Biliary Atresia in France 1986 to 2015: Long-term Results. *J Pediatr Gastroenterol Nutr* 2019;69:416–24.
13 Madadi-Sanjani O, Blaser J, Voigt G, *et al*. Home-based color card screening for biliary atresia: the first steps for implementation of a nationwide newborn screening in Germany. *Pediatr Surg Int* 2019;35:1217–22.
14 Santos JL, Carvalho E, Bezerra JA. Advances in biliary atresia: from patient care to research. *Braz J Med Biol Res* 2010;43:522–7.
15 Zheng J, Ye Y, Wang B, *et al*. Biliary atresia screening in Shenzhen: implementation and achievements. *Arch Dis Child* 2020;105:720–3.
16 Kong YY, Zhao JQ, Wang J, *et al*. Modified stool color card with digital images was efficient and feasible for early detection of biliary atresia-a pilot study in Beijing, China. *World J Pediatr* 2016;12:415–20.
17 Morinville V, Ahmed N, Ibberson C, *et al*. Home-Based Screening for Biliary Atresia Using Infant Stool Color Cards in Canada: Quebec Feasibility Study. *J Pediatr Gastroenterol Nutr* 2016;62:536–41.
18 Woolfson JP, Schreiber RA, Butler AE, *et al*. Province-wide Biliary Atresia Home Screening Program in British Columbia: Evaluation of First 2 Years. *J Pediatr Gastroenterol Nutr* 2018;66:845–9.
19 El-Shabrawi MH, Baroudy SR, Hassanin FS, *et al*. A pilot study of the value of a stool color card as a diagnostic tool for extrahepatic biliary atresia at a single tertiary referral center in a low/middle income country. *Arab J Gastroenterol* 2021;22:61–5.
20 Franciscovich A, Vaidya D, Doyle J, *et al*. PoopMD, a Mobile Health Application, Accurately Identifies Infant Acholic Stools. *PLoS One* 2015;10:e0132270.
21 Hoshino E, Hayashi K, Suzuki M, *et al*. An iPhone application using a novel stool color detection algorithm for biliary atresia screening. *Pediatr Surg Int* 2017;33:1115–21.
22 Angelico R, Liccardo D, Paoletti M, *et al*. A novel mobile phone application for infant stool color recognition: An easy and effective tool to identify acholic stools in newborns. *J Med Screen* 2021;28:230–7.
23 Akiyama T, Yamauchi Y. Use of near infrared reflectance spectroscopy in the screening for biliary atresia. *J Pediatr Surg* 1994;29:645–7.
24 Shen Z, Zheng S, Dong R, *et al*. Saturation of stool color in HSV color model is a promising objective parameter for screening biliary atresia. *J Pediatr Surg* 2016;51:2091–4.
25 Liao FM, Chang KC, Wu JF, *et al*. Direct Bilirubin and Risk of Biliary Atresia. *Pediatrics* 2022;149:e2021053073.
26 Harpavat S, Garcia-Prats JA, Anaya C, *et al*. Diagnostic Yield of Newborn Screening for Biliary Atresia Using Direct or Conjugated Bilirubin Measurements. *JAMA* 2020;323:1141–50.
27 Harpavat S, Ramraj R, Finegold MJ, *et al*. Newborn Direct or Conjugated Bilirubin Measurements As a Potential Screen for Biliary Atresia. *J Pediatr Gastroenterol Nutr* 2016;62:799–803.
28 Matsui A, Sasakia N, Arakawa Y, *et al*. Neonatal mass screening for biliary atresia: A pilot study in Tochigi Prefecture, Japan. *Screening* 1993;2:201–9.
29 Gong Z, Wu Y, Zheng L, *et al*. Can Free Carnitine or Bilirubin in Blood Be Used in Neonatal Screening for Biliary Atresia? *Eur J Pediatr Surg* 2020;30:459–64.
30 Zhao D, Han L, He Z, *et al*. Identification of the plasma metabolomics as early diagnostic markers between biliary atresia and neonatal hepatitis syndrome. *PLoS One* 2014;9:e85694.
31 Suzuki M, Muraji T, Obatake M, *et al*. Urinary sulfated bile acid analysis for the early detection of biliary atresia in infants. *Pediatr Int* 2011;53:497–500.

32 Madadi-Sanjani O, Petersen C. Aufruf zur Teilnahme an der Evaluation des Stuhlkartenscreenings. *Monatsschr Kinderheilkd* 2018;166:341–2.
33 Melter M, Felderhoff-Müser U. Das gelbe Baby. *Monatsschr Kinderheilkd* 2024;172:668–77.
34 Labberton M. *The infant stool color card as a screening tool for early detection of biliary atresia:a pilot study to determine the feasibility of the iscc in the dutch health-care system* [Thesis]. 2016
35 Ashworth J, Tavares M, Santos Silva E, *et al*. The Stool Color Card as a Screening Tool for Biliary Atresia in the Digital Version of the Portuguese Child and Youth Health Booklet. *Acta Med Port* 2021;34:632–3.
36 Witt M, Lindeboom J, Wijnja C, *et al*. Early Detection of Neonatal Cholestasis: Inadequate Assessment of Stool Color by Parents and Primary Healthcare Doctors. *Eur J Pediatr Surg* 2016;26:67–73.
37 Gaio P, Dalla Valeria F, Laverda R, *et al*. Acholic stools: are parents and general pediatricians aware of the importance of this clinical marker of cholestasis?. *ESPGHAN 50th Annual Meeting* 2017.
38 Santos Silva E, Moreira Silva H, Azevedo Lijnzaat L, *et al*. Clinical practices among healthcare professionals concerning neonatal jaundice and pale stools. *Eur J Pediatr* 2017;176:361–9.
39 Borgeat M, Korff S, Wildhaber BE. Newborn biliary atresia screening with the stool colour card: a questionnaire survey of parents. *BMJ Paediatr Open* 2018;2:e000269.
40 Madadi-Sanjani O, Kuebler JF, Uecker M, *et al*. Province-Wide Stool Color Card Screening for Biliary Atresia in Lower-Saxony: Experiences with Passive Distribution Strategies and Results. *Int J Neonatal Screen* 2021;7:75.
41 Griessmair L, Krumnow C, Slavetinsky C, *et al*. Recognition of acholic stools in biliary atresia – a deep learning approach. *ESPGHAN 55th Annual Meeting* 2023.
42 Mowat AP, Davidson LL, Dick MC. Earlier identification of biliary atresia and hepatobiliary disease: selective screening in the third week of life. *Arch Dis Child* 1995;72:90–2.
43 Cartledge P, Kevlani N, Shapiro L, *et al*. An audit of a community protocol for identifying neonatal liver disease. *Arch Dis Child* 2012;97:166–8.
44 Banakar MK, Subbarayan A. A study of prolonged jaundice screen in healthy term babies. *Indian J Clin Biochem* 2008;23:286–9.
45 Tyrell M, Hingley S, Giles C, *et al*. Impact of delayed screening for prolonged jaundice in the newborn. *Arch Dis Child Fetal Neonatal Ed* 2009;94:F154.
46 Rodie ME, Harry C, Taylor R, *et al*. Rationalized assessment of prolonged jaundice is safe and cost-effective. *Scott Med J* 2012;57:144–7.
47 Madsen SS, Kvist N, Thorup J. Increased conjugated bilirubin is sufficient to initiate screening for biliary atresia. *Dan Med J* 2015;62:A5114.
48 Hodgson JM, van Someren VH, Smith C, *et al*. Direct bilirubin levels observed in prolonged neonatal jaundice: a retrospective cohort study. *BMJ Paediatr Open* 2018;2:e000202.
49 Pedersen IB, Vestergaard ET, Petersen JP, *et al*. Evaluation of the diagnostic process in neonates with conjugated hyperbilirubinaemia. *Dan Med J* 2022;69:A08210650.
50 Gustafsson J, Alvelius G, Björkhem I, *et al*. Bile acid metabolism in extrahepatic biliary atresia: lithocholic acid in stored dried blood collected at neonatal screening. *Ups J Med Sci* 2006;111:131–6.
51 Mills KA, Mushtaq I, Johnson AW, *et al*. A method for the quantitation of conjugated bile acids in dried blood spots using electrospray ionization-mass spectrometry. *Pediatr Res* 1998;43:361–8.
52 Mushtaq I, Logan S, Morris M, *et al*. Screening of newborn infants for cholestatic hepatobiliary disease with tandem mass spectrometry. *BMJ* 1999;319:471–7.
53 Byrd DJ, Wiltfang A, Rodeck B, *et al*. The plasma amino acid profile and its relationships to standard quantities of liver function in infants and children with extrahepatic biliary atresia and preterminal liver cirrhosis. *Eur J Clin Chem Clin Biochem* 1993;31:197–204.
54 Uecker M, Prehn C, Janzen N, *et al*. Infants with biliary atresia exhibit an altered amino acid profile in their newborn screening. *Metabolomics (Los Angel)* 2024;20:109.
55 Chung PHY, Zheng S, Tam PKH. Biliary atresia: East versus west. *Semin Pediatr Surg* 2020;29:150950.
56 Schreiber RA, Harpavat S, Hulscher JBF, *et al*. Biliary Atresia in 2021: Epidemiology. *Screening and Public Policy J Clin Med* 2022;11.
57 Arshad A, Gardiner J, Ho C, *et al*. Population-based screening methods in biliary atresia: a systematic review and meta-analysis. *Arch Dis Child* 2023;108:468–73.
58 Gopal SH, Zebda R, Mohan A, *et al*. Population-based screening strategies for biliary atresia in the newborn: A systematic review and meta-analysis. *PLoS One* 2024;19:e0307837.
59 McKiernan PJ. Prompt diagnosis of biliary atresia: education has not succeeded, time to move to universal screening. *Arch Dis Child* 2020;105:709–10.
60 Lacaille F, Nicastro E, Czubkowski P, *et al*. Awareness, referral and age at Kasai surgery for biliary atresia in Europe: A survey of the Quality-of-Care Task Force of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2024;78:1374–82.