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Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: www.tandfonline.com/journals/ierh20

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To cite this article: Pietro Invernizzi, Alessio Aghemo, Vincenza Calvaruso, Ana Lleo, Marco Marzioni, Fabio Piscaglia, Cristina Rigamonti, Umberto Vespasiani Gentilucci, Stefano Brillanti, Marco Carbone, Nora Cazzagon & Pietro Lampertico (2026) Primary biliary cholangitis (PBC): evolving approaches and expert perspectives, Expert Review of Gastroenterology & Hepatology, 20:1, 17-28, DOI: 10.1080/17474124.2025.2601220

To link to this article: https://doi.org/10.1080/17474124.2025.2601220

EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
2026, VOL. 20, NO. 1, 17–28
https://doi.org/10.1080/17474124.2025.2601220

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CRITICAL PERSPECTIVES

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Primary biliary cholangitis (PBC): evolving approaches and expert perspectives

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ABSTRACT

Introduction: Primary biliary cholangitis (PBC) is a rare, chronic autoimmune cholestatic liver disease causing progressive destruction of intrahepatic bile ducts. Predominantly affecting women aged 35 to 70, PBC may remain asymptomatic for years before symptoms such as pruritus, fatigue, or sicca symptoms manifest. If untreated, PBC can progress to cirrhosis, liver failure and need for transplantation, significantly impacting life expectancy.

Areas covered: Ursodeoxycholic acid (UDCA) remains the only approved first-line therapy. The recent withdrawal of obeticholic acid (OCA) from the European market, the only available second-line agent since 2016, highlighting the need for alternative options. The recent European Medicine Agency (EMA) approval of new peroxisome proliferator-activated receptor (PPAR) agonists is promising for patients with suboptimal response to UDCA. A literature review was conducted to map the patient journey and examine current treatments.

Expert opinion: A panel of Italian expert hepatologists was involved to explore unmet needs along the patient journey and define clinical priorities. Focus areas included response monitoring, treatment evaluation timing, symptoms management – particularly pruritus and fatigue – and care of comorbid and high-risk patients. Many patients live with indolent disease, but some may require a more structured pathway, where emerging treatments can be an important turning point.

ARTICLE HISTORY
Received 28 July 2025
Accepted 4 December 2025

KEYWORDS
Primary biliary cholangitis; patient journey; UDCA; PPAR agonists; pruritus; fatigue

1. Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic autoimmune liver disease caused by destruction of the intrahepatic bile ducts [1,2]. The onset of the disease is usually asymptomatic but 51% of patients become symptomatic within 5 years, and 95% are symptomatic after 20 years [3], during which bile duct injury progresses silently. In the absence of therapeutic intervention, this can lead to symptomatic disease with significant impact on quality of life and may progress to cirrhosis, liver failure and death.

The global incidence of PBC is reported at 5,8 per 100.000 individuals per year [4], whereas in Italy the incidence is estimated at 5,31 per 100.000 people per year (3129 new cases in 2024) [3]. Instead, global prevalence of PBC is reported at 40,2 per 100.000 individuals, whereas in Italy it is estimated at 27,90 per 100.000 people (16.443 people in 2024) [4]. Women aged 35 to 70 are the demographic most affected by this condition.

The etiology of the disease remains unclear, although interaction between genetic susceptibility and environmental triggers has been implicated. Consistent with its autoimmune nature, approximately 95% of patients present with antimitochondrial antibodies (AMAs) targeting mitochondrial antigens and 30% of patients present Antinuclear Antibodies (ANAs), specifically antibodies (anti-gp210 and anti-Sp100) [5]. However, recent large-scale studies of blood donors and the general population have suggested that low-titer AMA positivity in the context of normal liver function tests is observed in approximately

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Article highlights

- Primary biliary cholangitis (PBC) is a rare autoimmune liver disease that primarily affects women and, if untreated, might progress to cirrhosis and liver failure.
- Ursodeoxycholic acid (UDCA) remains the only approved first-line therapy for PBC, highlighting the unmet need for second-line options following the withdrawal of obeticholic acid (OCA) from the European market.
- The European Medicines Agency (EMA) approval of peroxisome proliferator-activated receptor (PPAR) agonists offers a new targeted treatment for patients with inadequate response to UDCA.
- A continuum-based assessment of alkaline phosphatase (ALP), total bilirubin (TB) and alanine aminotransferase (ALT) over time allows for a more personalized evaluation of disease activity and treatment response, with particular attention to achieving biochemical normalization where possible.
- Fixed timelines for evaluation of UDCA response may prevent appropriate treatment changes. Earlier evaluation based on individual clinical features can provide the opportunity to intervene promptly to improve treatment.
- Pruritus and fatigue are common and debilitating symptoms in PBC that are often underestimated. A structured assessment of these symptoms can support earlier recognition and more effective management, ultimately improving patients' quality of life.

0.5% of the population. The clinical significance of this finding is currently unclear and requires further study. Previous research has shown that AMA-positive patients with normal liver tests often develop PBC during follow-up. Two studies have described features of PBC on liver biopsies of a cohort of AMA-positive patients with normal ALP; however, a subgroup of the included subjects presented with elevated GGT. Given the benign prognosis in patients with a positive AMA test and normal liver function, the guidelines do not recommend liver biopsy or ursodeoxycholic acid (UDCA) therapy. However, follow-up liver biochemistry and periodic (annual) monitoring with serum liver tests are recommended [5,6].

Bile duct injury is primarily mediated by CD4+ and CD8+ T lymphocytes, which attack biliary epithelial cells, resulting in chronic inflammation and progressive destruction of the intrahepatic bile ducts. This immune-mediated damage determines cholestasis and subsequent accumulation of toxic bile components, which contribute to hepatic injury, fibrosis and possible progression to cirrhosis and liver failure if left untreated or under-treated [1,7].

Clinically, PBC can be asymptomatic, but a broad spectrum of a spectrum of vague symptoms may occur such as: pruritus, fatigue, xerostomia and xerophthalmia, abdominal discomfort and arthralgia [8]. Regarding prognosis, it has been demonstrated that, at 10 years, transplant-free survival is 78% for patients treated with UDCA and 59% for untreated patients [9,10]. This highlights the importance of timely diagnosis and effective disease management.

Currently, there is no definitive cure for PBC, and the therapeutic approach is based on disease control with bile acid, specifically UDCA, the only approved first-line therapy, which has been shown to slow down disease progression. Due to the frequent coexistence of metabolic and/or autoimmune comorbidities, patients with PBC may present a complex clinical profile that requires a personalized approach to optimize outcomes and quality of life.

In 2024, the European Medicines Agency (EMA) revoked the marketing authorization for obeticholic acid (OCA) after study 747–302 failed to demonstrate that the benefits outweighed the risks, so there was no demonstrated proof of superior efficacy of OCA compared to placebo. Before then, OCA was the only licensed and approved second-line therapy for patients who do not benefit from UDCA monotherapy (defined as 'non-responders'). This disrupted the therapeutic landscape, leaving physicians without licensed alternatives for this subset of patients [11]. In such cases, off-label treatments, such as fenofibrates and bezafibrates, are currently used. However, the development of novel agents, such as peroxisome proliferator-activated receptor (PPAR) agonists, offers promising avenues for enhancing therapeutic efficacy and expanding treatment options [4].

This article aims to provide an expert-based overview of the PBC patient journey, highlighting unmet needs, integrating recent therapeutic developments and addressing challenges in care delivery, particularly for the selected patient category.

This Expert Opinion involved a panel of 12 Italian hepatologists and researchers with recognized expertise in PBC. The experts' perspectives were collected through a series of structured meetings, initially conducted virtually and subsequently complemented by an in-person session. Discussions were guided by the objective of identifying and commenting on the main unmet needs of patients with PBC, as emerging from a critical review of the available scientific literature. Consequently, the present paper primarily draws on international guidelines and published studies addressing the management and treatment of PBC.

2. Patient journey

The proposed algorithm (Figure 1) reflects the European patient journey with PBC; specifying geographic location is necessary as it influences the treatments approved by local healthcare organizations and the availability of resources for diagnosis and treatment.

The path of the patients affected by PBC can be summarized in three the main phases widely discussed below: suspicion and access, diagnosis and referral to the specialist, treatment and monitoring.

2.1. Suspicion and access

Clinical suspicion of PBC can arise through multiple diagnostic pathways, reflecting the heterogeneity of disease presentation and the high prevalence of asymptomatic cases at onset. The most common way of detection is through routine laboratory testing. In such cases, persistent elevations in cholestatic liver enzymes – particularly alkaline phosphatase (ALP) – are identified as a key biochemical hallmark of the disease. In the absence of other explanations for these abnormalities, further diagnostic workup with serological testing and liver imaging is typically warranted [15]. Some patients initially report vague yet characteristic symptoms such as chronic fatigue or pruritus. These

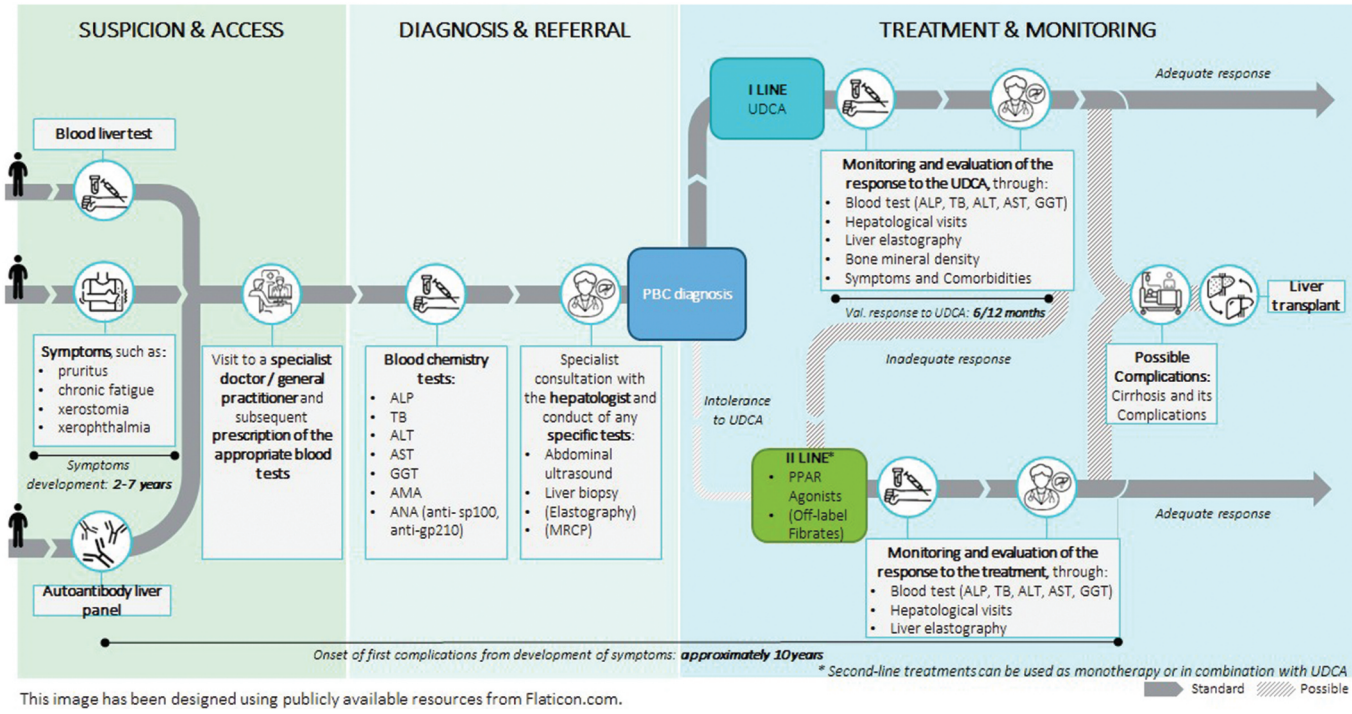

Figure 1. Summary of Patient Journey in European context, from diagnosis to therapy and follow-up, for patients affected by PBC. This is a generalized model based on the processing of various sources related to the patient care pathway [12–14]. In the picture there are some acronyms: ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: Aspartate Aminotransferase, AMA: anti-mitochondrial antibodies, ANA: antinuclear antibodies, GGT: gamma-glutamyl transferase, TB: total bilirubin, MRCP: magnetic resonance cholangiopancreatography. The box related to specific tests includes elastography and MRCP in brackets, as these are performed only in selected cases when necessary.

symptoms are often overlooked or misattributed to non-hepatic causes but make further investigation necessary, especially if accompanied by biochemical evidence of cholestasis. A third, less frequent pathway is the discovery of antimitochondrial antibodies (AMA) or other PBC-related autoantibodies during serological evaluations performed for unrelated conditions, often for pathologies with autoimmune or rheumatologic origin. In fact, the autoantibody panel allows for a diagnosis even in the absence of overt clinical symptoms, especially when coupled with biochemical evidence of chronic cholestasis. These varied diagnostic routes underscore the need for increased clinical vigilance and interdisciplinary collaboration to ensure early detection. AMA positivity can precede PBC development; however, in the absence of cholestasis, AMA reactivity alone is not sufficient to diagnose PBC. In such cases, European Association for the Study of the Liver (EASL) guidelines recommend annual follow-up of AMA positive patients with normal serum liver tests [16].

The EASL international guidelines recommend abdominal ultrasound to exclude extrahepatic cholestasis as a cause of abnormal liver tests [13]. It is important to note that this diagnostic test could also be performed to assess abnormal liver tests before consulting the hepatologist.

These varied diagnostic routes underscore the need for increased clinical vigilance and interdisciplinary collaboration to ensure early detection. Indeed, timely recognition of PBC is critical to initiate appropriate management strategies, prevent disease progression and improve long-term outcomes [5,17].

2.2. Diagnosis and referral

If the findings suggest a diagnosis of PBC, the patient is referred to an expert in hepatology or an expert in the management of liver disease for confirmation. According to international guidelines from both the EASL and the American Association for the Study of Liver Diseases (AASLD), the diagnostic criteria for PBC include the following [17]:

- persistent (>6 months) elevation in serum ALP levels in patients with a normal biliary tract ultrasound;
- positivity to AMA at a titer >1:40 using indirect immunofluorescence, or positivity to PBC-specific antinuclear antibodies (ANAs), namely anti-Sp100 and anti-gp210;
- histological evidence of nonsuppurative cholangitis with destruction of interlobular bile ducts.

A diagnosis of PBC can be established when at least two of the aforementioned criteria are met. AMA positivity remains central to PBC diagnosis, with its presence alongside elevated ALP yielding a positive predictive value above 95%, eliminating the need for liver biopsy. Biopsy is indicated in AMA and PBC-specific ANA-negative patients or when clinical and laboratory findings raise suspicion of an autoimmune hepatitis – PBC variant or other associated conditions [9,17].

International guidelines do not specify whether PBC-specific ANA – namely anti-gp210 and anti-sp100 – should be tested at the time of AMA and ANA determination, or only in cases of AMA negativity [18]. Importantly, it is

recognized that anti-gp210 positivity, whether alone or in association with AMA, has significant prognostic value, suggesting it may be an independent marker regardless of AMA status [19].

In accordance with EASL guidelines, when laboratory tests indicate cholestasis and abdominal ultrasonography excludes biliary obstruction or other extrahepatic causes, further evaluation should include measuring PBC autoantibodies, since PBC is the most common cause of chronic cholestasis in adult patients [13].

The diagnostic phase plays a central role in the management of PBC, as it provides the opportunity to identify additional risk factors to which the patient may be exposed, often related to age or the presence of other comorbidities. During the diagnostic phase, it is also important to monitor additional biochemical parameters, essential to describe the liver status. An increase in alanine aminotransferase (ALT), dissociated with ALP, can indicate a more active disease, and raise suspicion of a possible overlap with autoimmune hepatitis (AIH) or other concomitant liver disease. In these cases, a targeted diagnostic investigation is essential to clarify the diagnosis and define the most appropriate therapeutic approach.

2.2.1. Pre-treatment risk assessment

In addition to their diagnostic relevance, baseline biochemical and clinical parameters also have important prognostic implications. Indeed, parameters such as cholinesterase, bile acids, white blood cell count, total bilirubin and albumin provide complementary information on cholestasis, hepatocellular injury and hepatic synthetic function. They are therefore essential for building consolidated prognostic models that allow for a more granular stratification of individual risk, distinguishing high-risk from low-risk patients [20].

In addition to the above-mentioned parameters – such as ALP, ALT and total bilirubin (TB) – which are fundamental for the diagnosis of the disease, serum cholinesterase is an important marker of hepatic synthesis produced by hepatocytes. Reduced levels of this marker may indicate impaired liver synthetic function, therefore it is important to consider it in disease evaluation [21].

In this context, the GLOBE and UK-PBC scores, also used to assess response to UDCA, have shown high predictive value in assessing the likelihood of death or the risk of liver transplantation [13]. However, the Xi'an criteria stand out these include the following thresholds on parameters measured 1 month after initiation of UDCA therapy: ALP $\leq 2.5 \times$ ULN (Upper Limit of Normal), Aspartate Aminotransferase (AST) $\leq 2 \times$ ULN and TBIL $\leq 1 \times$ ULN. These criteria have demonstrated high reliability in identifying patients who have not responded to UDCA, with a 5-year adverse event-free survival rate of 64% in non-responders compared to 97% in responders [22].

The introduction of these models in the early stages of the disease provides clinicians with the tools not only to confirm the diagnosis, but also to anticipate long-term outcomes, identify high-risk patients and adapt treatment strategies accordingly [20].

2.2.2. Disease stage

Once a diagnosis of PBC has been confirmed, it is essential to define the disease staging for assessing the extent of liver damage, estimating prognosis and guiding treatment decisions. The first factor to consider is the degree of hepatic fibrosis, which can be established with biopsy or Non-Invasive Tests (NITs), and it ranges from early periportal inflammation to advanced cirrhosis. Current clinical guidelines do not recommend biopsy in the diagnostic process because a definitive diagnosis can be established through a combination of cholestatic liver enzyme patterns and specific autoantibodies. However, liver biopsy retains an important role in selected cases where the diagnosis is uncertain, when additional pathological information may alter management, or if staging by NITs remains inconclusive. NITs such as elastography techniques (e.g. vibration controlled transient elastography, VCTE) have become the standard for disease staging and for prognosis estimation, as these methods are less invasive, more reproducible and suitable for longitudinal monitoring. In fact, even if liver biopsy remains the historical gold standard for fibrosis assessment, several studies have shown that NITs demonstrate good diagnostic accuracy for advanced fibrosis and cirrhosis in PBC, with higher reproducibility and lower risk compared to biopsy. Nevertheless, their sensitivity in early-stage disease is lower, so, in these cases remains necessary the histological confirmation [23].

Accurate staging is especially important in identifying patients at increased risk of progression, liver decompensation or hepatocellular carcinoma. A periodic reassessment of liver fibrosis is essential because even patients with stable biochemical profiles may require therapeutic revisions [9,13,17]. The available literature provides extremely scarce evidence regarding the optimal timing for elastography reassessment, as no prospective studies are available in PBC and very few and limited retrospective studies have been carried so far. Consequently, defined intervals have not been established yet [24,25].

In light of the absence of data specifically addressed to PBC, the board recommends performing Fibroscan based on the stage of the disease and the patient's risk, as outlined in the EASL guidelines as a general approach to patients with chronic liver disease [26], supporting the use of the 10 kPa threshold to define advanced chronic patients. Specifically, for patients with liver stiffness values above 10 kPa, an annual assessment appears recommended. Likewise, an annual evaluation is also advised for those with values below 10 kPa, but who have not achieved a biochemical response, since they are at greater risk of more rapid evolution. In fact, given the current scenario – marked by the introduction of more effective second-line therapies – maintaining an annual elastography follow-up appears reasonable to enable early detection of disease progression that may warrant additional interventions, such as hepatocellular carcinoma surveillance or variceal screening.

Conversely, for patients with no evidence of advanced fibrosis, stable disease and complete biochemical response, a longer interval of 2–3 years between elastography assessments is considered appropriate, reflecting the lower risk of disease progression in this subgroup.

2.2.3. Comorbidity

In addition to the assessment of biochemical indices, it is essential to undertake an analysis of the comorbidities frequently associated with PBC [27], as they may influence both the progression of the disease and the tolerability of treatments. A range

of autoimmune diseases are observed in these cases, with the most frequently reported being the Sjögren syndrome, autoimmune thyroiditis and rheumatoid arthritis [28–30].

The strongest association of PBC is with Sjögren's syndrome (also known as sicca syndrome). Most patients present symptoms of dry eyes and mouth and even vaginal dryness. Treatment of the syndrome with hydration methods is essential, especially in patients with severe xerostomia who may develop dental caries and risk of oral candidiasis [13].

Autoimmune thyroid diseases occur in up to 25% of patients with PBC followed by rheumatoid arthritis, systemic sclerosis or limited scleroderma, celiac disease, autoimmune anemia and, less frequently, various autoimmune dermatological, pulmonary, renal and neurological diseases [5,27,31].

A recent meta-analysis reported a pooled prevalence of celiac disease of 1.53% among patients with PBC, like that observed in the general population (1%), thus not supporting routine screening for celiac disease in individuals with PBC [32]. Screening for concomitant autoimmune disorders such as celiac disease, thyroid disease and Sjögren syndrome at baseline is suggested by UK guidelines [5]. During follow-up, testing PBC patients for concomitant autoimmune diseases should be considered in those presenting with symptoms suggestive of a specific disease or in patients with fatigue that may be due to alternative causes such as anemia or hypothyroidism [5,13].

Patients with PBC have a significantly higher risk of osteoporosis (RR 2.79), bone fractures (OR 1.86) [33] and post-fracture mortality compared with the general population [34]. Therefore, baseline and regular screening every 2–3 years using dual-energy x-ray absorptiometry (DXA) is recommended, along with annual assessment of serum vitamin D, calcium (the integration of which is recommended [13]), phosphorus and parathyroid hormone (PTH) levels [7,9]. Recently, an open-label trial comparing denosumab and zoledronic acid in patients with PBC demonstrated that denosumab is a safe and effective treatment option for osteoporosis in this population [35].

Another common comorbidity in patients with PBC is hyperlipidemia affecting up to 80% of subjects; however, the mechanism underlying hyperlipidemia is different from that of other conditions. In fact, progressive intrahepatic cholestasis in these patients leads to impaired bile acid secretion into the duodenum, disrupting both endogenous and dietary lipid metabolism and transport. Altered bile acid homeostasis impairs cholesterol transport and excretion, leading to the formation of abnormal lipoprotein particles and disrupted cholesterol balance. These changes, along with elevated circulating triglycerides, contribute to broader lipid metabolism disorders and may increase cardiovascular risk [36]. When lipid imbalance occurs, lipid-lowering drugs should be administered according to standard clinical practice. However, if the imbalance persists after PBC treatment, the management of both PBC and the concurrent comorbidity should be reassessed based on the patient's overall condition [13,37].

Early recognition of such comorbidities is vital for comprehending the multifaceted nature of the patient's overall condition and establishing a personalized therapeutic approach. Therefore, the essential basis for defining an effective, safe and well-tolerated long-term therapeutic strategy lies in a thorough and multidimensional initial diagnosis, encompassing both the hepatological aspects and the entire clinical and metabolic profile.

2.3. Treatment and monitoring

The management of PBC currently relies on a therapeutic algorithm (Figure 2) tailored to individual patient responses,

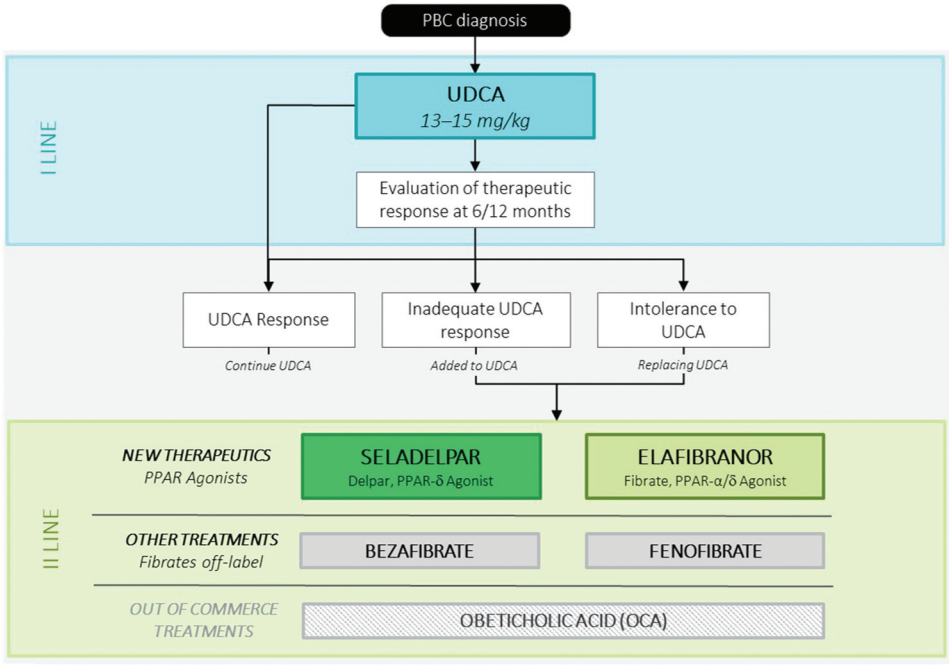

Figure 2. Treatment algorithm for patient with PBC in Europe [13,38].

encompassing first- and second-line treatment options. The only approved first-line therapy is UDCA: orally administered at an optimal dose of 13–15 mg/kg per day, either as a single daily dose or divided doses in cases of tolerability issues. UDCA has demonstrated efficacy in improving liver biochemistry, delaying histological progression, reducing the risk of esophageal varices and enhancing transplant-free survival [13]. Biochemical tests are combined with periodic hepatological visits and elastography to 1st line monitor the clinical condition of the patient over time.

However, patient response to UDCA therapy exhibits variability, necessitating evaluation through biochemical parameters such as ALP and bilirubin according to established response criteria [39]. Several criteria evaluate response to UDCA based on changes in biochemical markers such as ALP, gamma-glutamyl transferase (GGT), albumin and bilirubin after 6 to 12 months of therapy [17]. If tolerated, UDCA treatment is generally recommended to be lifelong [5]. It is observed that in about 25–40% of patients the drug is ineffective in reducing biochemical markers below a specific cut-off, particularly ALP. In addition, adverse events preventing therapy continuation occur in 3–5% of patients. In cases of incomplete response, therefore, access to second-line therapy in combination with UDCA is evaluated. In this case UDCA should be maintained at the same dosage, since it has been shown to reduce the occurrence of adverse liver outcomes even in those who do not respond adequately [10].

In addition to UDCA, adjunctive therapies targeting pruritus, osteopenia or osteoporosis are frequently employed, such as cholestyramine, rifampicin, bezafibrates, naltrexone and sertraline for cholestatic pruritus [17], as well as vitamin D supplementation and antiresorptive drugs or PTH analogs to address osteoporosis commonly associated with PBC, as previously stated.

Until June 2024, OCA represented the sole approved second-line therapeutic option for patients exhibiting an inadequate response or intolerance to UDCA, administered either in combination with UDCA or as monotherapy, respectively [9].

The recent withdrawal of OCA's marketing authorization by the EMA, and its subsequent removal from the US market following the Food and Drug Administration (FDA) request, has caused a therapeutic void in some countries, leaving clinicians without any authorized alternatives for this patient population. Moreover, the very reasons that led to the suspension of the drug's commercialization, namely, the failure to meet endpoints related to liver outcomes in the confirmatory trial [40], have sparked an ongoing and profound debate within the scientific community [41,42].

In clinical practice, off-label use of fibrates – originally approved for other indications – has become a common strategy for managing UDCA non-responders, further reinforced by the positive results of the French trial using bezafibrate [43].

The emerging second-line treatment options for PBC include new PPAR agonists, whose mechanisms of action – better detailed in the registration studies [44,45] —involve regulation of genes related to bile acid and fatty acid metabolism and inflammation. These effects allow for a reduction in bile acid synthesis and a decrease in inflammation caused by bile acid toxicity. Elafibranor, a first-in-class dual PPAR-α/δ agonist, received EMA approval in 2024 [46] while, seladelpar is a selective PPAR-δ agonist, approved by EMA in February 2025 [47]. The pivotal clinical trials investigating these novel therapies have been recently published. However, the data are still preliminary and not yet consolidated enough to be reported in detail. Efficacy outcomes and adverse events have been described in the respective trials and the mechanisms of action are referenced in the registration studies ELATIVE for elafibranor and RESPONSE for seladelpar [44,45].

When patients receive comprehensive clinical and pharmacological management, the disease can be effectively controlled over the long term, potentially throughout the patient's lifetime. Conversely, inadequate management can cause a clinical deterioration up to requiring liver transplantation. In fact, advanced PBC is a well-established indication for liver transplantation and accounts for about 3,6–9,7% of transplants in adults [9]. Importantly, even post-transplantation, pharmacological treatment remains essential. Evidence indicates that UDCA administration after liver transplantation reduces the risk of disease recurrence, which, although common, rarely progresses to a clinically significant state [5].

3. Clinical insights along the treatment path

Given the complexity of PBC and its management, several critical needs have emerged regarding the clinical and therapeutic facets of the condition. The following are insights into scientific evidence regarding the clinical aspects of PBC management, as well as regarding the challenges faced throughout the care continuum. These findings emphasize the importance of targeted interventions to improve clinical outcomes.

3.1. Monitoring of therapeutic response and prognostic biomarkers in PBC

For the evaluation and monitoring of therapeutic response in PBC, international clinical guidelines recognize ALP as the principal biochemical marker of disease progression. In fact, persistently elevated ALP levels reflect ongoing cholestasis and biliary inflammation and are associated with progressive ductopenia and advanced fibrosis. Failure to achieve an ALP reduction to less than 1.5×ULN, in combination with a normal serum bilirubin level, after 12 months of UDCA therapy, is linked to an increased risk of adverse clinical outcomes [13]. Conversely, patients with early-stage disease who achieve ALP levels below 1.5×ULN and maintain normal bilirubin values demonstrate significantly better transplant-free survival. Thus, ALP <1.5×ULN serves as a surrogate marker of a favorable biochemical response and a lower risk of disease progression [13]. However, recent studies have shown that ALP levels between 1.0×ULN and 1.67×ULN are still associated with approximately 7% lower survival compared to ALP ≤1×ULN [50,51]. These findings reinforce the concept that lower ALP levels correspond to improved long-term outcomes and underline, whenever possible, the importance of achieving complete normalization to maximize therapeutic benefit and transplant-free survival.

Even if biochemical thresholds have a consolidated prognostic value, complete normalization can become an important objective for some patients with PBC. This goal may be particularly meaningful in patients with high-risk profiles — such as younger individuals with longer life expectancy, those with advanced fibrosis stage [52] and/or those exhibiting high liver stiffness measurement (LSM) [53,54]. Nevertheless, interpreting ALP values solely in relation to a fixed cutoff may be overly simplistic. While the normalization of biochemical parameters, especially ALP, represents an ideal clinical endpoint, because the heterogeneity of PBC and the interindividual variability in treatment response limits the universal applicability of such stringent targets. The achievement of predefined cutoffs may not fully capture the complexity of disease trajectory. For this reason, a continuum-based therapeutic strategy, dynamic and longitudinal monitoring of biochemical markers and LSM is recommended and may allow a more specific and tailored approach. Moreover, it remains essential to exclude alternative, non-hepatobiliary causes of ALP elevation to prevent misinterpretation and guide appropriate diagnostic and therapeutic decisions.

Another important biochemical parameter to evaluate is TB which can be considered as a key marker of advanced liver disease. Rising bilirubin levels – particularly when accompanied by thrombocytopenia, hypoalbuminemia and elevated International Normalized Ratio (INR) – indicate compromised hepatic reserve and the presence of cirrhosis or severe ductopenia. Conversely, lower serum bilirubin levels are consistently associated with improved long-term outcomes, whereas values exceeding 1×ULN predict transition to advanced disease and poorer transplant-free survival. Importantly, the prognostic value of bilirubin remains significant even among patients receiving UDCA therapy [55]. It has been shown that attaining bilirubin levels ≤0.6 × ULN is associated with the lowest risk for liver transplantation or death in patients with PBC [50].

In addition to ALP and bilirubin, transaminases also provide clinically relevant information. Elevated aminotransferase levels may indicate a more pronounced inflammatory component [56] or raise suspicion of an autoimmune hepatitis – PBC overlap (AIH-PBC variant), which typically follows a more aggressive course and requires distinct therapeutic approaches. In particular, ALT activity may represent interface inflammation even in the absence of AIH-PBC variant, identifying a subgroup with a more aggressive and less treatment-responsive phenotype, including reduced responsiveness to treatment [56,57]. Recent data have further emphasized the prognostic relevance of liver function biomarkers, demonstrating that serum albumin, ALP and GGT are the strongest predictors of all-cause and cause-specific mortality [58].

Another important surrogate marker of disease severity and treatment response is LSM assessed by VCTE. Recent studies have confirmed that LSM is a robust predictor of clinical outcomes at baseline and during follow-up and may serve as a valuable surrogate endpoint in PBC research [53,59,60].

Regular monitoring of these biochemical and noninvasive markers enables timely evaluation of therapeutic response and early identification of patients at high risk of progression. In this context, achieving a 'deep response' – defined as normalization of ALP – can represent a clinically meaningful objective, particularly in younger patients or those with more aggressive disease phenotypes. Attaining such a response is associated with improved long-term transplant-free survival and preservation of liver function over time.

3.2. Non-optimized 1st line response evaluation times

First-line treatment involves the administration of UDCA, however, as previously stated, in around 30–40% of cases [17], treatment with UDCA results in an inadequate response, making it necessary to resort to second-line therapies.

The evaluation of the response to UDCA occurs through various specific evaluation scales. However, there is noticeable heterogeneity in the applicable criteria, both in terms of timing, parameters and the endpoints considered.

The evaluation of the response to UDCA can be performed using various criteria such as: Barcelona, Paris I, Rotterdam, Rochester-II, Toronto, Paris II, Rochester-I, Continuous GLOBAL PBC and UK-PBC. All criteria provide that the evaluation be done 12 months after the start of treatment with UDCA, except for Rochester I (after 6 months) and Toronto (after 24 months) [12]. The timelines defined by current treatment evaluation criteria may, in some cases, pose a clinical limitation. Delayed recognition of an inadequate response can postpone timely therapeutic adjustments, potentially contributing to disease progression [39].

Although there are no formal studies demonstrating a clinical benefit of earlier biochemical assessment of response to ursodeoxycholic acid (UDCA), early evaluation may support improved outcomes in certain patient categories. In fact, treatment reassessment as early as 6 months may be reasonable in patients with features suggesting higher risk of progression [25].

Therefore, early identification of patients likely to exhibit a suboptimal response to UDCA is of critical importance, as it may allow for the timely initiation of second-line therapies in appropriate cases. The future introduction in clinical practice of predictive models of 1st and 2nd line treatment response holds promising potential for PBC management [39,56].

3.3. Management of patients with high risk profile

Risk assessment is a critical component at every stage of the PBC patient journey. The diagnostic phase should include not only liver disease severity (based on liver biochemistry) and disease stage, but also comorbidities and potential treatment-related complications. Management must be personalized, as inappropriate choices can expose patients to significant harm.

More specifically, in patients with incomplete or inadequate response to UDCA, the introduction of off-label treatment with fibrates is a common practice, particularly in countries where UDCA is not readily available [61].

However, their benefit-risk profile must be carefully assessed, particularly in patients with reduced liver function. While fibrates may improve biochemical markers, they require close monitoring due to potential side effects [5].

It is important to underline that, except for cases of advanced cirrhosis, patients with PBC are not subject to an increased risk of adverse effects from statins compared to the general population. However, the combination of statins with fibrates, often used in cases of inadequate response to UDCA, may lead to an increased risk of myopathy [62].

Caution is also necessary in diabetic patients, in whom treatment may be underestimated for fear of hepatotoxicity. In this case, an inappropriate switch from metformin to insulin may occur, with weight gain and possible worsening of hepatic steatosis, so it is essential to maintain a balance between therapeutic efficacy and safety, avoiding changes that are not justified by the standard treatment for each disease.

Since the disease mainly affects women over 35, it is important to evaluate postmenopausal women on hormone replacement therapy (HRT). Despite concerns about cardiovascular risks, HRT is not contraindicated in PBC and coordinated care with gynecologists is recommended [63].

Finally, patients with cirrhosis – particularly those with decompensated disease – require careful consideration, given their increased risk of adverse events during treatment for PBC [9]. In compensated cirrhosis, available therapies have so far required caution due to their sometimes-unfavorable safety profile. In this context, the emerging of new therapeutic options, such as PPAR agonists, may offer an improved benefit – risk balance, as suggested by the clinical data available to date [44,45] — the results are limited but encouraging. These preliminary results represent a significant evolution in PBC management and provide a substantial contribution to addressing this current clinical need. However, the experience in patients with compensated cirrhosis remains limited and is based on a small subset of subjects included in registration trials, warranting confirmation in real-life settings. Conversely, the use of this agent in decompensated cirrhosis represents an off-label indication and is not currently recommended, as these patients should be evaluated for liver transplantation rather than pharmacological interventions. Overall, preliminary findings in compensated disease appear promising and could represent a meaningful advancement in addressing an important clinical need, provided that forthcoming real-world evidence substantiates their safety and efficacy in this fragile population.

4. Quality of life in PBC: the underrated burden of symptoms and opportunities for improved patient care

As a chronic condition, PBC requires careful attention and a comprehensive view – not only clinically but also psychosocially. Persistent symptoms such as fatigue and pruritus can severely impact emotional well-being, daily functioning and social engagement, leading to a notable decline in quality of life (QoL).

Pruritus affects up to 80% of PBC patients, with 20–35% of them experiencing severe itching involving areas such as the limbs, trunk, scalp and groin. Despite its high prevalence, pruritus is often underreported and poorly documented by clinicians, highlighting a critical gap in care. In fact, pruritus is strongly associated with poor sleep, depression, anxiety and diminished QoL, and chronic scratching can also lead to dermatologic complications such as excoriations and folliculitis [64–66].

Multiple reports highlight a suboptimal level of clinician recognition and documentation regarding pruritus [67]. Conscious and effective management is therefore essential to prevent both physical and psychosocial sequelae. Unfortunately, no specific drugs have yet been approved to treat pruritus in PBC. Indeed, first-line therapy with UDCA has been shown to have no significant effect on itching and in some cases even exacerbate the symptom [12]. An improvement in severity has been observed with bezafibrate treatment [5], as well as with PPAR agonists. The most relevant data, in fact, come from a study on seladelpar concerning patients with moderate-to-severe itching at baseline, with 93% showing statistically and clinically significant improvement after 1 year of treatment; in addition, 80% had an improvement in itch-related sleep disturbance [12].

Fatigue, though equally impactful, remains challenging to quantify due to its subjective, multifactorial nature. Patients may not spontaneously report fatigue or pruritus, either because they do not recognize them as disease-related or struggle to describe their symptoms clearly. Moreover, time-limited clinical encounters and a focus on biochemical metrics frequently lead to these symptoms being overlooked [68]. In this context as well, there are no licensed therapies for this symptom, and no drugs with proven efficacy have been identified [5,12].

To address this gap, clinicians should adopt a proactive and structured approach to symptom assessment. Active evaluation through targeted and contextualized questioning is critical, even in the absence of spontaneous patient reporting. This approach allows for the identification of subjective burdens that may otherwise remain hidden, particularly in patients who may minimize their complaints or struggle to articulate their experiences.

Currently, several symptoms assessment tools are available, such as the PBC-40; this scale is useful for general assessment of symptoms and the overall disease burden [13]. Additionally, pruritus-specific tools, such as the 5-D Itch Scale, the Visual Analog Scale (VAS) and the Numerical Rating Scale (NRS), are widely used in clinical trials [69–72]. There are also some fatigue-specific tools, such as the Fatigue Severity Score (FSS) and the Fatigue Impact Scale (FIS) [73]. However, a general low sensitivity to temporal changes in symptom severity is observed, which could be addressed with periodic symptom assessment.

Another important limitation for the application of these methods is the time required for completion, despite the possibility of adopting synthesized versions of these scales during the pre-visit wait (e.g. PBC-10 [74]). Consequently, these tools could be useful but may be limited in supporting a dynamic and contextualized assessment of symptoms, as periodic data collection is required. In this evolving landscape, the integration of patient-reported outcomes (PROs) and digital health technologies offers new opportunities to improve the systematic monitoring of symptom burden in PBC [75,76]. Mobile applications and other digital platforms

can support real-time symptom tracking, enable longitudinal monitoring outside the clinical setting and foster greater physician awareness of patient-reported data. These tools may ultimately improve therapeutic alignment with patient needs and enhance the overall quality of care. Importantly, the clinical visit should also be recognized as a critical moment to assess the broader psychosocial context of living with a chronic disease. The emotional and social implications of a PBC diagnosis can significantly influence symptom perception, treatment adherence and disease trajectory. Incorporating this dimension into routine care is essential to ensure a comprehensive, patient-centered approach that addresses both clinical and humanistic aspects of disease management.

5. Conclusion

In light of the evolving clinical management of PBC, a detailed and integrated analysis of the patient journey was presented, covering its principal stages – from diagnostic suspicion to specialist referral, from the assessment of autoimmune and metabolic comorbidities to the definition of a personalized and longitudinally monitored therapeutic strategy.

The discussion examines critical aspects of disease management, including the monitoring of treatment response through key biochemical markers, the limitations associated with standard timelines for evaluating UDCA therapeutic response, and the need for earlier and more individualized therapeutic interventions in high-risk patient subgroups. Particular attention is also given to the symptomatic burden of PBC – notably pruritus and fatigue – and its impact on patient quality of life, often underestimated or insufficiently addressed in clinical practice.

The analysis also examines how recent changes to the therapeutic algorithm – due to the withdrawal of obeticholic acid from the European market and the advent of new therapeutic options – affect the therapeutic approach to PBC.

6. Expert opinion

The evolving management of PBC calls for a more refined and tailored approach, particularly considering recent therapeutic developments.

The discussion emphasized the importance of accurate monitoring of biochemical response, focusing on key markers such as alkaline phosphatase, bilirubin, and transaminases, and on how their longitudinal trends should be interpreted as indicators of treatment response and disease stabilization. Indeed ALP, bilirubin, and transaminases should be interpreted together in the context of serial assessments and integrated with liver stiffness measurements. This allows for a better understanding of disease dynamics and treatment response, as it enables earlier detection of suboptimal responses and timely therapeutic adjustments. The panel emphasized the crucial role of liver elastography in monitoring, suggesting its use according to a risk-based approach: annual checks for patients with liver stiffness >10 kPa or with suboptimal biochemical response, while longer intervals (2–3 years) are considered adequate for stable patients with complete response. The expert panel reaffirmed that achieving complete ALP normalization is an important therapeutic goal especially for patients with adverse prognostic factors, such as younger age, advanced fibrosis or elevated liver stiffness. However, the panel cautioned against relying solely on fixed biochemical thresholds and emphasized the need for a longitudinal, patient-centered approach.

They identified total bilirubin as a key indicator of advanced liver dysfunction, particularly when accompanied by thrombocytopenia, hypoalbuminemia or elevated INR. The experts also highlighted ALT as a marker of ongoing inflammation, potentially reflecting active PBC or PBC-AIH overlap. Together, these parameters support a comprehensive, risk-based monitoring framework essential for optimizing long-term management in PBC.

In this context, experts also explored the potential benefit of anticipating the timing of treatment response assessment. While current practice typically foresees evaluation at 12 months following the initiation of UDCA, earlierassessment at 6 months – applicable to selected patient subgroups – may allow for timely identification of non-responders and early treatment escalation. This approach reflects a growing consensus toward more agile, individualized treatment paradigms, tailored to patient-specific risk profiles and disease trajectories.

Special attention was dedicated to patients with complex or high-risk profiles, whose clinical management is often more challenging due to advanced disease stage, comorbidities or suboptimal biochemical response. For these patients, early and tailored interventions may help prevent undertreatment and improve long-term outcomes and quality of life. It is the opinion of experts that patients with PBC should be managed using a multidimensional approach, in which the assessment of concomitant pathologies such as diabetes or hyperlipidemia must be carried out according to the same criteria followed for the general population, except for cases requiring specific attention. Hyperlipidemia should be treated following general guidelines, which include lifestyle changes, regular physical activity and use of statins, or, in case of intolerance, alternative oral lipid-lowering drugs after consulting with a specialist.

The active investigation of symptoms – particularly pruritus and fatigue – was also underscored as a clinical priority. Given their potential to significantly impair quality of life, clinicians are encouraged to systematically assess these symptoms, even when not spontaneously reported by the patient, to ensure a more comprehensive evaluation of disease burden. The panel encouraged a proactive and structured approach to evaluating both the physical and psychosocial symptom burden during clinical visits. They emphasized that systematic assessment is essential to comprehensively understand the patient's experience and guide more effective disease management.

These considerations gain further relevance in the current therapeutic landscape, following the withdrawal of OCA from the European market in 2024. At the same time, the availability of new PPAR agonists offers promising opportunities to address unmet needs and bridge the gap in the treatment algorithm.

Altogether, these insights pave the way for a more proactive, structured and patient-centered model of care, poised to

better address the clinical complexity of PBC and to enhance patient outcomes and quality of life in the years to come.

Declaration of interest

P Invernizzi, A M G Aghemo, V Calvaruso, A Lleo, M Marzioni, F Piscaglia, C Rigamonti, U Vespasiani Gentilucci, S Brillanti, M Carbone, N Cazzagon, and P Lampertico have acted as consultant for Gilead Sciences.

A M G Aghemo has served on Advisory Board, speaker and teacher, V Calvaruso has served on Advisory Board and speaker, A Lleo has acted as speaker, for Alfasigma.

P Invernizzi has served on Advisory Boards and has received honoraria for speaking and teaching, A M G Aghemo has received honoraria for speaking and teaching, V Calvaruso has acted on Advisory Board/Speaker Bureau, A Lleo has acted as consultant and speaker, M Marzioni has acted as consultant, F Piscaglia has acted on Advisory Board, C Rigamonti has acted as consultant/sponsored lectures/travel grants, U Vespasiani Gentilucci has acted as consultant, M Carbone has received founding, N Cazzagon has acted as consultant, speaker and travel grant for Ipsen Pharma.

P Invernizzi has served on Advisory Boards and has received honoraria for speaking and teaching, V Calvaruso has acted on Advisory Board and speaker, A Lleo has acted as consultant and speaker, C Rigamonti has acted as sponsored lectures/travel grants, U Vespasiani Gentilucci has acted as consultants, and N Cazzagon has acted as consultant and speaker, for Advanz Pharma.

A M G Aghemo has received speaker and teacher fees, and P Lampertico has served on Advisory Boards/Speaker Bureau for AbbVie.

A M G Aghemo has served on Advisory Boards, F Piscaglia and U Vespasiani Gentilucci have received honoraria or acted as consultants for Novo Nordisk.

P Invernizzi has served on Advisory Boards, V Calvaruso has acted as Advisor or Speaker Bureau member, A Lleo has acted as consultants, M Carbone has received founding, U Vespasiani Gentilucci has acted as consultants, for Mirum Pharmaceuticals.

P Invernizzi has served on Advisory Boards, V Calvaruso has acted as occasional consultants, A Lleo has acted as consultant and has received speaker fees, M Marzioni has acted as consultant, M Carbone has received founding, N Cazzagon has acted as consultant, and P Lampertico has acted on Advisory Board/Speaker Bureau for GSK.

V Calvaruso, F Piscaglia and P Lampertico have acted as Advisor Board/Speaker Bureau member for Roche.

V Calvaruso has acted on Advisory Board/Speaker Bureau and C Rigamonti has acted as sponsored lectures for Echosens.

A Lleo has received support for sponsored clinical studies (via Humanitas Research Hospital) and U Vespasiani has acted as consultant for Intercept Pharmaceuticals.

A M G Aghemo has acted on Advisory Board and F Piscaglia has received honoraria from Bristol Myers Squibb (BMS).

A Lleo has acted as consultant and speaker, F Piscaglia has acted on Advisory Boards and received honoraria from AstraZeneca.

P Invernizzi has acted on Advisory Board for Zydus Lifesciences and has served on Advisory Boards and speaker and teacher for Calliditas Therapeutics.

A M G Aghemo has served on Advisory Boards for Madrigal Pharmaceuticals, Mylan and Swedish Orphan Biovitrum AB (Sobi).

A Lleo has received speaker fees from Incyte Corporation, Gore PharmBIO, and has received funding from EU COST AcKon (CA22125), Italian Ministry of Health, and Italian Association for Cancer Research (AIRC), and has received support for sponsored clinical studies (via Humanitas Research Hospital) from: Dr. Falk Pharma, and UCB Pharma.

F Piscaglia has acted on Advisory Board and received honoraria from MSD, EISAI, Esaote, GE HealthCare, Samsung Healthcare, Bracco, Nerviano Medical Sciences, Signant Health, and Siemens Healthineers.

N Cazzagon has acted as consultant to Dr. Falk, speaker for Albireo Pharma and speaker, travel grant and Research grant for Orphalan.

P Lampertico has served on Advisory Boards/Speaker Bureau for Janssen Pharmaceutica, MYR GmbH, Eiger BioPharmaceuticals, Antios Therapeutics, Aligos Therapeutics, Vir Biotechnology, Grifols, Altona Diagnostics, Roboscreen GmbH.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All listed authors fully adhere to the authorship criteria established by the International Committee of Medical Journal Editors (ICMJE). Each author has made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; has participated in drafting or critically revising the manuscript for important intellectual content; has given final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring its accuracy and integrity.

Acknowledgments

The authors desire to acknowledge the members of Deloitte's Life Sciences Excellence Team, Milan, specifically Elisa Costantini, Marco Togni, Paolo Alberto Pinucci, Valeria Boccardo and Emanuella Colasuonno. They have participated in the writing and technical editing of the manuscript providing their contribute to the drafting of this document.

Funding

This publication was funded by Gilead Sciences, S.r.l. Italy. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AI-based tools and technologies declaration

No AI-based tools or technologies were used in the preparation of this manuscript.

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