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REVIEW

Long et al: Rare liver diseases

Rare liver diseases — Etiology, diagnosis and management: A review

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ABSTRACT

Rare liver diseases (RLDs) are diverse and often misdiagnosed conditions that impose significant clinical and public health challenges due to their variable presentations and limited treatment options. This study aims to synthesize contemporary evidence on the etiology, classification, diagnostics, and management of RLDs and to identify near-term research and implementation priorities. We conducted a systematic search of PubMed and Scopus for the years 2015 to 2025 using predefined keywords. We included peer-reviewed human studies, such as guidelines, randomized trials, and large registries, focusing on mechanisms, diagnostic strategies, and treatments. We excluded animal studies and non-peer-reviewed reports, extracting data on disease biology, diagnostic tools, outcomes, and molecular therapies. RLDs can be categorized into genetic/inherited, autoimmune cholestatic, and other vascular/metabolic entities. Care for these diseases is increasingly guided by structured pathways that integrate biochemistry and serology with magnetic resonance cholangiopancreatography (MRCP), elastography, targeted next-generation sequencing (NGS), and selective biopsy. Emerging biomarkers, such as circulating microRNAs, alongside machine learning in imaging techniques, enhance disease staging and prognostication. Key management strategies include the use of bile-acid modulators, surgical interventions, and ileal bile acid transporter (IBAT) inhibitors for progressive familial intrahepatic cholestasis (PFIC). Lifelong copper chelation is recommended for Wilson disease, with trientine preferred for neurologic phenotypes. Supportive care in alpha-1 antitrypsin deficiency (A1ATD) is complemented by the investigation of molecular chaperones. Additionally, gene-directed therapies, gene editing, RNA-based approaches, and cell therapies show early promise but raise concerns regarding durability, safety, and ethical considerations, particularly for pediatric patients. In conclusion, implementing precision medicine frameworks that rely on standardized diagnostics, multicenter registries, and equitable access is crucial for facilitating earlier detection and translating mechanism-targeted therapies into sustainable, globally accessible benefits.

Keywords: Primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, gene therapy, precision medicine.

INTRODUCTION

Rare liver diseases (RLDs) belong to a small subgroup of hepatic disorders with substantial clinical and public health challenges owing to their diagnostic inaccuracies, variable presentations, and restricted treatment options. When a disease affects fewer than 200,000 individuals in the United States or fewer than 1 in 2,000 people in Europe, it is considered as rare [1]. RLDs are uncommon; however, frequent misdiagnosis leads to liver injury before it is initially detected [2, 3]. Wilson disease (WD), alpha-1 antitrypsin deficiency (A1ATD), progressive familial intrahepatic cholestasis (PFIC), and primary biliary cholangitis (PBC) result from distinct genetic, metabolic, or autoimmune defects [4-7]. Some appear early in life and advance rapidly without treatment, while others remain dormant till advanced stages. WD is an autosomal recessive copper metabolism disorder that causes hepatic, neurological, and psychiatric symptoms [4, 8, 9]. A1ATD affects children and young adults and is often undiagnosed [10-12]. PFIC includes inherited cholestatic conditions from hepatocanalicular transporter gene mutations, leading to persistent cholestasis and cirrhosis [13-15]. Autoimmune cholestatic diseases, such as PBC, lead to progressive intrahepatic bile duct damage and are now reported in populations worldwide beyond Western regions [7, 16, 17]. Advances in molecular diagnostics, next-generation sequencing (NGS), and disease registries have improved the classification of the disease. Management includes pharmacologic therapy, transplantation, and supportive care, with outcomes influenced by underlying pathology [1, 2, 18]. Gene-based therapies, targeted biologics, and updated diagnostic strategies promote earlier detection and personalized treatment [19, 20]. This review outlines clinically relevant RLDs, underlying mechanisms, recent therapeutic progress, and future research directions to improve outcomes.

METHOD AND STUDY DESIGN

A complete search strategy was conducted with published literature on RLDs. Articles between 2015 to 2025 was searched systematically in PubMed, Scopus, using various keywords, including "*rare liver diseases," "Wilson disease," "alpha-1 antitrypsin deficiency," "progressive familial intrahepatic cholestasis," "primary biliary cholangitis," "primary sclerosing cholangitis," "autoimmune hepatitis," "gene*

therapy," "RNA therapy," and "precision medicine." Articles were included if they addressed etiology, diagnostic strategies, or management approaches for specific RLDs or provided clinical data relevant to therapeutic or molecular advances. Animal studies, non-peer-reviewed reports, and non-relevant publications were excluded. Data extraction focused on disease mechanisms, diagnostic tools, treatment outcomes, and molecular therapies, prioritizing evidence from clinical guidelines, randomized trials, and large registry-based studies.

CLASSIFICATION OF RARE LIVER DISEASES

RLDs are generally categorized into three major groups: genetic or inherited disorders, autoimmune liver diseases, and a range of structurally or metabolically distinct conditions (Table 1).

Genetic and inherited liver disorders

WD results from mutations in the *ATP7B* gene, which disrupts copper transport and leads to its toxic accumulation in the liver, brain, and other organs. Patients may develop hepatic failure, psychiatric changes, or neurological deterioration. Initial diagnosis with serum ceruloplasmin measurement, 24-hour urinary copper estimation, and liver biopsy is essential for chelation or zinc therapy, as delayed recognition is common due to variable clinical presentation in adolescents and young adults [4, 8, 9]. A1ATD, an inherited liver disorder, results from SERPINA1 mutations that block the secretion of AAT protein, causing its retention in hepatocytes and chronic liver injury. Pulmonary involvement is frequent, but hepatic disease is often missed. Patel et al. [11] reported low awareness of A1ATD as a cause of neonatal or chronic hepatitis and cirrhosis in PiZZ homozygotes. Management is mainly supportive, with liver transplantation as the only curative therapy in advanced disease [6, 12]. PFIC comprises autosomal recessive disorders caused by mutations in ATP8B1, ABCB11, or ABCB4 genes, leading to impaired bile secretion, early-onset cholestasis, pruritus, and progression to cirrhosis [14, 15]. Genetic testing has refined diagnosis and improved genotype–phenotype correlation. Intractable cases may require surgical biliary diversion or liver transplantation. Hemochromatosis includes genetic disorders with excessive intestinal iron absorption and hepatic iron deposition, resulting in fibrosis, cirrhosis, and hepatocellular carcinoma [21]. Most cases involve HFE

mutations, though non-HFE variants also contribute. Alagille syndrome, caused mainly by JAG1 and rarely NOTCH2 mutations, presents with reduced intrahepatic bile ducts, cholestasis, heart defects, facial dysmorphism, and vertebral anomalies [22, 23] Symptoms usually appear in infancy. Diagnosis is confirmed by genetic testing, and management focuses on symptomatic control and liver transplantation for progressive disease.

Autoimmune liver diseases

Autoimmune liver diseases are a group of rare hepatic conditions predominantly manifesting in adults. Autoimmune hepatitis (AIH) is characterized by immune-mediated destruction of hepatocytes, with elevated aminotransferases, hypergammaglobulinemia, and interface hepatitis on biopsy. Its diagnosis requires the elimination of viral and metabolic causes and should have reports with positive autoantibodies. Many patients respond well to corticosteroids and azathioprine, but some develop resistance and need other immunosuppressive drugs [2].

PBC involves progressive destruction of intrahepatic bile ducts, leading to cholestasis and cirrhosis. Tanaka et al. described its increasing prevalence in both Eastern and Western populations, especially among middle-aged women [7]. Antimitochondrial antibodies (AMAs) are the main diagnostic marker. Ursodeoxycholic acid is standard therapy, but 30–40% of patients respond incompletely and need obeticholic acid (OCA) [16, 24]. Recent guidelines have emphasized early stratification and integrated care pathways to optimize the results [24, 25]. In advanced disease, these guidelines also cover management of complications such as portal hypertension, with portal vein thrombosis as a major concern in cirrhosis [26]. Primary sclerosing cholangitis (PSC) is a chronic fibroinflammatory disorder of intrahepatic and extrahepatic bile ducts, often linked to inflammatory bowel disease. The disease progresses unpredictably, and no effective drug therapy exists. Lack of reliable biomarkers and disease-modifying treatments makes PSC one of the most challenging conditions in autoimmune hepatology [27].

Other rare liver conditions

Few liver diseases are as clinically significant for their severity and diagnostic complexity as Budd-Chiari syndrome. It results from hepatic venous outflow obstruction, usually due to thrombosis. Presentation varies from asymptomatic hepatomegaly to fulminant hepatic failure. Diagnosis relies on Doppler ultrasonography or CT venography, and treatment depends on disease severity [1]. Portal vein thrombosis (PVT) is a vascular complication often seen in cirrhosis and other prothrombotic states. It causes thrombotic blockage of the portal vein, leading to portal hypertension, variceal bleeding, and ascites. Diagnosis uses Doppler ultrasound or cross-sectional imaging, and treatment centers on anticoagulation and correction of underlying causes [26]. Congenital hepatic fibrosis is a developmental liver disorder marked by periportal fibrosis and abnormal ductal plate formation. It often coexists with polycystic kidney disease and appears in childhood with portal hypertension, splenomegaly, or variceal bleeding. Liver function remains stable until complications develop [28]. Glycogen storage diseases (types I and III) arise from enzyme defects causing hepatomegaly, hypoglycemia, and growth delay. Nutritional therapy remains standard, with gene therapy under study [1, 28].

PATHOPHYSIOLOGICAL MECHANISMS AND DISEASE ORIGIN

The pathogenesis of the RLDs depends on either genetic mutations that disturbs the metabolic and transport pathways and the dysregulated immune responses against hepatic tissue. Genetic mutations lead to altered protein function and disrupted cellular homeostasis in these diseases. Impaired enzyme activity, defective transport proteins, and buildup of toxic compounds drive disease progression. Figure 1 outlines main pathogenic mechanisms and diagnostic biomarkers for early detection and monitoring. Modifier genes and epigenetic factors, including DNA methylation and microRNAs, influence disease severity, clinical variability, and response to treatment [1, 19].

Copper metabolism diseases

In WD (caused by mutations in the ATP7B gene), the accumulated copper produces free radicals that damage the liver cells and mitochondria thus resulting in

hepatomegaly, fibrosis, and cirrhosis. When the liver can no longer store copper, this metal enters the bloodstream and accumulates in other organs, primarily in the basal ganglia and causes neuropsychiatric symptoms. Disturbed copper transport and weak antioxidant defense regulate the disease process, with modifier genes affecting its severity and clinical presentation [4, 9, 44].

Protein folding and aggregation disorders

A1ATD leads to the accumulation of misfolded alpha-1 antitrypsin polymers within hepatocytes. These deposits initiate the stress in the endoplasmic reticulum and activates the unfolded protein response thus leading to oxidative stress, inflammation, and fibrosis [45]. The process increases the risk of HCC. The clinical features vary from neonatal hepatitis to cirrhosis in adults [31, 46]. Genetic factors, including ERAD pathway defects and the HFE-H63D variant, affect disease severity and clinical expression [47].

Bile transport and cholestatic disorders

PFIC includes three genetic subtypes (types 1–3) caused by mutations in bile salt transporter genes ATP8B1, ABCB11, and ABCB4. Impaired bile acid transport results in accumulation within hepatocytes, causing cellular injury, chronic cholestasis, and severe pruritus [13, 33]. Early surgical biliary diversion or use of ileal bile acid transporter inhibitors can delay progression, but many affected children still advance to end-stage liver disease requiring transplantation [15, 23, 48].

Iron overload syndromes

In hereditary hemochromatosis, mutations in the HFE gene damage the hepcidin–ferroportin regulation and causes excessive intestinal iron absorption. The accumulation of iron deposits in hepatocytes leads to oxidative injury, activation of hepatic stellate cells, and progression to fibrosis and cirrhosis [22]. Some variants, including HJV, HAMP, and TFR2 genes also cause the disease state and leads to different degrees of iron loading and organ damage conditions [22, 34].

Autoimmune liver diseases

Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). AIH involves T cell–driven injury at the portal–parenchymal interface with hypergammaglobulinemia and autoantibodies such as ANA, SMA, and LKM1. Common symptoms are fatigue, jaundice, and raised aminotransferase levels [36]. PBC results from immune destruction of intrahepatic bile ducts directed against the pyruvate dehydrogenase complex and is strongly associated with anti-mitochondrial antibodies [7, 24]. PSC causes chronic inflammation and fibrosis of the bile ducts and is often associated with inflammatory bowel disease [27]. The disease process arises from loss of immune tolerance influenced by genetic background, environmental exposure, and epigenetic factors, with additional effects from gut–liver axis signaling [35, 49].

CLINICAL PRESENTATION AND DISEASE-SPECIFIC FEATURES

RLDs vary genetically and pathologically, often sharing features that delay diagnosis. Fatigue, pruritus, jaundice, and hepatomegaly are frequent. Severe, treatment-resistant pruritus occurs in PFIC and PBC. Intrahepatic bile retention causes right upper quadrant pain and liver injury. Neurological, hematological, and dermatological signs, including tremors, cognitive changes, and xanthomas, may accompany hepatic disease. In WD, tremors and behavioral changes often precede hepatic symptoms [4, 9]. PFIC presents in infancy with pruritus and growth failure [15, 33], while A1ATD may cause neonatal jaundice or remain undetected until adulthood [11, 46].

Biochemical and immunological diagnostics

Diagnosis of RLDs requires the incorporation of clinical, biochemical, serological, and imaging findings. In WD, low ceruloplasmin, high urinary copper, and hepatic copper measurement confirm diagnosis, while MRI often shows basal ganglia hyperintensities related to neurological symptoms [4, 9]. Disease-specific markers aid diagnosis: low serum alpha-1 antitrypsin with phenotyping in A1ATD [5, 6]; raised aminotransferases, IgG, and autoantibodies in autoimmune hepatitis [36]; elevated ALP with anti-mitochondrial antibodies in PBC [7, 24]; and characteristic cholangiography in PSC [27]. In A1ATD, periodic acid–Schiff–positive (PAS),

diastase-resistant inclusions with gene panel or whole-exome sequencing allow early and precise diagnosis, especially in pediatric or atypical cases, reducing the need for liver biopsy [5, 11]. Biopsy remains useful for histological confirmation, disease staging, and evaluating treatment response when non-invasive tests are unclear [15, 50]. AIH shows raised transaminases, increased IgG, and autoantibodies such as ANA, SMA, or LKM; the revised IAIHG criteria assist in confirmation and grading [36]. PBC presents with elevated ALP and M2-type AMA, often with raised GGT [7, 24]. PSC is characterized by cholangiographic evidence of multifocal bile duct strictures and a beaded appearance of the ducts on MRCP or ERC. Imaging methods, including ultrasound, elastography, MRI, and MRCP, support diagnosis and follow-up [26, 27, 50].

ETIOLOGY AND MANAGEMENT OF RARE LIVER DISEASES

The etiologies of RLDs are broadly categorized as genetic, autoimmune, or other uncommon causes, which are characterized by specific mechanisms, clinical course, and therapeutic considerations that facilitate the patient management strategies.

Genetic etiologies

Single-gene mutations cause several rare liver diseases, and WD is a well-known example. Mutations in the *ATP7B* gene impair biliary copper excretion, causing copper buildup in the liver and progressive injury [4, 8]. The diagnosis can be difficult because of varied clinical patterns. Chanpong et al.,[51] observed that about 30% of children present with acute liver failure, often without Kayser–Fleischer rings and stated the importance of genetic testing. Prolonged chelation with D-penicillamine or trientine is the standard treatment. The choice of initial drug is debated because D-penicillamine can worsen neurological symptoms in some patients [52]. Next-generation sequencing (NGS) has improved the diagnosis by directly identifying *ATP7B* mutations and identifying atypical cases [44]. Recent studies are evaluating small molecules like 4-phenylbutyrate to correct misfolded *ATP7B* protein. CRISPR/Cas9-based gene editing has also shown early success in experimental models [53, 54].

A1ATD is a protein misfolding disorder caused by *SERPINA1* gene mutations that lead to polymer accumulation in hepatocytes. This induces stress in the endoplasmic reticulum, causes inflammation, and progressive liver injury [45]. The hepatic impact is greatest in PiZZ homozygotes. Hamesch et al. [55] reported that 35% of adult Pi*ZZ individuals had significant fibrosis (≥F2) and 9% had advanced fibrosis (≥F3), confirming the toxic effect of retained Z-variant protein. Clinically, A1ATD often appears as unexplained neonatal cholestasis. Teckman et al. [46] observed a male predominance, with 73% of affected boys developing severe liver disease by adolescence. Liver transplantation is the only curative treatment for end-stage disease [56], while supportive management is also recommended. Joly et al. [47] identified *HFE-H63D* as a genetic modifier that worsens hepatic injury, explaining disease variability. Segeritz et al. [45] used iPSC-derived hepatocyte models to study unfolded protein response and inflammation, providing a platform for therapeutic testing. Ongoing studies are examining RNA therapies to reduce mutant protein production.

PFIC is a group of autosomal recessive liver disorders caused by mutations in hepatocanalicular transport genes. PFIC1 (*ATP8B1*), PFIC2 (*ABCB11*), and PFIC3 (*ABCB4*) impair phospholipid translocation, bile salt export, and phosphatidylcholine secretion thereby, leading to bile acid toxicity and liver injury [13, 14, 33]. Symptoms begin early, often in infancy, with severe itching and poor growth. Genetic classification is essential for prognosis and treatment planning. Vitale et al. [15] reported that surgical biliary diversion normalized bile acids and relieved pruritus in over 80% of selected PFIC1 and PFIC2 patients, preventing disease progression and reducing the need for transplantation. Davit-Spraul et al. [57] found that targeted genetic testing identified a molecular diagnosis in 68% of children with low-GGT PFIC. Genotype–phenotype patterns are well established; *ABCB11* mutations causing loss of BSEP protein led to rapid fibrosis and increased HCC risk [33, 48]. Liver transplantation is effective for end-stage disease but less successful in PFIC1 due the presence of extrahepatic symptoms and recurrent steatohepatitis from the *ATP8B1* defect [15, 23]. Current studies are investigating modifier genes and epigenetic factors that may explain clinical variability and guide future individualized therapies.

Autoimmune etiologies

AIH is a chronic immune-mediated liver disorder marked by elevated aminotransferases, hypergammaglobulinemia, and autoantibodies such as ANA, SMA, or LKM-1. It shows association with HLA-DR3 and HLA-DR4 alleles. Diagnosis requires excluding viral or metabolic causes and confirming interface hepatitis on histology. Corticosteroids and azathioprine remain first-line therapy, while second-line immunosuppressants are reserved for refractory cases [36]. Some more factors which are susceptible include polymorphisms in CTLA-4 and TNF-α, which may influence disease course [58]. Biologic agents such as rituximab and immune checkpoint–targeted therapies have expanded options for treatment-resistant disease. Epigenetic mechanisms, including altered DNA methylation and microRNA expression, are under investigation as potential biomarkers of disease activity and therapeutic response [35]. PBC is a chronic autoimmune cholestatic liver disease characterized by progressive destruction of small intrahepatic bile ducts. The condition predominantly affects middle-aged women and is strongly associated with AMAs. Bile duct injury leads to bile stasis, hepatocellular damage, fibrosis, and eventual cirrhosis. Ursodeoxycholic acid is the established first-line therapy; however, 30–40% of patients show incomplete biochemical response. Obeticholic acid (OCA) and fibrates serve as second-line treatments in these cases [7, 16, 24]. Epidemiological studies have demonstrated the increasing incidence in Asian populations, with emphasis on the recognized global distribution [17].

PSC involves chronic inflammation and fibrosis of intra- and extrahepatic bile ducts, producing multifocal strictures, cholestasis, and frequent association with ulcerative colitis. MRCP identifies characteristic ductal irregularities [27]. No curative therapy exists, and liver transplantation is the only definitive option for advanced disease [49, 56]. The higher risk of cholangiocarcinoma and other hepatobiliary cancers requires strict surveillance and coordinated care. Genomic studies link HLA variants and loci such as FUT2 and MST1 to bile acid metabolism and immune regulation [27]. Studies on molecular imaging, biomarkers, antifibrotic agents, and microbiome-based therapy is advancing early detection and treatment of rare liver diseases, while integration of genetic and multi-omics data through registries enhances precision care and clinical outcomes [59, 60, 61].

DIAGNOSTIC STRATEGIES AND CHALLENGES IN RARE LIVER DISEASES

Clinical evaluation and initial laboratory testing

Diagnosis of RLDs includes clinical exmination based on fatigue, jaundice, pruritus, hepatomegaly, or unexplained enzyme changes. Initial tests like liver function test to assess hepatocellular injury, coagulation studies for hepatic synthesis, and cholestatic markers such as ALP and GGT are conducted [2, 19]. Antinuclear (ANA), smooth muscle (SMA), antimitochondrial (AMA), and liver–kidney microsomal (LKM-1) antibodies confirm autoimmune causes like AIH or PBC [7, 36]. Sometimes overlapping biochemical patterns with elevated transaminases and cholestatic markers may lead to unclear differentiation [1, 19]. Absence of specific autoantibodies leads to the need for biopsy. Correlation of all the above factors are essential to ensure accurate diagnosis in RLDs.

Genetic testing

Genetic testing is needed for monogenic RLDs. NGS facilitates in rapid identification of pathogenic variants, improving diagnostic accuracy and thus allows early therapeutic intervention. ATP7B sequencing confirms WD and facilitates family screening [4, 8, 9]. PFIC diagnosis depends on ATP8B1, ABCB11, and ABCB4 mutations thus guiding the clinical decision amking ranging from pharmacologic therapy to biliary diversion or transplantation [23, 33, 48]. NGS achieves up to 68% diagnostic success in low-GGT PFIC and other cholestatic disorders [57]. However, there remains a gap in the diagnosis of RLDs as structural variants, deep intronic changes, or complex reorganizations may need additional approach [1, 45]. Variant interpretation also requires integration of clinical phenotype, segregation analysis, and functional validation to avoid misclassification. Limited bioinformatics resources and limited access to genetic counseling contribute to delayed diagnosis in low-resource settings [45].

Imaging modalities

Imaging is necessary to evaluate liver morphology, bile duct anatomy, and fibrosis staging in RLDs. Ultrasound detects hepatomegaly, splenomegaly, and biliary dilation

but lacks small-duct resolution, whereas MRCP provides radiation-free, gold-standard visualization of cholangiopathies like PSC, revealing multifocal strictures and characteristic ductal beading [27]. Transient elastography (FibroScan) provides bedside measurement of liver stiffness and shows fibrosis severity, but accuracy declines in obesity, inflammation, or ascites [19, 62]. Gan et al. [19] observed that these limitations may underestimate fibrosis stage, especially in cholestatic liver disease where bile duct proliferation confounds stiffness measurements. MRE enables whole-liver fibrosis assessment with higher sensitivity and specificity, particularly useful in PSC and advanced fibrotic disease. High cost, limited availability, and lack of platform standardization hinder widespread MRE use, as shown in multicenter studies. Some more drawbacks include overlap with common hepatic disorders, poor detection of small-duct cholangiopathies or early fibrosis, and restricted access in many centers [19, 62].

Histopathology and liver biopsy

Liver biopsy remains the gold standard for confirming diagnosis, staging disease, and excluding coexisting liver disorders. In WD, liver biopsy quantifies hepatic copper exceeding 250 μg/g dry weight, confirming diagnosis, while simultaneously assessing inflammation and fibrosis when biochemical or genetic results remain inconclusive [4, 9, 44]. In autoimmune liver diseases including autoimmune hepatitis, PBC, and PSC, histology assesses interface hepatitis, bile duct injury, and fibrosis, guiding therapy in antibody-negative cases or partial treatment responders [7, 27, 36]. Biopsy also establishes the diagnosis of alpha-1 antitrypsin deficiency by demonstrating characteristic PAS-positive, diastase-resistant hepatocytic inclusions [11, 30]. This is an invasive procedure, with risks of bleeding, pain, and sampling error, and thus skilled hepatopathologists are needed for accurate interpretation.

Integrated diagnostic workflow

A structured diagnostic algorithm increases accuracy in detecting RLDs and reduces unnecessary invasive testing. The assessment includes history, clinical examination and basic laboratory tests. Liver function tests assess hepatocellular injury, while raised ALP or GGT indicates cholestasis. Autoantibody tests help to identify autoimmune diseases, and low ceruloplasmin levels in the diagnosis of WD. Targeted

NGS confirms monogenic disorders like WD, PFIC, and A1ATD. MRCP identifies the biliary anatomy, and elastography estimates the fibrosis of the organ. A liver biopsy is effective in cases of unclear diagnoses, syndromes, or in assessing inflammation and fibrosis. This approach improves the diagnostic precision, supports treatment planning, and minimizes invasive procedures [2, 19].

Emerging diagnostic advances and challenges

New diagnostic approaches are improving early identification of RLDs. Circulating microRNAs and cytokine techniques are used as non-invasive biomarkers for monitoring fibrosis and inflammatory activity thus reducing the need for repetitive biopsies [51, 62]. Multi-omics methods with genomic, epigenomic, proteomic, and metabolomic data help in precise molecular classification and targets pathways relevant for appropriate treatment. Machine-learning-driven imaging tools enhance the detection of structural liver changes, quantify fibrosis, and help to predict disease progression or therapeutic response more accurately than conventional evaluation [61].

CURRENT MANAGEMENT STRATEGIES

In PBC, ursodeoxycholic acid (UDCA) 13–15 mg/kg/day is the standard first-line therapy, improving liver enzymes, slowing fibrosis, and extending transplant-free survival. The British Society of Gastroenterology/UK-PBC guidelines state that most patients adhering to UDCA achieve near-normal life expectancy [49]. Around 40% show incomplete biochemical response (ALP >1.67 × ULN after 12 months) and need further therapy [26, 49]. Obeticholic acid (OCA), a selective FXR agonist, is used as second-line treatment. In the ENHANCE trial [37], 46% of patients on OCA 10 mg met the composite endpoint versus 10% on placebo. Its use is restricted in advanced cirrhosis due to hepatic failure risk and frequent pruritus requiring dose adjustment [37]. This has driven the search for safer FXR agonists. In a randomized study, Schramm et al. [63] reported that tropifexor reduced ALP by a placebo-adjusted mean of −18.3% at a 60-µg dose, though pruritus remained frequent (45%). PPAR agonists offer an alternative mechanism. In the phase 3 ENHANCE trial, seladelpar achieved a −42.4% mean reduction in ALP at 3 months with only 14% incidence of pruritus, indicating better tolerability. However, high costs of emerging therapies continue to limit access for PBC patients in resource-constrained settings [19, 37].

In WD, lifelong copper chelation is standard, with ongoing debate regarding the choice of initial chelator. Mohr et al. [52] observed that D-penicillamine carries a higher risk of early neurological worsening, making trientine the preferred choice in neurologically presenting cases. Gene therapy using adeno-associated virus (AAV) vectors to deliver ATP7B (e.g., UX701) is under evaluation in early-phase clinical trials (Phase 1/2, NCT04884815). Pöhler et al. [53] demonstrated in vitro correction of ATP7B mutations with CRISPR/Cas9, restoring copper transport but with limited editing efficiency in hepatocytes. RNA-based treatments are experimental due to vague delivery and durability issues. mRNA and gene-editing approaches face challenges in achieving safe and repeatable hepatocyte delivery. Liver transplantation is the definitive treatment, with over 85% 5-year survival in Wilson disease thus highlighting the need for disease-modifying therapies to reduce transplant dependence [56, 64].

Pediatric considerations

Early diagnosis and targeted treatment are essential in pediatric RLDs. The identification of ATP8B1, ABCB11, and ABCB4 mutations guides the therapeutic approaches in PFIC. Vitale et al. [15] reported that biliary diversion normalizes bile acids and relieves pruritus in over 80% of PFIC1 and PFIC2 cases, thus preventing transplantation. WD may appear in childhood as acute liver failure rather than the usual adolescent form. Chanpong et al. [51] observed that about 30% of pediatric WD cases present this way, often with deficient Kayser–Fleischer rings or low ceruloplasmin, and require ATP7B sequencing for confirmation. In A1ATD, neonatal cholestasis can resemble biliary atresia. Teckman et al. [46] showed that male children (73%) with early cholestasis are more likely to develop severe liver disease, supporting early genetic testing and close follow-up to identify progression risk and guide timely intervention.

Disease progression and monitoring

Many RLDs remain undetected until significant damage occurs. In alpha-1 antitrypsin deficiency (A1ATD), the hepatic buildup of misfolded Z-variant protein induces cellular stress and fibrosis. Hamesch et al. [55] in a large adult Pi*ZZ cohort, reported liver fibrosis in 35% (F≥2) and advanced fibrosis in 9% (F≥3), confirming the direct

hepatotoxicity of the retained protein. Although ongoing surveillance is recommended, the most effective strategy is uncertain. Tamber et al. [50] reviewed biomarker performance and noted that serum indices, including the ELF score, vary in reliability across different liver pathologies. Semi-annual ultrasound is standard but lacks sensitivity in HCC. Finotti et al. [56] advised that in A1ATD-related cirrhosis, combining ultrasound with cross-sectional imaging enhances early tumor detection and addresses the limitations of conventional screening.

EMERGING THERAPEUTIC APPROACHES

Gene therapy and gene editing

Gene therapy has evolved for monogenic liver diseases, though safety and biological challenges restrict its clinical translation. AAV vectors (AAV9) allow targeted hepatocyte delivery. UX701 aim to restore copper regulation and are under clinical evaluation [37]. AAV genomes remain episomal, leading to transgene loss as hepatocytes divide and limits the durability in children [65, 66]. CRISPR-Cas9 offers a corrective approach by repairing mutations in genes such as ATP7B and SERPINA1, with successful ATP7B correction shown by Pöhler et al. [53] who achieved successful ATP7B correction in murine models [27, 32]. High-fidelity nucleases have improved editing accuracy, but ongoing genomic monitoring and long-term safety evaluation remain essential before routine clinical use [67].

RNA-based therapeutics

Management of RLDs emphasizes targeted therapy; in Wilson disease, lifelong copper chelation with regular hepatic, neurological, and psychiatric monitoring remains the standard approach [4, 9, 52]. A1ATD management focuses on preventing chronic liver injury, as no therapy corrects protein misfolding; transplantation remains the only curative option in end-stage disease [12, 56]. PFIC and Alagille syndrome present overlapping challenges, requiring multidisciplinary care for pruritus, malnutrition, and portal hypertension before surgical intervention or transplantation [25, 49, 68]. Studies have emphasized the mechanism-based therapies. Gene therapy and genome editing, including CRISPR/Cas9, help in the repair of the causal mutations in A1ATD and WD, with successful preclinical gene correction [34, 53, 66].

FXR and PPAR agonists (e.g., Seladelpar) improve cholestasis and inflammation in PBC [37, 63]. Progress depends on better diagnostics, personalized care, and global registries that enhance clinical precision [61, 69, 70].

Cell-based therapies

Cell-based therapies are under investigation for rare liver diseases as alternatives or bridges to transplantation. Hepatocyte transplantation restores partial metabolic function in Crigler–Najjar syndrome and urea cycle defects but faces donor shortage, low engraftment, and short-lived benefit [56]. Transplanted hepatocytes show limited proliferation and survival within fibrotic tissue, as reported in early studies [34, 69]. Induced pluripotent stem cell (iPSC) technology provides a renewable autologous source of hepatocyte-like cells. Segeritz et al. [45] demonstrated that iPSC-derived hepatocytes model A1ATD, reduce misfolded protein buildup, and improve cell function, though issues with maturation, tumor risk, and cost persist. Mesenchymal stem cells (MSCs) have shown immunomodulatory, antifibrotic, and reparative effects. Verbeke et al. [71] reported benefits in experimental cirrhosis and acute-on-chronic liver failure, though maintaining viability and long-term safety limits clinical application. Verbeke et al. [71] demonstrated benefits in experimental cirrhosis and acute-on-chronic liver failure. Ensuring sustained cell viability, functional integration, and long-term safety remains the major barrier to clinical translation.

Pharmacological innovations

New molecular therapies target core mechanisms in RLDs, including protein misfolding, inflammation, and metabolic dysfunction. In A1ATD, pharmacologic chaperones correct Z-variant SERPINA1 misfolding and reduce hepatic accumulation [11]. In cholestatic RLDs, FXR agonist obeticholic acid and PPAR agonist seladelpar improve biochemical responses in PBC and PFIC [7, 37]. The APASL 2022 clinical guidance supports these pathway-specific treatments and promotes the development of immunomodulatory agents [17]. Some other candidates targeting oxidative stress, fibrogenesis, and immune checkpoints are in development [19]. High-throughput screening and multi-omics tools are accelerating the discovery of precise, mechanism-based therapies for RLDs.

Precision medicine and pharmacogenomics

Precision medicine is transforming RLD management by matching treatment to each patient's genetic and molecular profile. Detailed genotyping refines diagnosis, prognosis, and the selection of therapy. In WD, ATP7B variants influence presentation and chelator response; missense mutations often show milder hepatic disease, whereas truncating variants relate to earlier neurological onset and intolerance to D-penicillamine [4, 9, 52, 72]. Pharmacogenomic data aid in dose optimization and prediction of adverse reactions. In autoimmune and cholestatic RLDs, gene polymorphisms affecting drug metabolism and immune pathways modify therapeutic outcomes [63, 73]. In A1ATD, pharmacologic chaperones target the misfolded Z-SERPINA1 protein [11]. Multi-omics integration genomics, proteomics, metabolomics, and epigenomics supports biomarker identification and mechanistic insight [7, 12, 51, 55]. Proteomic and metabolomic studies in A1ATD and PBC reveal inflammatory and fibrotic pathways valuable for early detection and personalized disease management [61].

Patient-centered outcomes and quality of life

RLDs involve multiple organ systems and lead to fatigue, pruritus, growth delay, and neurocognitive impairment, all of which reduce daily activity and quality of life [2, 19, 49]. These complications are often more evident in children, resulting in emotional and social stress. Patient-reported outcomes (PROs) are applied to assess the impact of the disease and treatment response apart from biochemical markers [12, 19, 46]. HRQoL evaluation helps to individualize therapy and guide psychological, nutritional, and social interventions [19, 72]. Commonly used instruments like the PBC-40 for adults with PBC focuses on fatigue and itching problems [7, 49]; the Itch-NRS for pruritus in PFIC, PBC, and PSC; and the SF-36 for overall health [30, 72]. The CLDQ assesses broad hepatic symptoms [12, 19], and the PedsQL measures pediatric HRQoL in PFIC, WD, and A1ATD [1, 15, 50].

Health economics and accessibility

Gene therapy and RNA-based drugs and treatments have improved the treatment options for RLDs but has major affordability and access challenges, especially in low-

and middle-income countries [1, 56]. Market-driven pricing has led to uneven global distribution, with most patients continuing to depend on established therapies such as chelation or UDCA, while advanced options are limited to specialized centers [7, 21]. Reducing these disparities requires international funding support, fair pricing systems, and inclusion of RLDs' care within universal health programs [1, 74]

LIMITATIONS AND FUTURE DIRECTIONS

Early identification of RLDs is still a major challenge, owing to their early manifestations which overlap with common hepatic disorders and limited standardized diagnostic protocols. Certain RLDs like A1ATD, PBC, and PFIC are misdiagnosed for viral or metabolic liver disease, with delayed assessment and treatment [7, 12]. The existing pharmacologic approaches often eliminate symptoms without preventing disease progression, and access to molecular or gene-based therapies remains restricted by cost and availability [1, 19]. In PBC, OCA reduces the biochemical markers but causes dose-limiting pruritus, which complicates prolonged adherence [26, 37]. Studies now emphasizes personalized therapy guided by genetic and molecular data. Biomarkers such as circulating miRNAs, EVs, and autoantibodies are under study for early diagnosis [51, 62]. Emerging multicenter registries and CRISPR-derived technologies are expected to refine patient stratification and advance targeted intervention strategies [70, 74].

CONCLUSION

Management of RLDs continues to depend on drug therapy, nutritional optimization, and coordinated multidisciplinary care to stabilize function and delay in progression. Earlier recognition requires improved awareness and broader access to genetic testing. Advances in molecular biology and genomics are shaping precision-based approaches that employ validated biomarkers for early detection and monitoring. Long-term correction of inherited defects through gene and RNA therapies is under clinical evaluation. Thus, strengthening international associations and confirming unbiassed access to advanced treatments are necessary for improving prognosis and providing improved quality of life in affected individuals.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Classification of rare liver diseases with significant features

Classification RLDs	Disease name	Pathophysiology	Clinical presentation	Diagnosis	Management	References
Genetic / inherited	**Wilson's disease**	Defective *ATP7B* gene causing copper accumulation	Hepatic failure, neuropsychiatric manifestations	Serum ceruloplasmin, 24-h urinary copper, liver biopsy	Chelating agents (D-penicillamine), zinc therapy, liver transplantation	[4, 9, 29]
	Alpha-1 antitrypsin deficiency	Mutated *SERPINA1* gene leading to hepatic AAT retention	Neonatal hepatitis, cirrhosis, hepatocellular carcinoma	Serum AAT levels, genotyping, liver biopsy	Supportive care; liver transplantation if decompensated	[30, 31]
	Progressive familial intrahepatic cholestasis (pfic)	Mutations in bile transporter genes impairing bile flow	Infantile cholestasis, pruritus, progressive liver failure	Liver function tests, genetic analysis	Medical therapy, partial biliary diversion, liver transplantation	[32, 33]

	Hereditary hemochromatosis	*HFE* gene mutation leading to iron overload	Fatigue, cirrhosis, diabetes mellitus, cardiomyopathy	Serum ferritin, transferrin saturation, *HFE* genotyping	Phlebotomy, iron chelation therapy	[21, 34]
	Alagille syndrome	*JAG1* or *NOTCH2* mutations causing bile duct paucity	Cholestasis, cardiac anomalies, butterfly vertebrae	Clinical assessment, genetic testing, liver biopsy	Nutritional optimization, liver transplantation in advanced disease	[22]
Autoimmune	**Autoimmune hepatitis (AIH)**	T-cell–mediated destruction of hepatocytes	Fatigue, jaundice, transaminase elevation	Autoantibody profile, serum IgG, liver biopsy	Corticosteroids, azathioprine	[35, 36]
	Primary biliary cholangitis (PBC)	Autoimmune destruction of intrahepatic bile ducts	Pruritus, fatigue, cholestatic pattern	Antimitochondrial antibody (AMA), elevated ALP	Ursodeoxycholic acid, obeticholic acid, seladelpar	[7, 24]

	Primary sclerosing cholangitis (PSC)	Chronic inflammation and fibrosis of intra- and extrahepatic bile ducts	Cholestasis, association with IBD, risk of cholangiocarcinoma	MRCP, liver biopsy (if indicated)	No curative drug therapy; liver transplantation in advanced disease	[27, 37]
Other rare conditions	**Budd–Chiari syndrome**	Hepatic vein thrombosis causing venous outflow obstruction	Ascites, hepatomegaly, liver failure	Doppler ultrasonography, CT/MRI venography	Anticoagulation, TIPS, surgical shunts	[38]
	Congenital hepatic fibrosis	Ductal plate malformation with periportal fibrosis	Portal hypertension, splenomegaly	Imaging, liver histology	Supportive care; management of portal hypertension	[39]
	Glycogen sTORAGE dISEASE (hepatic types)	Enzyme defects in glycogen metabolism	Hypoglycemia, hepatomegaly, growth retardation	Enzyme assay, genetic testing, metabolic screening	Dietary modification, surveillance for hepatic adenomas	[40-42]
	Lysosomal acid lipase deficiency (LAL-D)	*LIPA* gene mutation causing lysosomal lipid accumulation	Hepatosplenomegaly, dyslipidemia, liver fibrosis	LAL enzyme assay, *LIPA* genotyping	Enzyme replacement therapy (sebelipase	[43]

					alfa)	

Abbreviations: WD: Wilson disease; A1ATD: Alpha-1 antitrypsin deficiency; PFIC: Progressive familial intrahepatic cholestasis; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; AAT: Alpha-1 antitrypsin; AMA: Anti-mitochondrial antibody; ALP: Alkaline phosphatase; IgG: Immunoglobulin G; MRCP: Magnetic resonance cholangiopancreatography; CT: Computed tomography; MRI: Magnetic resonance imaging; IBD: Inflammatory bowel disease; TIPS: Transjugular intrahepatic portosystemic shunt; ATP7B: ATPase copper-transporting beta; SERPINA1: Serpin family A member 1; HFE: Homeostatic iron regulator; JAG1: Jagged 1; NOTCH2: Notch receptor 2; LAL-D: Lysosomal acid lipase deficiency; LAL: Lysosomal acid lipase; LIPA: Lipase A, lysosomal acid type.

Table 2. Summary of current therapeutic and supportive management approaches in rare liver diseases

Management approach	Description	Diseases	Key interventions	References
Pharmacological treatments	Disease-specific therapies targeting underlying mechanisms or symptoms.	PBC, Wilson's disease	UDCA improves cholestasis and delays progression (PBC); Obeticholic acid (FXR agonist) for UDCA non-responders (PBC); Copper chelators (D-penicillamine, trientine) and zinc for copper excretion (Wilson's disease)	[7, 9, 26, 49, 52]
Nutritional management	Supplementation to correct malabsorption and prevent deficiencies associated with cholestasis.	PFIC, PBC	Fat-soluble vitamin (A, D, E, K) supplementation; Medium-chain triglycerides (MCTs) to enhance caloric intake and absorption	[2, 15, 68]
Surgical Interventions	Procedures to manage advanced liver damage and complications.	End-stage liver disease, Wilson's disease, PFIC, A1ATD	Liver transplantation as definitive treatment; Biliary diversion to reduce pruritus and cholestasis; Post-transplant surveillance for recurrence or complications	[9, 15, 25, 49]
Multidisciplinary	Collaborative management	All RLDs	Coordination between hepatologists, geneticists,	[2, 19, 50,

care	involving multiple specialties to address systemic and psychosocial aspects.		nutritionists, surgeons, and allied teams; Genetic counseling and family screening; Nutritional monitoring, especially in children; Psychological and educational support	72]
Pediatric considerations	Age-specific management strategies to address early disease onset and progression.	PFIC, Wilson's disease, A1ATD	Early genetic testing and family screening; Nutritional optimization with vitamin and MCT supplementation; Early surgical evaluation or transplant when indicated	[15, 30, 46, 50]
Monitoring and surveillance	Continuous evaluation of disease activity and long-term complications.	All RLDs	Periodic liver biochemistry and elastography; HCC surveillance with ultrasound ± cross-sectional imaging in cirrhosis; Monitoring of therapy adherence, nutritional status, and psychosocial well-being	[12, 19, 26, 55, 56]

Abbreviations: RLDs: Rare liver diseases; PBC: Primary biliary cholangitis; PFIC: Progressive familial intrahepatic cholestasis; A1ATD: Alpha-1 antitrypsin deficiency; UDCA: Ursodeoxycholic acid; FXR: Farnesoid X receptor; MCT: Medium-chain triglycerides; HCC: Hepatocellular carcinoma.

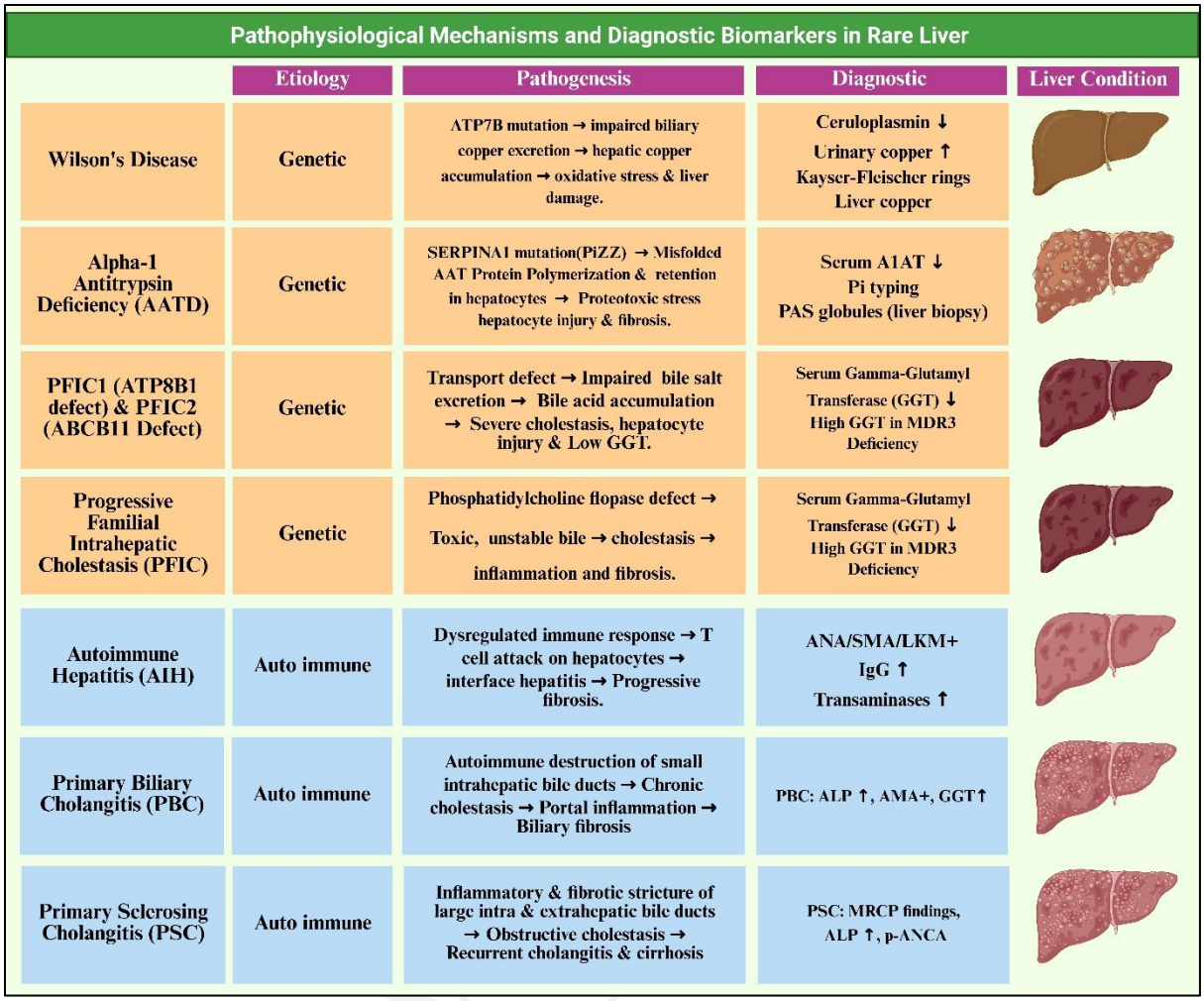

Figure 1. Pathophysiological mechanisms and diagnostic biomarkers in rare liver diseases. Schematic overview of key pathogenic pathways and diagnostic biomarkers enabling early detection and monitoring in rare liver diseases, with the influence of modifier genes and epigenetic regulators on disease severity, phenotypic variability, and therapeutic response.

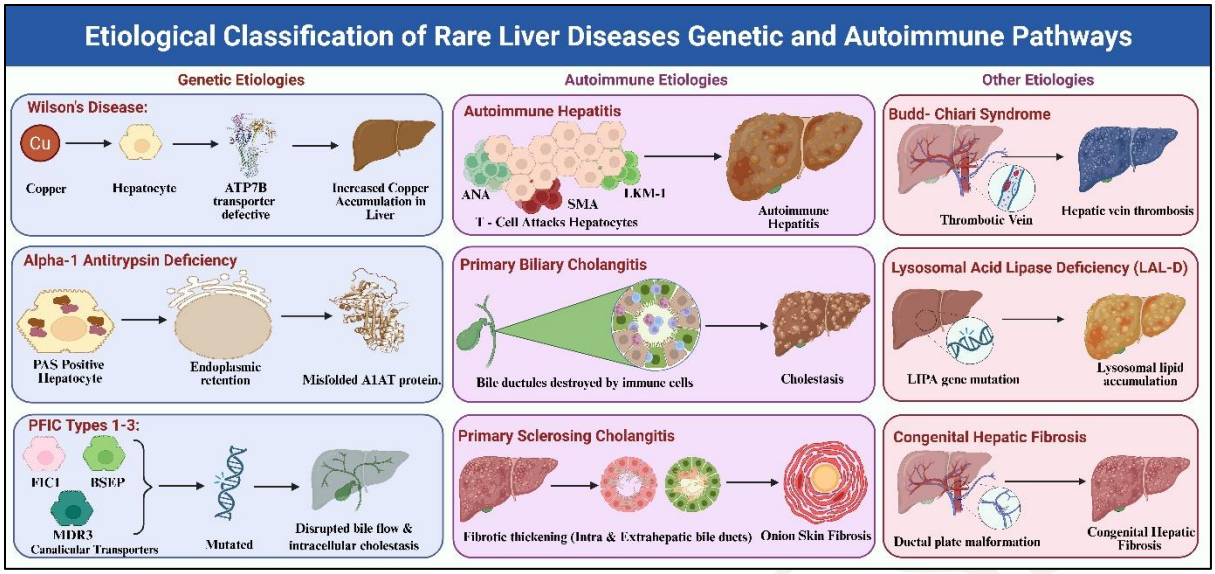

Figure 2. Etiological classification of rare liver diseases: Genetic and autoimmune pathways. Panels depict exemplar disorders within genetic (Wilson disease, A1ATD, PFIC1–3) and autoimmune (AIH, PBC, PSC) categories, highlighting key molecular defects and characteristic lesions. Abbreviations: A1ATD: Alpha-1 antitrypsin deficiency; PFIC: Progressive familial intrahepatic cholestasis; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

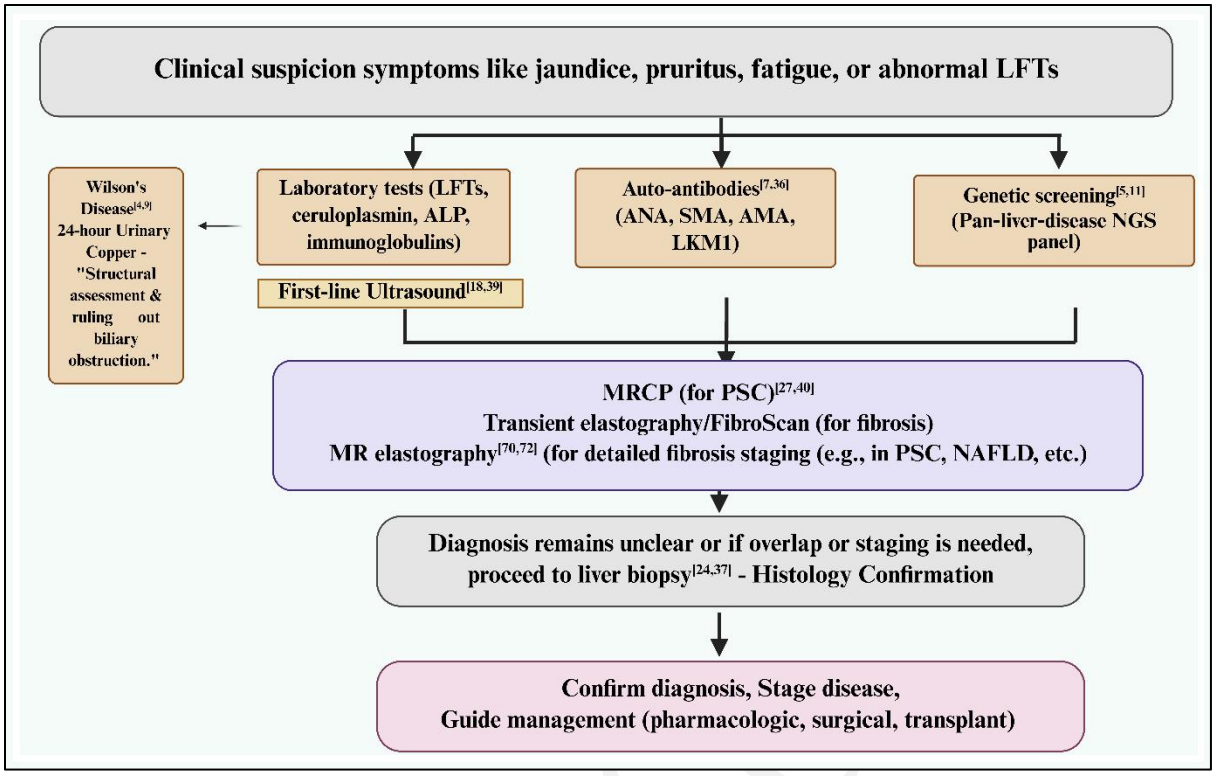

Figure 3. Stepwise diagnostic algorithm for rare liver diseases. From the initial clinical suspicion, the pathway incorporates baseline laboratory testing alongside first-line ultrasound, serologic autoantibody assessment, and targeted genetic screening. Cholangiopathy and fibrosis are evaluated using MRCP (for suspected PSC) and elastography—specifically transient elastography (FibroScan) and MR elastography. Testing for Wilson's disease, through 24-hour urinary copper measurement, is included when clinically indicated. If the diagnosis remains uncertain or if staging is necessary, a liver biopsy should be performed for histological confirmation. This process enables the confirmation of the diagnosis, staging of the disease, and guidance for pharmacological, surgical, or transplant management. Abbreviations: LFTs: Liver function tests; ALP: Alkaline phosphatase; ANA: Antinuclear antibody; SMA: Smooth muscle antibody; AMA: Anti-mitochondrial antibody; LKM1: Liver–kidney microsomal antibody type 1; NGS: Next-generation sequencing; MRCP: Magnetic resonance cholangiopancreatography; PSC: Primary sclerosing cholangitis; MR: Magnetic resonance; NAFLD: Non-alcoholic fatty liver disease.