

AGA SECTION

Multi-Society Expert Panel Consensus Guidance Regarding Clinical Assessment and Clinical Trial Endpoints in Adults With Alpha-1 Antitrypsin Deficiency–Associated Liver Disease



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Nomenclature & Diagnosis	Staging & Monitoring	Clinical Trials												
AATD-LD Alpha-1 antitrypsin deficiency-associated liver disease  adults with PiZZ genotype, elevated AST, ALT, or GGT, and/or $\geq$ F2 on NIT  Use biopsy only when needed. Prioritize non-invasive testing (NIT) for screening, diagnosis/staging and monitoring.	<table border="1"> <thead> <tr> <th>Risk</th> <th>VCTE LSM</th> <th>Monitoring</th> </tr> </thead> <tbody> <tr> <td>Low</td> <td>< 8 kPa</td> <td>2–3 yrs</td> </tr> <tr> <td>Intermediate</td> <td>8–15 kPa</td> <td>1–2 yrs</td> </tr> <tr> <td>High</td> <td>$\geq$ 15 kPa</td> <td>1 yr</td> </tr> </tbody> </table>	Risk	VCTE LSM	Monitoring	Low	< 8 kPa	2–3 yrs	Intermediate	8–15 kPa	1–2 yrs	High	$\geq$ 15 kPa	1 yr	Phase 3 primary endpoint: $\geq$ 1 stage improvement in fibrosis over 2 years  (secondary and exploratory endpoints also identified)
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Gastroenterology

BACKGROUND & AIMS: Alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD) remains underrecognized despite its significant contribution to morbidity and mortality in adults with the PiZZ genotype. Lack of standardized definitions, diagnostic criteria, and staging impedes timely diagnosis and therapeutic development. To address these gaps, a multi-disciplinary expert panel convened under the auspices of the American Gastroenterological Association in collaboration with the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Alpha-1 Foundation to develop consensus recommendations for nomenclature, diagnosis, staging, and clinical trial endpoints in AATD-LD. **METHODS:** An international multi-disciplinary expert consensus synthesized data from recent epidemiologic, histopathologic, and noninvasive biomarker studies related to AATD-LD. Expert

opinion was integrated with published evidence to establish case definitions, staging algorithms, and clinical trial endpoint criteria. **RESULTS:** AATD-LD is defined by the presence of liver enzyme (ie, aspartate aminotransferase, alanine aminotransferase, or γ -glutamyl transferase) elevations—which may be episodic—and/or liver fibrosis ($\geq$ F2) in adults with AATD, particularly those with the PiZZ genotype. Liver stiffness measurement by means of noninvasive elastography (eg, vibration-controlled transient elastography and magnetic resonance elastography) was identified as the preferred method for staging fibrosis, with liver stiffness measurement $\geq$ 8 kPa by means of vibration-controlled transient elastography as a threshold for clinically significant fibrosis. Aspartate aminotransferase-to-platelet ratio (<0.5) and fibrosis-4 index (<1.3) (low risk for advanced liver disease) were endorsed for risk stratification, although their sensitivity is

limited. A foundational, tiered algorithm was developed to guide longitudinal monitoring and staging, incorporating serial noninvasive testing and timely referral for liver transplantation evaluation. For clinical trial design, adults with F2–F4 fibrosis were recommended for inclusion in phase 3 trials; earlier stages (eg, F1) may be appropriate for phase 1–2 safety studies and patients with cirrhosis may be excluded, depending on therapeutic class. Preservation of pulmonary function was not deemed necessary for inclusion in trials of therapies that increase AAT levels via DNA or RNA editing. The consensus primary efficacy endpoint is a ≥ 1 -stage improvement in fibrosis. **CONCLUSIONS:** These consensus statements provide a unified framework for diagnosing, staging, and studying AATD-LD. Broad adoption will improve disease recognition, optimize clinical management, and facilitate therapeutic development.

Keywords: Chronic Liver Disease; Fibrosis; Liver Stiffness; Noninvasive Testing.

Alpha-1 antitrypsin deficiency (AATD) is a rare inherited disorder caused by sequence variations in the SERPINA1 gene, resulting in reduced serum levels and dysfunctional forms of the alpha-1 antitrypsin (AAT) protein. These sequence variations follow an autosomal codominant inheritance pattern and can lead to lung and liver disease, particularly in adults with severe deficiency. Although AATD is widely recognized for its association with early-onset pulmonary emphysema, its hepatic manifestations such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) are additionally significant in terms of morbidity and mortality, yet often remain underdiagnosed and underappreciated in clinical practice.^{1,2} The Z allele, which results in a Glu342Lys substitution in the AAT protein, is the most common pathogenic variant associated with AATD. Adults who are homozygous for the Z allele (PiZZ genotype) have a higher risk of developing liver disease, although the severity and onset can vary depending partly on additional genetic factors and, most importantly, environmental factors. Epidemiologic studies estimate that approximately 10% of adults with the PiZZ genotype develop clinically significant liver disease, including cirrhosis and HCC³ (Figure 1).

The pathogenesis of AATD-associated liver disease (AATD-LD) involves the accumulation of misfolded AAT protein within the endoplasmic reticulum of hepatocytes, leading to cellular stress, inflammation, and subsequent fibrosis. This "toxic gain-of-function" mechanism distinguishes hepatic involvement from the protease-antiprotease imbalance observed in pulmonary disease.⁴ Notably, the clinical presentation of AATD-LD is heterogeneous, ranging from asymptomatic elevations in liver enzymes to advanced liver fibrosis and cirrhosis. Factors such as age, male sex, metabolic syndrome, alcohol use, and other coexisting liver insults (eg, viral hepatitis)⁵ have been identified as modifiers of disease progression.

Despite its clinical significance, AATD-LD remains underdiagnosed, partly due to the lack of standardized nomenclature and diagnostic criteria and the absence of

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Liver disease is an underrecognized complication of alpha-1 antitrypsin deficiency (AATD), especially in adults with the PiZZ genotype, due in part to a lack of standardized definitions and diagnostic pathways and no approved therapies for the treatment of liver disease. Novel therapies are emerging for the treatment of liver disease associated with AATD.

NEW FINDINGS

This international consensus group proposed unified nomenclature, diagnostic criteria, staging algorithms, and clinical trial endpoints to better identify and manage liver disease associated with AATD. The safety, efficacy, and mechanisms of action of novel therapies for liver disease associated with AATD are discussed.

LIMITATIONS

Recommendations are based on available evidence and expert consensus but will require validation in large prospective or interventional studies across diverse patient populations.

CLINICAL RESEARCH RELEVANCE

This consensus guidance offers a practical framework for diagnosing and staging AATD-related liver disease using noninvasive tests. This is expected to assist clinicians to detect and manage liver disease in these patients earlier and more consistently, particularly in patients with the PiZZ genotype.

BASIC RESEARCH RELEVANCE

Misfolded Z-AAT accumulation in hepatocytes offers a tractable model for studying intracellular proteotoxic stress. This mechanism underpins AATD-associated liver disease and may share fibrogenic signaling pathways with other liver disorders. Ongoing research into these pathways may illuminate broader principles of hepatocyte injury, fibrosis, and therapeutic targets beyond AATD.

approved therapies for this liver condition. In addition, the variability in terminology and diagnostic approaches hamper the identification of affected adults and the development of targeted therapies. A previous report from a multi-stakeholder forum revised new biomarkers and clinical drug development in AATD, but did not address the variability in terminology and diagnostic approaches.⁶ To

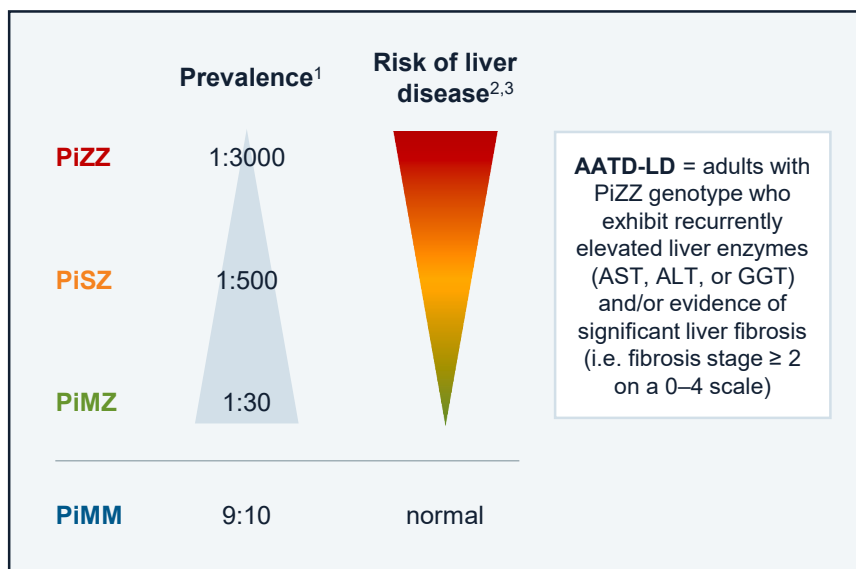
Abbreviations used in this paper: AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency; AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FIB-4, fibrosis-4 index; GGT, γ -glutamyl transferase; HCC, hepatocellular carcinoma; KCO, transfer coefficient of carbon monoxide; LSM, liver stiffness measurement; MALO, major adverse liver outcome; MRE, magnetic resonance elastography; NIT, noninvasive test; VCTE, vibration-controlled transient elastography; Z-AAT, misfolded Z-protein polymers.

 Most current article

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Figure 1. Risk of liver disease by AATD genotype. ¹Prevalence of AATD genotypes in White individuals. ²Risk of liver disease from genetic mutation alone. ³Of the AATD genotypes, PiZZ has the lowest prevalence but the highest risk of liver disease from the genetic mutation alone.



address these gaps, we convened a multi-disciplinary round table conference, hosted by the American Gastroenterological Association (in collaboration with the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Alpha-1 Foundation) to delineate a unified nomenclature and diagnostic framework for AATD-LD. This effort reflects a growing recognition of the need for precise classification to support early diagnosis, risk stratification, and therapeutic decision making.⁷ The consensus statement is timely because there are emerging novel therapies for liver disease associated with AATD that are anticipated to become (or are) available within the next year.

This article summarizes the outcomes of that meeting, including proposals for disease nomenclature, case definitions, and diagnostic criteria focused on adults. With the establishment of clear guidance, we aim to enhance clinical recognition, align research efforts, and ultimately improve outcomes for adults affected by AATD-LD.

Proposed Nomenclature: Alpha-1 Antitrypsin Deficiency–Associated Liver Disease

Patients with the PiZZ genotype have an approximately 20-fold increased risk (vs wild type) of advanced liver fibrosis compared with patients with heterozygous (ie, PiMZ) and compound heterozygous (ie, PiSZ) genotypes, who have 2 and 3 times elevated risks^{2,8} (Figure 1).

Because the risk of PiZZ-associated liver fibrosis is much higher, the term *alpha-1 antitrypsin deficiency-associated liver disease* would usually be applied to adults with the PiZZ genotype.⁸ However, patients with PiMZ and PiSZ genotypes often have additional comorbid conditions such as diabetes, obesity, or excessive alcohol use^{2,9} noted at the time of clinical liver disease diagnosis. Therefore, clinical trials that show efficacy coincident with

modification of the Z protein will be needed to determine how often patients with MZ and SZ genotypes have improvement and fall within the nomenclature boundaries for AATD-LD. Individuals with an AAT serum level <57 mg/dL with severe AATD-LD¹⁰ generally have the PiZZ genotype. Approximately 5% have non-Z alleles and may not have misfolded AAT production in the liver. Some variants such as the null variants may produce no protein and have no liver risks. Therefore, genotyping is important and recommended for all adults with liver disease and a low AAT serum level. An experienced AATD center should be involved for genotyping, family counseling, and management.

Although cross-sectional studies have described clinically significant liver fibrosis in 20%–36% of PiZZ genotypes,^{11,12} serum transaminases (ie, serum alanine aminotransferase [ALT] and aspartate transaminase [AST]) often remained within the normal range.^{2,11,12} For example, 3 cross-sectional studies^{2,11,12} reported elevated liver function tests only in 11%–24% of patients (AST, 13%–15%; ALT, 11%–19%; γ -glutamyl transferase [GGT], 13%–24%) with abnormal findings more common in patients with comorbid conditions, such as obesity or diabetes.²

The fact that liver function tests often remain within the normal range in patients with ZZ makes the detection of liver disease particularly challenging. As in other liver disorders, histologic evaluation of liver fibrosis remains the (imperfect) reference standard and is typically based on the METAVIR Histologic Scoring System.¹¹ Liver fibrosis assessment using blood-based tests, including AST-to-platelet ratio (APRI) or fibrosis-4 index (FIB-4), and imaging-based tests, which measure liver stiffness (liver stiffness measurement [LSM]) via vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) constitute noninvasive liver fibrosis tests that have been validated against liver biopsy^{11,13} and have been found to predict the

development of major adverse liver outcomes (MALOs) in a longitudinal study that assessed more than 700 adults.⁵ Ultrasound may be considered at the time of diagnosis of AATD-LD and is currently only recommended for HCC screening and surveillance in those with cirrhosis. Among liver function tests, GGT also correlated with both histologic fibrosis and MALO development, and AST and ALT appear to be somewhat less accurate.^{5,11,13} Notably, several studies found that persistently elevated liver function tests are associated with an increased risk of MALOs,^{3,5} thereby confirming their clinical relevance.

Although direct evidence linking histologic liver fibrosis to MALOs in adults with the PiZZ genotype is limited, as it is a rare disease, fibrosis stage has well-established prognostic value across many other chronic liver diseases.^{14–16} At the same time, LSM was proposed as the preferred noninvasive liver fibrosis surrogate by both a recent European Association for the Study of the Liver Clinical Practice Guideline and a recent expert Delphi panel study.^{7,10} Data concerning the intra-subject variability of LSM via transient elastography in AATD-LD will be accumulated in current clinical trials; however, limited reproducibility is known from other contexts and variability also occurs in liver biopsy sampling and scoring.^{17,18}

Proposed Definition: Adults With PiZZ Genotype Who Exhibit Recurrently Elevated AST/ALT/GGT and/or the Presence of Fibrosis

Based on the above considerations, we propose AATD-LD be defined as adults with PiZZ genotype who exhibit recurrently elevated liver enzymes and/or evidence of significant liver fibrosis (ie, fibrosis stage ≥ 2 on a 0–4 scale). Regarding the former, we propose considering elevations in AST, ALT, or GGT, given the established relevance of the former 2 parameters in various liver disorders and convincing data regarding the relevance of GGT in patients with the PiZZ genotype.^{5,19,20} For LSM, we propose a cutoff of 8 kPa via VCTE. This value is in line with current guidelines for noninvasive liver fibrosis testing, as well as with a Delphi panel study that recommended LSM as the preferred method of liver fibrosis evaluation in AATD.^{7,21,22} Notably, this cutoff is similar to the one used in a recent longitudinal study.⁵ Unlike LSM, less evidence is available for other noninvasive liver fibrosis tests. For APRI and FIB-4, cutoffs of 0.5 and 1.3 units,⁵ respectively, might be used to rule out AATD-LD. Although values below these cutoffs were associated with a very low risk of MALOs during a median follow-up of 3.5 years, an FIB-4 < 1.3 was seen in approximately 50% of the cohort and this fact limits its utility as a triage tool.⁵ Notably, similar cutoffs have been used in other liver disease etiologies.²² Although few data are available regarding the use of MRE in AATD,²³ a level of 3 kPa has been associated with clinically significant fibrosis in other liver diseases and is likely to be appropriate in AATD.²²

AATD-LD Case Detection

Chronic liver disease in patients with AATD is defined as repeatedly elevated liver enzymes and/or evidence of significant liver fibrosis by any means. The diagnostic evaluation of chronic liver disease should include testing for AATD by means of determining the serum AAT level. This is an inexpensive test that is typically abnormal in severe deficiency genotypes (eg, ZZ). The diagnostic approach for any patient who may potentially have AATD-LD should begin with levels $< 11 \mu\text{M}$ (57 mg/dL). Genotyping is necessary (Figure 2) to comprehensively determine carrier genotypes (MZ) because AAT is an acute-phase reactant and serum levels can be in the normal range under physiologic stress. Genotyping is more expensive but embraced by many liver centers. Notably, the diagnostic approach for any patient who may potentially have AATD-LD should begin with a presumed diagnosis. Importantly, suspected or confirmed evidence of steatotic liver disease does not preclude testing for AATD, as both conditions overlap, with the Z allele amplifying liver fibrosis progression.²⁵

In addition, AATD-LD case finding is indicated in patients with a family history of AATD or an individual history of neonatal cholestasis or associated extrahepatic conditions: emphysema, chronic obstructive pulmonary disease (COPD), asthma with airflow obstruction that is incompletely reversible, unexplained bronchiectasis, necrotizing panniculitis, or granulomatosis with polyangiitis²⁶ (Figure 2).

For case finding, low serum levels should be followed by confirmatory testing by genotyping (preferred) or alternatively phenotyping by isoelectric focusing, depending on local availability.¹⁰ Optimally, AAT levels should be determined in the absence of systemic inflammation (ie, normal C-reactive protein) because it is an acute-phase protein. However, some patients with chronic liver disease have a persistent slight elevation of C-reactive protein, which is reflective of systemic inflammation.^{27,28} A patient with MZ may have a normal serum level of AAT and require a genotype to diagnose. Severe AATD-LD is almost certain to be below the $< 11 \mu\text{M}$ (57 mg/dL) threshold.^{16,29,30} Given that heterozygosity for the Z allele (most commonly PiMZ) may contribute to liver disease progression, particularly in the presence of cofactors, and is associated with outcomes such as progression to cirrhosis in steatotic liver disease,²⁵ as well as development of hepatic decompensation,^{31,32} genotyping remains important not only for emerging clinical trials (Table 1), but also for family testing and risk stratification in adults with mild deficiency of AAT.

Proposed Algorithm for Diagnosis and Risk Stratification and Candidates for Treatment

AATD-LD Staging: How to Assess Liver Risk

Adults with the PiZZ genotype should undergo liver fibrosis staging using noninvasive means, including blood-based and imaging-based approaches. Although these tools have not been extensively validated against histology in AATD-LD, a recent

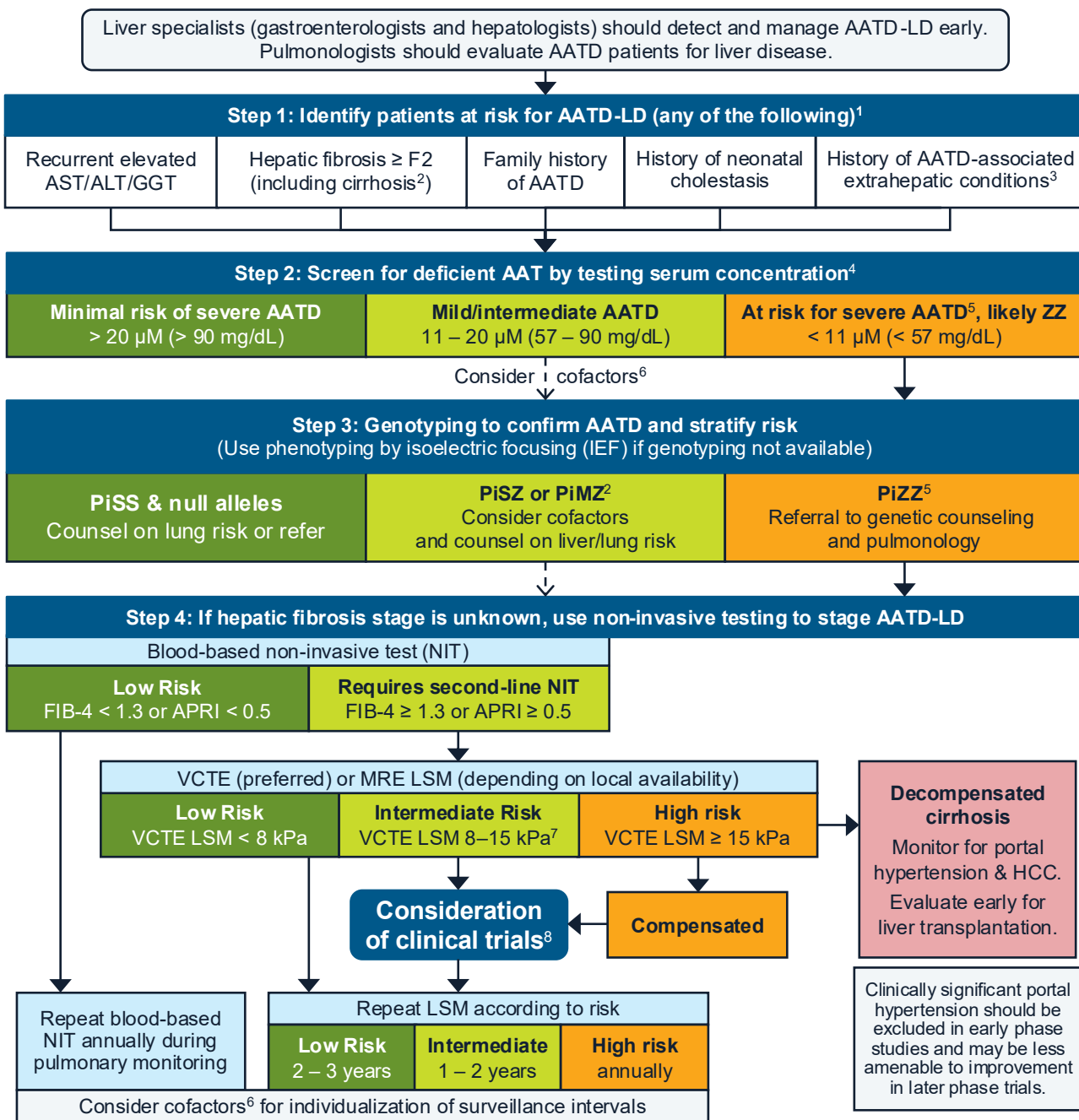


Figure 2. Algorithm for screening, diagnosis, and risk stratification of AATD-LD. ¹Can be used to identify candidates for treatment in clinical trials. ²Anyone with cirrhosis or being evaluated for liver transplantation should be tested for AATD. A presumed diagnosis of steatotic liver disease (SLD) does not preclude testing for AATD as both conditions overlap, with the Z allele amplifying liver fibrosis (progression).⁹ ³AATD-associated extrahepatic conditions: emphysema, COPD, asthma with airflow obstruction that is incompletely reversible, unexplained bronchiectasis, necrotizing panniculitis, or granulomatosis with polyangiitis.²⁴ ⁴AAT levels should be determined in the absence of systemic inflammation (ie, normal C-reactive protein) because it is an acute-phase protein. ⁵Severe AATD-LD (PiZZ) is almost certain to be below the $< 11 \mu\text{M}$ (57 mg/dL) threshold. ⁶Cofactors such as obesity, diabetes mellitus, and excessive alcohol consumption increase the liver risk. ⁷Consider liver biopsy for definitive diagnosis. ⁸Our focus is on F2–F4 for phase 3 trial design. Patients with cirrhosis may be excluded, depending on therapeutic class. F1 may be appropriate for phase 1–2 safety studies.

Table 1. Investigational Therapies for AATD in Human Trials^a

Target organs	Candidate	Mechanism of action	Approach/delivery system	Stage of development
Liver and lung	BEAM-302 (Beam Therapeutics)	DNA editing	Intravenous infusion	Phase 1/2b
	WVE-006 (Wave Life Sciences)	RNA editing	Lipid nanoparticle Subcutaneous injection	Phase 1/2b
	KRRO-110 (Korro Bio)	RNA editing	RNA editing oligonucleotide Intravenous infusion Oligonucleotide encapsulated in lipid nanoparticle	Phase 1/2a
Liver	Fazirsiran (Arrowhead and Takeda)	Small interfering RNA	Subcutaneous injection	Phase 3
	BMN-349 (BioMarin)	Chaperone	Silencing RNA Oral Stabilizer of monomeric Z-AAT to prevent polymerization in patients with PiMZ and PiZZ genotypes	Phase 1
Lung	Kamada-AAT (Kamada)	AAT protein replacement	Nebulized	Phase 3
	INBRX-101 (Sanofi)	AAT protein replacement	Daily delivery of AAT Intravenous infusion	Phase 2/3
	Alvelestat (Mereo BioPharma)	Neutrophil elastase inhibitor	Bivalent Fc fusion protein Oral	Phase 2
	KB-408 (Krystal Biotech)	Gene therapy	Protease inhibitor Nebulized Delivery of full-length SERPINA1 by an HSV-1 vector	Phase 1

^aIn order by target organ then stage of development, with most advanced first.

longitudinal study linked them to liver-related outcomes, supporting their utility for clinical risk estimation.⁵

Blood-based indices such as the FIB-4 score and the APRI can help identify adults at low risk of short-term liver-related events. In a European cohort, thresholds of FIB-4 <1.3 and APRI <0.5 captured 49%–77% of patients in this low-risk category.⁵ In such cases, second-line testing may not be necessary. Longitudinal reassessment using these same blood-based tools—such as during routine pulmonary follow-up—may offer a practical approach to ongoing liver disease monitoring in this population.

Alternatively, patients may also be directly referred for LSM via VCTE or MRE. The reasons for this are the rarity of the condition, which results in a low strain on health systems, and the broadening of the indication for second-line noninvasive tests (NITs), as well as the high pretest probability of liver fibrosis in patients with AATD-LD.

LSM assessed via VCTE from AATD-LD testing should be interpreted as a continuum of risk. Of note, patients with an LSM via VCTE <8 kPa are deemed low risk (significant fibrosis unlikely), LSM 8–15 kPa defines intermediate risk (likely significant to advanced fibrosis), and those with LSM ≥15 kPa are at high risk (likely cirrhosis) of MALOs. Although the currently available evidence does not allow firm recommendations on intervals for repeating LSM via VCTE, intervals of every 2–3 years seem reasonable for those with LSM <8 kPa, and closer follow-up (1–2 years) seems appropriate for those with LSM 8–15 kPa.⁷ In those

with LSM >15 kPa (ie, advanced chronic liver disease), yearly LSM assessment by means of VCTE as well as surveillance for HCC and management of portal hypertension are recommended (see below for details).^{7,33} The above-mentioned intervals for repeating LSM via VCTE should be individualized, considering risk factors for liver fibrosis (and thus, its presumed progression), in particular obesity¹² and potentially diabetes. Obesity is an important target for lifestyle intervention in AATD-LD, although the evidence supporting this recommendation is limited to its link to liver fibrosis (severity) assessed by means of NITs in observational studies. Although AATD-LD-specific data on the impact of alcohol consumption on liver fibrosis (progression) remain less conclusive,³⁴ alcohol consumption may be considered as a cofactor when deciding on surveillance intervals. Analogous to steatotic liver disease, patients with AATD-LD should be cautioned regarding the risks associated with consuming alcohol and those who are candidates for treatment should completely and permanently stop alcohol consumption.^{35,36}

Shear-wave elastography and MRE may serve as alternatives to VCTE for liver stiffness assessment in AATD-LD, depending on local availability and cost. Although these methods have not been specifically validated in this population, their utility is supported by broader experience in other liver diseases and a limited series of histologically evaluated AATD cases.²³ The enhanced liver fibrosis test has not been validated against liver biopsy or clinical

outcomes in AATD-LD, and its role in staging remains uncertain, although a recent study by Kappe et al³⁷ did find that enhanced liver fibrosis values correlated with advanced cirrhosis.

Liver biopsy is not required for establishing the diagnosis of AATD-LD, although it may be indicated in select cases to establish or exclude additional factors contributing to liver disease. Histologic staging of liver fibrosis is currently considered an imperfect reference standard. For the purpose of staging, NITs that have been validated vs histologic fibrosis and/or MALOs are preferable over liver biopsy in AATD-LD, as the latter is impractical for monitoring the longitudinal evolution in this genetic liver disease.

HCC Surveillance, Portal Hypertension Management, and Liver Transplantation

The indication for HCC surveillance^{38,39} and portal hypertension management^{33,40} should be based on published recommendations for the management of cirrhosis due to any etiology. Notably, after the development of first hepatic decompensation (ie, clinically evident ascites, variceal bleeding, or overt hepatic encephalopathy), patients with decompensated AATD-LD may have a higher risk of further decompensation, acute-on-chronic liver failure, requirement for liver transplantation, or death compared with other etiologies.⁴¹ Therefore, early consideration for liver transplantation is warranted in patients with decompensated AATD-LD. Given that liver transplantation is the only curative option for decompensated AATD-LD, and these patients may have higher risks of post-transplantation complications compared with other etiologies, early referral to a center with expertise in both transplant hepatology and AATD-LD is strongly recommended. Any patient with decompensation, including ascites, variceal bleeding, or hepatic encephalopathy, should be evaluated promptly to facilitate timely transplant listing and optimize pretransplantation care.

Proposed Changes to Clinical Trial Endpoints, Inclusion Criteria, and Exclusion Criteria

No regulatory guidance for AATD-LD drug development is available, but a critical need for an effective therapy remains. Liver transplantation is the only option for decompensated cirrhosis and is challenging in patients with pulmonary disease. A review of [ClinicalTrials.gov](https://clinicaltrials.gov) showed several investigational therapies are being tested in clinical trials (Table 1). For liver disease, results from phase 2 studies of a small interfering RNA inhibitor, fazirsiran, showed promise.^{42,43} For lung disease, novel forms of AAT protein replacement therapy are in phase 2b/3 trials. However, the tribulations of therapeutic drug development in AATD are revealed by the number of recently discontinued programs (Supplementary Table 1). An improved

understanding of disease mechanisms allows a variety of therapeutic targets for drug therapy.

Unique challenges are present in AATD, which require special consideration in clinical trial design. First, it is a rare disease, so patient identification and study recruitment will take additional time and effort. In fact, there are not sufficient numbers of identified patients with ZZ in the world to fill all the studies being planned.⁴⁴ Second, study sample sizes will necessarily be comparatively small, which may limit the ability to detect small but clinically relevant differences between treatment and placebo groups from a statistical point of view. Endpoints as well as assessment timepoints must therefore be thoughtfully selected, allowing for a substantial difference between treatment with placebo. Sponsors should focus on quality data collection to reduce noise and variability in outcome measurements. Third, adult onset of ZZ liver disease occurs after years without symptoms. Although knowledge of the natural history of liver disease in AATD has improved,^{5,45} gaps persist around time to progression of fibrosis. This is particularly relevant to phase 3 study length and when to measure outcomes. Fourth, there is considerable intra-individual variability in AAT levels. In a recent study, Haillot and colleagues⁴⁶ evaluated 255 patients with COPD in a community respirology practice. The between-measurement agreement was weak, and statistical analysis revealed wide limits of agreement. Finally, adults with AATD may also have clinically relevant lung disease, but patients should not be excluded from liver-directed therapy for this reason. Rather, trial design should harmonize the specific therapeutic mechanism's pulmonary safety concerns with enrolling a patient population representative of those who would benefit from an approved therapy because lung and liver disease overlap in many adults with ZZ and the historic median forced expiratory volume in 1 second (FEV₁) in the US population diagnosed with AATD is approximately 50% predicted.^{11,24}

Inclusion and Exclusion Criteria for Clinical Trials

Considering the burgeoning therapeutic landscape in AATD, what population of patients are appropriate for inclusion in clinical trials for AATD-LD? Trial design should attempt to mitigate the challenges outlined above while accounting for the following factors: phase of the clinical trial, mechanism of the investigational therapy, and safety profile of the investigational agent. It is beyond the scope of this document to address early-phase clinical trials, so our focus is on phase 3 trial design.

A consensus around broad study inclusion criteria shown in Table 2 was developed. For therapies that reduce the toxic accumulation of Z-AAT, such as small interfering RNA therapy, chaperones, and corrector molecules, the ideal study population would be adults with ZZ with significant liver fibrosis (F2–F4) and accumulated Z-AAT within the liver. LSMs are linked to hepatic outcomes in

Table 2. Inclusion and Exclusion Criteria for Clinical Trials

Inclusion criteria (all of the below)	Exclusion criteria
PiZZ genotype ^a	Decompensated liver disease Clinically significant portal hypertension should be excluded in early phase studies and may be less amenable to improvement in later phase trials.
Clinically significant liver fibrosis (F2–F4) ^b by any method (FIB-4, APRI, VCTE, MRE, or biopsy).	
FEV ₁ % predicted ^c >50% predicted for therapies that inhibit Z-protein production and require long-term treatment. Consider lower value with drug mechanisms that increase release of functional AAT into circulation. Consider adaptive trial designs when pulmonary safety is proven early. Enrollment should be more inclusive in later cohorts because many patients with AATD have very low lung function.	

^aPatients with PiZZ genotype have a much greater risk of advanced liver fibrosis. In the future, clinical trials that show efficacy coincident with modification of the Z protein will be needed to determine how often patients with MZ and SZ genotypes have improvement and fall within the nomenclature boundaries for AATD-LD.
^bOur focus is on F2–F4 for phase 3 trial design. Patients with cirrhosis may be excluded depending on therapeutic class. F1 may be appropriate for phase 1–2 safety studies.
^cMay change in future as additional long-term safety data emerge.

adults with ZZ.⁵ Thus, including patients with established liver fibrosis in clinical trials focuses therapeutic development on the ZZ population at highest risk for complications of liver disease.

When investigational therapies that involve DNA or RNA editing within the liver move into phase 2b/phase 3 studies, the trial design should consider a stepwise approach toward including adults with significant liver disease. Initial trial participants could have minimal risk of liver fibrosis by means of NIT. Expanding the study population to adults with fibrosis, and then eventually enrolling patients with cirrhosis, may be appropriate when safety data increase. This is an opportunity for sponsors and regulatory agencies to consider novel adaptive clinical trial designs to provide the evidence of benefit needed for regulatory approval, while serving the needs of all stakeholders.

Clinical Trial Endpoints

The pathway for drug approval is based on either a clinical benefit endpoint or a surrogate endpoint considered reasonably likely to predict a clinical benefit. The long duration over which AATD-LD clinical outcomes occur makes it impractical to design a trial with a clinical outcome as a primary outcome because AATD-LD is a rare disease and time to clinical events may take several years or even decades. Therefore, it is prudent to identify clinical trial endpoints that are reliable surrogates linked to disease pathogenesis and those that can be achieved within a reasonable timeframe. Early engagement with regulators to ensure that all parties understand these concepts is likely to be required.

Based on current understanding of the pathogenesis of AATD-LD, the accumulation of misfolded Z-protein (Z-AAT) in the hepatocytes is the probable driver or cause that is

associated with inflammation and progression of liver fibrosis, as well as development of cirrhosis and long-term morbidity and mortality in AATD-LD.^{9,47} It is anticipated that any treatment that reduces toxic accumulation of Z-AAT in the liver would diminish the risk of developing cirrhosis and its downstream complications. A reduction in liver Z-AAT is appealing as an endpoint because it is disease-specific and measurable, and it reflects changes in the disease process directly linked to disease pathogenesis. However, it has not been linked with clinical outcomes directly.^{48,49} For this reason, a reduction in Z-AAT would best be used as part of a composite outcome along with fibrosis reversal, which would add clinical meaning to sustained reduction in Z-AAT accumulation.

Based on current understanding of the natural history of AATD-LD, as well as the totality of evidence from all chronic fibrotic liver disease, the group unanimously recommended that a 1-stage improvement in fibrosis stage over 2-year time period using METAVIR Histologic Scoring System should be sufficient as a primary endpoint in phase 3 clinical trials. In addition, other AATD specific endpoints, such as globule or polymer reduction endpoint, may help overcome some of the challenges inherent in rare disease clinical trials. The potential for patients with ZZ with cirrhosis to decrease fibrosis by 1 stage is unknown, so it may be appropriate to limit fibrosis regression analysis to those with baseline F2 or F3 so that a trial enriched with F4 participants is not set up for failure (Table 3).

With these suggested endpoints, paired liver biopsies will be necessary in AATD-LD clinical trials for fibrosis assessment and intrahepatic Z-AAT measurement. The perils of histology endpoints are well known, including inherent inter- and intra-reader variability and sampling variability within the liver.^{18,51–53} Best practices for

Table 3. AATD Clinical Trial Endpoints

Endpoint	Criteria	Notes
Primary	1-stage improvement in fibrosis ^a using METAVIR Histologic Scoring System and paired biopsies ^b	Recommended trial duration of 2 y
Secondary	Reduction in hepatocyte Z-AAT accumulation	Anticipated decreased risk of developing cirrhosis and downstream complications ^c
	Reduction in hepatic globule burden	This endpoint may help overcome some of the challenges inherent in rare disease clinical trials
	Increase in functional AAT level	For DNA- and RNA-based studies to show proof of mechanism ^d
	1-stage improvement in fibrosis using NIT	Combination of blood- and imaging-based assessments Consideration should be given to incorporating novel proteomic and genomic measures
Exploratory	Reduction in circulating Z-polymer	As a biomarker to indicate risk of progression

^aThe potential for patients with PiZZ genotype with cirrhosis to decrease fibrosis by 1 stage is unknown, so it may be appropriate to limit fibrosis regression analysis to those with baseline F2 or F3 so that a trial enriched with F4 participants is not set up for failure.

^bFewer than 50% of patients with the PiZZ genotype would be willing to participate in a trial with more than 2 biopsies,⁵⁰ which may limit study participation.

^cThe long duration over which AATD-LD clinical outcomes occur make it impractical to design a trial with a clinical outcome as a primary outcome because AATD-LD is a rare disease and time to clinical events may take several years or even decades.

^dEstablishing the efficiency of gene and RNA edits in early-phase studies will require biopsies. Later-phase studies might be performed by means of measuring functional AAT levels as a primary outcome.

pathologic analysis can help mitigate the variability,⁵⁴ but high variability leading to a large placebo response in fibrosis in an AATD-LD trial has been reported in a phase 2b study.⁴² An additional consideration is that <50% of patients with ZZ would be willing to participate in a trial with more than 2 biopsies,⁵⁰ which may limit study participation. In conducting clinical trials for AATD, secondary or exploratory outcomes should encompass evaluations of liver fibrosis using blood tests and imaging-based assessments. In addition, consideration should be given to incorporating novel proteomic and genomic measures, with the ultimate aim of transitioning away from biopsy-based methods for assessing fibrosis. Emerging data suggest circulating Z-polymer is an AATD-specific biomarker related to liver disease severity and clinical outcomes,^{55,56} which would be an ideal way to assess treatment response, but it requires further validation in treatment studies. Lastly, for the DNA- and RNA-based studies in Table 1, measurement of a functional AAT level will ensure proof of mechanism. Establishing the efficiency of gene and RNA edits in early-phase studies will require biopsies. Later-phase studies might be performed by means of measuring functional AAT levels as a primary outcome.

Proposed Pulmonary Monitoring

Low serum levels of AAT are associated with an increased risk of pulmonary emphysema. Analysis from the RAPID trial suggests that even among adults with severe AATD, lower trough plasma levels of AAT are linked to a greater risk of emphysema progression.⁵⁷ Therefore, further reductions in plasma AAT concentrations may potentially elevate this risk.

However, the best way to monitor this risk remains unknown. Progression of emphysema has historically been measured by means of computed tomography densitometry, a direct measurement of the amount of tissue within the lung.⁵⁸ Reliance on lung function tests for this determination has much less power to detect clinically meaningful changes,⁴⁴ and has historically been done in COPD when lung function is severely impaired. In contrast, the inclusion criteria for silencing RNA therapies includes patients with near-normal lung function. In this group of patients with AATD, there may be significant bronchial hyperresponsiveness due to airways disease, a common endotype of AATD lung disease.⁵⁹

If lung function is to be used, then a minimum of 3 serial measurements over an appropriate period (eg, several months) is required to assess the slope of decline. However, even with extended follow-up, lung function tests have limited sensitivity. For example, in COPD, it is estimated that spirometric follow-up over 5 years offers only 50% sensitivity in identifying patients with rapid FEV₁ decline,⁶⁰ and 57% of patients whose computed tomography density declines will not exhibit measurable FEV₁ decline.⁶¹ Furthermore, the minimal clinically important difference of 100 mL that is often quoted in COPD⁶² is for population change, not for intra-individual data. Different patients may have impairment of the FEV₁ or diffusion capacity of carbon monoxide (or the transfer coefficient of carbon monoxide [KCO]) as emphysema progresses over time. Paradoxically, FEV₁ may increase in early emphysema as mild air trapping develops. These tests (FEV₁ and KCO) assess different aspects of lung function and may be differentially affected, depending on

the severity and distribution of emphysema.⁶³ Both FEV₁ and diffusion capacity of carbon monoxide (or KCO) exhibit high variability, making it difficult to identify consistent and significant deterioration.^{64,65} Studies in patients with AATD suggest that repeated lung function measurements, even over several years, have limited sensitivity for detecting emphysema progression, reflecting the variability of FEV₁ and its imperfect correlation with structural lung changes. More frequent lung function tests do not improve predictive accuracy due to the high correlation between repeated measurements and the slow progression of emphysema and the effort-dependent nature of the test. It has been shown that spirometric tests should be spaced at least 3 months apart to have any correlation with emphysema progression.⁶⁶ Furthermore, the typical patient with AATD has 2 exacerbations per year⁶⁷ that transiently cause problems for using lung function testing as a measurement tool for

safety monitoring. Lastly, overuse of a pulmonary function stopping rule based on variable lung function tests may generate lower power to detect drug efficacy.

Regarding what constitutes a significant change in FEV₁ and diffusion capacity of carbon monoxide, some studies reported intra-individual variability ranging from 2.5% to 4.2%. However, this may reach up to 10% depending on the device used, and can be even higher for KCO.⁶⁸ Day-to-day variation in FEV₁ ranges between 4% and 7%.⁶⁹ Consequently, a persistent change of $\geq 20\%$ is generally considered significant if confirmed in consecutive visits.

Recent prospective studies have found that death in AATD-associated lung disease increases significantly only when FEV₁% falls below 50% of the predicted value. Therefore, patients with FEV₁% $\geq 50\%$ may be safely included in clinical trials involving RNA interference therapies, provided they are closely monitored.⁵

Table 4. Summary of Recommendations

Category	Recommendation
Nomenclature	Alpha-1 antitrypsin deficiency–associated liver disease (AATD-LD)
Definition	We propose AATD-LD to be defined as adults with the PiZZ genotype who exhibit recurrently elevated liver enzymes (ie, AST, ALT, or GGT) and/or evidence of significant liver fibrosis (ie, fibrosis stage ≥ 2 on a 0–4 scale).
Case detection and diagnostic testing	The diagnostic evaluation of chronic liver disease should include testing for AATD by means of determining the serum AAT level. Genotyping is necessary to comprehensively determine carrier genotypes.
Staging and monitoring	Patients with the PiZZ genotype should undergo liver fibrosis staging using noninvasive means, including blood-based and imaging-based approaches (VCTE preferred). Longitudinal reassessment using NIT for liver fibrosis during routine pulmonary follow-up may offer a practical approach to ongoing liver disease monitoring. Patients with VCTE LSM < 8 kPa are deemed low risk and should be re-evaluated every 2–3 y, those with LSM 8–15 kPa are intermediate risk and should be re-evaluated every 1–2 y, and those with LSM ≥ 15 kPa are high risk and should be monitored yearly.
Liver biopsy	Liver biopsy is not required for establishing the diagnosis of AATD-LD, although it may be indicated in select cases to establish or exclude additional factors contributing to liver disease.
HCC surveillance and transplant referral	Early consideration for liver transplantation is warranted in patients with decompensated AATD-LD. Any patient with decompensation, including ascites, variceal bleeding, or hepatic encephalopathy, should be referred to a center with expertise in transplant hepatology and AATD-LD.
Clinical trial inclusion and endpoints	The ideal study population would be patients with PiZZ genotype with significant liver fibrosis (F2–F4). When investigational therapies targeting the liver move into phase 2b or phase 3 studies, the trial design should consider a stepwise approach toward including patients with significant liver disease. A 1-stage improvement in fibrosis stage over a 2-y time period should be sufficient as a primary endpoint in phase 3 clinical trials.
Pulmonary monitoring	If lung function is used as a stopping rule, a significant decline in FEV ₁ or KCO should require a reduction of $\geq 20\%$, confirmed on at least 2 consecutive tests. Low FEV ₁ % predicted inclusion criteria should be considered, particularly if patients are on augmentation therapy and carefully monitored.

In summary:

- Lung function measurements are an imperfect tool to use as stopping rules in clinical trials.
- If lung function is used as a stopping rule, a significant decline in FEV₁ or KCO should require a reduction of ≥20%, confirmed on at least 2 consecutive tests.
- The pulmonary risks of RNA interference therapies remain theoretic at this time. Because many eligible patients with liver disease from AATD have severely impaired lung function, low FEV₁% predicted inclusion criteria should be considered, particularly if patients are on augmentation therapy and carefully monitored. Although recent longitudinal observations can be used to estimate lung- and liver-associated risks,⁵ safety monitoring remains an important goal of all new AATD therapies.

Pediatric Considerations

Although this document is focused on adults, who tend to have presentations and disease courses different from most children with ZZ, some limited comments on the recommendations discussed here and their applicability to children can be made. First, the diagnostic path and the role of AATD in the differential diagnosis of liver abnormalities can be strongly considered to apply in children as well as adults. In addition, the concept of continued follow-up for liver abnormalities throughout life, regularly or annually, including the use of NITs, is reasonable to apply to children, although with the understanding that not all LSM modalities are readily available at all pediatric centers. Lung disease monitoring is not generally needed in children, unless they have asthma or are symptomatic in some other way, but it seems wise to refer patients with ZZ for a baseline adult pulmonary evaluation at age 18 years. Finally, at present, none of the AATD liver treatment trials are open to enrollment of participants younger than 18 years. Although caution, and US Food and Drug Administration recommendations, generally require safety data in adults for new drugs before trials in children begin, given the lack of any proven effective liver treatment other than liver transplantation, it would seem reasonable to advance to trials in younger ages as soon as possible.

Summary and Conclusions

AATD-LD is an underappreciated hepatic manifestation of a well-characterized genetic disorder. The burden of liver morbidity and mortality in adults with the PiZZ genotype—who account for the majority of severe AATD cases—has become increasingly apparent through recent longitudinal and cross-sectional studies. However, despite improved epidemiologic insights and advances in noninvasive diagnostics, clinical recognition, and standardized management of AATD-LD remain limited by the absence of clear diagnostic definitions, staging frameworks, and consensus-based monitoring strategies.

Table 5.AATD-LD Unmet Research Needs

Key research topics to advance the field and validate/undermine the proposed criteria for AATD-LD
Better define natural history of AATD-LD
Better define global incidence and prevalence of AATD-LD in various geographies and ethnic groups
Mechanism of injury in liver and lung
Potential role of gene silencing and gene editing in the treatment of AATD liver and lung disease
Understanding the performance of NITs in the detection of AATD-LD
Understanding which patients are likely to develop liver disease and why
Developing predictors of treatment response
Developing NITs that predict long-term clinical outcomes
Defining a uniform approach for assessing the presence and severity of metabolic dysfunction–associated steatotic liver disease in potential trial participants, along with clearly defined criteria for permissible levels of alcohol consumption for inclusion

This expert consensus initiative, convened by the American Gastroenterological Association in collaboration with international thought leaders, American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Alpha-1 Foundation, was designed to narrow these knowledge and practice gaps. Through critical review of emerging data and structured expert dialogue, the group developed a proposed nomenclature, case definition, and diagnostic algorithm for AATD-LD. The consensus supports using the term *alpha-1 anti-trypsin deficiency-associated liver disease* for adults with PiZZ genotype who exhibit recurrently elevated liver enzymes (ie, AST, ALT, or GGT) and/or evidence of significant liver fibrosis (ie, fibrosis stage ≥2 on a 0–4 scale). These criteria are based on consistent associations between these biomarkers and progression to major adverse liver outcomes.

The consensus also established a preferred approach to fibrosis staging and monitoring. LSM by means of VCTE was prioritized due to its demonstrated ability to predict liver-related outcomes in adults with phenotype and its utility across all stages of fibrosis. Blood-based fibrosis scores such as APRI and FIB-4 may serve as triage tools, although their limitations in sensitivity and coverage of the population are acknowledged. The proposed staging framework uses a risk-stratified approach to define monitoring intervals and guide decisions around HCC surveillance and early referral for transplantation in decompensated patients.

Recognizing the urgent need for disease-modifying therapies, the group also outlined a research agenda for clinical trial design in AATD-LD. Phase 3 studies should focus on adults with F2–F4 fibrosis and not restrict enrollment according to lung function thresholds unless the therapy is likely to negatively impact the lung. Endpoints

should include changes in fibrosis stage and reduction in intrahepatic Z-AAT polymer accumulation. Importantly, biopsy-based endpoints may be supplemented or replaced by emerging biomarkers such as serum Z-polymer levels and elastography-based surrogates, with the goal of decreasing reliance on invasive sampling. Table 4 includes a summary of the recommendations developed by this expert consensus initiative.

Although several knowledge gaps remain—including the longitudinal trajectory of fibrosis, the precise role of heterozygous genotypes, and the interplay of metabolic cofactors—the consensus statements provide a clear framework for harmonizing care, facilitating earlier diagnosis, and expediting therapeutic development. Adoption of these recommendations can support a broader clinical and regulatory ecosystem capable of improving outcomes for adults with AATD-LD. In addition, we have identified a number of unmet research needs in this field, as shown in Table 5.

Future efforts should include real-world validation of these criteria, integration into clinical practice guidelines, and coordination among hepatologists, pulmonologists, and genetic counselors to ensure early identification and comprehensive management of this complex multi-system disease.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2025.12.012>.

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All authors were involved in manuscript conception, writing, editing, and approval of the final document.

Conflicts of interest

These authors disclose the following: Rohit Loomba: serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse bio, Inipharm, Intercept, Inventiva, Ionis, Janssen Inc., Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics; and has stock options in Sagimet Biosciences; his institution received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Intercept, Hammi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals; he is co-founder of LipoNexus Inc. Virginia Clark: served as a consultant to Vertex and Takeda Pharmaceuticals; has research grant support paid to the institution from Arrowhead Pharmaceuticals, Hammi, Takeda, 89 Bio, and Novo Nordisk. Mattias Mandorfer: received grant support from Echosens; served as a speaker and/or consultant and/or advisory board member for AbbVie, AstraZeneca, Echosens, Eli Lilly, Gilead, Ipsen, Takeda, and W. L. Gore & Associates; and received travel support from AbbVie and Gilead. Marc Miravittles: received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Glenmark Pharmaceuticals, Menarini, Kamada, Takeda, Zambon, Tabuk Pharmaceuticals, CSL Behring, Zambon, Specialty Therapeutics, Sanofi/Regeneron, Grifols and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, BEAM Therapeutics, GondolaBio, Chiesi, GlaxoSmithKline, CSL Behring, Ferrer, Korrobio, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi/Regeneron, Zambon, Zentiva and Grifols, and research grants from Grifols. Mark Brantly: serves as consultant for Takeda, WAVE, Sanofi, Beam, Vertex and Grifols and is a board member of the Alpha 1 Foundation, and AlphaDetect. Saul J. Karpen: served as consultant for Mirum and Ipsen. Aleksander Krag: served as speaker for Novo Nordisk and Norgine and participated in advisory boards for Boehringer Ingelheim, GSK, W4Cure, and Novo Nordisk, all outside the submitted work, and received research support from Astra, Siemens, Nordic Bioscience, GSK, and Echosense and is a board member and co-founder of Evido. Paul Y. Kwo: Aligos: consultant; Arbutus; Consultant; AusperBio consultant; Durect: consultant, stockholder; Gilead: consultant, Research Grant HepQuant: consultant; Inventiva: consultant, grant support; Madrigal: research grant; Mallinckrodt: consultant; Mirum: consultant; Novo Nordisk: research grant, consultant; Precision BioSciences: consultant; Takeda: research grant; Target RWE: research grant, Tune Therapeutics: consultant Ultragenyx: research grant. Don C. Rockey: received research support from the following: Akero, AstraZeneca, Durect, Galectin Therapeutics, Gilead Sciences, Intercept Pharmaceuticals, Ipsen, Novo Nordisk, Salix Pharmaceuticals. Consultant; Takeda: DSMC - orexin program. Mark W. Russo: consultant to Lilly. Antonio J. Sanchez: grant/research support from Takeda, Gilead, GSK, Boehringer Ingelheim, Merck, Mirum, 89Bio, and Inventiva. Consultant for Madrigal. Suzanne R. Sharpton: grant/research support paid to her institution from Boehringer Ingelheim, AstraZeneca, and Takeda Pharmaceuticals. Charlie Strange: grant support paid to the Medical University of South Carolina for studies related to Alpha-1 from the Alpha-1 Foundation, Beam, BioMarin, Grifols, Krystal, Sanofi, Takeda, and Vertex; consultant to Grifols, Morair, Sanofi, Takeda, and Vertex in Alpha-1 and medical director at AlphaNet. Jeffrey H. Teckman: grants and consulting honoraria active from Abbvie, Beam, BioMarin, Congruence, Critical Path Institute, Ipsen, KorroBio, Takeda, Tessera, Vertex, Alpha-1 Foundation, National Institutes of Health. Alice M. Turner: grants and/or honoraria from CSL Behring, Grifols, Takeda, Vertex, Chiesi, GSK, AZ, Beam, and AiRNA. Hugo E. Vargas: research support from Takeda, Arrowhead; consultant for Sequana Medical; prior research funding from Mallinckrodt, DURECT and Ocelot. Pavel Strnad: reports grants and honoraria from Arrowhead Pharmaceuticals, CSL Behring, Grifols Inc; consulting fees or honoraria from AiRNA Pharmaceuticals, Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, BioMarin Pharmaceutical, Dicerna Pharmaceuticals, GondolaBio, GSK, Intellia Pharmaceuticals, Korro Bio, Takeda Pharmaceuticals, Novo Nordisk, Tessera Pharmaceuticals and Ono Pharmaceuticals; participates in leadership or fiduciary roles in Alpha1-Deutschland, Alpha1 Global, and material transfer support for Vertex Pharmaceuticals and Dicerna Pharmaceuticals. The remaining author discloses no conflicts.

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