

## REVIEW

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# Wilson disease: a summary of the updated AASLD Practice Guidance

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## Abstract

Wilson disease (WD) is caused by autosomal variants affecting the *ATP7B* gene on chromosome 13, resulting in alterations in physiological copper homeostasis and copper accumulation. Excess copper clinically manifests in many organs, most often in the central nervous system and liver, ultimately causing cirrhosis and death. Often considered a pediatric or young adult disease, WD actually affects patients of all ages, and aging patients need to be regularly managed with long-term follow-up. Despite over a century of advances in diagnosis and treatment, WD is still associated with diagnostic challenges and considerable disability and death, in part due to delays in diagnosis and limitations in treatment. Standard-of-care treatments are considered generally effective when the diagnosis is timely but are also limited by efficacy, safety concerns, multiple daily dosing, and adherence. This expert perspective review seeks to facilitate improvements in the awareness, understanding, diagnosis, and management of WD. The objectives are to provide a full overview of WD and streamline updated diagnosis and treatment guidance, as recently published by the American Association for the Study of Liver Diseases, in a practical way for clinical use.

## INTRODUCTION

Wilson disease (WD) is a pediatric and adult liver disease first described in 1912 by Kinnear Wilson as “progressive lenticular degeneration”.<sup>[1]</sup> WD is a genetic disease of copper metabolism<sup>[2]</sup> that demonstrates an autosomal recessive pattern of inheritance. Excess copper accumulates in various body tissues and, if left

untreated, may cause several systemic manifestations, including central nervous system dysfunction, acute/acute on chronic liver disease, cirrhosis, and ultimately, death. Despite over a century of significant advances in diagnosis and treatment, WD is still associated with considerable disability and death. Several factors may contribute to this, including the rarity of the disease; multisystemic involvement; clinical heterogeneity, which

**Abbreviations:** AE, adverse event; AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AASLD, American Association for the Study of Liver Diseases; INR, international normalized ratio; KF, Kayser-Fleischer; MCV, mean corpuscular volume; NCC, nonceruloplasmin copper; qd, once-daily; UWDRS, Unified WD Rating Scale; WD, Wilson disease; WBC, white blood cell count.

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complicate and often delay the diagnosis; uncertainty surrounding the best possible choice of treatment; and significant treatment nonadherence with the necessary lifetime medical therapy.

This expert perspective review seeks to facilitate improvements in the awareness, understanding, diagnosis, and management of WD. This paper provides a full overview of WD, streamlines updated diagnosis and treatment guidance recently published by the American Association for the Study of Liver Diseases (AASLD)<sup>[3]</sup> in a practical way for clinical use, recommends how to incorporate these guidelines into clinical practice, and analyzes new developments in WD.

## Epidemiology and pathophysiology

The most frequently reported prevalence of WD is ~1 in 30,000 people worldwide, with an expected number of 8300–11,000 cases in the United States; thus it is classified as a rare disease.<sup>[4,5]</sup> Studies in the UK indicate a WD genetic prevalence of ~1:7026–~1:20,000,<sup>[6,7]</sup> indicating that the actual clinical prevalence could be higher than projected. Discrepancies in prevalence may be attributed to misdiagnoses of WD as other hepatic, neurological, or psychiatric disorders.<sup>[8]</sup> Another possible explanation is that WD does not have full penetrance, so the gene variants do not always correspond to severely impaired copper metabolism and actual clinical manifestations. However, in most fully studied patients, evidence of phenotypical disease can be found. The usual age of presentation is 4–40 years of age, but the disorder has been detected in children as young as 3 and in adults as old as 70 years. WD affects males and females in equal numbers of all races and ethnic groups.<sup>[8]</sup>

The pathophysiology and clinical manifestations of WD are attributed to alterations in copper homeostasis. Copper, taken in through the diet at a recommended intake of 1.5–3.0 mg per day (for adults),<sup>[9]</sup> is an important cofactor for many physiological/enzymatic reactions in critical metabolic pathways and is thereby considered an essential trace element.<sup>[10,11]</sup> Copper homeostasis is maintained through<sup>[1]</sup> the gut, which is responsible for dietary copper uptake and use;<sup>[2]</sup> the liver, which removes excess copper in the bile, where it is excreted in the stool; and<sup>[3]</sup> metabolic pathways designed to maintain copper homeostasis.<sup>[10,11]</sup> With regard to liver involvement, hepatocytes use copper for metabolic needs, incorporate copper into nascent ceruloplasmin, and transport excess copper into bile. Most excess copper is excreted through this biliary pathway into feces; only a minor amount is excreted through the kidneys. Therefore, impaired biliary copper excretion can lead to hepatic copper retention.<sup>[2]</sup>

WD is caused by the presence of 2 autosomal mutations (one on each allele) in the *ATP7B* gene on

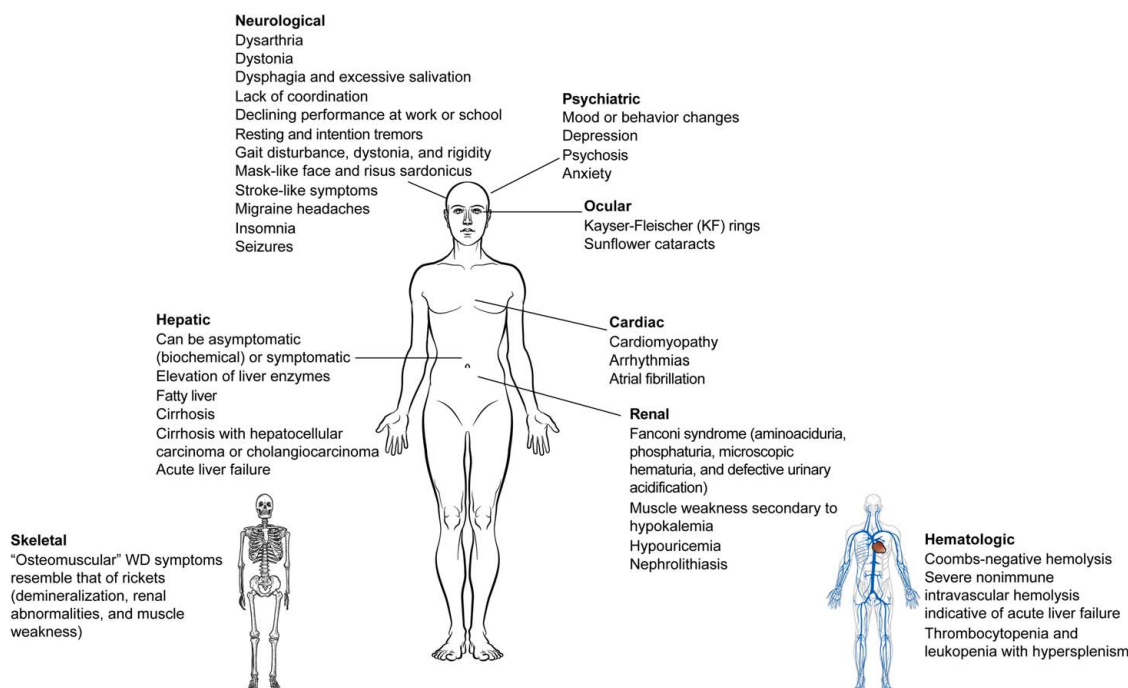
chromosome 13, a copper-transporting ATPase in hepatocytes that is responsible for excreting copper into bile.<sup>[12]</sup> A meta-analysis identified 782 *ATP7B* variants, with 216 considered “likely pathogenic”;<sup>[13]</sup> it is approximated that 1 in 90 people may be carriers of disease-causing variants.<sup>[14,15]</sup> The distinction between “disease-causing” variants and variants of uncertain significance is sometimes challenging, so these estimates are evolving. What is established is that the loss of functional *ATP7B* alters hepatocellular copper excretion through the bile, as well as the biosynthetic incorporation of copper into ceruloplasmin, a serum ferroxidase that is responsible for 90% of copper transport from the liver.<sup>[16]</sup> Loss of functional *ATP7B* also diminishes hepatocellular copper incorporation into ceruloplasmin. The resulting apoceruloplasmin has a shorter circulating half-life, causing lower steady-state levels of circulating ceruloplasmin.<sup>[17]</sup> Excess copper, due to reduced biliary copper excretion, leads to the generation of free radicals, which causes oxidation of vital proteins and lipids, alterations in methionine metabolism with consequent DNA hypomethylation and epigenetic changes,<sup>[18,19]</sup> and early damage affecting the mitochondria, nuclei, and peroxisomes.<sup>[12]</sup> As 95% of copper excretion is through the liver, excess copper first accumulates in the liver, causing various degrees of liver damage, and eventually accumulates in other organs, mainly the brain and cornea.<sup>[11]</sup> Without treatment, advanced liver disease, among other manifestations, ensues.<sup>[13,21]</sup>

## Clinical presentation/manifestations

### Signs and symptoms

In concordance with the pathogenesis of WD, copper accumulates in different organs and causes a wide range of signs and symptoms, as indicated in [Figure 1](#).<sup>[3,20–24]</sup>

As a result, WD can be considered a systemic disease. With regard to hepatic manifestations, symptoms are nonspecific and, therefore, require an accurate approach to differential diagnosis.<sup>[21–23]</sup> WD can present as asymptomatic or symptomatic.<sup>[21–23]</sup> Patients with asymptomatic WD are typically diagnosed serendipitously during the screening of family members; findings include elevated aspartate aminotransferase and alanine aminotransferase. Patients with symptomatic hepatic disease can present with an insidious onset of vague symptoms, including fatigue and lack of appetite, followed by jaundice. Additional findings include acute hepatitis with sharp elevation in liver enzymes, portal hypertension with or without bleeding varices, incidental evidence of hepatomegaly, and ultimately, compensated and decompensated cirrhosis. Approximately 3%–5% of patients with WD present with acute liver failure (ALF),<sup>[3,25]</sup> some with underlying fibrosis or



**FIGURE 1** The clinical manifestations of WD impact on several organ systems.<sup>[3,20–24]</sup> Abbreviation: WD, Wilson disease.

cirrhosis that went undetected until their acute clinical presentation.<sup>[26]</sup> ALF associated with WD typically presents with jaundice, nonimmune (Coombs negative) intravascular hemolysis, coagulopathy, ascites, progressive encephalopathy, altered ratios of alkaline phosphatase to bilirubin ( $<1:4$ ) and aspartate aminotransferase to alanine aminotransferase ( $>2.2$ ), and rapid progression of renal dysfunction.<sup>[3,26]</sup> Without liver transplantation, mortality rates of ALF due to WD approach 100%.<sup>[27]</sup>

The typical neurological manifestations of WD are listed in [Figure 1](#) and characteristically manifest at a mean age of 20 years<sup>[21–23]</sup> or later. A less common but unique finding characteristic of WD is the “face of the giant panda” sign on brain MRI, comprising increased T2 signal in the midbrain.<sup>[3]</sup> However, this is only found in patients with advanced neurological presentation.<sup>[20]</sup> Ocular manifestations commonly include Kayser-Fleischer (KF) rings, which are usually seen as a golden brown ring in the peripheral cornea caused by the deposition of excess copper on the inner surface of the cornea in the Descemet membrane.<sup>[28]</sup> KF rings are present in 90% of patients with neurological manifestations<sup>[13,24,25]</sup> and absent in ~60% of patients with hepatic manifestations.<sup>[13,24,25]</sup> Sunflower cataracts, with a 1.2% prevalence in newly diagnosed patients, are considered a very rare manifestation of WD. These cataracts resemble a sunflower with thin, centralized opacification located under the anterior capsule, and secondary opacifications arranged in ray-like structures around it. Sunflower cataracts do not affect visual acuity and are typically reversible after treatment.<sup>[29]</sup>

WD can also present with hematologic, cardiac, renal, skeletal, and endocrine manifestations ([Figure 1](#)<sup>[3,20–23]</sup>). Hematological features of untreated WD typically involve hemolysis, which is a result of copper-associated damage to erythrocyte membranes. Severe nonimmune intravascular hemolysis, demonstrated by a sudden severe drop in hemoglobin, is a classic feature of ALF in WD. Thrombocytopenia and leukopenia with hypersplenism may occur in accordance with hepatic WD and portal hypertension.<sup>[3]</sup> Renal abnormalities have been characterized as nephrolithiasis, a potentially presenting feature; Fanconi syndrome; hypokalemia; and secondary and hypouricemia due to excess urinary loss of urate.<sup>[3,30–34]</sup> Patients with the rarely observed “osteomuscular” WD demonstrate skeletal changes that are uncommon yet distinctive. The clinical manifestations resemble rickets and include demineralization, renal abnormalities, and muscle weakness.<sup>[3]</sup> Potential cardiac problems associated with WD include cardiomyopathy, arrhythmias, and atrial fibrillation.<sup>[35–38]</sup> Endocrine abnormalities in patients with WD include hypoparathyroidism, infertility, and frequent miscarriages.<sup>[3,39–43]</sup>

## Sex-specific considerations

Three studies on patients with WD, detailed in [Table 1](#),<sup>[44–46]</sup> consistently found that hepatic symptoms are slightly more predominant in female patients (57%), whereas neurological symptoms are more predominant in male patients (60%).<sup>[44–46]</sup> Female patients with WD are more likely to develop ALF than male

**TABLE 1** Observed differences in WD clinical manifestations based on sex

| Study                                                                                                                                                                                   | Signs/symptoms | Sex-related findings                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A retrospective study of 627 patients with confirmed WD, included in ~50 y registry (1958–2010), in which the influence of sex differences on the disease was evaluated <sup>[46]</sup> | Overall        | <ul style="list-style-type: none"> <li>• A male predominance was observed overall (327 male patients vs 290 female patients; <math>p &lt; 0.05</math>)</li> </ul>                                                                                                                                                                                                                                                                  |
|                                                                                                                                                                                         | Hepatic        | <ul style="list-style-type: none"> <li>• Hepatic presentations were predominant in female patients (57%) versus male patients (43%) (<math>p &lt; 0.01</math>)</li> <li>• Lower mean age in male patients at first symptom onset of the hepatic form (22.9 y vs 24.3 y in female patients)</li> <li>• Same mean age at diagnosis of the hepatic form for male patients and female patients (26.2 y)</li> </ul>                     |
|                                                                                                                                                                                         | Neurological   | <ul style="list-style-type: none"> <li>• Neurological presentations (eg, rigidity tremor, rigidity, and dystonic) were predominant in male patients (60%) versus female patients (40%) (<math>p &lt; 0.01</math>)</li> <li>• Mean age at onset was younger for male patients (27.1 y) versus female patients (29.4 y)</li> <li>• Mean age at diagnosis younger for male patients (29.8 y) versus female patients (32 y)</li> </ul> |
| A 21-question survey was distributed within the WD Association patient network; 97 (11%) patients responded <sup>[44]</sup>                                                             | Hepatic        | <ul style="list-style-type: none"> <li>• Liver-related signs and symptoms were more commonly reported in female patients (56%) than male patients (44%)</li> </ul>                                                                                                                                                                                                                                                                 |
|                                                                                                                                                                                         | Neurological   | <ul style="list-style-type: none"> <li>• CNS-related symptoms were more commonly reported in male patients (55%) than female patients (45%)</li> </ul>                                                                                                                                                                                                                                                                             |
| The clinical manifestations of 1357 WD patients were studied <sup>[45]</sup>                                                                                                            | Hepatic        | <ul style="list-style-type: none"> <li>• Hepatic presentations were more common in female (56.5%) than male patients (48.3%)</li> <li>• The female-to-male ratio of ALF was <math>&gt; 2:1</math>–<math>4:1</math></li> </ul>                                                                                                                                                                                                      |
|                                                                                                                                                                                         | Neurological   | <ul style="list-style-type: none"> <li>• Neurological presentations were more common in male patients (38.1%) versus female patients (29.8%)</li> </ul>                                                                                                                                                                                                                                                                            |

Abbreviations: ALF, acute liver failure; CNS, central nervous system; WD, Wilson disease.

patients.<sup>[45,47–49]</sup> Data are limited on sex differences in WD, but most recently, a post hoc analysis of sex differences in WD examined 51 patients on maintenance treatment with trientine for 12 months. The neurological disease burden, measured by means of an investigator-rated Unified Wilson Disease Rating Scale (UWDRS), found that sex differences in the UWDRS decrease were significant ( $p = 0.02$ ) in the longitudinal model extended by sex as a covariate. Specifically, the trend of continuous improvement in neurological symptoms was mainly seen in female patients with WD, even after long-term therapy (for females, a mean UWDRS was 10.6 ( $n = 34$ ) at baseline, 8.6 ( $n = 34$ ) at 6 months, and 8.0 ( $n = 34$ ) at 12 months and for males, a mean UWDRS was 12.6 ( $n = 17$ ) at baseline, 11.9 ( $n = 16$ ) at 6 months, and 10.4 ( $n = 17$ ) at 12 months).<sup>[50]</sup>

Female patients with WD require special consideration and counseling regarding conception, pregnancy, and breastfeeding. Preconception counseling should communicate the possibility of impaired fertility, the risk of spontaneous abortion, the discussion of medication safety and compliance in pregnancy, and the need for genetic counseling (detailed in the AASLD guidance).<sup>[3]</sup> Anticopper therapy in pregnant patients with WD is generally considered safe. One retrospective multicenter

study reviewed 282 pregnancies in 136 patients with WD and determined that the overall spontaneous abortion rate in the study cohort was 73 of 282 (26%). However, patients with an established diagnosis of WD receiving medical treatment experienced significantly fewer spontaneous abortions than patients with undiagnosed WD [OR, 2.853 (95% CI: 1.634–4.982)].<sup>[51]</sup> Patients with current/previous decompensated cirrhosis should be discouraged from conceiving, as advanced liver disease poses a significant health risk to the mother and the fetus.<sup>[3,52]</sup>

## Age-specific considerations

As average life expectancy increases, so does the population of aging patients with WD. Although, according to AASLD guidance, age alone does not contravene a WD diagnosis, and recommendations for diagnosis are the same regardless of the stage of the patient's journey,<sup>[3]</sup> there is much interest in the transition of care throughout this journey. Overall, the age of presentation for symptomatic WD, which is mainly, but not exclusively, 3–55 years old, is both younger and older than generally appreciated. Symptoms at any age are frequently nonspecific,<sup>[2]</sup> but it has



been observed that WD presents with isolated liver disease more often in children and younger adult patients than in older adults.

In patients with WD, progressive accumulation of copper in the liver begins in infancy when copper-containing foods are introduced into the diet;<sup>[23]</sup> however, WD is rarely symptomatic before the age of 5 years.<sup>[20,39,40]</sup> Neurological manifestations are rare in children younger than 10 years,<sup>[21–23]</sup> but mild impairments in memory and language development are frequently reported.<sup>[20,23]</sup> KF rings are generally absent in children with asymptomatic or mild liver disease but are typically observed in children with neurological symptoms.<sup>[12,23]</sup> WD most often manifests when patients are in their 20s or 30s,<sup>[53]</sup> and neurological manifestations are more common in adults. Because geriatric presentation of WD is rare and data are mostly limited to case reports, the upper age limit for consideration of WD is generally 55 years. The oldest patients with WD, confirmed by molecular studies demonstrating *ATP7B* mutations, were in their early 70s.<sup>[19,36,37]</sup> One study investigated 46 patients with WD who became symptomatic at older than 40 years of age. Of the 27 patients with available liver biopsy specimens, 19 had cirrhosis and 3 had no liver abnormalities. Investigators found that the diagnostic features and frequency of late-onset WD gene mutations were not different from those in patients with an earlier onset of disease.<sup>[54]</sup> All patients who have signs and symptoms indicative of WD should be further evaluated regardless of age.<sup>[3,55]</sup>

## Ethnicity-specific considerations

WD has been described on all continents. All races and ethnicities are affected. A retrospective study of 52 WD probands, followed at The Hospital for Sick Children in Canada, examined data from 1962 to 2021. Patients were predominantly Caucasian (48%), with 23% South African and 29% from other ethnicities. Compared with 27 non-Caucasians, Caucasians had a later disease onset (14 vs 10 y,  $p = 0.002$ ) and presented more often with decompensated cirrhosis (38% vs 7%,  $p = 0.01$ ). South Africans were younger than non-South Africans ( $n = 40$ ) at presentation (10.5 vs 13 y,  $p = 0.03$ ) but less likely to present in decompensated cirrhosis (0% vs 28%,  $p = 0.04$ ). Ethnicity did not play a role in long-term outcomes.<sup>[56]</sup>

Recent therapeutic advances derived from clinical trials on WD conducted on patients from Europe and North America have brought subjects of Caucasian descent to the forefront of WD treatment. Even large clinical trials could not or did not plan to include diverse groups of studied subjects, likely due to the understandable limitation of conducting trials on a rare disease. This should be the focus of future studies.<sup>[57–59]</sup>

## Applying guidance recommendations to clinical practice

“A Multidisciplinary Approach to the Diagnosis and Management of Wilson Disease: 2022 Practice Guidance on Wilson Disease from the American Association for the Study of Liver Diseases” provides a contemporary approach to the diagnosis and management of WD.<sup>[3]</sup> It serves to replace the prior AASLD guidance on the same topic published in 2008.<sup>[22]</sup> To facilitate its use in clinical practice, the following section provides a summary of the recommendations set forth in the guidance.

## Diagnosis

1. The AASLD recommends that WD be considered when the patient presents with one or more of the following:<sup>[3]</sup>
  - Liver abnormalities of uncertain cause, regardless of age.
  - Unexplained liver disease associated with neurological or psychiatric disorder(s).
  - ALF with nonimmune hemolytic anemia, including acute intravascular hemolysis.
  - Recurrent self-limited nonimmune hemolysis.

Timely identification of patients with WD is essential. Patients with cirrhosis, neurological manifestations, and KF rings are relatively easily diagnosed as they present with overt clinical signs and symptoms. However, about half of the patients presenting with liver disease do not possess two of these 3 criteria, posing a challenge in trying to establish a diagnosis.<sup>[20]</sup> Neurological symptoms occur later than hepatic abnormalities but are typically the first clinical symptoms leading to diagnosis. Initial neurological symptoms occur in up to 68% of patients. The mean age at onset of symptoms is 20–30 years, but a wide range (6–72 y) of presentation of new neurological symptoms is observed.<sup>[18]</sup> Therefore, the broad spectrum of liver disease necessitates heightened clinical suspicion for diagnosis.<sup>[3]</sup> In asymptomatic patients, organ damage may be present, and symptomatic WD is likely to follow if patients are untreated. Clinicians need to be vigilant regarding the effects of WD on other organ systems, as symptomatic WD may go beyond the liver and nervous system<sup>[3]</sup> if the diagnosis and treatment are delayed. The AASLD guidance recommends diagnostic tests based on indexes of suspicion and presents scenarios where additional specialty consults are warranted (eg, neurology and ophthalmology). A topline overview of these recommendations will be streamlined in this

section and will conclude with a table detailing the most common real-world clinical scenarios seen in patients presenting to a hepatologist/gastroenterologist with corresponding diagnostic recommendations.

2. Once WD is considered, a detailed personal and family medical history should be conducted, and a physical examination focused on evidence of liver, neurological, and psychiatric disease should be performed. Assessment should include the following:<sup>[3]</sup>

- Liver biochemistries.
- Complete blood count and international normalized ratio.
- Serum ceruloplasmin.
- Basal 24 hours urinary copper excretion.
- Slit-lamp or optical tomography examination for KF rings.
- Neurological evaluation.
- Molecular genetic investigation of ATP7B.

A gold standard diagnostic test does not exist for WD, so a combination of assessments is recommended. For example, serum ceruloplasmin is typically decreased in WD, with values in WD typically <14 mg/dL (normal >20 mg/dL).<sup>[21]</sup> However, the predictive value in this setting is poor. Many patients with low ceruloplasmin do not have WD, and normal ceruloplasmin values do not exclude a WD diagnosis. Therefore, relying exclusively on serum ceruloplasmin levels is not sufficient to establish a diagnosis. Non-ceruloplasmin copper levels could be a representation of actual organ damage and a helpful diagnostic and monitoring test; however, although their reliable measurement is currently not clinically available, it is the subject of extensive research.<sup>[59]</sup> Measuring the amount of copper excreted in the urine in a 24-hour period (basal 24 h urinary excretion) is an important part of WD diagnosis, as it reflects the amount of nonceruloplasmin-bound copper in the circulation. Basal 24-hour urinary excretion of copper levels are >100 µg (>1.6 µmol)/24 hours in symptomatic patients with WD. A lower reference value of >40 µg/24 hours (>0.6 µmol/24 h) may indicate WD in asymptomatic individuals or children and, therefore, requires clinical correlation and further investigation. A multidisciplinary approach is warranted for certain assessments. Specifically, examination of the eyes through a slit-lamp requires a skilled observer and detection of neurological signs or symptoms warrants referral to a neurologist or movement disorder specialist.<sup>[3]</sup>

3. Early differential diagnosis is essential in WD, particularly for ruling out hepatic disorders that resemble WD.

Patients with WD, especially younger patients, may have clinical features and histologic findings on liver biopsy that are indistinguishable from autoimmune hepatitis (AIH). WD should be excluded in children with apparent AIH and in patients with a diagnosis of AIH that is unresponsive or only partially responsive to corticosteroid therapy. In rare cases, AIH and WD may coexist.<sup>[60–62]</sup> The diagnosis of WD can be especially difficult in patients with multiple etiologies of chronic liver disease, including NAFLD and alcohol-associated liver disease. It is important to maintain a thorough differential in patients with an already established diagnosis and more obvious etiologies of liver disease. Patients with WD may also present with manifestations of multiple etiologies of liver injury. Hepatic steatosis in WD may be as severe as in NAFLD and, in some cases, NASH. Basal 24-hour urinary copper excretion and hepatic copper may be low in NAFLD, thus allowing for differentiation.<sup>[63]</sup> Given the increased prevalence of obesity, it is becoming more common to observe both WD and NAFLD in patients. Alcohol-associated liver disease, acute viral hepatitis, and underrecognized rare liver diseases (eg, lysosomal acid lipase deficiency and alpha-1 antitrypsin deficiency) should also be considered in the differential diagnosis.<sup>[3]</sup>

More details on establishing a diagnosis of WD in the real-world setting are presented in [Table 2](#). With regard to asymptomatic WD, the AASLD guidance does not delineate the definition of asymptomatic WD with and without organ damage. In hepatology clinical practice, the definition of organ damage is based on elevation in liver enzymes (biochemical evidence) and the presence of liver steatosis or fibrosis, as assessed by noninvasive tests that can evaluate for steatosis and measure liver stiffness, or by liver biopsy (histological evidence).

4. Genetic testing for ATP7B mutations may be performed as part of a routine evaluation. It can provide diagnostic confirmation when biochemical testing is not definitive and is efficient for screening first-degree relatives of a proband.

Genetic analysis is not required for the diagnosis of WD, but it is useful to confirm WD or in difficult cases with no clear clinical manifestations and to facilitate the subsequent screening of family members. A molecular genetic strategy using direct mutation analysis may be particularly effective in identifying affected siblings of probands with 2 identified ATP7B mutations. Considerations of genetic testing include availability and costs. Genetic counseling to help explain testing results and their current and future implications to the patient and family complement discussions with other clinical providers.

Patients in whom genetic testing is inconclusive require clinical and biochemical evaluations.<sup>[3]</sup>

**TABLE 2** WD diagnostic recommendations for patients presenting to hepatology/gastroenterology practices

| Presentation                      | Copper parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Histological features                                                                                             | Differential diagnosis                                                                                                                                                        |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Asymptomatic with no organ damage | <ul style="list-style-type: none"> <li>• Low or mildly low ceruloplasmin (between 14 and 20 mg/dL)</li> <li>• Mildly increased 24 h urinary excretion of copper (&gt; 40 µg/24 h)</li> <li>• Increased NCC</li> <li>• Increased hepatic copper (&gt; 75 µg/g)</li> </ul>                                                                                                                                                                                                                                                                                                                                                             | Normal liver histology                                                                                            | Not applicable                                                                                                                                                                |
| Hepatitis                         | <ul style="list-style-type: none"> <li>• Low or normal ceruloplasmin</li> <li>• Increased 24 h urinary excretion of copper (&gt; 100 µg/24 h)</li> <li>• Increased NCC</li> <li>• Increased hepatic copper (&gt; 250 µg/g)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                | Acute or chronic inflammatory infiltrate                                                                          | <ul style="list-style-type: none"> <li>• Viral hepatitis</li> <li>• AIH</li> <li>• Drug-induced liver injury</li> </ul>                                                       |
| Steatosis                         | <ul style="list-style-type: none"> <li>• Low ceruloplasmin (&lt; 14 mg/dL)</li> <li>• Increased 24 h urinary excretion of copper (&gt; 100 µg/24 h)</li> <li>• Increased NCC</li> <li>• Increased hepatic copper (&gt; 250 µg/g)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                          | Hepatocyte steatosis, mainly macrovesicular                                                                       | <ul style="list-style-type: none"> <li>• Nonalcoholic Steatohepatitis</li> <li>• Alcohol-associated steatosis</li> </ul>                                                      |
| Cirrhosis                         | <ul style="list-style-type: none"> <li>• Low or very low ceruloplasmin (&lt; 5 mg/dL)</li> <li>• Increased 24 h urinary excretion of copper (&gt; 100 µg/24 h)</li> <li>• Increased NCC</li> <li>• Increased hepatic copper (&gt; 250 µg/g)</li> <li>• Thrombocytopenia</li> <li>• Increased INR</li> </ul>                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>• Bridging fibrosis</li> <li>• Cirrhotic nodules</li> </ul>                | <ul style="list-style-type: none"> <li>• Nonalcoholic steatohepatitis</li> <li>• Alcohol-associated steatosis</li> <li>• AIH</li> <li>• Cholestatic liver diseases</li> </ul> |
| ALF                               | <ul style="list-style-type: none"> <li>• ALP: total bilirubin &lt;4 and AST: ALT &gt;2.2</li> <li>• Low or elevated ceruloplasmin</li> <li>• Increased NCC</li> <li>• Increased 24 h urinary excretion of copper (&gt; 100 µg/24 h)</li> <li>• Increased hepatic copper (&gt; 250 µg/g)</li> <li>• Hemolysis indicated by decreased haptoglobin levels, Coombs negative hemolytic anemia (high reticulocyte count and MCV).</li> <li>• Low hemoglobin may be present if hemolysis occurs.</li> <li>• Low WBC and thrombocytopenia develop in those with hypersplenism due to portal hypertension</li> <li>• Increased INR</li> </ul> | <ul style="list-style-type: none"> <li>• Hepatocyte necrosis</li> <li>• Acute inflammatory infiltrates</li> </ul> | <ul style="list-style-type: none"> <li>• Drug-induced liver injury</li> <li>• AIH</li> </ul>                                                                                  |

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MCV, mean corpuscular volume; NCC, nonceruloplasmin copper; WD, Wilson disease; WBC, white blood cell count.

5. In patients not meeting classic descriptions of WD, diagnostic scoring systems may aid in establishing or refuting a WD diagnosis. Prognostic scoring systems may help to determine the potential for successful medical therapy for WD.

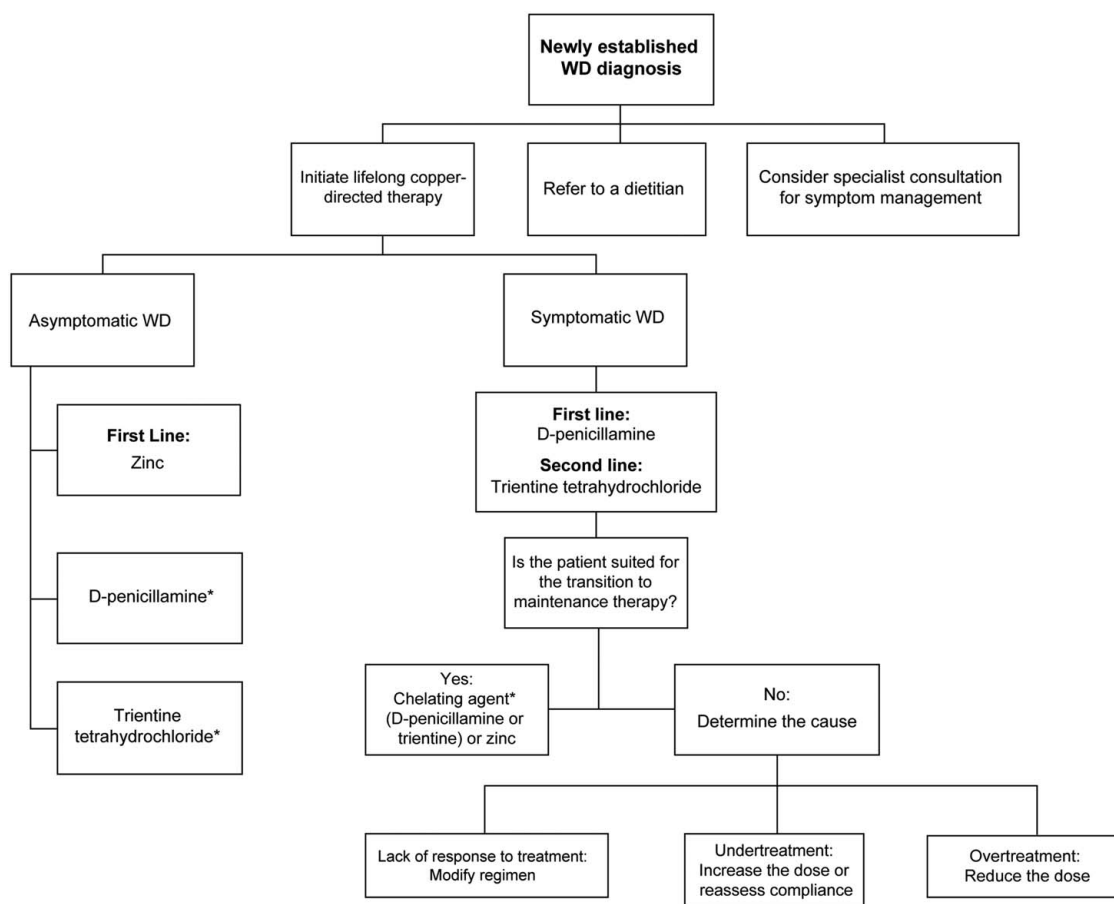
The Leipzig score is useful in facilitating the diagnosis of WD. This arithmetic scoring system comprises clinical and biochemical findings and has been validated in children and adults.<sup>[3,64]</sup> Prognostic scoring systems are used to predict when patients with WD will fail medical therapy. The first of these scoring systems was the Nazer score, which is based on serum bilirubin, aspartate aminotransferase, and prothrombin time.<sup>[3,65]</sup> The New Wilson Index supersedes the Nazer score and differs from it by including white blood cell count, serum albumin, and international normalized ratio (not prothrombin time).<sup>[3]</sup> AASLD guidance can be

consulted for recommendations on the use of these diagnostic and prognostic scoring systems.<sup>[3,66]</sup>

## Treatment

1. All patients with a newly established diagnosis of WD should be initiated on lifelong medical therapy for WD [Figure 2](#).<sup>[3]</sup>

The primary treatment of WD is copper directed and involves pharmacotherapy through the chelation of copper or blockage of copper absorption ([Table 3](#)).<sup>[3]</sup> Failure to comply with lifelong therapy typically leads to recurrent or new symptoms (including neurological or psychiatric as well as hepatic), liver failure, and ultimately, liver transplantation or the new onset or



**FIGURE 2** AASLD recommendations for the treatment of WD. \*Maintenance doses are recommended. Abbreviations: AASLD, American Association for the Study of Liver Diseases; WD, Wilson disease.

worsening of neuropsychiatric symptoms.<sup>[3]</sup> An Austrian retrospective analysis ( $n = 229$ , age range, 2–61 y) observed the effects of chelation therapy in patients with WD and demonstrated the importance of treatment before progressive liver disease ensues. The mean observation period was  $14.8 \pm 11.4$  years (range, 0.5–52.0 y), resulting in 3116 patient years. Of the 162 patients on chelation therapy, 26% fully recovered, 24% improved, 25% had stable disease, and 15% deteriorated despite therapy. Nonadherence to chelation therapy led to worsening liver disease (1 death, 1 transplantation, and 1 development of decompensated cirrhosis). Cirrhosis at diagnosis was the best predictor of death (OR, 6.8; 95% CI: 1.5–31.03;  $p = 0.013$ ) and the need for liver transplantation (OR, 0.7; 95% CI: 0.016–0.307;  $p < 0.001$ ). Only 84% of patients with cirrhosis survived 20 years after diagnosis (compared with healthy Austrians,  $p = 0.008$ ). The investigators concluded that early diagnosis at a precirrhotic stage might increase survival and reduce the need for liver transplantation.<sup>[49]</sup>

The previous guidance advised a reduced copper content in the diet of patients with WD, but limited data support this approach. The updated guidance encourages consultation with a registered dietitian to design a

personalized dietary plan for maintaining a copper intake at  $<0.9$  mg/day. Dietary counseling should complement pharmacotherapy.<sup>[3]</sup>

- Initial treatment for symptomatic patients with WD should include a chelating agent. Trientine may be better tolerated than *D*-penicillamine.<sup>[3]</sup>

Chelating agents (Table 3) act by chelating copper and promoting urinary copper excretion. *D*-penicillamine was the first available oral treatment for WD and is indicated as the primary treatment for WD. The numerous adverse effects of *D*-penicillamine, including worsening neurological symptoms, led to discontinuation in almost one-third of patients. Initial incremental dosing may enhance tolerability, but the “low and slow” approach has not been studied in controlled trials.<sup>[3]</sup> Trientine, which exhibits the same mechanism of action as *D*-penicillamine, is especially indicated in patients who are intolerant of *D*-penicillamine. Oral trientine tetrahydrochloride was approved in 2022 as a maintenance therapy for adults with stable WD who are tolerant of penicillamine. This milestone represents the first new drug approval for WD in more than 50 years.<sup>[67]</sup> The approval of trientine tetrahydrochloride was based



**TABLE 3** Oral pharmacotherapy for the initial and maintenance treatment of WD<sup>[3]</sup>

| Mechanism of action     | Treatment               | Dosing                                                                                                                                                                                                                                                                                      | Clinical considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 24 h urinary copper excretion goals                                                                                                |
|-------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Copper chelation        | <i>D</i> -Penicillamine | Initial treatment: <ul style="list-style-type: none"> <li>Start at 250–500 mg/kg/d, increase by 250 mg increments every 4–7 d to ~1000–1500 mg/d (15–20 mg/kg/d to a maximum of 2000 mg/d) in 2–4 divided doses</li> </ul>                                                                  | <ul style="list-style-type: none"> <li>Take on an empty stomach (food inhibits absorption by 50%)</li> <li>Associated with severe or “paradoxical” worsening of neurological symptoms</li> <li>The first 1–3 wk of treatment are associated with early sensitivity reactions (fever, cutaneous eruptions, lymphadenopathy, neutropenia, or thrombocytopenia, and proteinuria)</li> <li>Associated with iron and zinc chelation; avoid these supplements</li> <li>Associated with pyridoxine inactivation; administer supplemental pyridoxine (vitamin B6), 25–50 mg PO qd</li> </ul> | Immediately after initiating therapy: 1000–2000 µg/24 h (~16–32 µmol/24 h)<br>In stable patients: 200–500 µg/24 h (~3–8 µmol/24 h) |
|                         |                         | Maintenance treatment <ul style="list-style-type: none"> <li>Adults: 10–15 mg/kg/d (~750–1000 mg/d) in 2 divided doses</li> <li>Pediatrics: 20 mg/kg/d (rounded to the nearest 250 mg) in 2–3 divided doses, started incrementally; the dose may reduce to 10–15 mg/kg over time</li> </ul> | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | —                                                                                                                                  |
|                         | Trientine               | Initial treatment: <ul style="list-style-type: none"> <li>20 mg/kg/d (to 2000 mg daily maximum) in 2–3 divided doses, with incremental increases over 2–3 wk</li> </ul>                                                                                                                     | <ul style="list-style-type: none"> <li>Initial paradoxical worsening of neurological symptoms seems less common than with <i>D</i>-penicillamine</li> <li>Associated with limited AEs</li> <li>Colitis and lupus-like reactions are rare</li> <li>No hypersensitivity reactions have been reported</li> <li>Esophageal irritation may occur; take with ample fluid</li> <li>Associated with iron and zinc chelation; avoid these supplements</li> </ul>                                                                                                                              | Immediately after initiating therapy: > 1000 µg/24 h (> 16 µmol/24 h)<br>In stable patients: 150–500 µg/24 h (~2.4–8 µmol/24 h)    |
|                         |                         | Maintenance treatment <ul style="list-style-type: none"> <li>Adults: 10–15 mg/kg/d in 2–3 divided doses</li> <li>Pediatrics: 20 mg/kg/d (rounded to the nearest 250 mg) in 2–3 divided doses, started incrementally.</li> <li>Doses &gt; 20 mg/kg/d may increase AEs</li> </ul>             | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | —                                                                                                                                  |
| Block copper absorption | Zinc (zinc salts)       | Initial treatment<br>Adults and larger children $\geq 50$ kg: 150 mg/d in 3 divided doses<br>Smaller children <50 kg older than 5 y: 75 mg/d in 3 divided doses.<br>Smaller children <50 kg $\leq 5$ y: 50 mg/d in 3 divided doses                                                          | Take on an empty stomach (food inhibits absorption)<br>Associated with limited AEs, with gastric irritation or gastritis being the most common<br>Early paradoxical neurological deterioration is uncommon but may occur<br>Elevation in serum lipase or amylase, without clinical or radiologic evidence of pancreatitis, may occur                                                                                                                                                                                                                                                 | In stable patients: <100 µg (< 1.6 µmol)/24 h)                                                                                     |

Abbreviations: AEs, adverse events; qd, once daily; WD, Wilson disease.

on the randomized, open-label, noninferiority phase 3 CHELATE trial. Investigators demonstrated the noninferiority of trientine tetrahydrochloride compared with penicillamine in maintaining nonceruloplasmin copper levels. In addition, the clinical trial presented data about speciated-serum copper bound to ceruloplasmin versus other serum components, proposing a test with potential clinical validity to monitor labile copper levels.<sup>[57]</sup>

Trientine seems to have fewer overall adverse effects than *D*-penicillamine, including paradoxical neurological worsening after treatment initiation. Adverse effects due to *D*-penicillamine tend to resolve and do not recur when trientine tetrahydrochloride is substituted for *D*-penicillamine. However, neurological worsening after *D*-penicillamine may not resolve after switching to trientine tetrahydrochloride. These observations are based on accumulated clinical experience. A head-to-head comparison between *D*-penicillamine and trientine for the initial therapy of WD has never been performed.<sup>[3]</sup>

3. The treatment of asymptomatic patients with WD can be a chelating agent (*D*-penicillamine or trientine at a lower dose than for initial therapy) or zinc.<sup>[3]</sup>

Oral agents (Table 3) were developed for the treatment of symptomatic WD, but their role has evolved to include asymptomatic patients and long-term maintenance therapy. All asymptomatic patients require treatment, but the urgency is greater if organ damage is evident. Zinc was traditionally reserved for the maintenance treatment of WD, but is used most commonly, and is now recommended by the AASLD as a first-line therapy for asymptomatic patients. Zinc can also be considered a first-line treatment as well as a maintenance treatment for patients with prevalent neurological manifestations. The slow onset of action and mechanism of action are typically not associated with paradoxical worsening of neurological signs and symptoms. Zinc inhibits the intestinal uptake of copper by inducing the intestinal copper chelator enterocyte metallothionein. Copper is then excreted into the feces, thereby creating a negative copper balance. Zinc may also reduce hepatic copper toxicity by inducing the expression of hepatocellular metallothionein, which will potentially sequester copper in a nontoxic form or less prone to oxidative stress. In the event of zinc treatment, urine copper determination will be low, which is also an indication of compliance with treatment or treatment adequacy.

In general, zinc demonstrates equivalent efficacy to *D*-penicillamine. However, a retrospective analysis of 288 treated patients with WD found that hepatic treatment failure occurred more often from zinc therapy (14/88 treatments) than from chelator therapy (4/313 treatments;  $p < 0.001$ ). Patients who did not respond to zinc therapy showed hepatic improvement after

reintroduction of a chelating agent. One limitation of this study was that compliance was not assessed, which may have contributed to these outcomes.<sup>[68]</sup> Zinc is generally well tolerated, uncommonly associated with early paradoxical neurological deterioration, and advantageous in patients with impaired renal function when chelation, requiring urinary copper excretion, might be ineffective. Frequent daily dosing on an empty stomach affects long-term adherence to zinc treatment in some patients.<sup>[3]</sup>

4. Regular monitoring of treatment while on medication is recommended and involves the following:

- 24-hour urinary copper excretion.
- Biannual assessment of the following:
  - i. Liver biochemistries.
  - ii. International normalized ratio.
  - iii. Complete blood count.
  - iv. Routine urinalysis (especially for those on chelation therapy with *D*-penicillamine or trientine).
- Serum copper and ceruloplasmin for trends.
- Signs of overtreatment, including anemia, neutropenia, and increased ferritin levels.
- Indications of nonadherence in the setting of treatment failure.

Adequacy of treatment is assessed through clinical and biochemical improvement and subsequent stability, and by measuring 24-hour urinary copper excretion on treatment (Table 3). Immediately after treatment, copper excretion is high but then normalizes. Serum copper and ceruloplasmin may be followed for trends: very high serum copper disproportionately high for simultaneously measured serum ceruloplasmin may indicate excessive copper intake. Lower serum copper and ceruloplasmin could indicate overtreatment and total-body depletion; newer methodology is in development to accurately measure nonceruloplasmin-bound bioavailable copper. The development of cytopenias, an increase in serum ferritin, and/or disproportionately low 24-hour urinary copper excretion [ $< 100 \mu\text{g}/24 \text{ h}$  for chelation therapy;  $\leq 20 \mu\text{g}/24 \text{ h}$  ( $< 0.3 \mu\text{mol}/24 \text{ h}$ ) for zinc therapy] may be indicative of overtreatment. Overtreatment can be corrected by dose reduction or a brief interruption in treatment. Patients who are nonadherent to therapy typically demonstrate worsening clinical and biochemical findings and increased urinary copper over time, but poor drug absorption, insufficient dosing, or intercurrent acute liver injury should be ruled out. True treatment failure requires adjustments to pharmacological therapy and, ultimately, liver transplantation in advanced diseases.<sup>[3]</sup> Data support the efficacy of liver transplantation in patients with WD.<sup>[69]</sup>

5. Although effective treatment may sufficiently restore normal copper balance and improve WD symptoms, adjunctive medical treatment may be required to alleviate neurological symptoms and control the complications of advanced liver disease.

Although the primary method of alleviating neurological symptoms is to remove excess copper, many neurological symptoms are at least partially responsive to adjunctive medical management. Medications to treat parkinsonism, dystonia, and chorea have proven effective in WD. If psychiatric symptoms do not resolve with the primary treatment of WD alone, or if they are severe, psychotropic medication or psychotherapy can be used along with pharmacotherapy for WD. Specialist consults (eg, neurologist, psychiatrist, speech, physical, and occupational therapists) are recommended in these situations. Patients with advanced liver disease must be treated for any complications of portal hypertension, screened for hepatocellular carcinoma, immunized against hepatitis A and B, and followed regarding the maintenance of general good health.<sup>[3]</sup>

6. The suitability for transition to maintenance therapy for WD includes time-on-therapy (generally more than 1 y) and favorable clinical and biochemical response to therapy. Maintenance therapy may be a lower dose of the chelating agent (*D*-penicillamine or trientine) or full-dose zinc.

Transitioning to maintenance therapy entails clinical and biochemical monitoring in the first 2–6 months by checking liver enzymes, 24-urinary copper, and frequent neurological examinations (as opposed to standard 6 mo intervals) to ensure effective therapy. Regardless of the choice of maintenance therapy (Table 3), regular follow-up is required to ensure compliance and to monitor for late treatment failures.<sup>[3]</sup>

## CONCLUSIONS

Although educational initiatives and updated guidance recommendations will improve WD management, the limitations of current WD therapies remain. Standard-of-care treatments are associated with limited efficacy, safety concerns, multiple daily dosing, and nonadherence.<sup>[39]</sup> Novel therapies under investigation seek to fulfill the urgent need for new therapies that control free copper. An example of a novel pharmacological therapy is ALXN1840 (bis-choline tetrathiomolybdate, formerly WTX101)<sup>[58,59,70]</sup> and examples of novel gene therapies include VTX-801<sup>[71–73]</sup> and UX701.<sup>[74,75]</sup> Approval of these novel therapies is greatly anticipated, with the hope that they will make a positive difference in the lives of patients with WD.

In conclusion, new medical advancements are reshaping how we take care of patients with WD and their families. These include a better understanding of sex differences in presentation, the use of genetic testing to confirm the diagnosis in indeterminate cases, and its use in first-degree relatives in the hope of finding new therapeutic approaches, including gene therapy. (Figure 2)

## CONFLICTS OF INTEREST

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