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Metabolism and Target Organ Damage

Review

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An initiative to promote the integration of artificial intelligence in transforming the diagnosis and management of Wilson disease in the 21st century

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Abstract

Wilson disease (WD) is a rare genetic disorder characterized by the excessive accumulation of copper in the body, leading to metabolic alterations and subsequent health complications due to mutations of the *ATP7B* gene. Despite advancements in medical science, diagnosing this condition remains challenging due to its variable presentation and overlap with other disorders. Traditional diagnostic methods are helpful in establishing WD, although in some cases, conflicting results may necessitate invasive procedures. The practicing physician may not always utilize the known diagnostic parameters or may not weigh their significance due to a lack of experience with the rare population of WD patients. In such cases, artificial intelligence (AI) can facilitate the diagnosis and management of WD, avoiding individual misinterpretation. By leveraging advanced algorithms and machine learning techniques, AI enhances diagnostic accuracy through predictive modeling and data analysis, while also facilitating personalized treatment plans tailored to individual patient profiles. Additionally, AI tools are reshaping disease monitoring through wearable technology and remote systems that provide real-time data integration with electronic health records. However, ethical considerations such as data privacy concerns and algorithmic bias must be addressed to ensure responsible implementation of AI in healthcare settings. The potential for broader applications across various genetic disorders further emphasizes the importance of continued research and interdisciplinary

collaboration among tech developers, clinicians, and researchers. Ultimately, this paper highlights how AI can significantly improve patient outcomes and modulate copper metabolism in such a way that WD patients have a normal and worthwhile life expectancy.

Keywords: Artificial intelligence, Wilson disease, *ATP7B*, ATPase, copper, diagnostic trees, liver, brain

INTRODUCTION

Overview of Wilson disease

Wilson disease (WD) is a rare genetic disorder characterized by the excessive accumulation of copper in the body, primarily affecting the liver, brain, and other vital organs[1]. This condition arises from mutations in the *ATP7B* gene, which disrupts the body's ability to regulate copper levels effectively. Understanding WD is important because it can help prevent severe health complications through appropriate therapy. The complications in WD include liver failure, neurological disorders, and psychiatric issues. Early diagnosis and effective intervention are crucial to mitigate these risks and improve patient outcomes. In this review, we have compiled information from previous papers found in the PubMed database that utilized artificial intelligence (AI) for the diagnosis and management of WD. We conducted a search using the keywords "Wilson disease" and "artificial intelligence". However, the search yielded papers that were, in most cases, highly specific. Therefore, we only discuss and cite those that are of more general interest.

Current challenges in diagnosis and management

Despite advancements in medical science, diagnosing WD remains challenging due to its variable presentation and overlap with other conditions. In WD, metabolic alteration primarily occurs due to the accumulation of copper in the liver, leading to hepatocellular damage. The liver plays a critical role in the body's metabolism by processing nutrients absorbed from the digestive tract, converting them into energy, and storing essential substances such as glycogen, lipids, and minerals including iron and copper. Additionally, it is responsible for detoxifying harmful substances, regulating blood sugar levels, and synthesizing proteins necessary for various bodily functions, making it vital for overall metabolic health. Therefore, ongoing damage to the liver can lead to severe and numerous health complications, ultimately compromising overall bodily functions and quality of life[2]. In addition, many patients with WD experience nonspecific symptoms such as fatigue, abdominal pain, or behavioral changes that can lead to misdiagnosis or delayed treatment[3]. Traditional diagnostic methods often require invasive procedures like liver biopsies or extensive laboratory testing, which even may not always yield definitive results[1,4]. These challenges highlight the need for more efficient diagnostic tools and management strategies that can provide timely interventions tailored to individual patient profiles.

Introduction to AI in healthcare

AI is emerging as a transformative force in healthcare, offering innovative solutions to complex medical problems[5]. By leveraging advanced algorithms and machine learning techniques, AI can analyze vast datasets rapidly and accurately, capabilities that are especially advantageous in areas like diagnostics and disease management. In the context of WD, AI has the potential to enhance diagnostic accuracy through predictive modeling based on patient data while also improving personalized treatment plans by integrating various clinical information sources[6].

Purpose of this perspective

The purpose of this paper is to explore how AI is revolutionizing the diagnosis and management of WD in the 21st century. Compared to previous papers, we have included pathogenetic and pathophysiological aspects to explain the diagnostic features and their importance in establishing WD. We also provide a

rationale for its treatment. We discuss the current challenges that healthcare professionals face in effectively diagnosing and managing WD. Furthermore, we will delve into specific applications of AI technology within this field, highlighting its role in enhancing diagnostic accuracy, personalizing treatment strategies, monitoring disease progression, and addressing ethical considerations surrounding its use. By shedding light on these aspects, this paper aims to underscore the importance of continued research and collaboration between technologists and clinicians for advancing care for individuals affected by WD.

UNDERSTANDING WD

Physiology of copper metabolism

Copper plays a catalytic role in cellular respiration as part of the oxygen-handling proteins, known as cytochromes[7]. In the blood, copper is present as a copper cluster within ceruloplasmin, which is synthesized in the liver. Ceruloplasmin is responsible for oxidizing iron from a Fe^{2+} state in ferritin to a Fe^{3+} state, allowing it to bind to transferrin[8]. We consume about 900 µg of copper daily in its cupric form (Cu^{2+})[8]. To be transported into the system, copper must be converted (reduced) to Cu^{+} at the apical side of mucosal cells, which is the form that can pass through cell membranes via the copper transporter 1 (Ctr1). Within the cells, the toxic Cu^{+} is bound to copper chaperones such as ATOX1 or, in cases of excess intracellular copper, to metallothionein. ATOX1 releases its Cu^{+} to the ATP7A (Menkes ATPase) at the basal side of mucosal cells for delivery to the blood, where it is taken over by albumin[9]. In the liver, after the reduction of Cu^{2+} at the basal plasma membrane, Cu^{+} is absorbed from albumin by Ctr1 and then transferred to ATOX1. When in excess, Cu^{+} is stored in metallothionein. The Cu^{+} bound to ATOX1 is presented to ATP7B (Wilson ATPase) for translocation to the trans-Golgi network (TGN). In the TGN, copper is loaded onto apoceruloplasmin with its six copper binding sites before ceruloplasmin is secreted into the blood via a vesicular pathway. Once the capacity for copper incorporation into apoceruloplasmin or other less abundant copper-containing proteins is met, any remaining copper leaves the TGN through a vesicular export route, passing through the canalicular plasma membrane into bile as an unabsorbable complex[10] [Figure 1].

Genetic basis and pathophysiology

WD is caused by mutations in the *ATP7B* gene located on chromosome 13, which encodes the Wilson ATPase *ATP7B*[11] [Figure 2]. This defective protein impairs the translocation of Cu^{+} to the TGN, hindering the incorporation of copper into ceruloplasmin and its excretion into bile. Consequently, copper accumulates primarily in hepatocytes, initially stored in metallothionein, whose synthesis is stimulated by the excess copper.

When this rescue pathway is overwhelmed, excess copper is deposited in lysosomes (Rhodanine-positive granules), leading to cellular damage over time due to oxidative stress and even necrosis or apoptosis[10] [Figure 3].

This pathophysiological process ultimately leads to liver cirrhosis with hepatic dysfunction. In addition to the lack of ceruloplasmin synthesis and the absence of biliary copper secretion, albumin-bound copper is no longer taken up by the liver. Unlike ceruloplasmin, copper bound to albumin is only loosely associated and can exchange with histidine, a copper-binding amino acid (albumin-histidine shuttle)[13]. This represents the non-ceruloplasmin bound or “free” copper. An excess of free copper can enter various parenchymal cells and is responsible for a plethora of clinical symptoms, particularly neurological manifestation when copper deposits affect brain tissue[10].

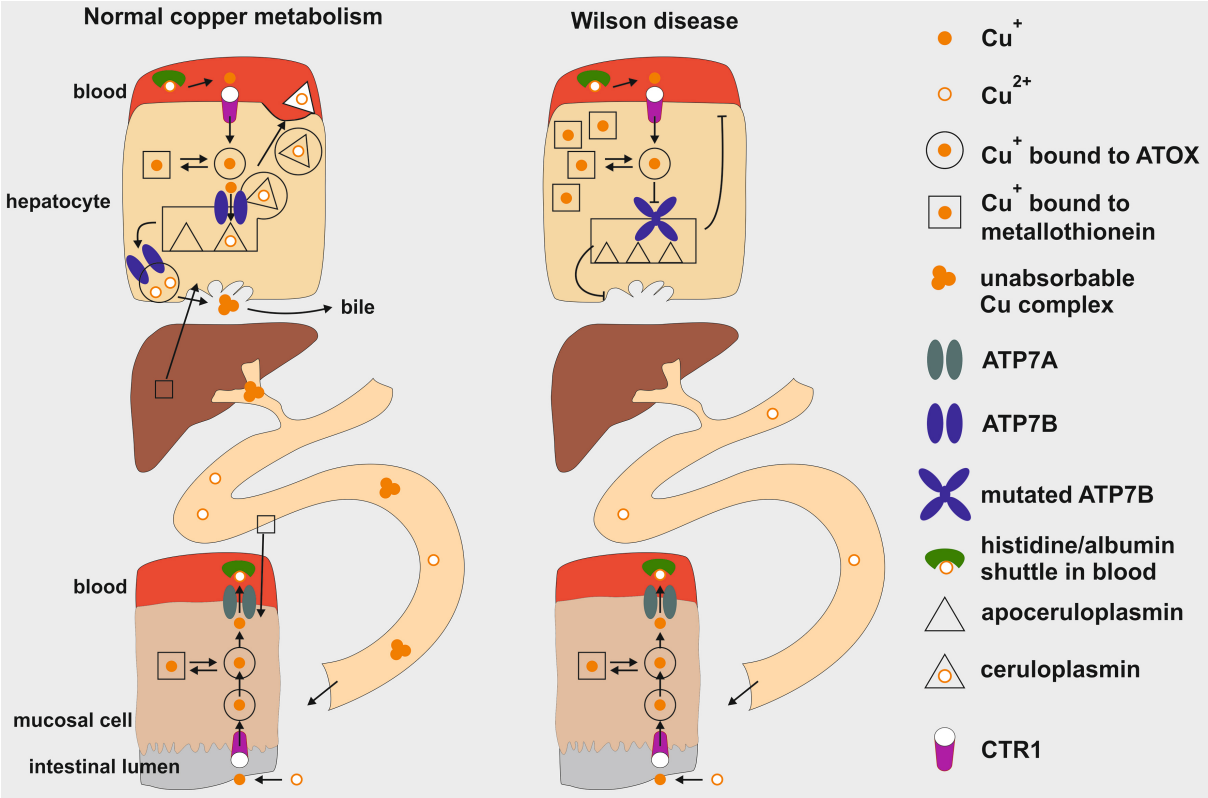

Figure 1. Schematic representation of copper metabolism in healthy individuals compared to Wilson disease. The regulation of copper levels involves absorption in the upper gastrointestinal tract and excretion by liver cells (hepatocytes) into bile as an insoluble complex. Key components include the mucosal cell and the hepatocyte. This diagram illustrates the processes of cellular uptake, intracellular transport, storage, metabolic processing within the liver, and cellular excretion. In Wilson disease, a mutation in the *ATP7B* gene leads to a defective copper transporter at the trans-Golgi network, hindering proper loading of apoceruloplasmin with copper, resulting in decreased serum copper levels. Additionally, impaired biliary excretion causes copper accumulation in hepatocytes, initially bound to metallothionein. Cu^{+}: Cuprous form; Cu^{2+}: cupric form; ATOX1: antioxidant copper chaperone; ATP7A: ATPase copper transporter alpha; ATP7B: ATPase copper transporter beta; CTR1: copper transporter 1.

There are other rare genetic diseases resembling WD, as summarized in Table 1. Each of them has a different clinical picture due to varying pathophysiology and requires a distinct therapeutic approach. This information can be utilized in AI analysis for cases of disturbed copper metabolism unrelated to WD[4].

Epidemiology and prevalence

The prevalence of WD varies globally but is estimated to be around 1 in 30,000 individuals overall[4]. However, certain populations exhibit higher rates due to founder effects or consanguinity patterns that increase mutation frequency within families or communities. It affects both males and females equally. The disease typically presents between ages 5-35 years, but manifestations can occur earlier in life or as late as 70 years, when symptoms become apparent due to significant copper accumulation over time without appropriate treatment measures taken during earlier life stages. It is emphasized that early detection plays a critical role in preventing irreversible organ damage[1,4].

Traditional diagnostic methods

Diagnosing WD involves a combination of clinical evaluation alongside laboratory tests aimed at assessing abnormalities in copper metabolism in suspected patients[1,4]. The clinical presentation can involve multiple organs with various symptoms that, on their own, are not necessarily indicative of WD. However, when

Table 1. Rare genetic diseases resembling Wilson disease[1]

Disorder	Gene	Cytogenetic location[2]	Serum ceruloplasmin	Hepatic Cu	24-h basal urinary Cu	Possible mechanism (s)	Type
Aceruloplasminemia	*CP*	3q24-q25.1	Absent	Normal; Fe ↑	Normal	No production of ceruloplasmin	Clinical
MDR3 deficiency	*ABCB4*	7q21.12	Normal	NN	May be ↑	Cu retention due to cholestasis	Clinical
MEDNIK syndrome	*AP1S1*	7q22.1	Very low	May be ↑	↑ (2.5 μ mol/24-h)	Abnormal protein production and metal (Cu) excretion	Mechanistic
Mn retention-1	*SLC30A10*	1q41	Normal	Slightly ↑	NN	Hepatic Mn excretion abnormality	Mechanistic
Mn retention-2	*SLC39A14*	8p21.3	Not reported	NN	NN	Abnormal hepatic Mn uptake	Mechanistic
Nieman-Pick type C	*NPC1, NPC2*	18q11.2; 14q24.3	Low or slightly low	Mildy ↑ (100-250 μg/g dry weight)	Normal	Defective interaction with ATP7B	Mechanistic
PGM1-CDG	*PGM1*	1p31.3	Low	Mildy ↑ (50-250 μg/g dry weight)	Normal	(Golgi dysfunction)	Clinical, mechanistic
CCDC115-CGD	*CCDC115*	2q21.1	Low or very low	Slightly ↑	Normal or mildly ↑	Abnormality in protein production pathway affecting ATP7B function (Golgi dysfunction)	Clinical, mechanistic
TMEM119-CDG	*TMEM199*	17q11.2	Low	Not reported	Normal or mildly ↑	(Golgi dysfunction)	Clinical, mechanistic

[1]Data were taken in modified form from[4]; [2]The cytogenetic locations were obtained from the OMIM database[14]. ↑ : Increase. *ABCB4*: ATP-binding cassette, subfamily B, member 4; *AP1B1*: adaptor-related protein complex 1, beta 1 subunit; *AP1S1*: adaptor-related protein complex 1, sigma 1 subunit; *CCDC115*: coiled-coil domain-containing protein 115; *CP*: ceruloplasmin; *NPC1*: NPC intracellular cholesterol transporter 1; *NPC2*: NPC intracellular cholesterol transporter 2; *SLC30A10*: solute carrier family 30 (zinc transporter), member 10; *SLC39A14*: solute carrier family 39 (zinc transporter), member 14; *TMEM119*: transmembrane protein 119; NN: not known.

considered in combination, they can be a useful tool in suspecting the diagnosis [Figure 4].

However, any unexplained liver disease - particularly in childhood and adolescence - should be considered as WD. This is also true for Coombs-negative hemolytic anemia with high bilirubin levels. Finally, liver enzyme elevation and signs of hepatic architectural changes observed on ultrasound, in association with a movement disorder (e.g., tremor), should also raise suspicion for WD. A family history of WD is a very strong indicator of this copper overload disease[1,4]. The challenge lies in identifying asymptomatic cases, as early therapy can prevent complications and provide a normal life expectancy. Thus, alongside clinical suspicion, a laboratory examination is essential. Initial evaluations include measuring serum ceruloplasmin levels (which are low, mostly clearly reduced or at least below the lower level of normal). Since ceruloplasmin is the predominant copper-containing protein in blood, serum copper is also reduced. Urinary copper excretion is elevated due to the above-mentioned release of "free" copper. In normal individuals, only 10%-20% of copper is "free", while in untreated WD, it represents up to 60%-80% of serum copper. Unfortunately, due to technical reasons, it is not directly measurable[15]. In cases with low serum ceruloplasmin levels (< 0.1 g/L), there is a formula that can estimate the free copper with sufficient accuracy[10]:

free Cu (μg/dL) = total Cu (μg/dL) - ceruloplasmin (mg/dL) × 3.15.

According to the elevated, filterable free copper, urinary copper is increased without further stimulation by D-penicillamine, making it a very reliable diagnostic parameter[1,4] [Table 2].

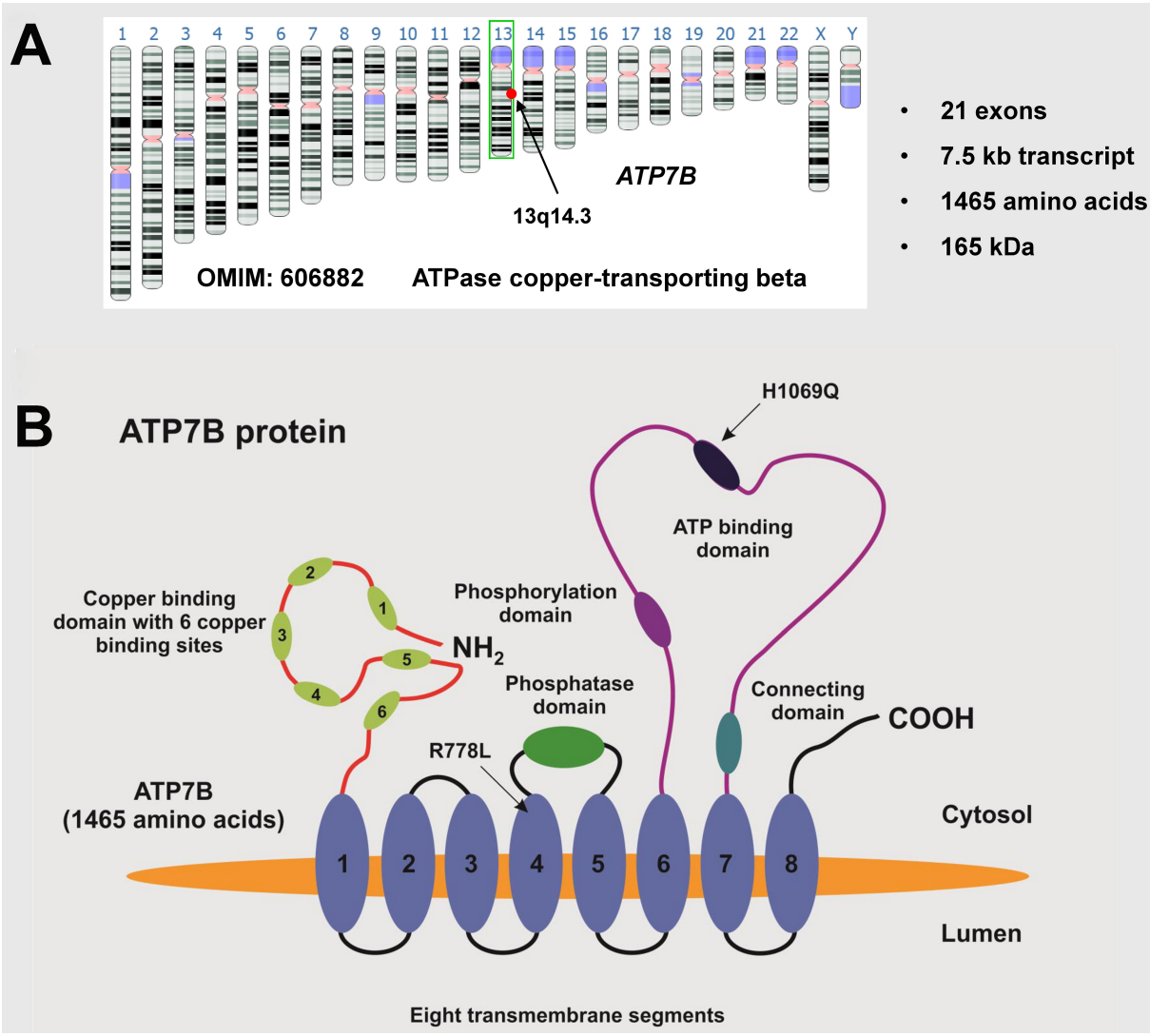

Figure 2. The *ATP7B* gene. (A) The *ATP7B* gene (OMIM: 606882) is located on the long arm (q-arm) of human chromosome 13, specifically in region q14.3. It consists of 21 exons, encoding a transcript of approximately 7.5 kb that translates into a 1,465 amino acid protein with an estimated molecular weight of around 165 kDa; (B) The ATP7B protein, known as ATPase copper-transporting beta, contains a phosphatase domain, a phosphorylation domain, an ATP binding domain, a metal binding domain, and eight transmembrane segments. The ideogram image shown in (A) was obtained from the Genome Data Viewer of the National Library of Medicine[12]. There are over 500 known disease-causing mutations, with the most common European mutation being H1069Q and the most common mutation in the Chinese population being R778L. The location of these mutations is shown.

Clinical presentation can vary from asymptomatic cases to severe manifestations in terms of hepatic and neurological symptoms. Hepatic manifestations range from simple hepatomegaly with hyperechogenicity, often with elevated transaminases, to acute liver injury/failure, and cirrhosis (compensated or decompensated). Neurological manifestations typically manifest as movement disorders (tremors, involuntary movements, rigid dystonia), dysphagia, dysarthria, pseudobulbar palsy, drooling, dysautonomia, seizures, and sleep disorders. Psychiatric manifestations include depression, bipolar disorders, personality changes, and psychosis. Other manifestations include Kayser-Fleischer rings, sunflower cataracts, renal abnormalities, skeletal manifestations (osteoporosis, arthritis), cardiomyopathies and arrhythmias, pancreatitis, hypoparathyroidism, infertility, and miscarriages. The wide range of possible manifestations and their overlap with other diseases pose a challenge in defining the diagnosis. Therefore, a

Table 2. Diagnosis of Wilson disease[1]

Parameter	Criteria to diagnose Wilson disease
Ceruloplasmin	< 0.2 g/L
Serum copper	< 70 μg/dL (12 μmol/L)
Urinary copper	> 60 μg/d (> 0.94 μmol/d)
Free copper	> 15 μg/dL (0.23 mmol/dL)
D-Penicillamine 2 mg × 500 mg	Urinary copper increase to > 20× of basal value, > 1,600 μg/d in children
Liver copper	> 250 μg/d dry weight
Kayser-Fleischer rings	Sensitivity 50%; Specificity 95%
Genetic analysis	Sensitivity 90%; Specificity 100%

[1]Data taken from[11].

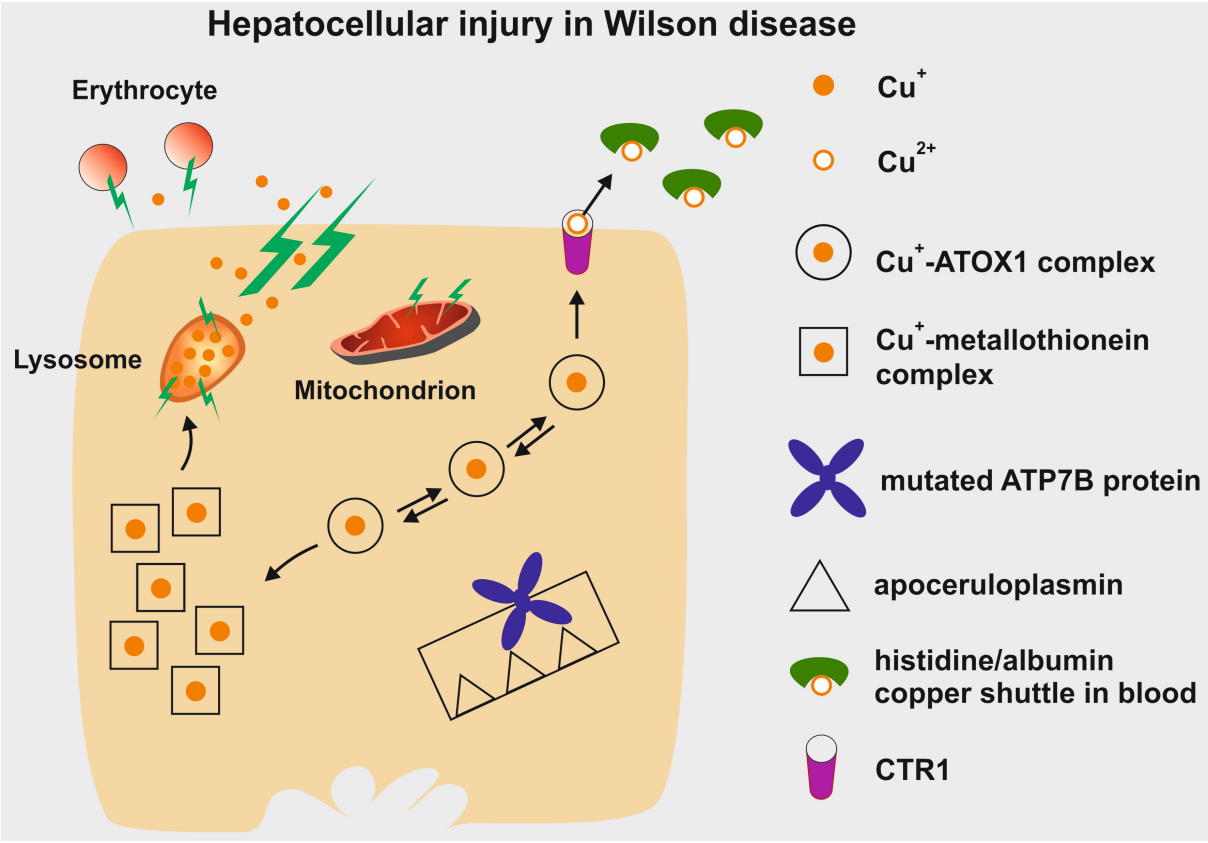

Figure 3. Depiction of the potential hepatotoxic effects of copper accumulation in Wilson disease. Initially, excess copper is sequestered within cytosolic metallothionein. Once these stores are full, copper can be re-excreted through CTR1 into the bloodstream. From there, it is transported as non-ceruloplasmin-bound copper within a histidine/albumin shuttle complex to other organs, such as the brain, and eventually excreted in urine. In hepatocytes, additional copper buildup leads to lysosomal deposition, which can be detected by positive Rhodanine staining. The reactive nature of Cu^{+} damages the lysosomal membrane, causing rupture and the release of Cu^{+} into the cytoplasm, resulting in damage to hepatocytes. This process also renders the plasma membrane permeable, allowing Cu^{+} to leak into the bloodstream and contribute to erythrocyte membrane destruction (hemolysis). Cu^{+}: Cuprous form; Cu^{2+}: cupric form; ATOX1: antioxidant copper chaperone; ATP7B: ATPase copper transporter beta; CTR1: copper transporter 1.

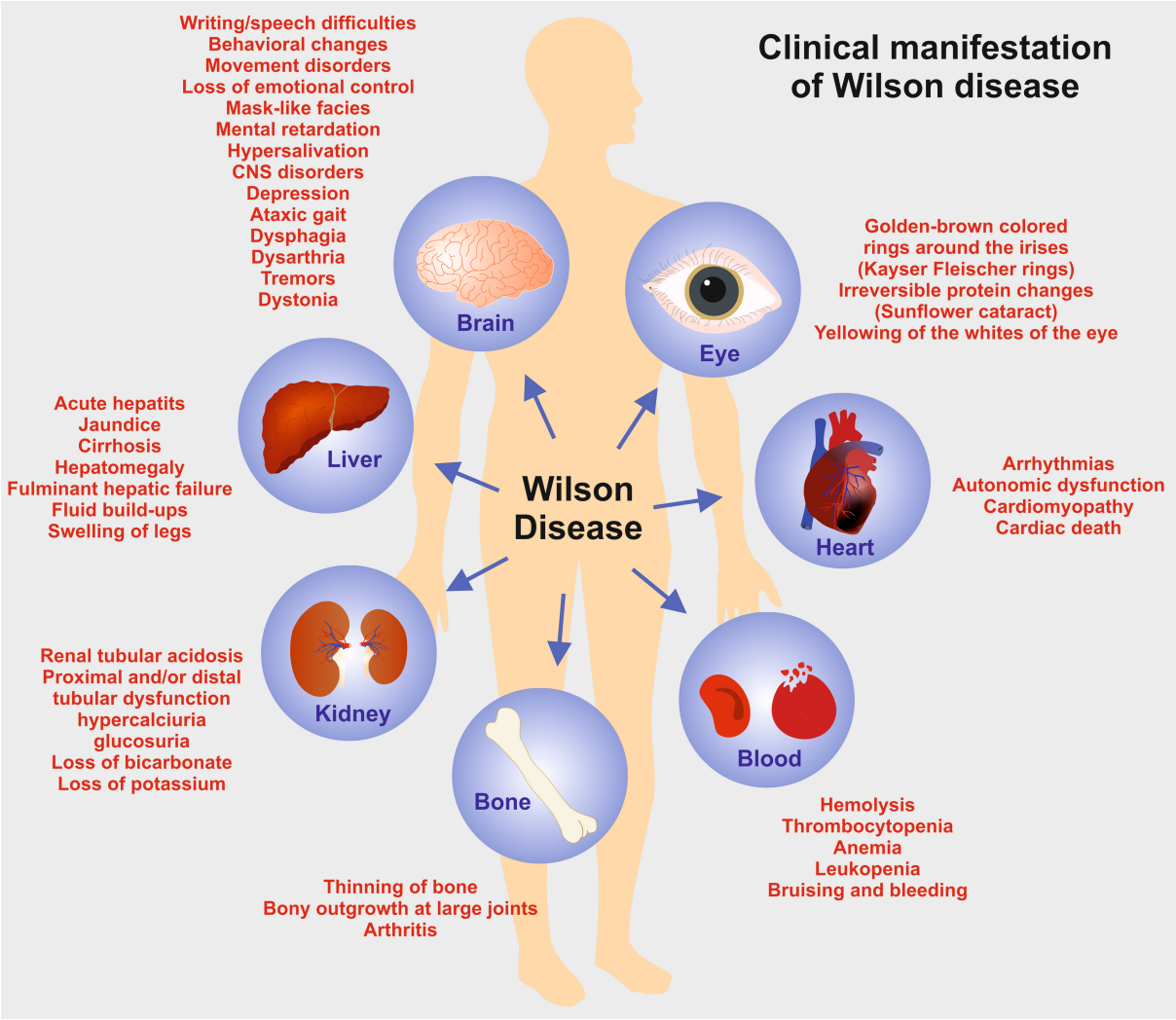

Figure 4. Diverse organ manifestations and symptoms associated with Wilson disease. Wilson disease presents a wide range of symptoms that can vary significantly among individuals, affecting multiple organs. The key areas of manifestation include the liver, where copper accumulation leads to hepatotoxicity, and the brain, which can experience neurological disturbances due to copper deposition. Additional effects may be observed in the eyes, such as Kayser-Fleischer rings, as well as in the kidneys, heart, bones, and hematological system. This variability in clinical presentation underscores the complexity of Wilson disease and highlights the difficulty of early diagnosis and comprehensive management.

panel of experts evaluated various clinical and laboratory parameters with indicative values for the presence of WD and provided a Leipzig scoring system for establishing a diagnosis, which can be used as a helpful diagnostic algorithm, including for AI applications [Table 3][1]. Nevertheless, it must be considered that the Leipzig score is simply a tool to aid in diagnosis. There are limitations to be aware of, such as cholestatic diseases that result in the buildup of copper in the liver. In these cases, elevated urinary copper excretion is the most sensitive and specific indicator (refer to pathophysiology). However, in cases of fulminant hepatic failure in WD, urinary production may decrease or even stop, making urinary copper excretion unreliable or unmeasurable (see below).

Due to the autosomal recessive mode of inheritance, heterozygous carriers of the mutation show discrete changes in laboratory parameters but no clinical signs of disease manifestation[1,4]. In these cases which are hard to differentiate from asymptomatic early cases of homozygous carriers, no therapy is indicated because

Table 3. Leipzig scoring system for diagnosis of Wilson disease[1]

Typical clinical symptoms/signs		Other tests/Score points	
Kayser-Fleischer rings	Score	Liver copper (in the absence of cholestasis)	Score
Present	2	5× ULN (> 4 μmol/g)	2
Absent	0	0.8-4 μmol/g	1
		Normal (< 0.8 mol/g)	-1
		Rhodanine-positive granules[2]	1
Neurologic symptoms[3]	Score	Urinary copper	Score
Severe	2	Normal	0
Mild	1	1-2× ULN	1
Absent	0	> 2× ULN	2
		Normal, but > 5× ULN after D-Penicillamine	2
Serum ceruloplasmin	Score	Mutation analysis	Score
Normal (> 0.2 g/L)	0	On both chromosomes detected	4
0.1-0.2 g/L	1	On one chromosome detected	1
< 0.1 g/L	2	No mutation detected	0
Coombs-negative hemolytic anemia	Score	Total score	Diagnosis
Present	1	≥ 4	Established
Absent	0	3	Possible, more tests needed
		≤ 2	Very unlikely

[1]This information is adapted from[1]; [2]If quantitative liver copper levels are not available; [3]or if typical abnormalities are observed on brain magnetic resonance imaging. ULN: Upper limit of normal.

of the absence of disease. The presence of WD can be confirmed by sophisticated copper kinetics (mostly not available) or imaging techniques, which are particularly significant for detecting the neurological manifestations typical of WD.

The presence of neurocognitive features along with Kayser-Fleischer rings is often sufficient for diagnosing WD. Accumulated experience has shown that magnetic resonance imaging (MRI) abnormalities are almost always present in individuals with neurological manifestations of WD[16-18]. Pathognomonic MRI features include the "Face of the giant panda" (14.3%), tectal plate hyperintensity (75%), central pontine myelinolysis-like abnormalities (62.5%), and simultaneous signal changes in the basal ganglia, thalamus, and brainstem (55.3%).

Diagnosis of WD through genetic analysis is typically performed at specialized centers. By sequencing the entire *ATP7B* gene, known mutations in the family can be confirmed. There are also libraries available that can assess the pathogenicity of a specific *ATP7B* variant [Table 4]. However, it is important to note that not all mutations detected are necessarily associated with disease manifestation. Therefore, genetic analysis may not always be the definitive method for diagnosis.

Indeed, in some instances, uncertainty regarding the diagnosis of WD persists. In these cases, physicians may utilize invasive procedures such as liver biopsies aimed at evaluating the histologic pattern of liver affection. More importantly, the demonstration of excess hepatic copper deposition by Rhodanine staining or, more precisely, quantifying hepatic copper content (higher than 250 μg/g dry weight, or in mild cases, higher than 75 μg/g dry weight) is crucial. This analysis is still considered the gold standard of diagnosis. However, the risk of bleeding as a complication of the biopsy procedure must be considered[1,4]. There are still cases where the diagnosis remains unclear due to sampling error by biopsy or performing the biopsy too early in life when full-blown copper accumulation has not yet occurred.

Table 4. Representative resources available for evaluating *ATP7B* gene variants[1]

Public domain databases		
	URL	Comments
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/	Hosted by the NCBI; aggregates information about genomic variation and its relationship to human health
gnomAD	https://gnomad.broadinstitute.org/	The Genome Aggregation Database, originally launched in 2014 as the ExAC, aggregates exome and genome sequencing data from various large-scale sequencing projects
VarSome	https://varsome.com/	A search engine that aims to share global expertise on human variants. It also offers a suite of bioinformatics tools for processing and annotating NGS data
Proprietary databases		
HGMD	https://www.hgmd.cf.ac.uk/ac/index.php	Hosted by the University of Cardiff, which systematically collates published gene lesions responsible for human inherited diseases. Established in 1996, its goal is to facilitate the scientific study of mutational mechanisms in human genes underlying inherited diseases
WilsonGen	https://clingen.igib.res.in/WilsonGen/	WilsonGen is a comprehensive resource of genetic variants in the *ATP7B* gene, manually curated from literature and data resources. It is systematically annotated using the ACMG and AMP guidelines for assessing the pathogenicity of genetic variants. WilsonGen serves as a central point for clinicians and geneticists working on Wilson Disease. It is a compilation of six datasets: Wilson Disease Mutation Database University of Alberta, NDDVD, ClinVar, *ATP7B* mutations database (UMD), LOVD, HGMD and publications
University of Alberta Wilson Disease Mutation Database	Formerly available at: https://www.medgen.med.ualberta.ca/database.html	Data in this database are now integrated into the WilsonGen database
International Wilson Disease Mutation Database	https://wilsondisease.azyfy.com/home/Blog/index1	This database, officially launched on September 23, 2022, contains almost all the *ATP7B* mutations reported in articles included in the PubMed and Embase databases updated to May 31, 2022, including both Chinese and international databases

[1]Part of these data are taken from[4]. NCBI: National Center for Biotechnology Information; ExAC: Exosome Aggregation Consortium; NGS: Next-Generation Sequencing; HGMD: Human Gene Mutation Database; ACMG: American College of Medical Genetics; AMP: Association of Molecular Pathology; NDDVD: Neurodegenerative Diseases Variation Database; UMD: Universal Mutation Database; LOVD: Leiden Open Variation Database; HGMD: Human Gene Mutation Database.

THE ROLE OF AI IN DIAGNOSIS

AI algorithms for data analysis

In the realm of WD, AI algorithms are revolutionizing data analysis by enabling more accurate and efficient diagnosis and management[19-24]. These algorithms are accessible to practicing physicians, making them easily available to affected patients, without the need for specialized WD specialists. They leverage vast datasets, including genetic information, clinical symptoms, and biochemical markers, to identify patterns that may be overlooked by traditional methods. Machine learning techniques, such as supervised and unsupervised learning, facilitate the development of predictive models that can assess disease progression and treatment responses in real time. By integrating AI-driven insights into clinical workflows, healthcare professionals can make informed decisions tailored to individual patient profiles, ultimately enhancing outcome prediction for those affected by WD. The application of AI not only streamlines data processing, but also fosters a deeper understanding of the complexities of diseases. This paves the way for new pathogenetic mechanisms, such as urea-Krebs´ cycle abnormalities, the central role of mitochondria, and mechanisms of hepatic injury[19]. Moreover, innovative new therapeutic strategies may emerge.

Enhancing diagnostic accuracy

WD is a well-characterized condition with a comprehensive list of reported clinical symptoms, as shown above [Figure 4]. However, the diagnostic significance is not outlined in this compilation. Which symptoms are common in WD and which are rare? This responsibility lies with experts in the field who create corresponding guidelines[1,4]. These guidelines cover both clinical asymptomatic patients and symptomatic

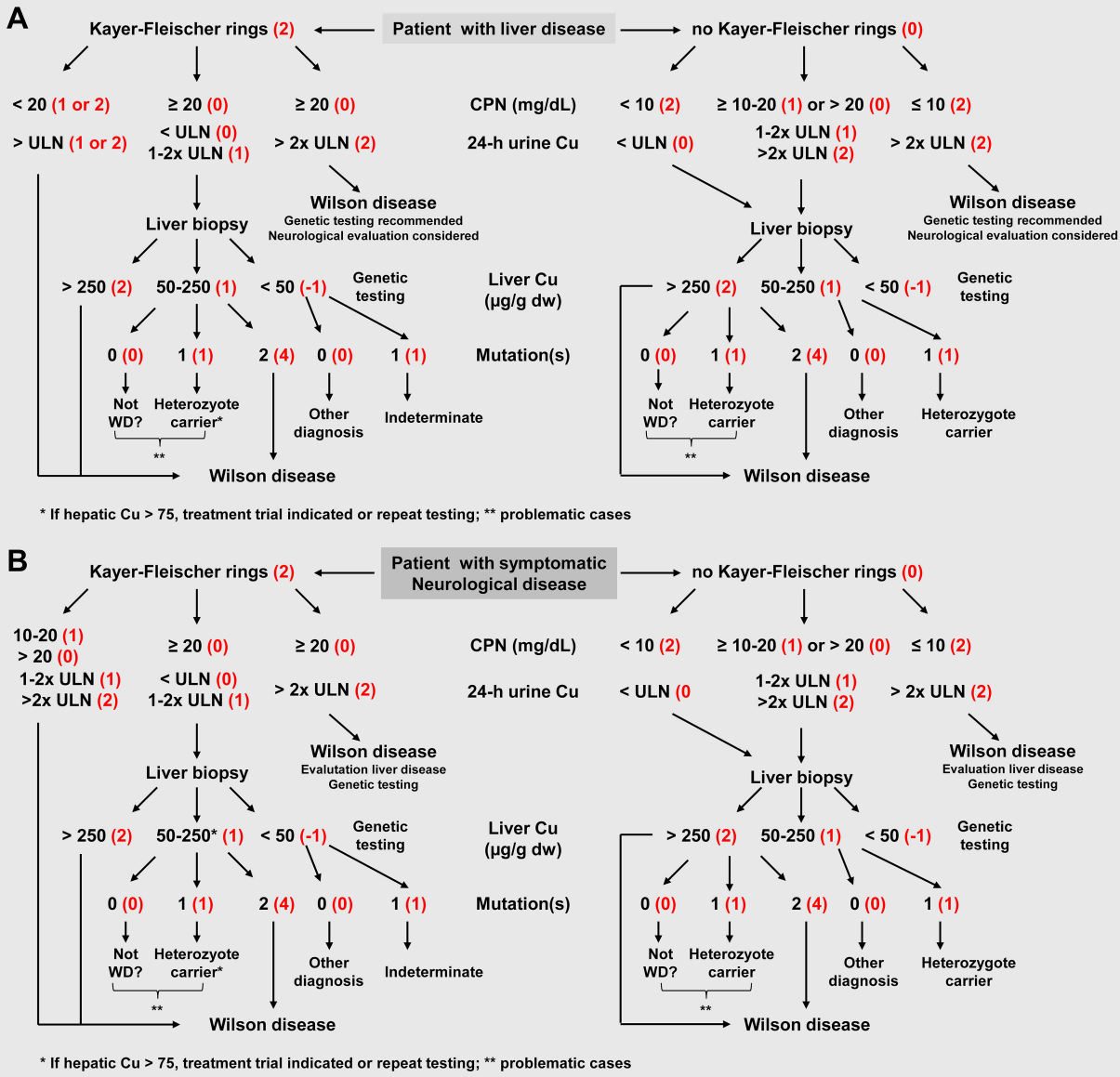

Figure 5. Diagnostic algorithms for Wilson disease. The algorithms for patients with (A) unexplained liver conditions and (B) neurological symptoms are depicted. The numbers in parentheses correspond to the Leipzig score, where a total score of 4 or higher indicates a strong likelihood of Wilson disease. The minimum ULN for basal 24-h urinary Cu excretion is set at 40 µg/24 h. Genetic testing involves examining the *ATP7B* gene sequence to identify any disease-associated mutations present on each allele. The manifestation of Wilson disease as a neurological disorder without the presence of Kayser-Fleischer rings is uncommon, yet it poses significant diagnostic challenges. These schemes were adapted from[4]. ULN: Upper limit of normal; Cu: copper; CPN: ceruloplasmin.

cases with hepatic and neurological manifestations, outlining the most suitable approach [Figure 5][4].

Screening first-degree relatives of patients with WD is crucial due to the hereditary nature of this genetic disorder, which impairs copper metabolism and can lead to severe liver and neurological complications. Since WD follows an autosomal recessive inheritance pattern, siblings and children of affected individuals have a 25% chance of being affected themselves and a 50% chance of being carriers. Early detection through screening can facilitate timely intervention, potentially preventing the onset of symptoms or reducing disease severity in those who are diagnosed. Moreover, understanding their carrier status can help in family

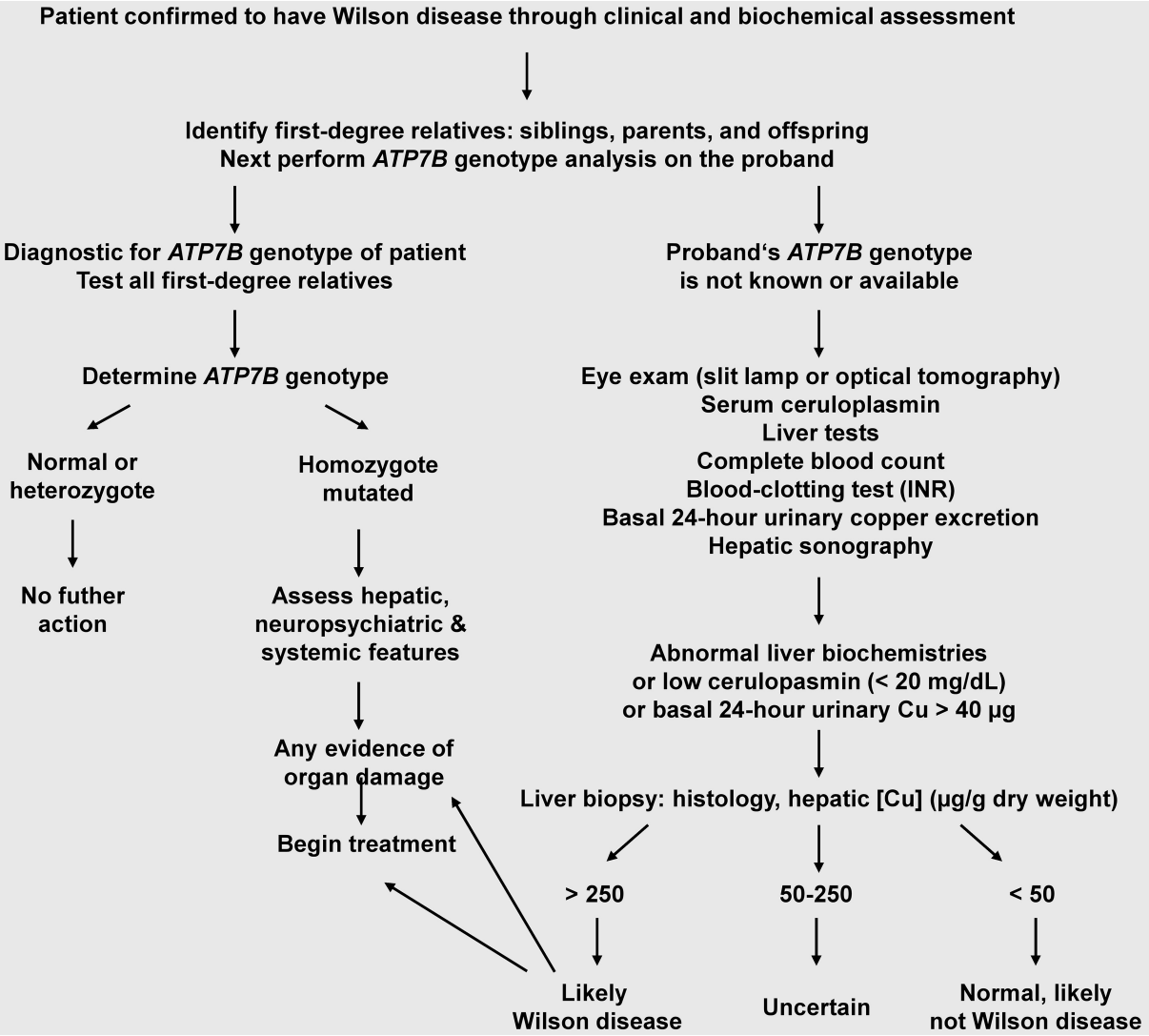

Figure 6. Screening for Wilson disease in first-degree relatives of a diagnosed individual (proband). The initial step involves identifying all first-degree relatives. If the proband's genotype related to Wilson disease (ATP7B) is known, genetic testing serves as the most effective screening method. In cases where the genotype is not available, clinical assessments are necessary. Should clinical evaluations yield inconclusive results and genetic testing not an option, a follow-up noninvasive assessment should be conducted after 6 to 12 months. A treatment trial may also be considered at this stage. Genetic testing entails analyzing the *ATP7B* gene sequence to check for disease-associated mutations on each allele. This scheme was adapted from[4]. ATP7B: Adenosine triphosphatase copper-transporting beta; CPN: ceruloplasmin; INR: international normalized ratio; Cu: copper.

planning decisions. A strategy for screening first-degree relatives is depicted in Figure 6.

There are still areas of uncertainty in establishing a diagnosis, which are summarized in Table 5[4].

Another area that could benefit from AI technology is the specific diagnostic features of acute hepatic failure in WD. This is indeed a challenging diagnosis, especially in young patients (e.g., 14 to 24 years of age), predominantly in females without any previous signs of liver disease. They rapidly develop jaundice with elevated levels of conjugated and unconjugated bilirubin due to hepatic failure or hemolysis, respectively. Alkaline phosphatase is often low for unexplained reasons, but not in all cases[25,26]. Liver function is compromised (cholinesterase, albumin, and coagulation parameters). Thrombocytopenia is

Table 5. Checklist for dealing with "gray areas" in the provided diagnostic algorithms[1]

Type of problem	Specific issues	Action
Accuracy of laboratory data	Serum ceruloplasmin - potential confounders to consider 24-h urinary copper - ensure complete collection and potential contamination Liver [Cu] - was the specimen large enough? Stored properly Thoroughness of genetic analysis	Confirm the technical adequacy of the assay Check the creatinine level Repeat testing Check the report and/or discuss it with the pathologist Review protocols Consult a clinical geneticist Confirm trans (not cis) mutations
Adequacy of clinical assessment	Neurological assessment Presence of Kayser-Fleischer rings Psychiatric assessment (only implied in algorithms)	Expert review to specify relevant findings Brain MRI Request an exam or optical tomography to determine the presence Expert consultation/review
Data available but not accounted for in algorithms	Liver function tests Liver tissue examination (histology)	Normal LFTs would likely preclude a liver biopsy Abnormal LFTs support WD or some other liver disorder: biopsy may be performed Findings may support WD or provide a basis for an alternative diagnosis Consider examining ultrastructure (by EM) as findings may support WD, especially in children
Emerging problem not well accounted for in algorithm	Hepatic Cu < 250 μg/g dry weight but above suggested revisions of that threshold (e.g., > 75 μg/g dry weight) and well above normal Only one mutation found, but along with a VUS Screening reveals an affected infant/toddler who is entirely healthy	Reevaluate, with genetic analysis if not yet performed Treatment trial Repeat clinical/biochemical evaluation in 6-12 months or until a clear diagnosis is reached *In silico* assessment of VUS Reevaluate every 6 months and plan to start treatment at 3 years old unless earlier evidence of organ damage

[1]Data were taken in modified form from[4]. Cu: Copper; EM: electron microscopy; LFT: biochemical liver test; MRI: magnetic resonance imaging; VUS: variant of unknown significance; WD: Wilson disease.

frequently present. The course is characterized by the rapid development of hepatic encephalopathy, often within 3-4 days, leading to a fatal outcome. Therefore, immediate registration for liver transplantation is crucial and can be life-saving. However, establishing a diagnosis of underlying WD is often challenging. Inflammatory parameters (transaminases) are only mildly to moderately elevated, while functional parameters are significantly reduced (high bilirubin, low coagulation parameters, low albumin, low cholinesterase, high ammonia). Due to liver failure, ceruloplasmin levels may be decreased, as in non-Wilsonian acute liver decompensation, while free copper levels are elevated. This can be difficult to detect as it is not typically provided by standard laboratories. Calculating free copper is unreliable as it requires very low ceruloplasmin concentrations (< 0.1 mg/dL)[11]. Urinary copper excretion is a valuable parameter, as it reflects the free copper in the blood. However, some patients may have compromised urinary excretion due to hepatorenal syndrome, leading to low copper excretion, which could impede the diagnosis. Liver biopsy for quantifying liver copper, considered the gold standard of diagnosis, is challenging due to impaired coagulation (low plasma coagulation and low platelets). Genetic analysis can be time-consuming for logistical reasons and is not always reliable. The diagnostic features of fulminant hepatic failure are summarized in Table 6.

AI can help increase the likelihood of establishing the correct diagnosis. For fulminant hepatic failure due to WD, liver transplantation is often a curative option with better post-transplant survival rates compared to other reasons for liver transplantation, possibly due to the young age of the patients[1,4]. Furthermore, AI is significantly enhancing the diagnostic accuracy of WD by providing advanced analytical tools that assist clinicians in interpreting complex medical data. AI could also be useful in analyzing various influencing factors. For instance, the impact of estrogen on the increase of ceruloplasmin levels could be taken into account during diagnostic evaluations. Traditional diagnostic methods often rely on subjective assessments

Table 6. Introducing the NWI: a prognostic scoring system for Wilson Disease using conventional units[1]

Points assigned	0	1	2	3	4
Bilirubin, mg/dL Bilirubin, µmol/L	0-5.8 0-100	5.9-8.7 101-150	8.8-11.7 151-200	11.8-17.5 201-300	> 17.5 > 300
INR	0-1.29	1.3-1.6	1.7-1.9	2.0-2.4	≥ 2.5
AST, IU/L	0-100	101-150	151-200	201-300	> 300
WBC (×10^6/mL)	0-6.7	6.8-8.3	8.4-10.3	10.4-15.3	≥ 15.4
Albumin, mg/dL	> 4.5	3.4-4.4	2.5-3.3	2.1-2.4	≤ 2.0
A score ≥ 11 is a strong predictor of mortality without liver transplantation					

[1]Data were taken from[4]. AST: Aspartate aminotransferase; INR: international normalized ratio; MELD: Model of End-Stage Liver Disease; WBC: white blood cell count; NWI: New Wilson index.

and limited laboratory results, which can lead to misdiagnosis and, thus, delayed treatment.

AI algorithms, particularly those employing deep learning techniques, analyze a multitude of factors including genetic profiles, imaging studies, and biochemical tests to identify subtle indicators of the disease[19-24]. Examples of diagnostic algorithms for WD have already been proposed in the practice guidelines by the American Association for the Study of Liver Diseases (AASLD)[4] [Figure 5].

Predictive modeling based on patient data enables the development of sophisticated algorithms that can forecast disease progression and treatment responses by identifying patterns across large datasets. Additionally, image analysis techniques using advanced MRI technology for brain and liver scans play a crucial role in this process. AI systems can analyze these images with exceptional precision, detecting early signs of hepatic damage or copper accumulation that may not be visible to the naked eye. By synthesizing information from diverse sources and recognizing intricate patterns within the data, AI systems can flag potential cases of WD earlier and more reliably than conventional approaches. This increased precision not only facilitates timely intervention but also minimizes the risk of complications associated with late diagnosis, ultimately improving patient outcomes and quality of life for individuals affected by this condition. As AI continues to evolve, its integration into clinical practice promises to further refine diagnostic processes and enhance our understanding of WD complexities.

Case studies or examples of successful AI implementations

The implementation of AI in the diagnostic management of WD should begin with a basic assessment of clinical features, followed by an examination of laboratory data that focuses on detecting liver diseases and metabolic changes, especially those related to copper metabolism. Another challenge is related to the classification of genetic variants in the *ATP7B* gene and their pathogenetic significance. It is essential to analyze the involvement of both the liver and brain. It is important to consider the patient's age, whether they are a child, adolescent, or adult. AI algorithms could utilize the information provided in the text, figures, and tables presented here, but they need to be consistently updated with new findings and recommendations from consensus conferences.

Diagnostic procedures and evaluation of liver involvement

Several case studies highlight the successful implementation of AI in the diagnosis and management of WD, showcasing its transformative potential[19,22]. One notable example involves a research team that developed an AI-driven diagnostic tool utilizing machine learning algorithms to analyze patient data from multiple healthcare institutions[5,6]. This tool demonstrated a remarkable accuracy rate in identifying WD, significantly reducing the time taken for diagnosis compared to traditional methods. In another instance, a

collaborative project between radiologists and data scientists employed deep learning techniques to evaluate MRI scans of patients suspected of having WD. The AI system was able to detect early signs of liver damage with higher sensitivity than human experts, enabling earlier intervention and improved patient outcomes. Additionally, predictive modeling applications have been utilized to assess treatment responses based on historical patient data, allowing clinicians to tailor therapies more effectively for individual patients.

Tools to detect brain affection

Agarwal *et al.* designed and validated seven types of advanced, high-performing AI-based computer-aided design (CADx) systems for classifying and characterizing brain magnetic resonance images from patients with WD against control groups. They addressed challenges posed by subtle intensity changes in MRI scans[20]. The AI models were evaluated using metrics such as area under the curve (AUC), diagnostic odds ratios (DOR), reliability, stability, and benchmarking against other machine learning methods like k-NN, decision trees, support vector machines (SVM), and random forests (RF). An improved deep convolution neural network (iDCNN) achieved a diagnostic accuracy of 98.28% ± 1.55% with an AUC of 0.99 in identifying WD. Additionally, the study utilized CNN-based feature map strength alongside bispectrum signal processing techniques for characterization purposes, showcasing a novel way to analyze MRI features indicative of WD. Power analysis indicated that a dataset size above 60% was necessary for generalization without compromising accuracy[20]. Overall, this research highlights the potential of advanced AI methodologies in improving early diagnosis and characterization of WD through effective image analysis techniques based on deep learning frameworks.

Similarly, Yang *et al.* focused on developing a predictive model for neurological symptoms in patients with WD using advanced machine learning techniques[23]. In their study, they analyzed data from 185 WD patients, 163 of whom exhibited neurological symptoms, and utilized various clinical indicators such as imaging results, blood tests, and clinical scale measurements. Among the machine learning methods tested, the eXtreme Gradient Boosting (XGB) algorithm showed the best performance, achieving an accuracy of 92.9%, an area under the receiver operating characteristic curve (AUROC) of 0.835, and an area under the precision-recall curve (AUPRC) of 0.975. Key predictors identified through this model included brainstem damage, creatinine levels, age, indirect bilirubin levels, and ceruloplasmin levels. The study used Shapley Additive Explanations (SHAP) to interpret feature importance, revealing that higher values of creatinine and indirect bilirubin and older age increased the likelihood of neurological symptoms, while lower ceruloplasmin levels also correlated with symptom onset[23]. This example demonstrates that machine learning enhances clinical decision making by identifying critical indicators associated with neurological complications in WD patients.

Likewise, Zhang *et al.* utilized AI-based techniques to explore the potential of using resting-state functional magnetic resonance imaging (rs-fMRI) data, specifically the amplitude of low-frequency fluctuations (ALFF), which reflects the intensity of spontaneous brain activity, as a biomarker for diagnosing WD[21]. The study included 30 healthy controls and 37 WD patients, with ALFF values obtained from rs-fMRI data preprocessing. Four significant clusters were identified where WD patients showed abnormal ALFF z-values compared to healthy controls, particularly in regions like the thalamus and caudate nucleus. Three machine learning models [RF, SVM, and logistic regression (LR)] were developed to classify these groups based on ALFF data. The models exhibited good performance, achieving AUC values greater than 0.80 for several clusters, indicating their effectiveness in distinguishing between WD patients and healthy individuals[21]. Importantly, the integration of multimodal information did not significantly improve model performance beyond what was achieved using only ALFF data.

Metabolic predictors for clinical courses

Another important example in which AI was used to address challenges in the diagnosis of WD was presented by Medici *et al.*[19]. By integrating clinical and molecular data, including serum metabolite levels, the artificial neural network (ANN) was trained to identify patterns associated with different WD phenotypes, which differ in hepatic, neurological, and asymptomatic manifestations. Notably, plasma levels of specific amino acids such as glutamate, asparagine, taurine, and ratios like Fischer's ratio emerged as critical indicators for diagnosing WD[19]. The final ANN achieved high accuracy in distinguishing between healthy individuals and those with WD, while suggesting that many patients might have undiagnosed neurological issues even when asymptomatic. This innovative approach not only facilitates earlier diagnosis but also provides insights into underlying metabolic dysfunctions related to hepatic mitochondria in WD pathology.

Parameters to predict progression and prognosis

Liang *et al.* conducted a retrospective cohort study using US Optum EHR data from 2007 to 2020. The research employed advanced AI techniques, including LASSO Cox regression, Random Survival Forest (RSF), and XGBoost (XGB) models. These methods were utilized to identify significant predictors for adverse outcomes in WD patients[22]. Key findings revealed that factors such as age at diagnosis, alcoholism, AST and bilirubin levels shortly after diagnosis, along with neurologic and hepatic conditions, were strong predictors of progression. Among the machine learning models tested, XGB demonstrated slightly superior predictive performance compared to RSF. The resulting models were validated on an independent cohort using metrics like C-index and dynamic AUC. The study reported dynamic AUC values indicating good predictive accuracy over time for cirrhosis (0.78 at year 1), liver failure (0.82 at year 1), and death (0.81 at year 1)[22]. This example also demonstrates that the integration of machine learning into this research enhances understanding of WD disease natural history and offers potential benefits for clinical trial design and personalized patient care through individualized risk assessments based on identified clinical predictors.

AI application of genetic analysis in the diagnosis of WD

Recently, Vatsyayan *et al.* introduced a new machine learning framework aimed at classifying genetic variants of the *ATP7B* gene lined to WD as either pathogenic or benign[24]. By leveraging two sophisticated algorithms, TabNet and XGBoost, the authors trained their models on a comprehensive dataset sourced from the WilsonGen database. Both models demonstrated high accuracy rates, with TabNet achieving 99% accuracy and XGBoost achieving 98.6% accuracy when validated against independent datasets. This innovative approach enables the swift classification of numerous genetic variants, including those previously categorized as variants of uncertain significance (VUS), thus expediting clinical interpretations and deepening our understanding of the genetic landscape of WD[24]. Moreover, by showcasing superior performance in comparison to existing tools, this study highlights the potential of deep learning methodologies in genomic medicine, particularly in navigating the complexities of variant classification in rare diseases such as WD.

Perspective

As AI technologies continue to evolve and integrate into clinical practice, they hold the promise of transforming how WD is diagnosed and treated in the 21st century. AI can analyze complex datasets, including genetic risk factors, changes in metabolic profiles, and conspicuous features in imaging data. This can enhance diagnostic accuracy and facilitate early intervention strategies for patients with WD.

AI MANAGEMENT STRATEGIES

Personalized treatment plans using AI insights

AI is paving the way for personalized treatment plans in WD by harnessing insights derived from extensive patient data. The actual treatment options are limited. A first supportive step is maintaining a diet that avoids copper-rich food. This includes innards, nuts, raisins, chocolate, cacao, mushrooms, soy-based products, and shellfish. Respective lists can be found online. WD cannot be exclusively treated with dietary restriction. According to the pathophysiology described above, the ultimate goal of therapy is to prevent copper-induced cellular injury, rather than necessarily removing copper from the body, which is only partially achievable[10,11]. Treatment options recommended by European and American expert panels include the chelators D-penicillamine and trientine (only when D-penicillamine is not tolerated), or oral zinc preparations (3 mg zinc × 50 mg zinc daily)[1,4]. Other treatment options, such as dimercaprol, were deemed more harmful or less effective, so they will not be discussed further.

Table 7 summarizes the therapeutic options, but they only represent the authors' recommendations. For a more detailed guideline of the individual treatment options, including children and adolescent doses, as well as dosage in pregnancy, lactation, and concomitant diseases, we refer to the published guidelines[1,4] and instruction leaflets of the applied medications.

Chelators bind "free" copper in the blood (copper not bound to ceruloplasmin) to facilitate its excretion in urine. This binding of toxic copper is a cellular protective mechanism. Both chelators also induce the synthesis of metallothionein, which binds and neutralizes toxic Cu^{+} within cells[27]. In the intestine, the induction of metallothionein inhibits copper absorption, helping to achieve a negative copper balance. D-penicillamine is often associated with adverse effects, such as an initial worsening of neurological symptoms and a higher risk compared to trientine or zinc therapy. Early sensitivity reactions, as well as nephrotoxicity or bone marrow toxicity, can also occur. Dermatological toxicity, such as collagen disorders or pemphigus, may develop. The dosage should be slowly increased from 150 mg to 1,200 mg daily. Trientine is as effective as D-penicillamine but may require a higher dose with fewer side effects[11].

Zinc (3 mg × 50 mg for adults, 3 mg × 25 mg for children and adolescents) is the safest and most effective therapy for WD. It induces metallothionein, which provides cellular protection and inhibits copper absorption. The only potential drawback may be dyspepsia, but this can be minimized by providing zinc as a complex with amino acids, such as histidine. Pancreas irritation (enzyme elevation) may also occur. However, if tolerated, it is an excellent therapy for WD. Therapy progress is monitored by normalizing copper excretion in urine (24-h collection) while taking zinc or after a 2-day pause in chelator therapy[11]. If copper in urine is undetectable, a gradual reduction in the initial dosage of the therapies can be considered, with close monitoring of urinary copper levels. An ideal parameter for balanced and effective therapy would be measuring free copper levels, which should be normal under effective therapy. However, this is a technically challenging laboratory analysis and is not yet routinely available. The calculated free copper estimation is only reliable when ceruloplasmin is < 0.1 g/dL (as mentioned above).

A final therapeutic option for WD is liver transplantation. This is only applicable in cases of advanced cirrhosis, mostly untreated cases with severe liver function failure, or in rare cases of hepatocellular carcinoma if transplantation is deemed suitable for limited disease extension. The second indication is acute hepatic failure in fulminant WD, which occurs in 5% of all cases. The outcome of liver transplantation in these cases is usually better compared to other indications, as it corrects the metabolic defect in the liver, eliminating the need for further therapy[28,29]. However, there is still a mortality rate of 10%-20% within the first year after transplantation. This is why liver transplantation is not recommended for the general WD

Table 7. Therapy of Wilson disease

Chelator therapy	Zinc therapy
(1). D-Penicillamine Begin with 150-300 mg daily, increasing by 300 mg increments every 7 days up to 1,200 mg on an empty stomach For children and adolescents: 10 mg/kg In case of adverse events: (2). Trientine - dihydrochloride - tetrahydrochloride Starting with 200 mg daily, increasing by 200 mg every 7 days up to 800-1,600 mg on an empty stomach; for children and adolescents, use half of the adult dose (10 mg/kg)	Oral zinc (optimal zinc histidine) Start with 50 mg daily, increasing by 50 mg increments every 7 days up to 150 mg on an empty stomach For children and adolescents: Start with 25 mg daily, increasing by 25 mg increments every 7 days up to 75 mg on an empty stomach

population, as with available treatment options, normal life expectancy can be achieved[30]. Whether gene therapy may become a therapeutic option for the general WD population remains to be seen[31]. The issue may be immunologic reactivity, which could impact efficacy, especially if gene therapy can only be applied once in a lifetime.

By analyzing genetic, biochemical, and clinical information, AI algorithms can identify specific disease patterns and predict individual responses to various therapeutic interventions. This enables healthcare providers to tailor treatment strategies that are uniquely suited to each patient's needs, optimizing efficacy while minimizing potential side effects and dosage adaptation for patients in special periods of their disease and other life circumstances[19-24]. For instance, machine learning models can evaluate the likelihood of a patient responding positively to chelation therapy based on their unique metabolic profile and disease severity. As a result, patients benefit from more targeted therapies that not only enhance treatment outcomes but also improve adherence by aligning with their personal health circumstances and preferences.

Monitoring disease progression with AI tools

AI tools are revolutionizing the monitoring of disease progression in WD through innovative applications such as wearable technology and remote monitoring systems. These devices can continuously track vital signs and symptoms, providing real-time data that are crucial for assessing changes in a patient's condition[32]. By integrating this continuous stream of information with electronic health records (EHRs), clinicians can gain comprehensive insights into a patient's health trajectory over time. Furthermore, advanced data analytics can identify trends and anomalies that may indicate worsening liver function or neurological involvement, allowing for timely interventions before complications arise. This proactive approach not only enhances patient safety but also empowers individuals to take an active role in managing their own health[33]. It should be noted that WD research could also greatly benefit from AI technology. For example, our laboratory investigates copper overload in experimental WD models by using innovative laser ablation inductively coupled plasma mass spectrometry[34]. Data management in this technology requires a significant amount of hands-on work, and it would be highly beneficial if AI could simplify the overall workload associated with this methodology. In particular, the programs require sophisticated methods of calibration, standardization, and normalization to quantify copper concentrations in tissues. The abundance of mass spectrometry data processing programs actually differs widely in terms of quality, usability, integrated features, workflow, reliability, system requirements, speed of data processing, and price[35]. All of these features could be harmonized and better adapted for routine use by AI technologies.

Decision support systems for clinicians

Decision support systems powered by AI are becoming invaluable tools for clinicians managing WD, offering evidence-based recommendations that enhance diagnostic accuracy and treatment effectiveness[19-24]. These systems analyze vast amounts of clinical data alongside established guidelines to

provide actionable insights tailored to individual cases. For example, an AI-driven decision support tool could assist physicians in determining optimal drug regimens based on a patient's specific biochemical markers or genetic predispositions, thereby reducing the risk of adverse reactions or ineffective treatments. Additionally, these systems facilitate collaboration among multidisciplinary teams by synthesizing input from various specialties involved in patient care, such as hepatology, genetics, and neurology, ensuring a holistic approach to management[36].

ETHICAL CONSIDERATION AND CHALLENGES

As AI continues to revolutionize the diagnosis and management of WD, several ethical considerations and challenges must be addressed to ensure its responsible implementation in healthcare settings[33]. One of the foremost concerns is data privacy, as AI systems rely on vast amounts of sensitive patient information to function effectively. The collection, storage, and processing of these data raise questions about consent, confidentiality, and the potential for unauthorized access. Healthcare institutions must establish robust protocols to protect patient data while complying with regulations such as General Data Protection Regulation (GDPR) or Health Insurance Portability and Accountability Act (HIPAA)[36]. Ensuring transparency in how patient information is used by AI algorithms will be crucial for maintaining trust between patients and healthcare providers.

Data privacy concerns

Data privacy concerns are particularly significant in the context of AI applications for WD, where sensitive health information is essential for accurate diagnosis and treatment planning[5]. Patients may feel hesitant about sharing their medical history or genetic data due to concerns about misuse or breaches of confidentiality. To address these concerns, healthcare organizations must prioritize implementing strict security measures to protect patient data throughout its lifecycle, from collection to analysis[37]. Additionally, promoting a culture of informed consent is essential. Patients should be informed about how their data will be used in AI systems and have the option to opt out if they wish. Addressing these privacy issues is not only necessary for compliance but also crucial for ensuring patient engagement and trust in AI-driven healthcare solutions.

Algorithmic bias and its implications in healthcare

Another significant ethical challenge associated with AI in healthcare is algorithmic bias, which can lead to disparities in diagnosis and treatment outcomes for individuals with WD. If training datasets lack diversity, whether due to underrepresentation of certain demographic groups, AI algorithms may produce skewed results that do not accurately reflect the characteristics or needs of all patients[38]. This bias can exacerbate existing inequalities within healthcare systems, potentially leading to misdiagnosis or suboptimal treatment plans for marginalized populations. To combat this issue, developers must prioritize creating inclusive datasets that encompass a wide range of demographics and clinical presentations related to WD[5]. Ongoing monitoring and validation of AI algorithms are essential to identify biases early on and ensure equitable care across all patient groups.

The role of healthcare professionals alongside AI

Despite the advancements offered by AI, the role of healthcare professionals remains indispensable in managing WD effectively. While AI can provide valuable insights and support decision-making processes, it cannot replace the nuanced understanding that clinicians possess regarding individual patients' needs, preferences, and circumstances[37]. Healthcare professionals play a crucial role in interpreting AI-generated recommendations within the broader context of a patient's health status and personal values. Furthermore, they serve as advocates for their patients by ensuring that ethical considerations, such as informed consent and addressing algorithmic biases, are prioritized during implementation processes. Collaboration between

AI technologies and human expertise will ultimately enhance diagnostic accuracy and treatment efficacy while safeguarding ethical standards in patient care[38].

FUTURE DIRECTIONS

Emerging technologies in AI for WD management and broader applications

The future of WD management is poised for significant transformation through the integration of emerging technologies in AI. Innovations such as natural language processing (NLP) and advanced machine learning algorithms are being developed to analyze unstructured clinical data, such as physician notes and patient-reported outcomes[39]. These technologies can enhance diagnostic accuracy by providing a more comprehensive view of a patient's condition, allowing for earlier detection of WD and more personalized treatment plans. Additionally, advancements in AI-driven imaging techniques are expected to improve the precision of liver assessments and other diagnostic imaging modalities, ultimately leading to better monitoring of disease progression and therapeutic responses[40].

The methodologies developed for applying AI in WD management hold promise for broader applications across various genetic disorders. As researchers refine AI algorithms tailored specifically to the complexities of WD, similar approaches can be adapted for conditions like cystic fibrosis, Huntington's disease, or sickle cell anemia[41]. By leveraging insights gained from the unique characteristics of each disorder, healthcare providers can develop targeted interventions that address specific challenges associated with these diseases. This potential expansion underscores the importance of continued investment in AI research within genetics and rare diseases, as it may lead to breakthroughs that improve patient care on a much larger scale.

Collaboration among AI developers, clinicians, and researchers

To fully realize the benefits of AI in managing WD and beyond, collaboration among AI developers, clinicians, and researchers will be essential[40]. Interdisciplinary partnerships can facilitate the sharing of knowledge and expertise necessary for creating effective AI solutions tailored to clinical needs. By involving healthcare professionals in the development process from the outset, technologists can ensure that their tools are user-friendly and aligned with real-world workflows. Moreover, ongoing dialogue between these stakeholders will foster an environment conducive to innovation while addressing ethical considerations related to data privacy and algorithmic bias[38]. As these collaborations evolve, they will play a pivotal role in shaping the future landscape of genetic disorder management through AI advancements.

LIMITATIONS

We acknowledge that we are listing only established facts for diagnosing and treating WD. AI has been introduced to help critically evaluate available facts, creating a new, practical scoring system for physicians to use with input from individual patients. It is now the responsibility of AI experts to create algorithms that can input necessary data to determine the validity of the diagnosis and potential treatment options. Although we have compiled all relevant data on WD in this manuscript, the AI template for its practical application still needs to be developed. This initiative aims to encourage the implementation of AI to revolutionize the diagnosis and management of WD.

CONCLUSION

In summary, the integration of AI into the diagnosis and management of WD represents a significant advancement in healthcare that has the potential to transform patient outcomes. This paper has explored the complexities of WD, highlighting its genetic basis, symptoms, and current challenges faced in traditional diagnostic methods. We have examined how AI algorithms enhance diagnostic accuracy through advanced data analysis and predictive modeling while also providing personalized treatment plans that cater to

individual patient needs. Furthermore, we discussed the ethical considerations surrounding AI implementation, such as data privacy concerns and algorithmic bias, emphasizing the critical role healthcare professionals play alongside these technologies. The importance of continued research and development in this area cannot be overstated. As emerging technologies evolve, they will not only refine our understanding of WD but also pave the way for broader applications across various genetic disorders. Collaborative efforts among tech developers, clinicians, and researchers will be essential to ensure that AI tools are effectively integrated into clinical practice while maintaining ethical standards and prioritizing patient care. By fostering innovation in this field, we can look forward to a future where AI significantly enhances diagnosis and management strategies for WD and other complex conditions, ultimately leading to improved quality of life for affected individuals.

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Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Stremmel W, Weiskirchen R

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Conflicts of interest

Weiskirchen R is Associate Editor and Stremmel W is an Editorial Board member of the journal *Metabolism and Target Organ Damage*. Both authors serve as Guest Editors for the Special Issue titled "*Metabolic Mysteries: The Role of Copper Dysregulation in Liver Disease*". Weiskirchen R and Stremmel W were not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making.

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Not applicable.

Consent for publication

Not applicable.

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