REVIEW ARTICLE

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Current and Emerging Issues in Wilson's Disease

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The history of Wilson's disease reflects modern biomedical progress. Samuel Kinnier Wilson's 1912 description of "progressive lenticular degeneration," a lethal neurodegenerative disorder associated with inapparent hepatic cirrhosis, was based on clinical and pathological observations. The disorder was subsequently renamed "hepatolenticular degeneration," reflecting the importance of the hepatic component. At mid-century, advances in biochemistry had established the etiologic role of copper and the diagnostic relevance of ceruloplasmin. Lifesaving medical treatment was introduced in the mid-1950s. Liver transplantation became an option in the 1970s. Subsequent advances in genetics led to the identification of *ATP7B* (ATPase copper transporting beta), the gene associated with Wilson's disease. Recently devised scoring systems quantitatively describe the disorder, facilitate its diagnosis, or prognosticate the clinical outcome. Innovative diagnostic methods, treatments, and monitoring approaches are in development, serving as bellwethers for future biomedical advances. Comprehensive contemporary reviews are available elsewhere.[1-3]

Clinical Presentation

Wilson's disease may present as liver disease, a neurologic disorder, a psychiatric illness, or a combination of these disorders. Hepatic Wilson's disease, which tends to develop earlier than neuropsychiatric Wilson's disease, ranges from mild liver disease to cirrhosis; in children, fatty liver is common. Infrequently, Wilson's disease manifests as acute liver failure. In patients with Wilson's disease, neurologic movement disorders involve either increased movement, with tremor or dystonia, or decreased movement, resembling parkinsonian rigidity. Tremors, poor coordination, and loss of fine motor control may occur early. Dysarthria is often the first prominent symptom. Drooling and difficulty swallowing indicate pseudobulbar involvement. Sleep disorders and restless legs syndrome are increasingly recognized. In general, cognitive function is intact; however, subtle deficits in executive ability[4,5] or integrative capabilities[6] may occur. Clumsiness, loss of athletic skills, or deterioration in school performance may be initial features in adolescents. Psychiatric Wilson's disease is highly variable, although depression is common. Bipolar disorder may occur, and psychosis may develop.[7,8] Anxiety disorders, including phobias and compulsive behaviors, have been reported, as has aggressive or antisocial behavior. Kayser–Fleischer rings are the main ophthalmologic sign. Other manifestations include renal, cardiac, musculoskeletal, and endocrine conditions (Fig. 1). Wilson's disease can manifest at any age, although usually before the age of 50 years; older age does not rule it out.

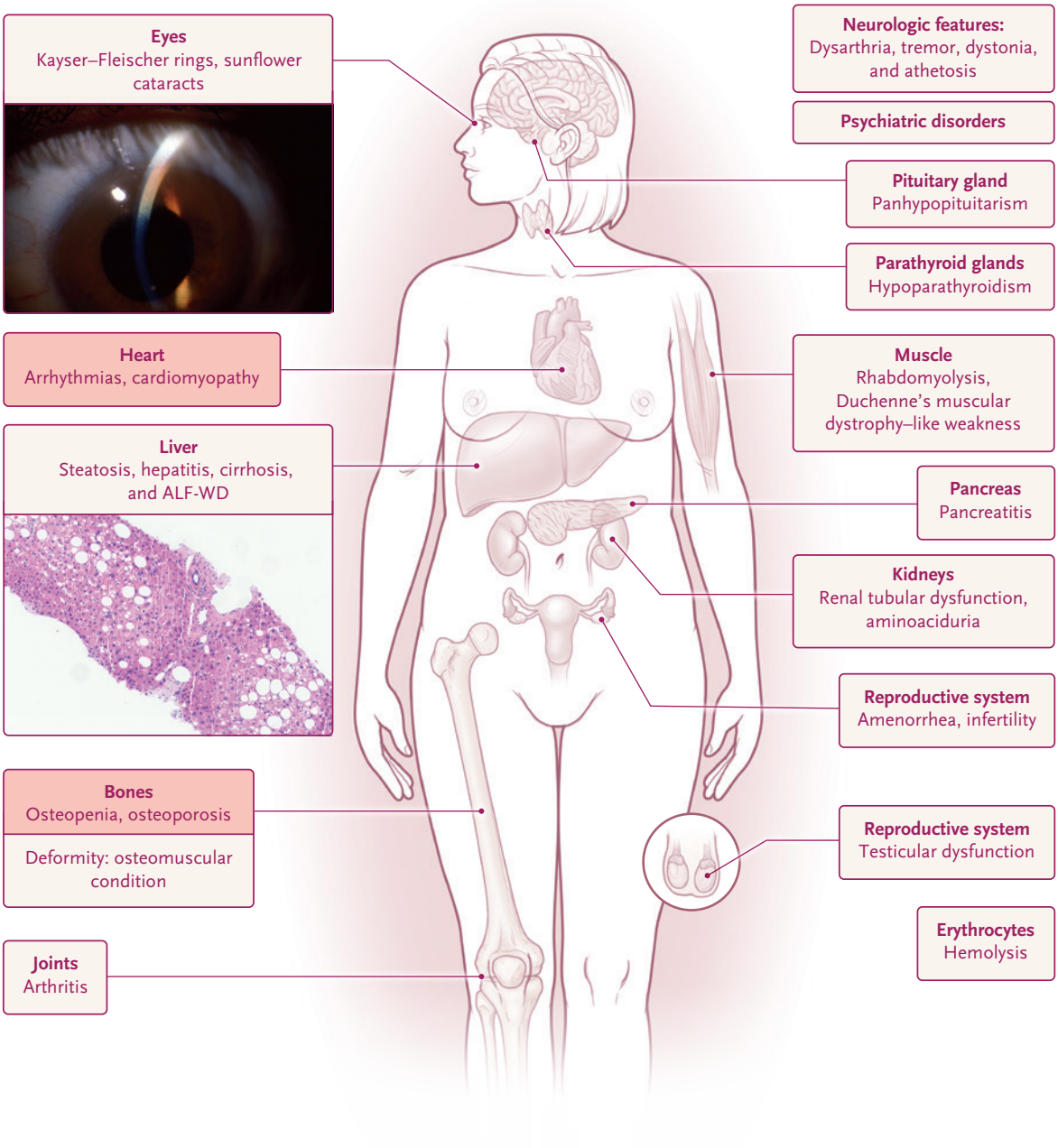
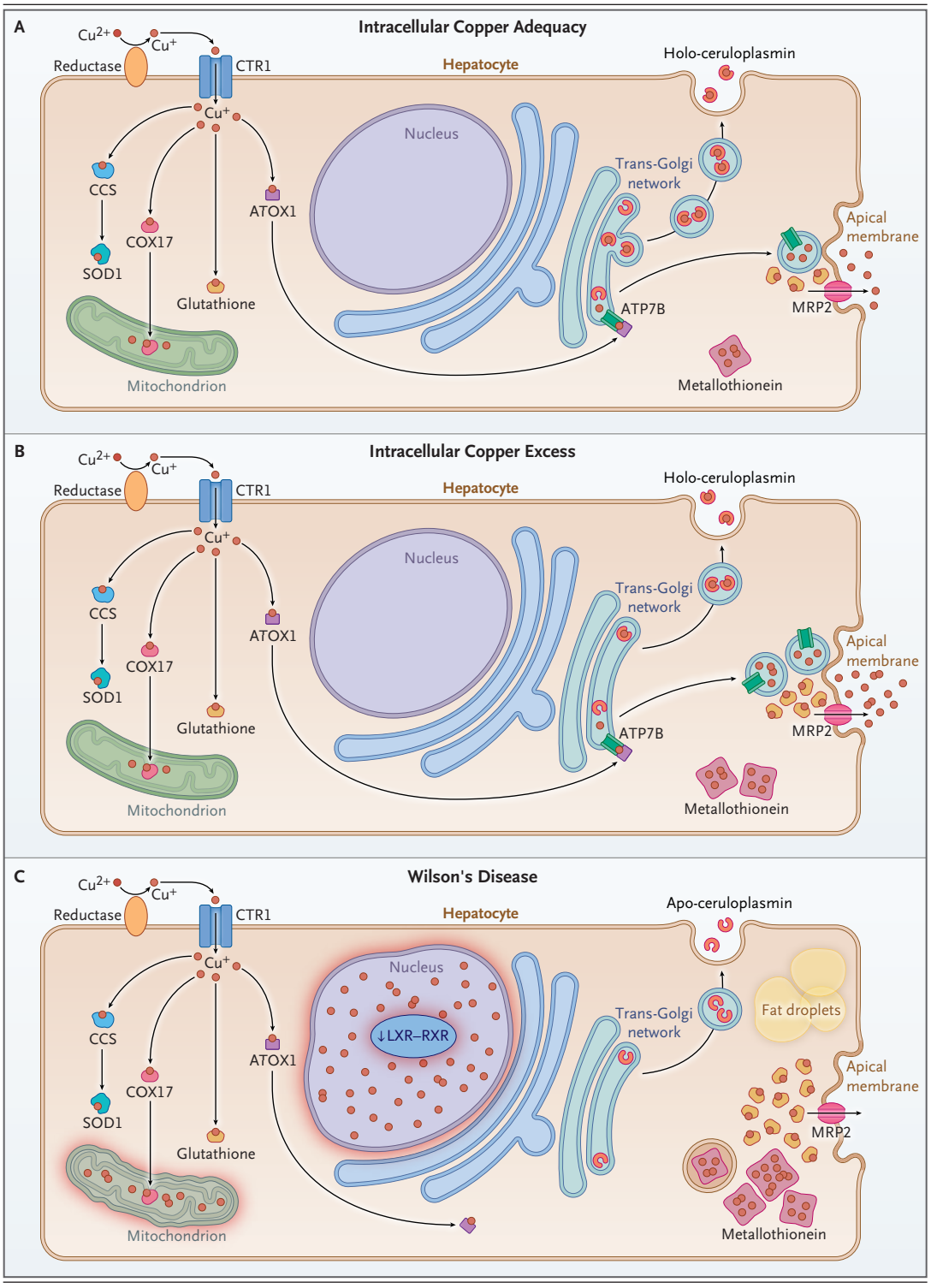


Figure 1. Clinical Manifestations of Wilson's Disease.

Wilson's disease may have manifestations apart from typical hepatic and neuropsychiatric features. The salmon-colored boxes indicate features that may be present initially or develop despite treatment. Acute liver failure due to Wilson's disease is more common in women than in men (female to male ratio, 2–4:1). Sunflower cataracts are radiating, multicolored central opacities in the lens. Tremor in neurologic Wilson's disease can range from a fine tremor of the hands to tremor involving the head to the characteristic "wing beating" tremor. ALF-WD denotes acute liver failure due to Wilson's disease. The photograph of the Kayser–Fleischer ring on slit-lamp examination is courtesy of Jeffrey G. Odel, M.D., from the Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, and the photomicrograph of liver histologic findings showing mild steatosis in Wilson's disease (hematoxylin and eosin staining) is courtesy of Dhanpat Jain, M.D., from the Department of Pathology, Yale University.



PATHOGENESIS AND GENETICS

ATP7B, on chromosome 13q14, is the only gene with mutations that are associated with Wilson's disease.[9,10] The gene product ATP7B is a multifunctional, intracellular P_1-type ATPase, found mainly in the liver. In hepatocytes, ATP7B expedites biliary copper excretion when intracellular

Figure 2 (facing page). Hepatocellular Disposition of Copper in Healthy Persons and in Those with Wilson's Disease.

As shown in Panel A, under conditions of intracellular copper adequacy, copper is taken up from the portal circulation, where it is loosely attached to albumin and other molecules, by interacting with one or more reductases and CTR1 (copper transporter 1) on the hepatocellular membrane. CTR2 (copper transporter 2), not shown, is also involved in copper disposition, but its actions are not fully understood. Copper is not "free" within the hepatocyte: metallochaperones direct it to targets (CCS [copper chaperone for superoxide dismutase] to SOD1 [superoxide dismutase type 1], COX17 (cytochrome *c* oxidase copper chaperone) to mitochondria, and ATOX1 [antioxidant 1 copper chaperone] to ATP7B [ATPase copper transporting beta] in the trans-Golgi network), or it may interact with glutathione, which is abundant in the cytoplasm. Other mechanisms besides COX17 appear to contribute to mitochondrial uptake of copper. The disposition of copper within mitochondria is complicated, governed by various transporters, metallochaperones, and accessory proteins. Some copper is sequestered in metallothionein. ATP7B mainly expedites the transfer of copper in nascent holo-ceruloplasmin, which is secreted into the plasma compartment but also contributes to biliary excretion of copper. As shown in Panel B, under conditions of intracellular copper excess, CTR1 function is reversibly decreased, and ATP7B migrates from the trans-Golgi network in vesicles of the endosomal–lysosomal compartment and directly promotes biliary excretion of copper, which may also be excreted as copper–glutathione through MRP2 (multidrug resistance–associated protein 2, also called cMOAT [canalicular multispecific organic anion transporter 1]). ATP7B thus appears to have a sensing capability for intracellular copper levels. As shown in Panel C, in Wilson's disease, functional ATP7B is absent. Copper is taken up from the portal circulation. A condition of extreme intracellular copper excess develops, shown here at an early-to-intermediate stage of development. CTR1 function is substantially reduced, in part reflecting decreased CTR1 expression. Metallothionein is induced and binds copper, until saturated, in the cytoplasm. Copper is transiently taken up into the nucleus, leading to its enlargement and altered gene expression. Lipid metabolism is disturbed, giving rise to fat droplets. Decreased expression or action of the liver X receptor–retinoid X receptor (LXR–RXR) complex may contribute to abnormal lipid metabolism and the cellular inflammatory response. Mitochondria become overloaded with copper and structurally damaged; COX17 is not down-regulated. ATP7B-mediated biliary excretion of copper is absent. The MRP2 pathway only partially compensates. Copper is not incorporated into nascent ceruloplasmin; thus, apo-ceruloplasmin is secreted into the circulation, where it has a shorter half-life than holo-ceruloplasmin. Over time, some copper–metallothionein aggregates are taken up by lysosomes, in which copper is detectable histochemically.

copper levels are elevated (Fig. 2). In addition, ATP7B transports copper into the Golgi apparatus for incorporation into apo-ceruloplasmin, producing the ferroxidase holo-ceruloplasmin, a metalloprotein containing most of the copper in the circulation under physiologic conditions. In Wilson's disease, functional ATP7B is decreased or absent, and excessive copper accumulates in hepatocytes. Serum copper levels are low because of decreased holo-ceruloplasmin levels. As copper-induced liver injury progresses, extrahepatic sites — notably, the central nervous system — are affected. Animal models of Wilson's disease include the toxic milk mouse, the Atp7b$^{-/-}$ mouse, and the Long–Evans Cinnamon rat and its related LPP rat.

Numerous *ATP7B* variants have been identified, including approximately 600 pathogenic variants.[11] The most common gene alterations are missense mutations, deletions, and insertions, occurring in nearly all 21 exons of *ATP7B*. Most persons with Wilson's disease are compound heterozygotes. Determining the pathogenicity of any given gene alteration or, with compound heterozygosity, the functional effect of paired different mutations, is difficult. Pathogenic mutations typically cause nonproduction of ATP7B, misfolded ATP7B that is subject to degradation, or messenger RNA dysfunction, but some mutations result in structurally normal yet nonfunctional ATP7B.[11] No convincing genotype–phenotype correlation has been found. Variants that do not produce any ATP7B or that produce nonfunctional ATP7B may cause earlier, more severe liver disease.[12,13] The role of epigenetic factors is being investigated.[14]

Wilson's disease occurs worldwide, with an estimated prevalence of approximately 30 cases per 1 million population.[15,16] Some data suggest a higher allelic prevalence,[17-19] raising the possibility of variable penetrance. The predominant pathogenic variant in northern European populations is p.H1069Q.[20] Some geographically isolated populations have limited sets of *ATP7B* mutations.[16] Molecular genetic evaluation can be an efficient strategy for diagnosing Wilson's disease in such populations or in pedigrees for which the proband's genotype is known. *ATP7B* analysis helps in distinguishing Wilson's disease from other genetic and metabolic disorders. In general, analysis of the entire gene and its promoter region is preferred, with attention to intron–exon

boundaries and the possibility, although rare, of large deletions.

Given the evidence of possible variable penetrance in Wilson's disease,[16,20] differentiating genetic Wilson's disease — the isolated finding of a genotype that is consistent with the disease — from asymptomatic Wilson's disease associated with organ damage is particularly important because this distinction influences treatment. This issue poses challenges for managing cases of Wilson's disease that are identified by means of general population screening or newborn screening.

CLINICAL DIAGNOSIS

The clinical diagnosis of Wilson's disease involves a detailed medical history taking and physical examination focused on liver, neurologic, and psychiatric disease. Laboratory assessment includes liver biochemical and serum ceruloplasmin levels and basal 24-hour urinary copper excretion. The serum ceruloplasmin level alone is not adequate for diagnosis, although a very low level (<5 mg per deciliter) strongly suggests Wilson's disease. Ceruloplasmin levels of less than 14 mg per deciliter in one study (from Hong Kong)[21] and less than 11.5 mg per deciliter in another study (from Spain)[22] were identified as diagnostic cutoff points. The ceruloplasmin level can be normal in Wilson's disease, although a normal value is uncommon. Basal 24-hour urinary copper excretion is typically more than 40 μg, with higher values in symptomatic patients.

Kayser–Fleischer rings, due to corneal copper deposition in Descemet's membrane, are visualized by means of slit-lamp examination or optical tomography. The rings are often absent in younger patients and are also absent in 50% of patients with hepatic Wilson's disease. Liver biopsy for histologic examination and copper quantification establishes the degree of liver damage and rules out competing diagnoses. Metallothionein immunohistochemical staining may be informative.[23] The hepatic parenchymal copper level is classically more than 250 μg per gram of dry weight, but values exceeding 70 μg per gram warrant further investigation.

In many patients with Wilson's disease and neurologic findings, brain magnetic resonance imaging (MRI) identifies structural abnormalities in the basal ganglia and elsewhere,[24] ruling out other diagnoses. The Unified Wilson's Disease Rating Scale (UWDRS)[25] and the Global Assessment Scale for Wilson's Disease[26] (both described in the Supplementary Appendix, available with the full text of this article at NEJM.org) are descriptive neurologic scoring systems for standardizing neurologic findings in patients with Wilson's disease. Identifying and characterizing *ATP7B* mutations may aid in the diagnosis. A genotype with two *ATP7B* pathogenic variants (in trans) is compelling evidence of Wilson's disease.

EMERGING DIAGNOSTIC APPROACHES

New diagnostic strategies are in development. One candidate approach involves determining the relative exchangeable copper (REC). The REC is the ratio of circulating exchangeable copper (CuEXC), representing bioavailable copper not bound within ceruloplasmin, to total serum copper. In patients with Wilson's disease, the REC exceeds 18.5%.[27,28] More extensive validation of the REC as a diagnostic tool is needed, including critical assessment of CuEXC measurement.

A novel approach to diagnosis involves proteomics-based methods developed initially for newborn screening. Selected ATP7B peptides were quantified in proteolyzed dried blood spots by combining immunocapture involving monoclonal antibodies to ATP7B with targeted mass spectroscopy involving multiple reaction monitoring. Levels of recovered ATP7B peptide were lower in patients with Wilson's disease than in controls.[11,29] Further validation of initial diagnostic cutoff points was largely successful in distinguishing patients from carriers and unaffected controls. This technology may be useful for interpreting the functional effect of *ATP7B* variants of unknown significance.

Another diagnostic approach uses positron emission tomography (PET) to quantify copper incorporation into ceruloplasmin, which was previously evaluated with plasma ratios.[30] Recent studies in humans with the use of ^{64}Cu PET examined differences between oral and intravenous administration of radiocopper, especially with respect to the effect on copper distribution in organs.[31,32] In addition to distinguishing among patients with Wilson's disease, simple heterozygotes, and unaffected persons, this technology could be used to evaluate the efficacy of cell trans-

plantation or gene therapy for the treatment of Wilson's disease.[33]

DIAGNOSTIC SCORING SYSTEMS

LEIPZIG SCORE

The Leipzig score, devised in 2001, is based on clinical and laboratory findings, including the *ATP7B* genotype.[34] It was validated in adults and children[35,36] and critiqued, leading to a minor modification.[37] A more extensive modification has been developed specifically for children,[38] with the exclusion of some components, including *ATP7B* analysis, which may be unavailable, delaying the diagnosis. A novel measure — a triad of a low-for-age serum alkaline phosphatase level, a serum zinc level of less than 11 μmol per liter, and a ratio of aspartate aminotransferase to alanine aminotransferase of 2 or higher — was substituted. Initial validation looked promising. False positive Leipzig scores have been encountered with some disorders that mimic Wilson's disease.

DIAGNOSIS OF ACUTE LIVER FAILURE DUE TO WILSON'S DISEASE

Acute liver failure due to Wilson's disease is typically characterized by distinctive clinical findings: severe coagulopathy and hepatic encephalopathy, acute intravascular hemolysis, moderate elevations of serum aminotransferase levels, normal or subnormal serum alkaline phosphatase levels, and progression to renal failure. Acute liver failure may be the first manifestation of Wilson disease, despite established underlying chronic liver damage. Analysis of data from the multicenter Acute Liver Failure Study Group showed that a combination of two ratios (a ratio of alkaline phosphatase to total bilirubin of <4 and a ratio of aspartate aminotransferase to alanine aminotransferase of >2.2) was 100% sensitive and specific for diagnosing Wilson's disease in the study cohort.[39] Further validation of these ratios is in progress. Two studies indicate that the combined ratios may not work well for diagnosing acute liver failure due to Wilson's disease in children and adolescents.[40,41]

DISORDERS THAT MIMIC WILSON'S DISEASE

Several disorders resemble Wilson's disease closely enough to be included in the differential diagnosis. These disorders include autoimmune hepatitis and metabolic dysfunction–associated steatotic liver disease, both of which are problematic, especially in children. Genetic disorders with a clinical presentation that can resemble hepatic Wilson's disease include MDR3 deficiency and various congenital disorders of glycosylation. Since the Leipzig score may not distinguish MDR3 deficiency from Wilson's disease,[42,43] genetic testing is required. Aceruloplasminemia may resemble neurologic Wilson's disease clinically but is characterized by a normal level of copper in the liver; genetic testing is definitive.

Recently, disorders that mimic Wilson's disease mechanistically have been identified (Table 1). These very rare disorders, which share pathogenic cellular mechanisms with Wilson's disease, occur primarily in children. They somewhat resemble Wilson's disease and warrant diagnostic consideration in the right clinical setting.[44-47] However, one of these disorders, the Huppke–Brendel syndrome, was misdiagnosed as Wilson's disease in an adult.[48]

SCREENING OF FIRST-DEGREE RELATIVES

Accurate and timely diagnosis of Wilson's disease is important for the first-degree relatives of an affected person. Screening of all first-degree relatives, not just siblings, is mandatory. Identifying other persons with Wilson's disease in the pedigree positions them for the most favorable treatment outcomes.[49-51] The assessment may be based on the *ATP7B* genotype analysis, a comprehensive clinical and biochemical evaluation, or both.[3]

PROGNOSIS

Clinically evident Wilson's disease is relentlessly progressive and ultimately fatal, if untreated. With consistent, effective medical treatment, however, the longevity of patients with Wilson's disease is close to that of the general population.[51-53] This "treated natural history" is very favorable but is dependent on treatment adherence and numerous social factors, including political and socioeconomic stability and medication that is available and affordable. Both hepatocellular carcinoma and cholangiocarcinoma can develop, but the risk is lower among patients with Wilson's disease

Table 1. Rare Genetic Diseases Mimicking Wilson's Disease.*

Disorder	Gene	Clinical Features	Onset	Serum Ceruloplasmin	Basal 24-hr Urinary Copper	Hepatic Parenchymal Copper	Hepatic Histologic Assessment
Clinical mimics							
Aceruloplasminemia	*CP*	Neurologic disorder, iron accumulation in liver	Adulthood	Absent	Normal	Normal	Iron overload
MDR3 deficiency (progressive familial intrahepatic cholestasis type 3)	*ABCB4*	Cholestatic liver disease, normal biliary system, possible jaundice and gallstones, cholestasis of pregnancy	Childhood; less often, adulthood	Normal	Increased	May be increased	Cholestasis
Mechanistic mimics							
MEDNIK syndrome	*AP1S1*	Neurologic disorder with intellectual disability, deafness, peripheral neuropathy; hepatic copper retention	Childhood	Very low	Increased	Increased	Chronic injury, cirrhosis
MEDNIK-like syndrome	*AP1B1*	Similar to MEDNIK but with no apparent hepatic damage	Childhood	Low	NA	Normal	NA
Hypermanganesemia with dystonia							
Type 1	*SLC30A10*	Parkinsonian movement disorder; fatty liver, cirrhosis; polycythemia; severe hypermanganesemia	Childhood; less often, adulthood	Normal	Normal	Normal or mildly increased	Cirrhosis, fatty liver, some stainable copper
Type 2	*SLC39A14*	Developmental delay; progressive dystonia and bulbar dysfunction; parkinsonian features	Infancy, toddlerhood, or childhood	Normal	NA	Normal	No hepatic involvement
Niemann–Pick type C	*NPC1*, *NPC2*	Neurologic disorder: dysarthria, ataxia; oculomotor abnormalities	Childhood or young adulthood	Low or slightly low	Normal or possibly increased	May be moderately increased	Possible fatty liver

Both clinical and mechanistic mimics							
PGM1-CDG	*PGM1*	Systemic form: hepatopathy, bifid uvula (with or without cleft palate and with or without Pierre Robin sequence), growth retardation, rhabdomyolysis, hypoglycemia, dilated cardiomyopathy	Childhood or adulthood	Low	Normal	NA	Steatosis, cholestasis; possible slight fibrosis
CCDC115-CDG	*CCDC115*	Hepatosplenomegaly; psychomotor disability, hypotonia, or both; dysmorphism; hypercholesterolemia; possible liver failure	Childhood or adulthood	Low or very low	Normal or mildly increased	May be mildly increased	Steatosis, fibrosis, necrosis; progressive cholestatic liver disease
TMEM119-CDG	*TMEM119*	Mild hepatopathy, hypercholesterolemia	Childhood or adulthood	Low	Normal	Normal or mildly increased	Steatosis, mild fibrosis; abnormal mitochondria (fragmented cristae) possible
COG2-CDG	*COG2*	Mild hepatopathy; developmental delay, microcephaly, spastic quadriplegia	Infancy	Low	NA	NA	NA
Unclassified mimic							
Huppke–Brendel syndrome	*SLC33A1*	Congenital cataracts, hearing loss, developmental delay, cerebellar hypoplasia	Childhood; adulthood (rare)	Low or very low	Increased†	Normal†	Normal

* Data are from Schilsky et al.[3] CDG denotes congenital disorder of glycosylation; MEDNIK intellectual (mental) disability, enteropathy, deafness, neuropathy, ichthyosis, and keratoderma; NA not available; and PGM1 phosphoglucomutase 1.
† This information is based on one case in an adult. Data are not available for these values in children.

than among those with other chronic liver diseases.[54,55]

Prognostic scoring systems attempt to identify patients who are seriously ill with hepatic Wilson's disease and are not likely to have an adequate response to medical treatment. The New Wilson Index (NWI), which includes measures of hepatic damage and inflammatory response, replaced the Nazer score. The NWI, validated in adults and children, has some unreliability at the breakpoint (i.e., scores near or straddling the dividing line between favorable and unfavorable outcomes [survival vs. liver transplantation or death]). It may be most informative when applied serially. Similar scores that have been developed more recently[40,56] require broader validation. Currently, none of the prognostic scoring systems are validated for neurologic or psychiatric Wilson's disease. Standard MRI cannot be used to predict the outcomes with treatment, although larger destructive brain lesions typically carry a worse prognosis. Preliminary data suggest that quantitative analytic techniques may reveal prognostic information in patients with neurologic Wilson's disease.[24] Scoring systems such as the UWDRS can help document clinically detectable neurologic deficits. Serial application of these scoring systems may define the disease trajectory.

Functional MRI (fMRI), which measures changes in connectivity within the brain, has prognostic potential for patients with neurologic Wilson's disease. A pilot study comparing 30 patients who had neurologic Wilson's disease with appropriate controls showed structural and functional changes on MRI and fMRI, irrespective of the clinical neurologic manifestations of the disease.[57] The findings were diverse and included thinning in the bilateral prefrontal cortex. Structural changes, including altered functional connectivity, were more extensive and numerous in patients with neurologic Wilson's disease (as defined by an abnormal UWDRS score) than in those with isolated hepatic disease. Longitudinal fMRI data may reveal more about the prognosis and response to treatment.

CURRENT TREATMENT

MEDICAL THERAPY

The advent of oral chelators revolutionized treatment for Wilson's disease: both penicillamine (provided as D-penicillamine) and trientine (dihydrochloride) remain the principal treatments (Tables 2 and 3). The recently approved tetrahydrochloride version of trientine, which was shown to be noninferior to penicillamine,[59] is stable at ambient temperatures. Zinc salts are effective as maintenance therapy. Extensive European experience indicates that zinc can serve as primary therapy; however, it may not always be effective for hepatic Wilson's disease in the long term.[60] Neurologic worsening may occur when any of these drugs (most notably, penicillamine) is started. Thus, the starting dose of oral chelators is low and gradually increased.

Once the diagnosis of Wilson's disease is established, lifelong medical therapy should begin, preferably with a chelator in symptomatic patients. Asymptomatic patients with evidence of organ damage on imaging studies, histologic assessment, or biochemical tests should also be treated with chelation. Those without evidence of organ damage can be treated with lower-dose chelation therapy or zinc. When to initiate treatment in children younger than 3 years of age (and what treatment to choose) remains unclear.[61] Treatment should be individualized according to the degree of organ damage, but the need for adequate copper availability in early development must be considered. Wilson's disease cannot be treated successfully by dietary modification alone. Copper-rich foods should be avoided. Supervision by a registered dietitian is valuable for patients with Wilson's disease who are on restricted diets, such as vegetarians.

ORTHOTOPIC LIVER TRANSPLANTATION

Most patients with Wilson's disease can be treated medically; however, liver transplantation can be lifesaving. It should be reserved for patients with acute liver failure or decompensated chronic liver disease who do not have a response to medical treatment. Neurologic Wilson's disease as the primary indication for transplantation remains controversial. Unaffected (simple) heterozygotes may serve as living donors for segmental liver transplantation. Outcomes with respect to patient and graft survival are excellent.[3]

TREATMENT MONITORING

Establishing clear treatment targets, along with criteria for insufficient treatment and overtreatment, is critical. Treatment monitoring is based

on clinical evaluation, along with liver biochemical testing and measurement of 24-hour urinary copper excretion (Table 2). New elevations in serum aminotransferase levels are often the earliest signal of treatment failure. When treatment is initiated or modified or when symptoms are highly variable, monitoring is performed more frequently and is individualized on the basis of symptom severity or disease complications. Subsequently, during maintenance therapy, clinical examination and biochemical monitoring are used to verify ongoing clinical stability and detect any treatment failure, including that from nonadherence or concurrent disease.

New monitoring methods focus on accurate assessment of a patient's copper status during treatment. Non–ceruloplasmin-bound copper, the bioavailable fraction of circulating copper loosely associated with albumin, histidine, and various proteins, is used for cellular uptake and for renal excretion. Bioavailable copper plays an important role in the pathogenesis of extrahepatic Wilson's disease. However, measuring it is difficult. The calculated estimate, although previously promoted for monitoring, is notoriously unreliable and has never been validated as a diagnostic test.[30,62] With inadequate or failed treatment of Wilson's disease, non–ceruloplasmin-bound copper is increased. Monitoring of non–ceruloplasmin-bound copper and urinary copper excretion in patients receiving chelation or zinc therapy should reflect the adequacy of treatment and even predict overtreatment. Recent studies have focused on accurate measurement of non–ceruloplasmin-bound copper with the use of chromatographic protein speciation and inductively coupled plasma–mass spectrometry.[63,64] Such an assay for non–ceruloplasmin-bound copper was used as a primary end point in a recent clinical trial,[59] but it requires validation for broader use in guiding therapy.

EMERGING TREATMENTS

Emerging treatments include new chelators and novel interventions aimed at curing Wilson's disease by rehabilitating the abnormal ATP7B or correcting the genetic abnormality (Table 3). The objective of curative therapy is to make pharmacotherapy and dietary restriction unnecessary. Some emerging treatments may serve as adjunctive therapy to existing treatments, and others represent improvements in existing pharmacotherapies. Treating concurrent hepatic disorders also improves clinical outcomes.

NEW CHELATORS

Tetrathiomolybdate (TTM) is a well-known copper-specific chelator with very high affinity for binding copper (approximately 10^{-19} kD). The bis-choline salt, which is more stable than ammonium-TTM, appeared to be effective in mobilizing tissue copper in Wilson's disease,[65] but its further development was recently discontinued.

Methanobactin, a peptide produced by the bacterium *Methylosinus trichosporium OB3b*, binds copper with very high affinity ($10^{-19\text{-}21}$ kD).[66] Administration of methanobactin to LPP rats during the phase of acute liver injury decreased hepatic copper and increased biliary excretion of copper, thus halting the process and lessening hepatic mitochondrial injury.[67] Another study in LPP rats showed that methanobactin attenuated the cumulative oxidative injury from diet-induced hepatic steatosis, added to copper-induced injury.[68] These findings underscore the importance of hepatic mitochondria in Wilson's disease and show the convergence of copper-induced mitochondrial oxidative injury with other cytotoxic processes.

RESTORATION OF ATP7B FUNCTION

Restoring or improving ATP7B transport function is a goal for both repurposed older therapeutics and new therapeutics that have been tested only in vitro. Curcumin was used in vitro to rescue the subcellular localization of the misfolded gene products such as p.R778L and several other ATP7B mutants.[69,70] Some molecules — namely, inhibitors of stress kinases p38 and JNK, which are currently in development — restore the intracellular trafficking of mutated ATP7B. In these cell models, the mutated ATP7B protein is confined to the endoplasmic reticulum; the pharmacologic effect involves inhibiting some degradation pathways of the endoplasmic reticulum.[71] Only specific mutations would be susceptible to such rehabilitation; eligible mutations include p.H1069Q and p.R778L.

AMELIORATION OF COPPER-INDUCED HEPATIC INJURY

Reducing copper-induced cellular injury is another option for augmenting treatment in patients with Wilson's disease. In Atp7b$^{-/-}$ mice, activa-

Table 2. Current Drug Therapy for Wilson's Disease.*

Variable	General Chelators to Increase Renal Excretion of Copper		Metallothionein Inducer to Inhibit Intestinal Absorption and Promote Fecal Excretion of Copper
	Penicillamine	Trientine (Dihydrochloride)	Elemental Zinc
Dosage†	Initial dose: 15–20 mg/kg/day (maximum, 2000 mg/day) in 2–4 divided doses; maintenance dose: 10–15 mg/kg/day in 2 divided doses (total dose, approximately 750–1000 mg/day)	Initial dose: 15–20 mg/kg/day (maximum, 2000 mg/day) in 2–3 divided doses; maintenance dose: 10–15 mg/kg/day in 2 divided doses	Initial dose: 50 mg thrice daily; maintenance dose: 50 mg thrice daily
Consequences of initiation of treatment	Urinary copper increases; paradoxical neurologic worsening in 10–20% of patients	Urinary copper increases; paradoxical neurologic worsening in 10–20% of patients	Urinary copper stays the same, then decreases; paradoxical neurologic worsening uncommon
Adverse effects	Early: fever, rash, proteinuria, lupus-like reaction; over time: aplastic anemia, leukopenia, thrombocytopenia, nephrotic syndrome, degenerative changes in skin, elastosis perforans serpiginosa, serous retinitis, colitis, hepatotoxicity	Gastritis, aplastic anemia (rare), sideroblastic anemia, colitis, hepatotoxicity (rare)	Gastritis, biochemical pancreatitis, zinc accumulation, possible changes in immune function
Target for monitoring during treatment: urinary copper excretion	Approximately 200–500 μg/24 hr (3–8 μmol/24 hr)	Approximately 150–500 μg/24 hr (2.4–8.0 μmol/24 hr)	<100 μg/24 hr (<1.6 μmol/24 hr)
General considerations	Should be taken apart from food intake; start at 5–10 mg/kg/day and increase gradually over 2–4 wk to full initial dose; routinely given with oral pyridoxine (25–50 mg/day); temporarily decrease dose by 25–50% for pregnancy or surgery to avoid interference with wound healing	Dose is for the conventional dihydrochloride formulation (tetrahydrochloride formulation pending); should be taken apart from food intake; start at 5–10 mg/kg/day and increase gradually over 2–4 wk to full initial dose; temporarily decrease dose by 25–50% for pregnancy or surgery to avoid interference with wound healing; may also inhibit intestinal absorption of copper	Specific salt does not affect efficacy but may affect tolerability; should not be taken with food; thrice-daily dosing preferred; twice-daily dosing is minimal effective dose; once-daily dosing is ineffective; no dose reduction for pregnancy or surgery; indicators of adherence: urinary zinc excretion >2 mg/24 hr with typical adult dosage; serum zinc level >125 μg/dl
Signs of treatment failure with long-term therapy‡			
Urinary copper excretion	>500 μg/24 hr (previously within target range)§	>500 μg/24 hr (previously within target range)§	>100 μg/24 hr (previously within or close to target range)
AST and ALT	Elevated (previously improved or failing to improve from start of treatment)	Elevated (previously improved or failing to improve from start of treatment)	Elevated (previously improved or failing to improve from start of treatment)

Signs of overtreatment with long-term therapy			
Urinary copper excretion	<100 μg/24 hr	<100 μg/24 hr	<20 μg/24 hr
Serum ceruloplasmin level as compared with baseline level	Very low	Very low	Very low
Other features	Sideroblastic anemia, leukopenia, iron accumulation; in rare cases, new neurologic features of copper deficiency	Sideroblastic anemia, leukopenia, iron accumulation; in rare cases, new neurologic features of copper deficiency	Sideroblastic anemia; leukopenia; iron accumulation; in rare cases, new neurologic features of copper deficiency

* Data are from Schilsky et al.[3] ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Doses shown are for adults. Dosing in children is as follows: penicillamine — start at 5 to 10 mg per kilogram of body weight per day, gradually increasing over 2 to 4 weeks to 20 mg per kilogram per day in 2 to 4 divided doses; trientine — start at 5 to 10 mg per kilogram per day, gradually increasing over 2 to 4 weeks to 20 mg per kilogram per day in 2 to 4 divided doses (>20 mg/kg/day associated with adverse effects); zinc — 25 mg thrice daily, except that in small children, the dose is 25 mg twice daily (dose for infants not determined). Teenagers can take the adult dose for zinc.
‡ Treatment failure may be due to nonadherence, drug failure, or intercurrent liver injury.
§ The 24-hour urinary copper excretion may initially drop below the achieved target range because of loss of cupriuresis, reflecting drug failure or nonadherence. With the continuation of ineffective treatment, 24-hour urinary copper excretion increases gradually over time and exceeds the target range. Reinstitution of an oral chelator will yield a sizable increase in urinary copper excretion, whereas initiation of zinc therapy will lead to decreased urinary excretion of copper.

tion of the liver X receptor–retinoid X receptor complex by the liver X receptor agonist T0901317 decreased markers of liver fibrosis and inflammatory cytokines, improving liver function, lipid profiles, and liver histologic features.[72] It may be possible to reduce inflammation and injury by targeting other cellular pathways involved in the injury response to copper. Copper-induced downregulation of nuclear receptor farnesoid X receptor and retinoid X receptor function was reversed by zinc treatment in Atp7b$^{-/-}$ mice.[73]

GENE THERAPY AND GENE REPAIR

Advances in molecular genetics and gene therapy give hope that a cure for Wilson's disease is possible. Liver transplantation provided the proof of principle that targeting the liver alone will restore normal copper balance. Preclinical studies using viral vectors with modified *ATP7B* constructs in rodent models of Wilson's disease showed restoration of copper balance and prevention of copper-induced hepatic injury. Naturally hepatotropic viral vectors, such as lentivirus, allow direct targeting of liver cells and provide the opportunity for a one-time treatment. However, current experience with lentiviral gene delivery is limited. Concerns persist about the potential for off-target DNA integration of introduced DNA. Use of adeno-associated virus for extrachromosomal delivery of DNA was initially limited by the size of the DNA that could be packaged. However, smaller yet functional *ATP7B* constructs[74] have been created and can now be used for Wilson's disease. Successful hepatocyte transfection and correction of the metabolic defect in rodent models, as defined by prolonged survival, improved histologic features, and decreased hepatic copper levels, was shown independently by various groups.[74-76]

Unresolved questions for the use of this therapy in humans are dosing, which is dependent on vector packaging and transfection efficiency, and the duration of transgene expression. It is not yet known whether barriers to use in patients with prior exposure to specific serotypes — notably, patients with neutralizing antibodies that can block uptake — can be overcome so that the therapy could be administered repeatedly. Phase 1 and 2 studies using adeno-associated virus vectors for Wilson's disease are ongoing (ClinicalTrials.gov numbers, NCT04884815 and NCT04537377).

Table 3. Status of Current and Future Therapies for Wilson's Disease.*

Therapy	Status	Comments
Medical therapy		
Chelators: penicillamine, trientine, zinc (acetate, gluconate, sulfate, or another salt); temperature-stable trientine	Available	Lifelong administration required; reversal of liver damage can occur over time
New chelators		
Bis-choline TTM	Development discontinued	Lifelong administration required
Methanobactin	In development	May be suitable for intermittent therapy; capable of decreasing hepatic parenchymal copper through biliary excretion
Pharmacologic rehabilitation of mutated ATP7B	In development	
Augmentation of cell-protective responses	In development	
Liver transplantation		
Deceased donor; living donor (segmental transplantation)	Available	Copper metabolism restored to normal; requires lifelong immunosuppression with its potential complications; donor may be simple heterozygote (one *ATP7B* mutation)
Auxiliary transplantation	Available	Developed for patients with acute liver failure; limited immunosuppression may be possible
Transplantation of hepatocytes from unaffected person	In development	Requires lifelong immunosuppression; may require cells from more than one donor; may need to be repeated if cell survival not adequate or if cell population does not expand; safe techniques for selective expansion of the population of donor cells must be developed
Hepatocyte transplantation plus gene repair (through CRISPR technology) or gene replacement		
Patient's induced pluripotent stem cells treated to repair *ATP7B* mutation or replace with wild-type *ATP7B*, then transformed into hepatocytes and reintroduced	In development	Lifelong immunosuppression probably not needed; safe techniques for selective expansion of the population of repaired cells must be developed
Patient's hepatocytes reprogrammed into liver progenitor cells, treated to repair *ATP7B* mutation or replace with wild-type *ATP7B*, then transformed into hepatocytes and reintroduced	In development	Lifelong immunosuppression probably not needed; safe techniques for selective expansion of the population of repaired cells must be developed
Gene replacement: wild-type *ATP7B* expressed in patient's hepatocytes after being introduced in vivo	In development	Transfection of all hepatocytes probably not necessary, but high transfection rate desirable; safety of integrating delivery virus into recipient's genome not clear; potential for development of antibodies to viral or transfected proteins in recipient; unknown whether multiple transfections will be required

* Data are from Schilsky.[58] CRISPR denotes clustered regularly interspaced short palindromic repeats, and TTM tetrathiomolybdate.

Gene repair is another attractive future application for Wilson's disease.[77] Somatic gene modification can be achieved with the use of such methods as CRISPR-Cas (clustered regularly interspaced short palindromic repeats associated with a Cas endonuclease) genome editing, allowing correction of suitable *ATP7B* mutations and thereby restoring functional copper transport in hepatocytes. The goal is to achieve copper transport equivalent to that in an unaffected simple heterozygote without altering the germline cells. The large number of pathogenic *ATP7B* variants makes

it potentially costly to establish the technique for patients who have uncommon mutations. Newer technology may permit repair by substitution of larger segments that encompass regions with multiple mutations, potentially reducing the cost of development and expanding the number of patients who would be candidates for this treatment. Since certain types of mutations are not suitable for gene repair, this therapeutic approach would be limited to a subgroup of patients with Wilson's disease.

INNOVATIVE STRATEGIES FOR LIVER-CELL TRANSPLANTATION

Hepatocyte transplantation has been tested in rodent models of Wilson disease.[78,79] At present, human hepatocyte transplantation requires immunosuppression to prevent rejection of the transplanted cells. Unlike liver transplantation, hepatocyte transplantation may not correct complications of portal hypertension. Innovative cell transplantation strategies to avoid the need for immunosuppression are being developed. The suitability of autologous liver progenitor cells (generated from hepatocytes) or nonhepatic stem cells, either of which can be transformed into hepatocytes, is being investigated. Ex vivo gene therapy to express wild-type *ATP7B* or repair existing *ATP7B* mutations is performed before cells are reintroduced into the patient. The results of proof-of-principle studies in animal models for each strategy were recently reported.[80,81]

MANAGEMENT OF WILSON'S DISEASE

In general, the diagnosis and treatment of Wilson's disease benefit from a team approach. The team typically is customized according to the patient's needs. It may include specialists in hepatology, neurology, psychiatry, and clinical genetics; an internist, general pediatrician, or family physician; and ancillary specialists such as a registered dietitian, physiotherapist or occupational therapist, speech therapist, and genetic counselor. Adjunctive medical therapies for neurologic symptoms of Wilson's disease, such as parkinsonism, dystonia, and chorea, may be warranted. Some patients may benefit from psychotropic medication or counseling. A dietitian can streamline meal patterns and help prevent undue anxiety about excess dietary copper intake. Physical and occupational therapists can assist with strategies to meet special needs at school and in the workplace. Patients with Wilson's disease and cirrhosis should undergo screening for hepatic neoplasia, and treatment for portal hypertension and its complications may be warranted.

The importance of a multidisciplinary team is especially evident with respect to pregnancy. Fertility appears to be normal and pregnancy outcomes are typically favorable in treated patients with Wilson's disease that is clinically stable.[82-84] Treatment must be continued throughout pregnancy. The teratogenic risk of available medications is poorly established, except for penicillamine. The doses of both penicillamine and trientine should be reduced by 25 to 50% during pregnancy. Associated liver disease may require management by a specialist. Wilson's disease can manifest initially during pregnancy and must be distinguished from the HELLP (hemolysis, elevated liver-enzyme levels, and a low platelet count) syndrome, thrombotic thrombocytopenia purpura, and similar rare disorders.

ADHERENCE AS AN EMERGING ISSUE

The importance of adherence to treatment for Wilson's disease is increasingly recognized. Adherence is a major challenge for patients, who must take, at a minimum, twice-daily medication for the rest of their lives or risk severe clinical deterioration.[85] Although patients who receive an early diagnosis by means of molecular genetic testing have the best outcome with well-tolerated, effective treatment, such patients are also likely to become nonadherent, since they may not recognize the risks associated with untreated Wilson's disease. Innovative methods for supporting adherence are being developed for other chronic diseases and warrant testing for Wilson's disease.

Factors in achieving good adherence include regular clinical assessments and a broadly supportive approach that is team-based, if possible. Improved methods for monitoring treatment, along with clear benchmarks for treatment adequacy, facilitate general management. Monitoring should be closer in patients for whom nonadherence is suspected. Concurrent disease, increased dietary copper, taking medication too close to meals, or societal barriers to obtaining medication (supply shortages and cost) may account for treatment failure that is otherwise attributed to nonadherence. Strong family and social supports

are essential, with clear communication to all health care providers and the patient.

CONCLUSIONS

Current advances in the diagnosis, treatment, and multidisciplinary management of Wilson's disease are important. Future population screening is likely to identify patients earlier in the course of the disease. Novel treatments will address unmet needs and furnish new options for individualizing treatment. Gene therapy or gene repair has the potential to provide the first cures for Wilson's disease, apart from liver transplantation. Fine-tuned monitoring will establish the effectiveness and durability of these therapies. Continued efforts to describe the complicated pathobiology of Wilson's disease entail expanding the focus on gene expression and mutated gene-product dysfunction to include an assessment of how different tissues respond to intracellular alterations caused by defective ATP7B. This approach enlarges the scope from genomic to postgenomic issues and will further enhance our understanding of Wilson's disease.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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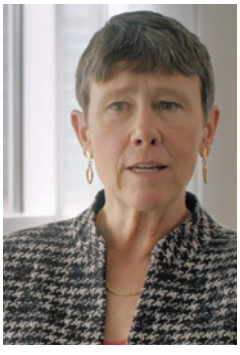
Double Take Video: **Understanding and Preventing Type 2 Diabetes**


In this first episode of "Type 2 Diabetes — Controlling the Epidemic," a four-part Double Take video miniseries, Drs. Jane Reusch, Dale Abel, and Monica Peek discuss the pathophysiology of the disease and its common complications. The experts also review prediabetes and the importance of engaging at-risk communities for diabetes screening and prevention.