Wilson Disease: Diagnosis and Management Across the Age Spectrum

Kris V. Kowdley MD
Director, Liver Institute Northwest
Clinical Professor
Elson S. Floyd College of Medicine
Washington State University

Liver Institute Northwest

Elson S. Floyd College of Medicine
Washington State University

Disclosures

- **Grants/Research Support:** Gilead, HighTide, Mirum, Pliant; Genfit, CymaBay, GSK, Viking, Pfizer, Intercept, NGM Bio, 89Bio, Celgene, BMS, Corcept, Metacrine, Hanmi, Terns, Madrigal, Enanta, PTG
- **Principle Investigator for a Drug Study:** Gilead, HighTide, Mirum, Pliant; Genfit, CymaBay, GSK, Viking, Pfizer, Intercept, NGM Bio, 89Bio, Celgene, BMS, Corcept, Metacrine, Hanmi, Terns, Madrigal, Enanta, PTG
- **Consultant:** Gilead, Intercept, HighTide, Mirum, Genfit, CymaBay; Inipharm, Madrigal, NGMBio
- **Speakers Bureau:** AbbVie, Gilead, Intercept
- **Advisory Board Membership:** 89Bio, Pfizer, Enanta, 89Bio, Pfizer, Enanta
- **Stockholder:** Inipharm
- **Editorial Board Involvement:** Hepatology Communications
- **Other Financial or Material Support:** UpToDate-Royalties

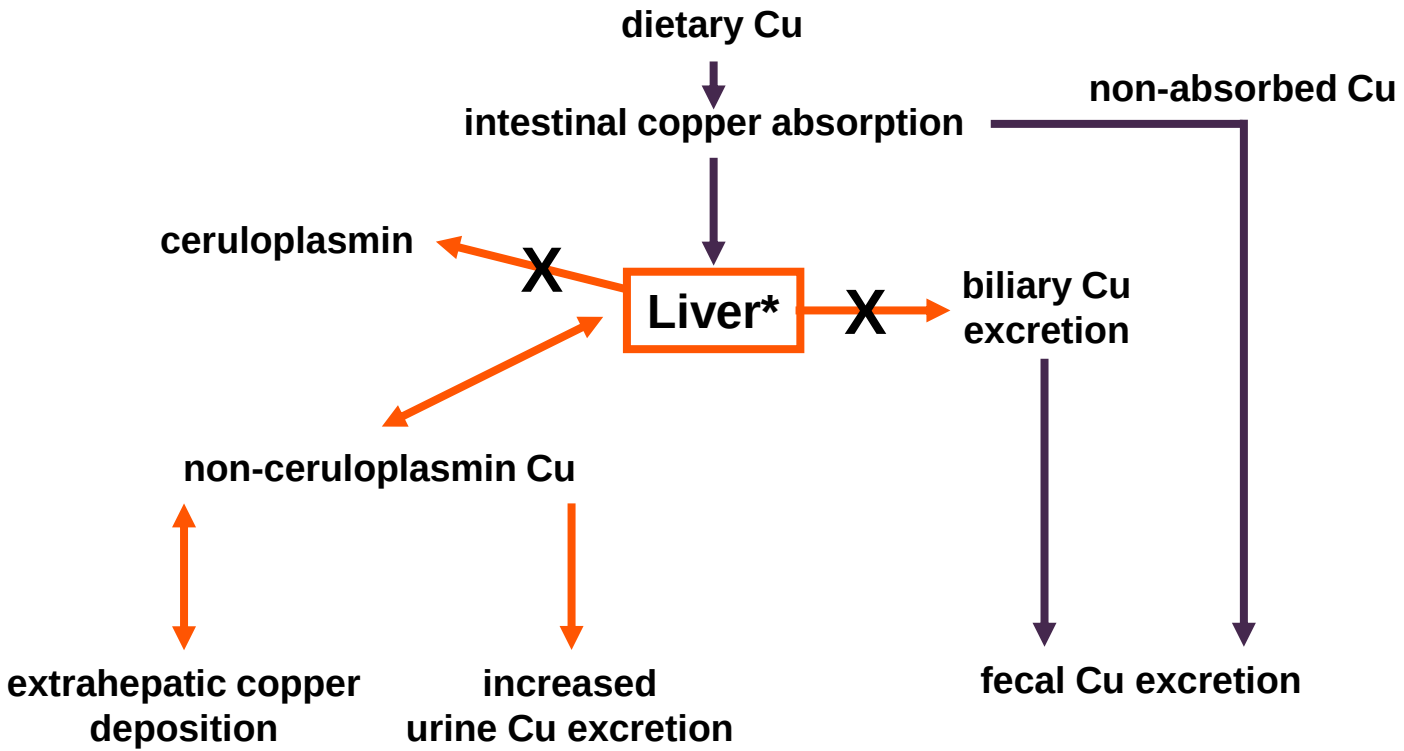
Acknowledgement

- Thanks to Michael Schilsky, MD for several of the slides in this presentation

Learning Objectives:

- Understand the approach to Wilson disease diagnosis
- Discuss treatment options for Wilson disease
- Improve your monitoring of Wilson disease treatment
- Understand what future options lie ahead for treatment and monitoring of Wilson disease patients

Wilson Disease Pathophysiology



*ATP7B highly expressed but absent or non-functional in WD patients.

Wilson Disease Should Be Suspected in:

- Persons with unexplained serum aminotransferase elevation, chronic hepatitis with steatosis, poorly responsive autoimmune hepatitis, cirrhosis, or acute liver failure
  most between 3–55 years, but age alone should not exclude the diagnosis
- First degree relative with a diagnosis of Wilson disease
- Unexplained Coombs-negative hemolytic anemia
- Neurological symptoms of unexplained origin with liver disease
- Psychiatric disease with signs of hepatic or neurologic disease
- Incidental detection of Kayser–Fleischer rings
- Brain imaging suggestive of Wilson disease
- Detection of 2 ATP7B disease specific mutations (trans)

Orange highlighted items frequent in pediatric patients.

Leipzig Scoring System Aids in Wilson Disease Diagnosis*

Typical clinical symptoms and signs	Other tests	TOTAL SCORE Evaluation:
KF rings Present 2 Absent 0 **Neurologic symptoms**** Severe 2 Mild 1 Absent 0 **Serum ceruloplasmin** Normal (> 0.2 g/L) 0 0.1–0.2 g/L 1 < 0.1 g/L 2 **Coombs-negative hemolytic anemia** Present 1 Absent 0	**Liver copper (in the absence of cholestasis)** > 5x ULN (> 4 µmol/g) 2 0.8–4 µmol/g 1 Normal (< 0.8 µmol/g) -1 Rhodanine-positive granules* 1 **Urinary copper (in the absence of acute hepatitis)** Normal 0 1–2x ULN 1 > 2x ULN 2 Normal, but > 5x ULN after D-penicillamine 2 **Mutation analysis** On both chromosomes detected 4 On 1 chromosome detected 1 No mutations detected 0	**4 or more – diagnosis established** **3 – diagnosis possible, more tests needed** **2 or less – diagnosis very unlikely** *If no quantitative liver copper available, **or typical abnormalities at brain magnetic resonance imaging. KF, Kayser–Fleischer; ULN, upper limit of normal.

*Incorporated into EASL guideline for Wilson disease, as a guide in AASLD 2021 Guidance;
Non-WD exceptions with diagnostic score: PFIC3, glycosylation defects.
From Ferenci et al. *Liv Int*. 2003.

Approach to Wilson Disease Diagnosis

To be released: New AASLD Guidance – Diagnosis and Treatment of Wilson disease

What is new regarding disease diagnosis:

- Updated algorithms for approaching the diagnosis of Wilson disease
- Important for pediatrics and family screening: emphasize utility of molecular genetic testing for ATP7B mutations
- Acknowledge that the frequency of molecular diagnosis is rising
- Use of optical tomography for evaluation for Kayser-Fleischer rings
- Incorporating non-invasive methodology for evaluating for hepatic fibrosis

What's New:
Use of Optical Tomography for KF Ring Detection

Optical tomography

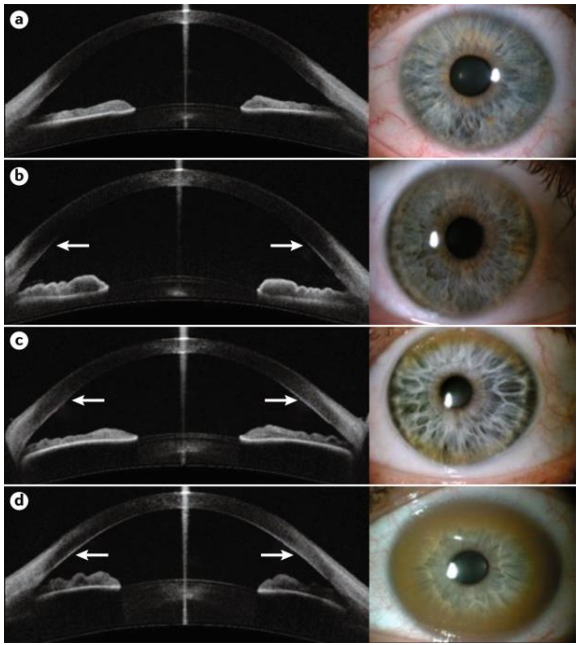


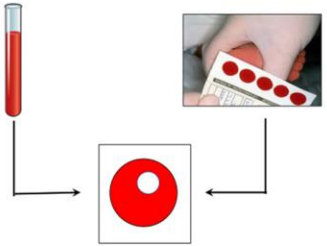
Fig. 8: Kayser-Fleischer rings in WD
Images courtesy of K. Broniek and J. Szaflik, the Department of Ophthalmology, Medical University of Warsaw, Warsaw, Poland.
Członkowska A et al. Wilson disease. *Nat Rev Dis Primers*. 2018. doi:10.1038/s41572-018-0018-3.

*Coming Soon for WD Diagnosis:

ATP7B Peptide Analysis Identifies Wilson Disease Patients

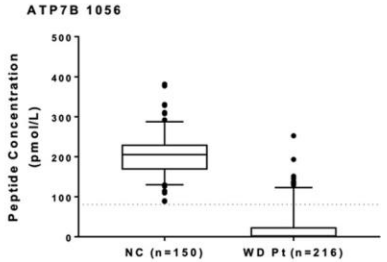
216 WD Patients
(130 Unique Variants)

211 With Genetic Results
- 143 (68%) genetically confirmed
- 68 (32%) genetically ambiguous



Dried Blood Spots

Antibody-Mediated
Enrichment
of ATP7B Peptides



ATP7B peptide deficient in:
- 199/216 (92%) of all patients
- 64/68 (94%) genetically ambiguous
- 130/143 (91%) genetically confirmed
- 14/16 (88%) with normal ceruloplasmin

Gastroenterology

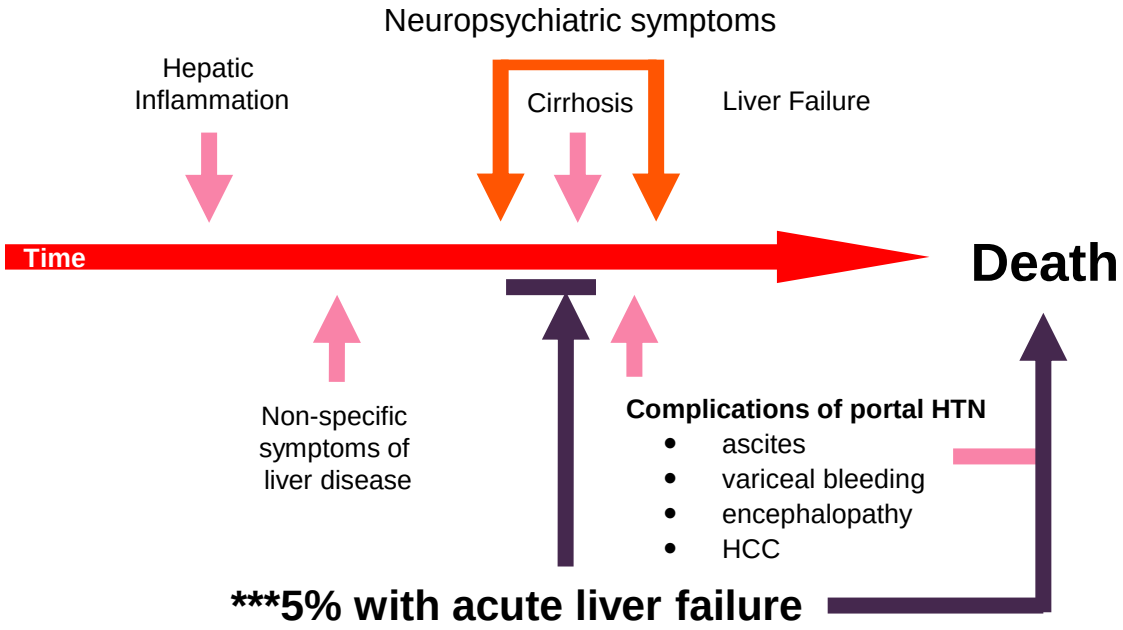
*experimental

ELSEVIER

What Hasn’t Changed:

- Need to consider the disease in the differential diagnosis
- Serum ceruloplasmin remains a useful screening test but is not sufficient for diagnosis
- 24 h urine copper threshold for basal excretion of 40 mcg/day remains useful
- Ultrastructural analysis of liver tissue in the early phase of the disease may be helpful for difficult to diagnose cases
- Establish the diagnosis firmly as medical treatment is lifelong

2021 Guidance for Diagnosis and Treatment of Wilson Disease
Treatment Goals With Respect to the Liver Are Phase of Disease Dependent



Goals: **Prevention** **Treatment** **Rescue**

Wilson Disease Treatments – Timeline for Introduction

Samuel Alexander Kinnier Wilson (1878–1937)

1912 — No Available Therapy

1951 — BAL — Treat symptomatic

1956 — D-penicillamine — Treat pre-emptively

1961 — Zinc

1969 — Trientine

1973 — Liver Transplant

1979 — Ammonium TTM*

2017 — Choline TTM*

2021 — Gene therapy* — Proteonomic

Future

*Treatment trials

Treatment Options for Wilson Disease

Primary

- Diet
- Pharmacotherapy
  - **Chelation**
    - d-penicillamine
    - Trientine
    - TTM*
  - **Zinc**
- Transplantation

Secondary

Treat if present:

- Complications of portal HTN
- Screening for HCC?
- Treat neurological symptoms
- Treat psychiatric symptoms

*Experimental

Treatment Options for Wilson Disease

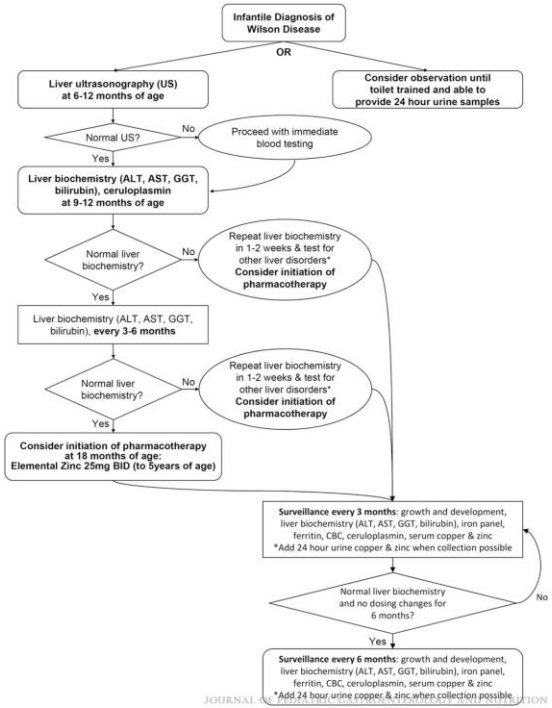
What's new:

- Concept of trial of "Intensive therapy" for those in need of "Rescue therapy"

"Intensive therapy":

- Chelation and zinc temporally separated
- Use of pheresis/hemofiltration or other acute copper lowering therapies

Management of Wilson Disease Diagnosed in Infancy After Genetic Diagnosis



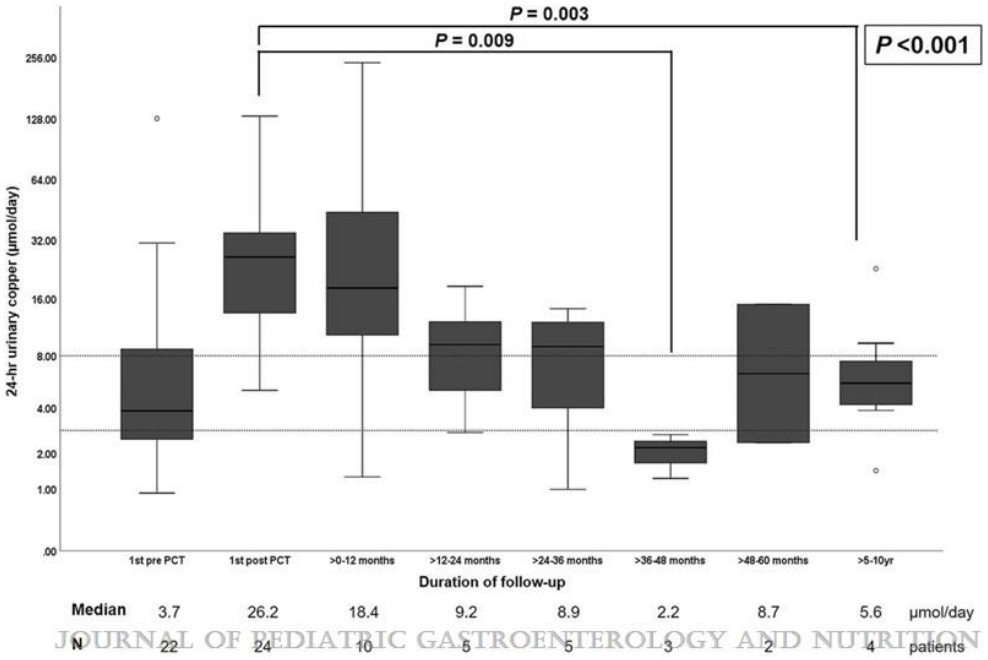
Proposed surveillance and treatment algorithm for infants with genetically diagnosed Wilson disease.
*Etiologies of other liver disorders include alpha-1-antitrypsin deficiency, viral hepatitis B and C, and autoimmune liver diseases.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase.
Valentino PL, Roberts EA, Beer S, Miloh T, Arnon R; Vittorio JM, Schilsky ML. *Journal of Pediatric Gastroenterology and Nutrition*. 2020;70(5): 547–554. doi: 10.1097/MPG.0000000000002608.

Long-Term Urinary Copper Excretion on Chelation Therapy in 28 Children With Wilson Disease

Male, n (%)	17 (60.7)
Age, y	11.4 (9.4–13.9)
Duration of follow-up, y	6.9 (3.8–10.4)
Presentation, n (%)	
Asymptomatic	8 (28.6)
Chronic liver disease	11 (39.1)
Acute liver failure	9 (32.1)
Laboratory results at first visit	
Total bilirubin, μmol/L	17.5 (9.3–33.8)
AST, IU/L	116.0 (71.8–198.3)
ALT[□], IU/L	115.0 (42.3–436.0)
Albumin, g/L	42.5 (26.5–45.0)
INR	1.14 (1.03–1.99)
White cell count, 10^9/L	6.2 (5.1–8.4)
Ceruloplasmin, g/L	0.07 (0.05–0.17)
NCC[†], μmol/L	3.1 (0.6–5.6)
Liver copper content[‡], μg/g dry weight liver	445.0 (194.3–1028.5)
24-h urinary copper excretion	
Pre-penicillamine[□], μmol/day	3.4 (2.3–8.8)
Post-penicillamine[§], μmol/day	26.2 (13.4–35.9)
Wilson prognostic index	4.0 (1.0–7.0)
Penicillamine, n (%)	18 (64.3)
Trientine, n (%)	8 (28.6)
Liver transplantation, n (%)	2 (7.1)

Chanpong A and Dhawan A. *Journal of Pediatric Gastroenterology and Nutrition*. 2021; 72(2): 210–215.

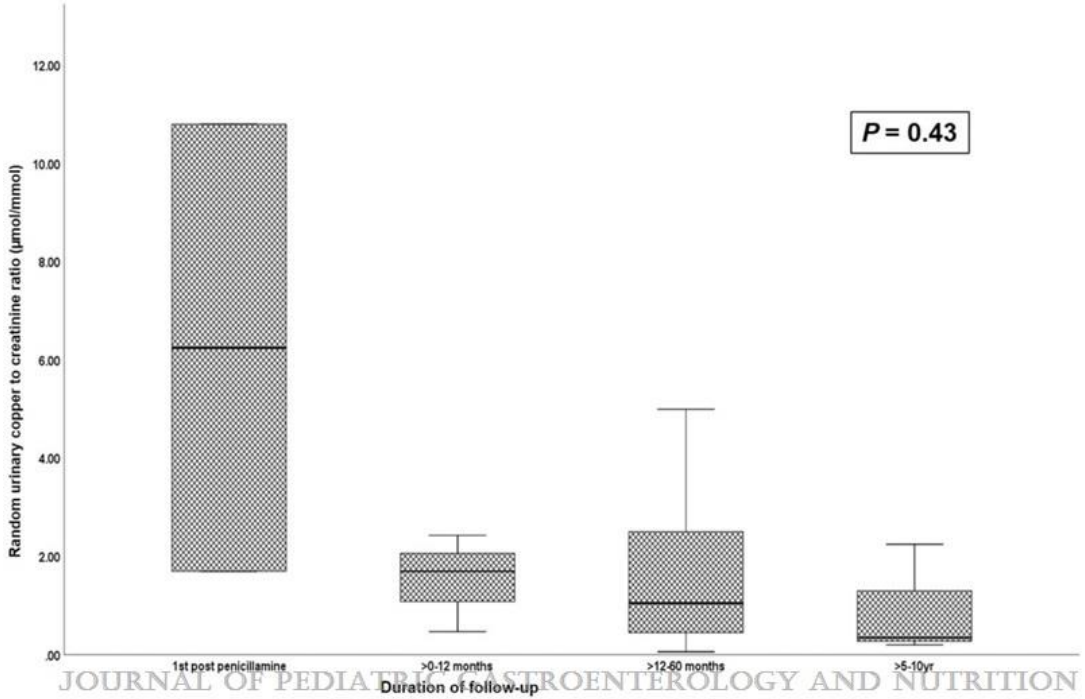
Twenty-Four-Hour Urinary Copper Excretion



24 WD patients
WD = Wilson disease

Chanpong A and Dhawan A. *Journal of Pediatric Gastroenterology and Nutrition*. 2021; 72(2): 210–215.

Spot Urinary Copper to Creatinine Ratio



11 followed-up patients

Chanpong A and Dhawan A. *Journal of Pediatric Gastroenterology and Nutrition*. 2021; 72(2): 210–215.

When to Use “Intensive Therapy” – Advanced Liver Disease, ALI

- Examined patients with ALI and WD entered into the ALFSG registry study
- Measures examined:
  - Outcome day 21
  - Survival without transplantation
  - Scoring systems for ALI and ALF
  - Results – some patients survived
  - With medical therapy and did not
  - Progress to ALF

Case no.	Gender	Age	Transplanted	AST/ALT > 2.2	ALP/TB < 4	Modified WD Score	ALI Prog Score	MELD Score	APRI Score
1	Male	19	N	N	N	9	0.53	23	3.3
2	Male	19	N	N	N	9	0.618	22	1.6
3	Female	49	N	N	N	13	0.636	25	9.2
4	Female	57	Y	Y	Y	12	0.668	24	4.7
5	Female	21	Y	Y	Y	15	0.67	30	1.2
6	Female	18	Y	Y	Y	15	0.774	33	1.6
7	Female	25	Y	N	N	17	0.764	32	19.8

*Survivors were treated with trientine or trientine and zinc treatment: “intensive therapy”.
Table 3: Diagnostic and Prognostic Scores; Y = Yes, N = No.
Camarata et al. Outcomes of Acute Liver Injury in Adults Due to Wilson's Disease: Is Survival Without Transplant Possible? Liver Transpl. 2020; 26: 330–336.

Gene Therapy: Building on Prior Observations

- WD is a monogenic disease
- Heterozygotes do not have pathologic copper overload
- ATP7B is highly expressed in hepatocytes
- Liver transplant corrects the metabolic defect in WD
- Hepatocyte transplant studies in animal models of WD showed that partial replacement is adequate to restore copper balance

Research Article

JOURNAL OF HEPATOLOGY

Long-term metabolic correction of Wilson's disease in a murine model by gene therapy

Oihana Murillo[1,2,†], Daniel Moreno Luqui[1,2,†], Cristina Gazquez[1,2], Debora Martinez-Espartosa[2,3], Iñigo Navarro-Blasco[2,7], Jose Ignacio Monreal[2,3], Laura Guembe[2,4], Armando Moreno-Cermeño[2,5], Fernando J. Corrales[2,5,6], Jesus Prieto[1,2,3,†], Ruben Hernandez-Alcoceba[1,2,†], Gloria Gonzalez-Aseguinolaza[1,2,*,†]

[1]Gene Therapy and Regulation of Gene Expression Program, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; [2]IDISNA, Instituto de Investigacion Sanitaria de Navarra, Spain; [3]Clinical Chemistry Department, University Clinic of Navarra, University of Navarra, Pamplona, Spain; [4]Department of Morphology, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; [5]Hepatology Program, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; [6]CIBERehd, University of Navarra, Pamplona, Spain; [7]Department of Chemistry and Soil Sciences, University of Navarra, Pamplona, Spain

Editorial

JOURNAL OF HEPATOLOGY

Gene therapy of Wilson disease: A "golden" opportunity using rAAV on the 50th anniversary of the discovery of the virus

Jayanta Roy-Chowdhury[1,*], Michael L. Schilsky[2]

[1]Department of Medicine (Gastroenterology and Liver Diseases), Department of Genetics and Marion Bessin Liver Research Center, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA; [2]Division of Digestive Diseases and Transplantation and Immunology, Departments of Medicine and Surgery, Yale University, New Haven, CT 06520, USA

See Article, pages 419–426

HEPATOLOGY AASLD

Original

Liver expression of a miniATP7B gene results in long-term restoration of copper homeostasis in a Wilson's disease model

Oihana Murillo, Daniel Moreno, Cristina Gazquez, Miren Barberia, Itziar Cenzano, Iñigo Navarro, Iker Uriarte, Victor Sebastian, Manuel Arruebo, Veronica Ferrer, Bernard Bénichou ... See all authors

First published: 01 February 2019 | https://doi.org/10.1002/hep.30535

GATEWAY Clinical Trial

Oct 2020: FDA Clearance of IND for GATEWAY Phase 1/2 Trial with VTX-801, Vivet's Investigational Gene Therapy for Wilson Disease

Investigational Sites:
Yale
University of Michigan
UC Davis

Initial studies on 18–60 years of age

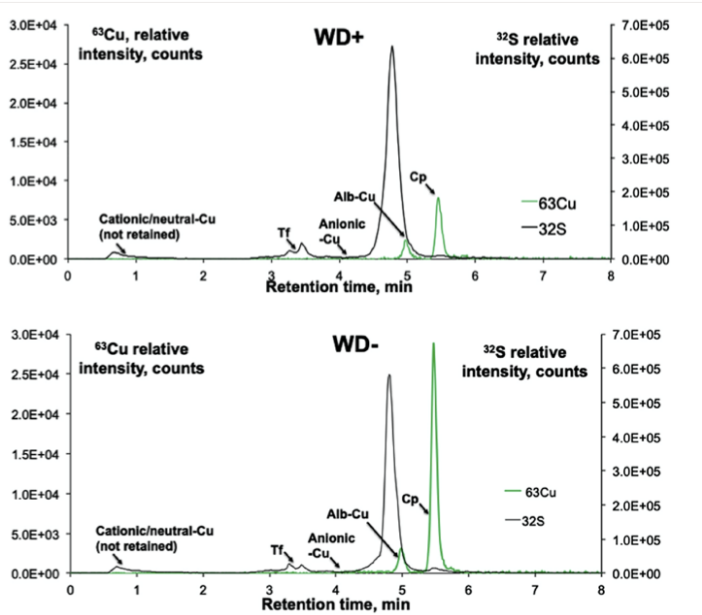
https://clinicaltrials.gov/ct2/show/NCT04537377?term=schilsky&cond=wilson%27s+disease&draw=2&rank=2

Improve Your Monitoring of Wilson Disease Treatment

What's new from the 2021 Guidance:

- De-emphasis of NCC by estimate (total Cu – CPNx3.12)
- New publications on accurate NCC determination and AASLD 2021 poster
- Use of new NCC methodology in clinical study
- Better definitions for treatment failure, overtreatment
- Other: use of urine copper excretion for monitoring and dose adjustment is still very useful but must be carefully interpreted for the particular therapy and stage of disease
- Chelation: higher copper excretion occurs after start of chelation and lowers with time
- Zinc: start with higher copper excretion or normal value before treatment, lowers or stays < 100 mcg daily on therapy
- What should **not** change: continue to monitor liver tests, clinical examination, use of medication at regular intervals – for pediatrics, especially during adolescence, focus on adherence

Improve Your Monitoring of Wilson Disease Treatment



What's new from the 2021 Guidance:

- De-emphasis of NCC by estimate using current commercial assay (total Cu – CPNx3.12)

Direct determination of ceruloplasmin copper:

- Isolation of the ceruloplasmin and accurate determination of copper in ceruloplasmin – allows for accurate NCC determination

Solovyev et al. Biomedical copper speciation in relation to Wilson's disease using strong anion exchange chromatography coupled to triple quadripole inductively coupled plasma mass spectroscopy. *Analytica Chimica Acta*. 2020; 15: 1098: 27–36.

Understand What Future Options Lie Ahead for Treatment and Monitoring of Wilson Disease Patients

Future treatment:

- Chelate study: Non-inferiority of trientine (TETA4) to d-penicillamine for maintenance therapy(AASLD oral presentation Nov 2021)
- TTM for neurologic Wilson disease and for maintenance therapy (results of phase3 study soon, trials of TTM in pediatrics beginning soon)
- Gene replacement therapy (trials with AAV just begun)

Future monitoring:

- Use of new NCC assays – needs validation as biomarker
- Use of drug holiday and UCE determination off therapy