Wilson Disease: Overview and Update

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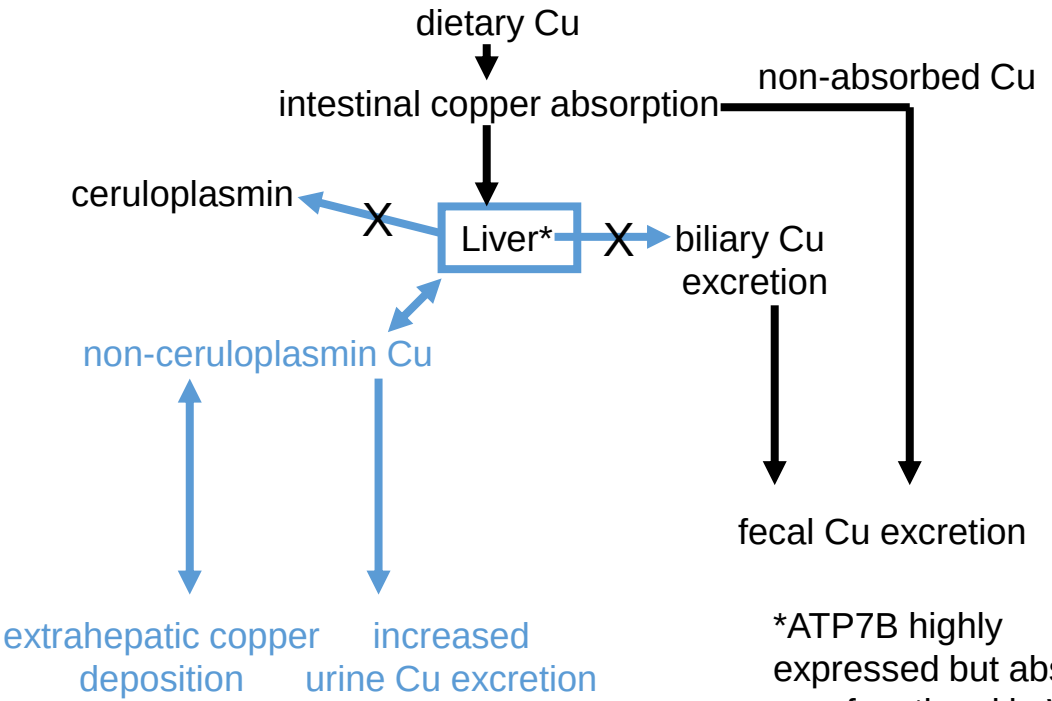
Disclosures

- Grant support: Alexion, GMPO (Orphalan), Vivet Therapeutics, Wilson Disease Association
- Chair, Medical Advisory Committee Wilson Disease Association
- No conflicts with any of the material presented today

Learning Objectives

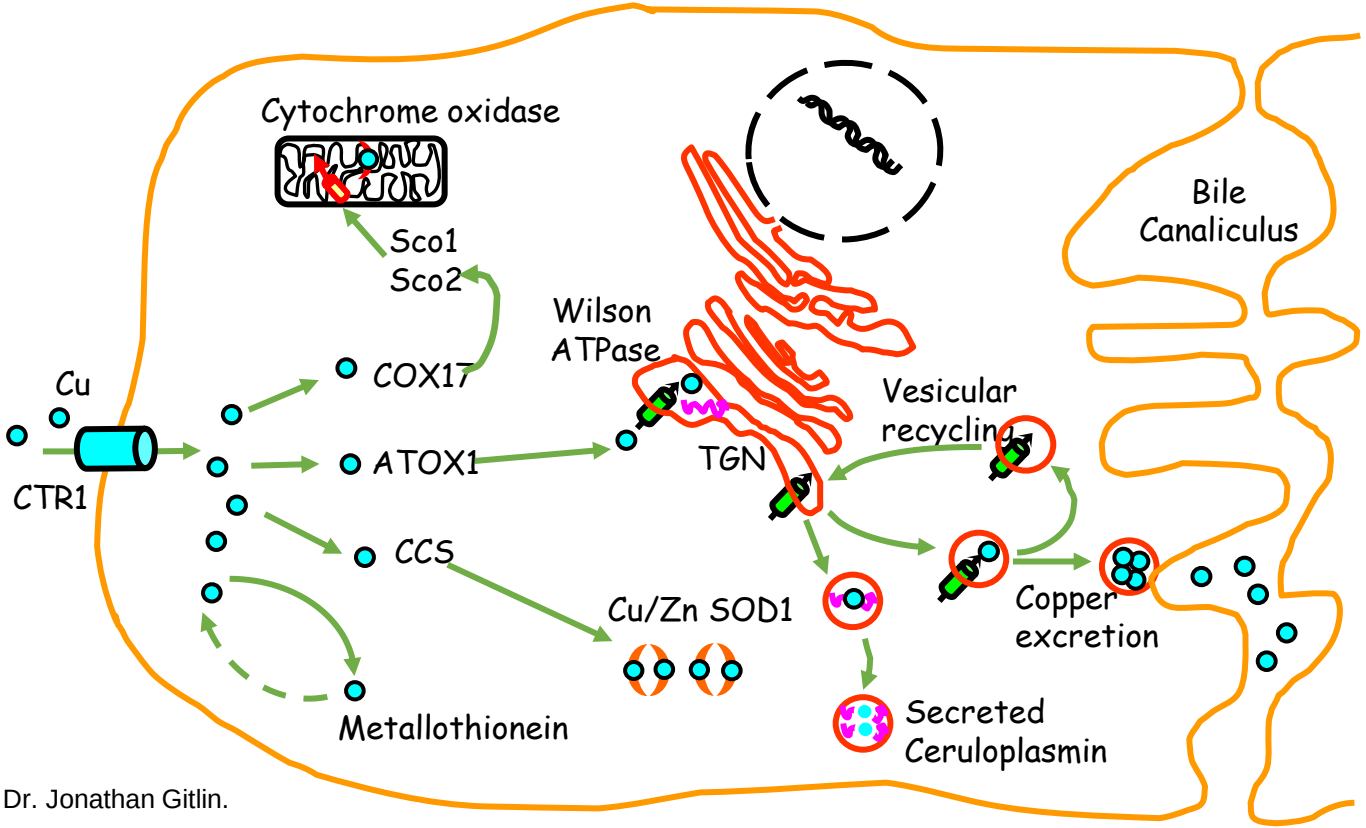
- Understand the pathophysiologic defect leading to Wilson disease
- Learn about diagnostic testing for Wilson disease
- Discuss new treatment options for Wilson disease and unmet needs for therapy

Wilson Disease Pathophysiology



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

Hepatocyte Copper Metabolism



Courtesy Dr. Jonathan Gitlin.

Wilson Disease – Diagnosis

Samuel Alexander Kinnier Wilson (1878–1937)

1912 Rumpel Liver Cu Elevated

1913

1921 Hall "familial" pattern

1948 Urine copper elevated

1952 Scheinberg Gitlin Bearn Kunkel Low CPN

1958 Percutaneous liver biopsy

1979 Frydman Chr 13

1993 Gilliam Cox Gitlin *ATP7B*

2021 Hahn ATP7B Peptide

Future

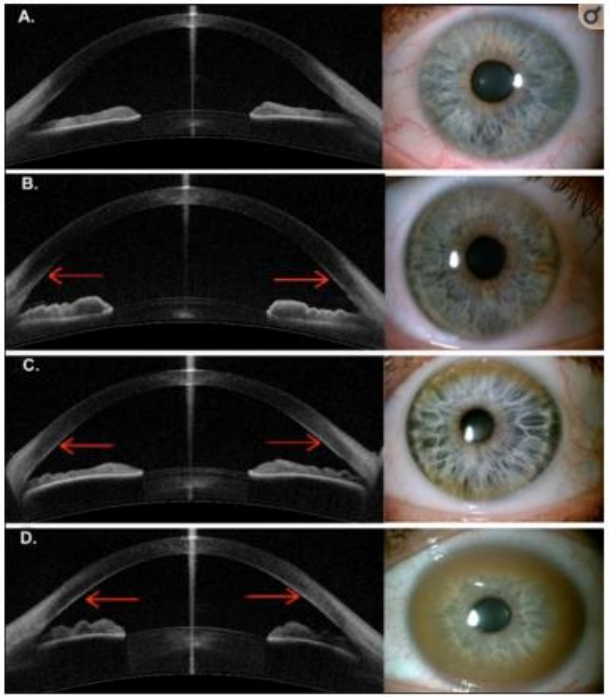
Clinical syndrome

Biochemical definition

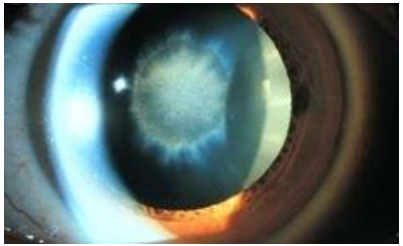
Molecular diagnosis

Proteonomic

Ocular Findings in Wilson Disease



Kayser Fleischer rings
Neurologic 98% Hepatic 50%



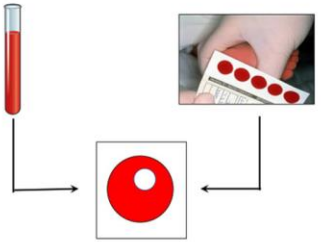
sunflower cataracts

What's new:
Optical tomography

*Coming soon for WD diagnosis:
ATP7B Peptide Analysis Identifies Wilson Disease Patients

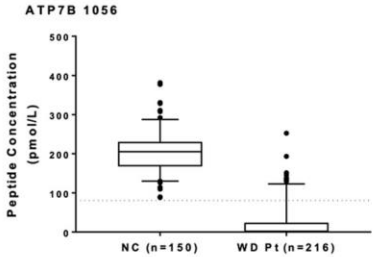
216 WD Patients
(130 Unique Variants)

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

Gastroenterology. 2021;1602367-2382.


Wilson's Disease
Centennial Symposium
Friday 5th and Saturday 6th October 2012
The Royal College of Physicians
THE ROYAL COLLEGE OF PHYSICIANS

Treatment for Wilson Disease

Primary

- Diet
- Pharmacotherapy
- Transplantation

Secondary

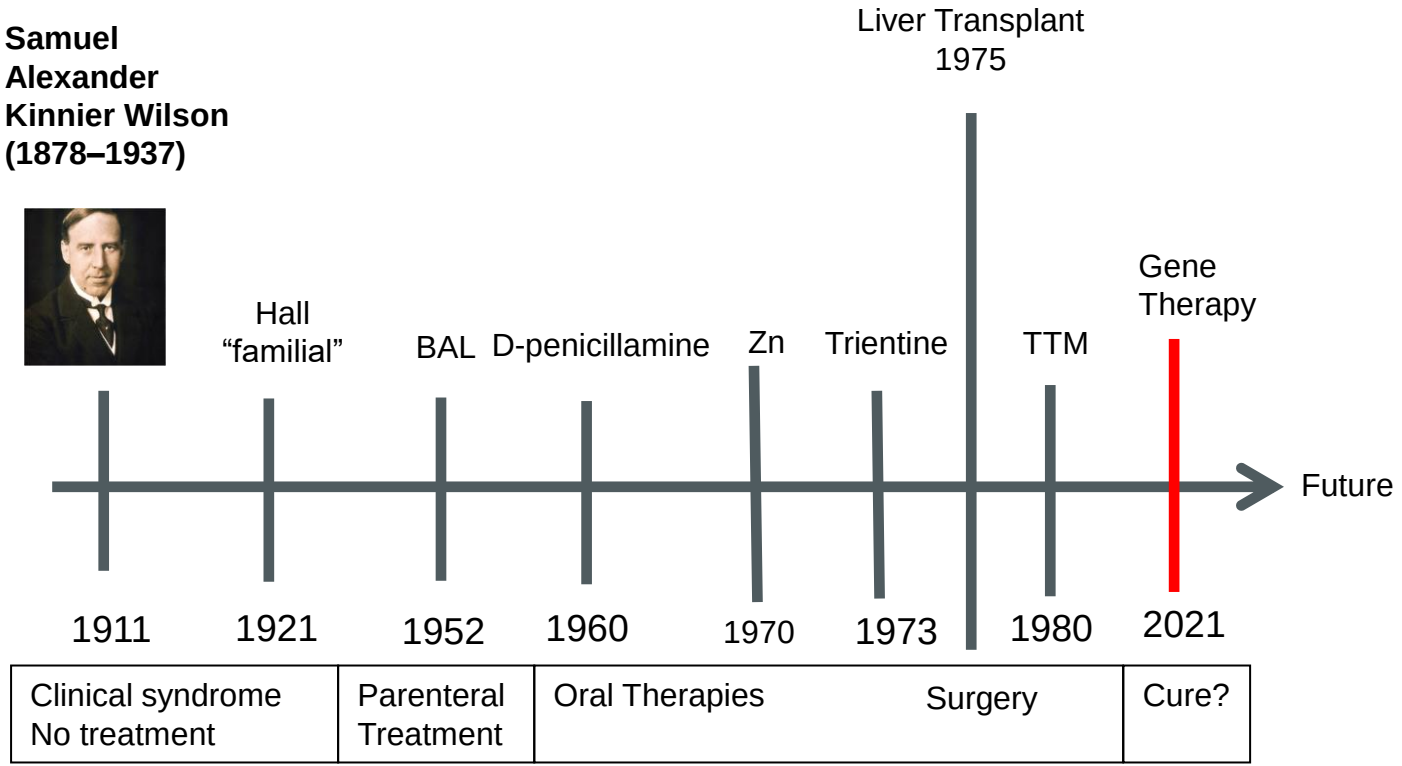
Treat if present:

- Complications of portal HTN
- Neurological symptoms
- Psychiatric symptoms

Perform:

- Screening and surveillance for hepatoma

Timeline: Treatment of Wilson Disease



Treatment Goals With Respect to the Liver Are Phase of Disease Dependent

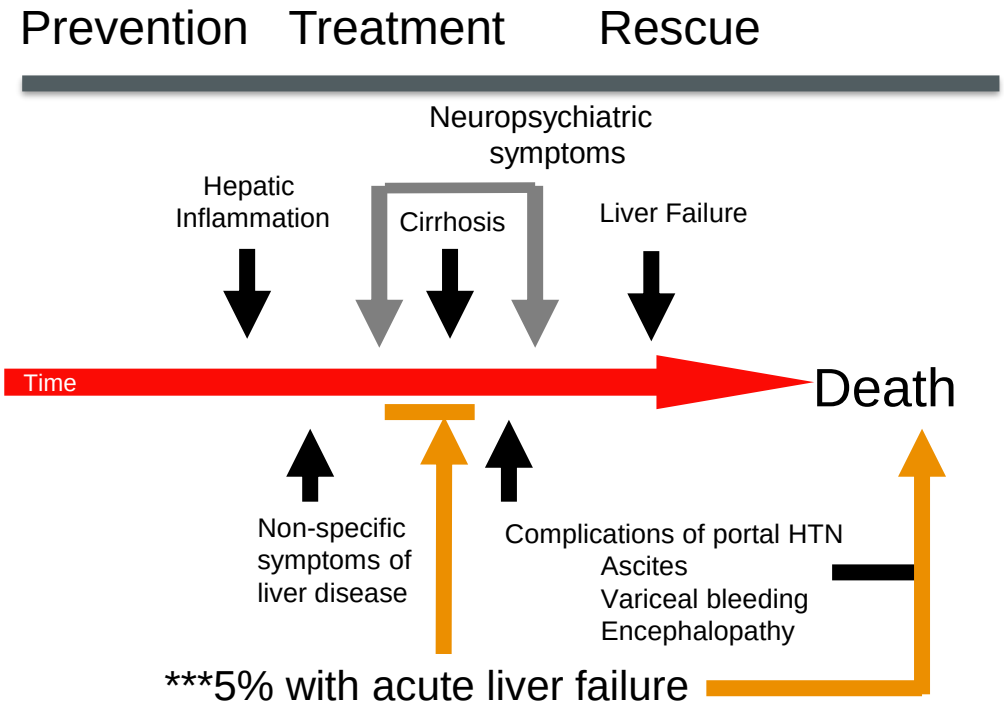


Figure will appear in new AASLD Guidance 2021.

Outcome Measures
Efficacy – Safety

- Control of copper metabolism
- Improvement, stabilization or maintenance of liver function
- Improvement, stabilization or maintenance of neurologic and/or psychiatric function
- Safety

Medical Treatment for Wilson Disease

- Initial treatment – symptomatic, asymptomatic*
- Maintenance therapy
- Rescue therapy – medical, transplantation

*lack of strict definitions.

FDA Approved Treatments of Wilson Disease

- d-Penicillamine – initial therapy, maintenance
- Trientine dihydrochloride – for use if intolerant of d-Penicillamine
- Zinc acetate – maintenance

How to Decide If Medical Therapy Will Succeed? Prognostic Score

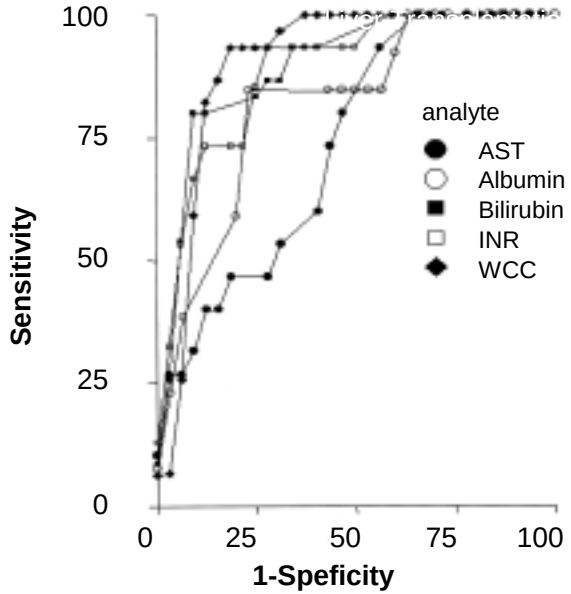


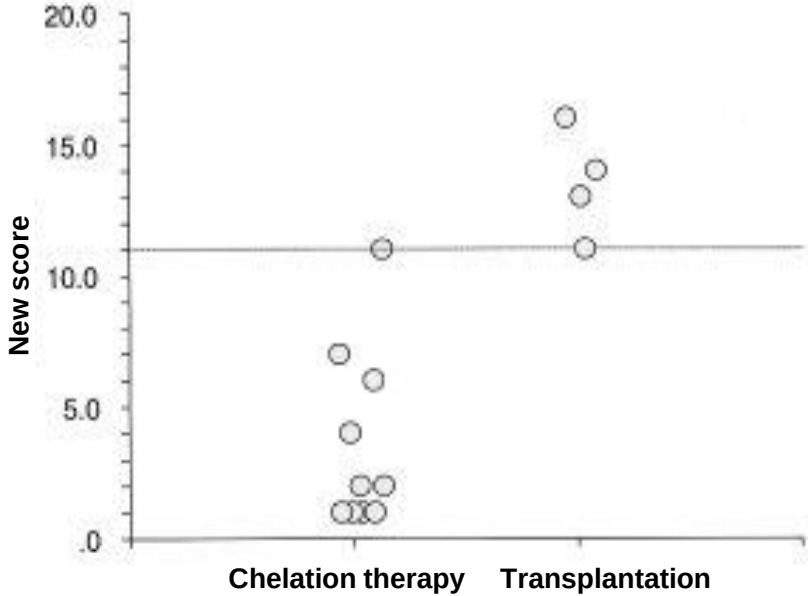
Table 3. Prognostic index in Wilson's disease [40], modified by Dhawan *et al.* [41].

	1*	2*	3*	4*
Serum bilirubin (μmol/L)	100-150	151-200	201-300	>300
AST (U/L)	100-150	151-300	301-400	>400
INR	1.3-1.6	1.7-1.9	2.0-2.4	>2.4
WBC [10^9/L]	6.8-8.3	8.4-10.3	10.4-15.3	>15.3
Albumin [g/L]	34-44	25-33	21-24	<21

*= score points, upper limit of normal for AST = 20 IU/ml (at King's College). A score ⩾11 is associated with high probability of death without liver transplantation.

57 pediatric patients reviewed retrospectively
14 validated prospectively (4 transplanted)
Note – original Nazer score 1986

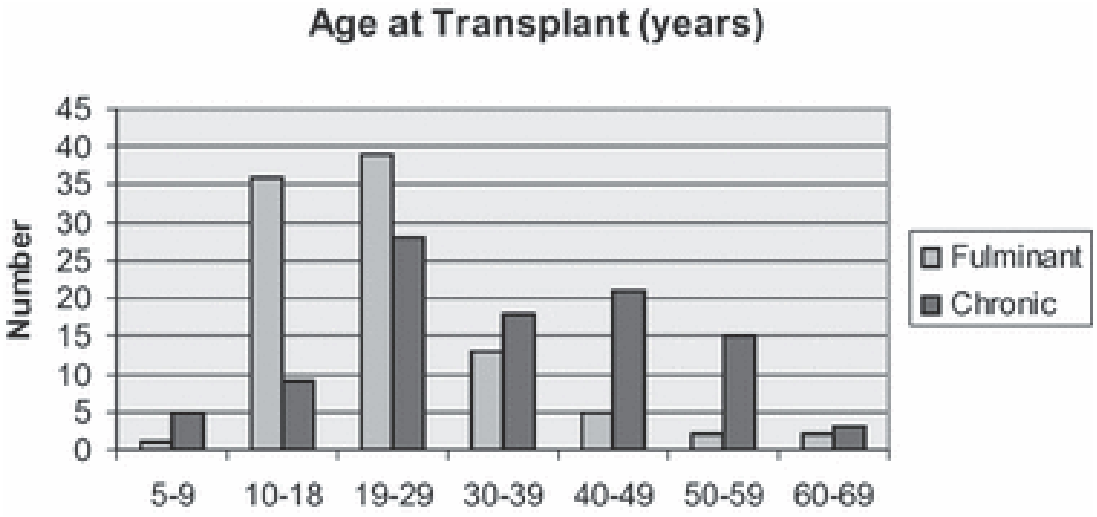
Dhawan A, Taylor Rm, Cheeseman P, De Silva P, Katsiyannakis L, Mieli-Vergani G. Wilson's Disease in Children: 37-Year Experience and Revised King's Score for Liver Transplantation. *Liver Transplantation*. 2005.



Dhawan et al. *Liver Transplantation*. 2005.

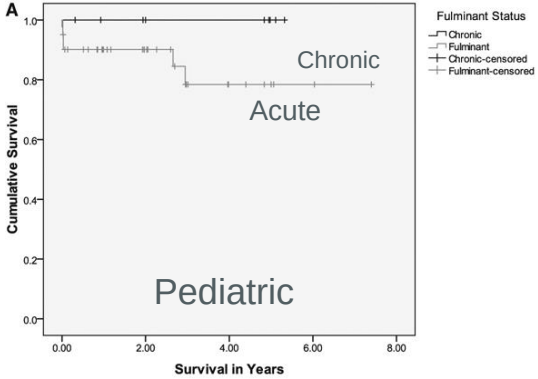
Liver Transplantation for Children With Wilson Disease: Comparison of Outcomes Between Children and Adults

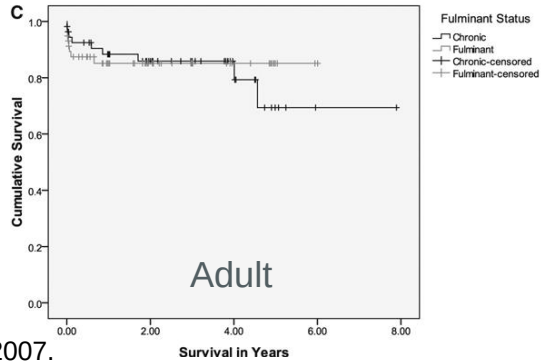
From 1987 to 2008, 170 children and 400 adults 0.6% of all liver transplants
70% children female; 49% adults female



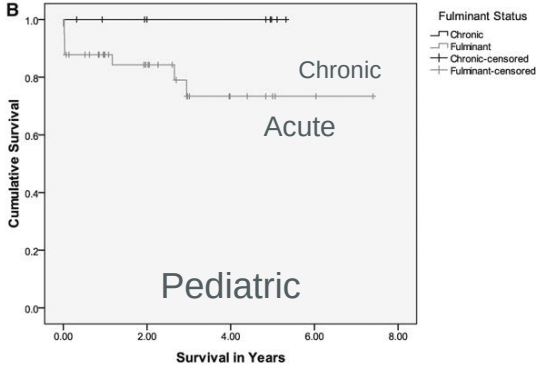
Arnon R, Annunziato R, Schilsky M, Miloh T, Willis A, Sturdevant M, Sakworawich A, Suchy F, Kerkar N. *Clinical Transplantation*. 2011; 1: E52-60.

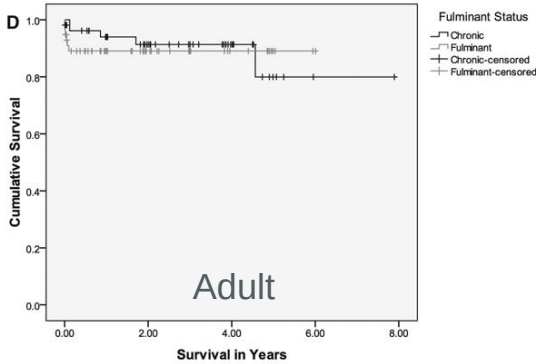
GRAFT Survival





PATIENT Survival





Arnon et al. *Clin Transplant*. 2007.

New Treatments: Landscape

- FDA approved medications:
  - d-Penicillamine
  - Trientine dihydrochloride
  - Zinc acetate
- Non- prescription medications
  - Zinc salts
- Under development:
  - Choline tetrathiomolybdate – Phase 3
  - Trientine tetrahydrochloride – Phase 3
  - Gene therapy – AAV phase 1 / 2 started 2021

WTX101 in Patients Newly Diagnosed With Wilson Disease: Final Results of a Global, Prospective Phase II Trial

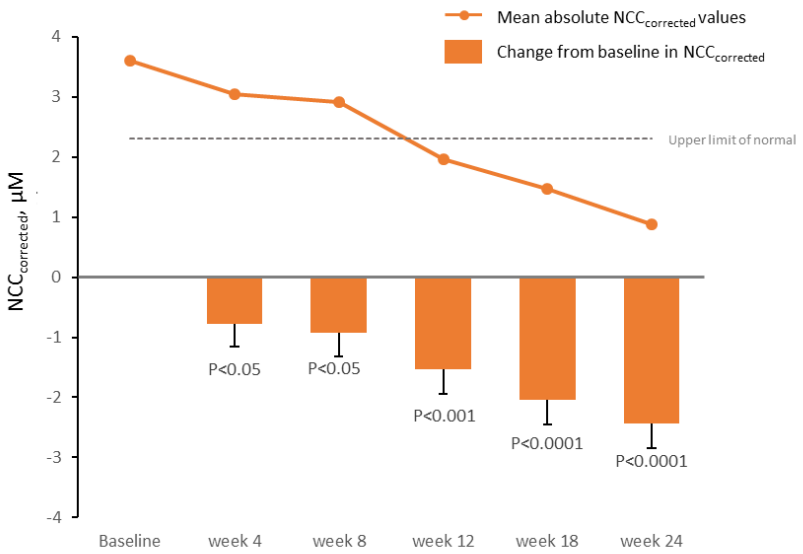
Bis-choline tetrathiomolybdate (WTX101 – now ALXN1840)

- Oral, once daily administration
- Specifically binds to copper (not iron or zinc) with high affinity
- Tetrathiomolybdate (TTM) removes copper from intracellular metallothionein (MT) copper stores by forming TTM-Cu complexes
- TTM augments Cu excretion into bile
- TTM expands endogenous copper buffering capacity by forming stable TTM-Cu-albumin complexes in blood

Karl Heinz Weiss, Frederick K. Askari, Peter Ferenci, Aftab Ala, Anna Czlonkowska, David Nicholl, Jeffrey Bronstein, Danny Bega, Michael L. Schilsky for the WTX101-201 study group; *Lancet Gastro Hep*. 2017; 2: 869-876.

Reductions in Non-Ceruloplasmin Bound Copper Levels

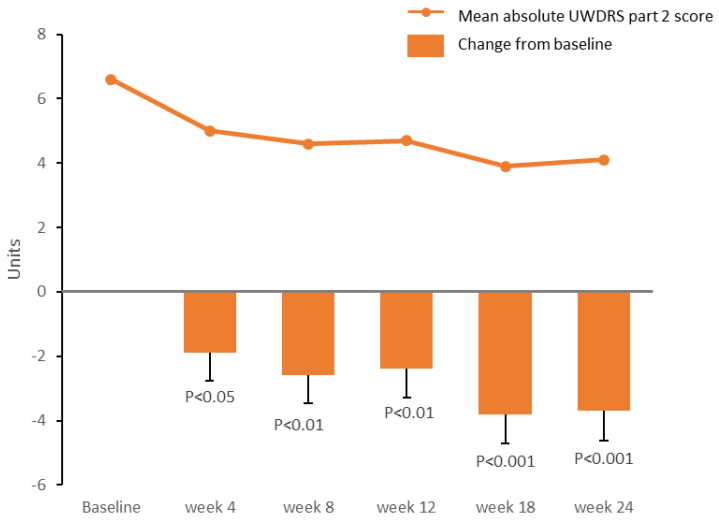
- Rapid improvements in $NCC_{corrected}$ with WTX101
  - Mean levels were within the upper limit of normal by week 12
- 71% of patients met the primary endpoint at week 24 ($P < 0.001$)
  - 57% achieved or maintained normalized levels of $NCC_{corrected}$
  - 14% had ≥ 25% reduction in $NCC_{corrected}$ from baseline
- Overall, mean $NCC_{corrected}$ was significantly reduced by 72% at week 24 vs baseline ($P < 0.0001$)



Change from baseline data are least squares mean (LSM) ± standard error (SE) for 23 to 25 patients at each time point.
P values vs baseline.

Improvements in Neurological Disability

- Unified Wilson Disease Rating Scale Part 2 can be used to measure patient-reported disability in Wilson disease[1]
  - Based on elements of the Barthel Index
- With WTX101, there were significant improvements in UWDRS Part 2 score at week 24 vs baseline (P < 0.001)

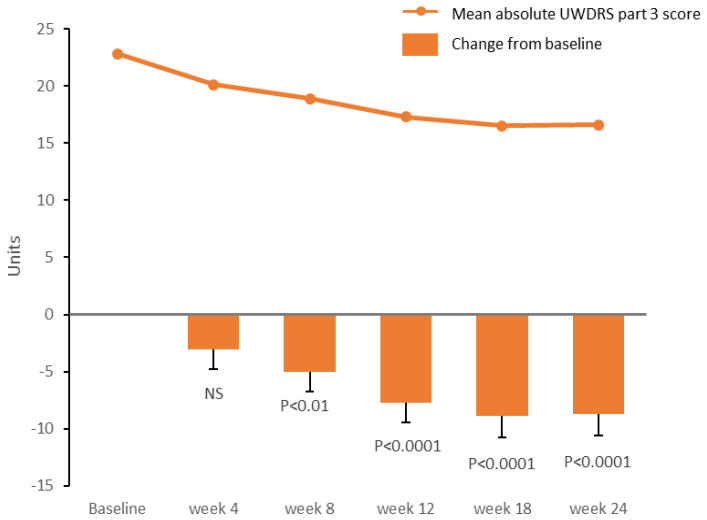


Change from baseline data are LSM ± SE for 21 to 28 patients at each time point.
P values vs baseline.

1. Członkowska A et al. *Neurol Neurochir Pol*. 2007; 41: 1-12.

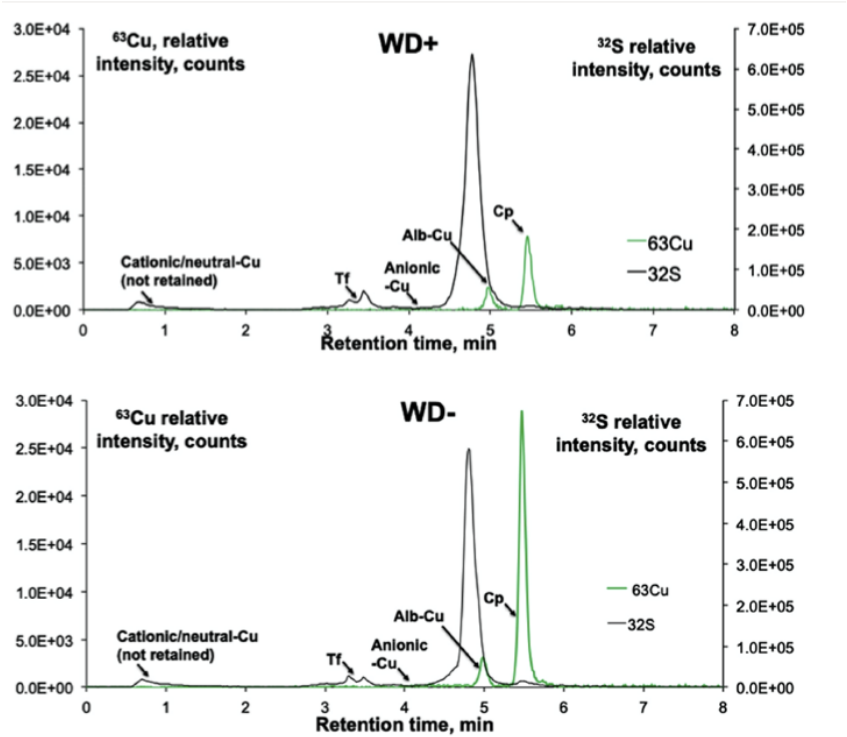
Improvements in Neurological Status

- Unified Wilson Disease Rating Scale Part 3 is a composite clinical score to assess neurological status in Wilson disease[1]
  - Scale ranges from 0 (no impairment) to 143 (maximally impaired)
- With WTX101, there were significant improvements in UWDRS Part 3 score at week 24 vs baseline (P < 0.0001)
- No paradoxical neurological worsening attributed to the study drug was observed



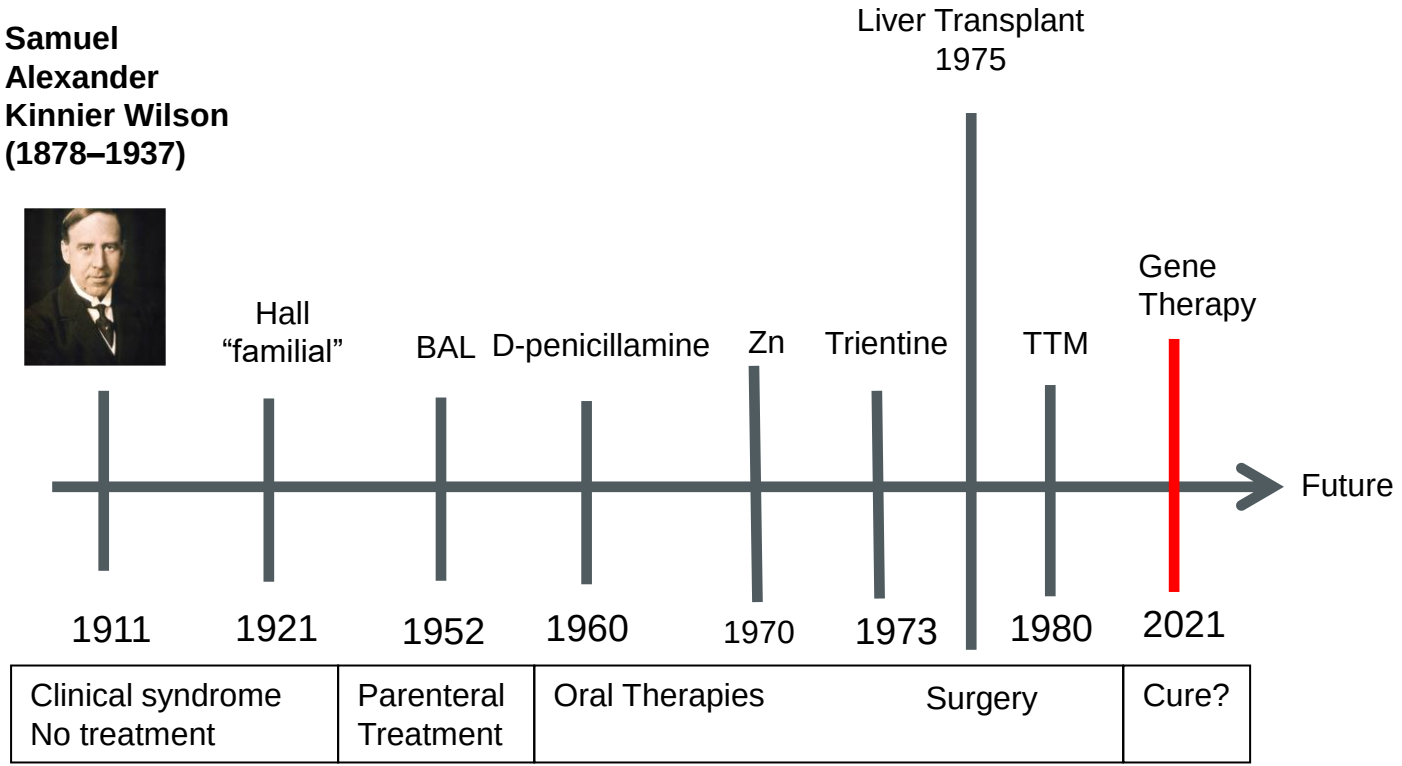
NS, not significant.
Change from baseline data are LSM ± SE for 21 to 28 patients at each time point.
P values vs baseline.

1. Członkowska A et al. *Neurol Neurochir Pol*. 2007; 41: 1-12.



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; 1098: 27-36.

Timeline: Treatment of Wilson Disease



Summary

- Medical treatment is effective for most patients with Wilson disease, but is life-long
- Pre-emptive treatment prevents disease manifestations
- Symptomatic patients are treated with chelation or combination therapy, asymptomatic and maintenance therapy for patients with reduced dosage chelation or zinc salts
- Phase 3 data are being analyzed to determine if TTM is non-inferior or superior to current standard of care for WD
- Gene therapy studies are beginning, and may open the door for a “cure” for WD

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