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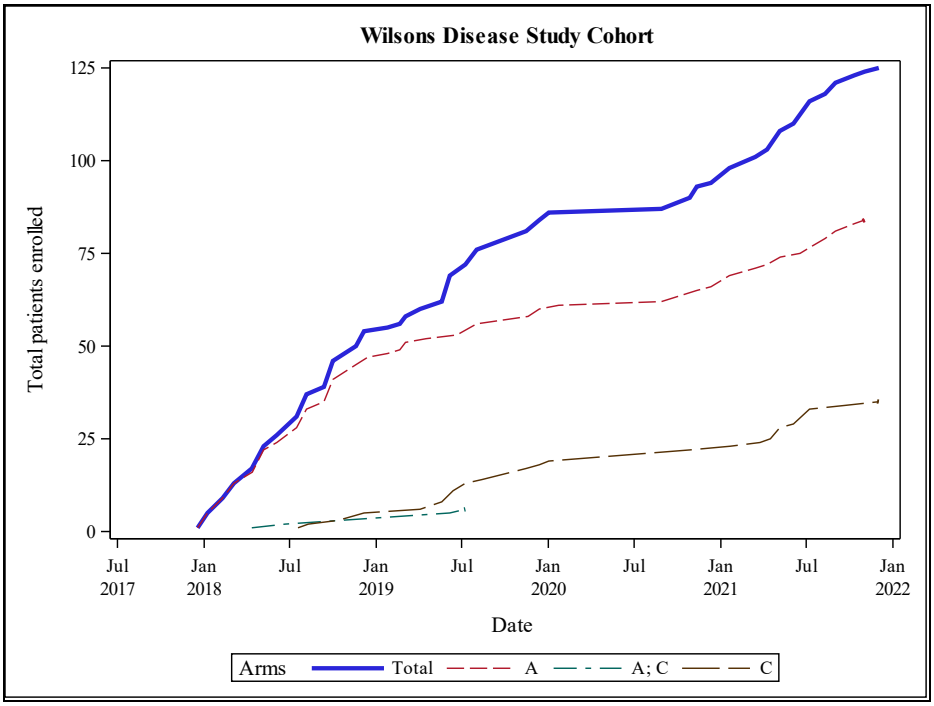
Dear Wilson Disease Association Board Members,

We would like to again thank you for your support for the Wilson Disease Registry (WDR) Study as we welcome the new year, 2022. This year marks the beginning of the fourth year of the opening of the registry at Yale, but many of our other site openings were staggered. This, along with the current pandemic due to SARS-COV2 accounted for the delay in achieving initial enrollment targets. Despite these challenges we are reaching important thresholds – we enrolled over 30 pediatric patients and are approaching the 40th pediatric enrollment. As we discussed at the recent Board meeting, we view this work on pediatric patients as a very important part of our overall mission. This work will help to define the diagnostic challenges and natural history of the youngest Wilson disease patients. A subgroup was formed to analyze the initial data and will report on their findings in a future publication. In addition, we have examined liver tests at enrollment into the study of our adult registrants and found that a surprising number of individuals have abnormal liver tests despite many years of therapy. We will begin to explore this further by taking a deeper dive into the data. We are analyzing the use of the modified neurologic rating scale and the current UWDRS scale used in the study, and presentations and a manuscript is expected for this in the coming months. Our collaborative work goes on with the metal analysis laboratory run by Chris Harrington in Surrey, UK, and we hope to share more of the findings in the coming year. The following is a more detailed description of the activities for the registry project:

As of December 6, 2021, the number of subjects enrolled to the Wilson Disease Registry Study in four national and two international sites reached 125. Despite the hindering effect of the COVID-19 pandemic, since January 2021 we enrolled 33 new patients (20 adults and 13 children) and completed return visits for 56 subjects. Out of 125 subjects, 4 patients were discontinued for follow up. One is deceased, one received a liver transplant, and two withdrew their consent.



The demographic and study site locations for our registry patients are shown below:

Gender				
GENDER	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Female	59	47.20	59	47.20
Male	66	52.80	125	100.00

	N	Mean	Std	Min	Max
Age at On Study	125	30.91	19.05	0.00	74.00
Age of diagnosis of Wilson disease	122	16.48	12.37	0.00	64.00
Leipzig Score	121	6.78	2.95	0.00	13.00

*(Leipzig Score > 4 is criteria for diagnosis of Wilson disease and study entry.)

Study Site				
STUDY SITE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Baylor College of Medicine	11	8.80	11	8.80
Florida Hospital	12	9.60	23	18.40
Heidelberg University Hospital, Germany	10	8.00	33	26.40
Seattle Children's Hospital Research Institute	2	1.60	35	28.00
University of Surrey	5	4.00	40	32.00
Yale University	85	68.00	125	100.00

The return rate among our study participants remains excellent, however there were disruptions in follow-up due to COVID-19 restrictions in access to the study sites. The table below shows the number of follow up visits per pediatric (C) and adult (A) study subjects stratified by their time (months) following enrollment (12, 24 and 36 months). Those marked A;C began as pediatric and transitioned to adult subjects.

Table of LAST VISIT by ARMS				
Last Visit	Arms			
Frequency	A	A; C	C	Total
EOS	2	0	0	2
Enrollment	26	0	18	44
M12	13	2	7	22
M24	13	2	7	22
M36	30	2	3	35
Total	84	6	35	125

Shown are the numbers of patients removed from the study, and these number 4 (3.2%).

Table of CURRENT STATUS by ARMS				
Current Status	Arms			
Frequency	A	A; C	C	Total
EXPIRED	1	0	0	1
OFF STUDY	3	0	0	3
ON STUDY	80	6	35	121
Total	84	6	35	125

Serum copper analysis: Dr. Harrington's group recently developed an approach for the determination of the main copper protein, ceruloplasmin, which uses a separation method joined to a measurement instrument. In the publication, we highlight a new, dependable indicator, for the clinical management of Wilson disease, the 'accurate non-ceruloplasmin bound copper' concentration. We think this will help clinicians in the diagnosis and treatment of patients, and it is also scheduled to be used in some clinical trials of new drug treatments. The manuscript on their work is in preparation and will be submitted to will be submitted early next year to Clinical Chemistry.

ATP7B mutation analysis: We are continuing to make sure that all of our patients have analysis for ATP7B mutations. This will be helpful in our analysis of use of the Leipzig criteria for diagnosis and allows correlation with patient phenotype in the future.
Cirrhosis assessments: As a part of our efforts to develop a more standardized patient evaluation, we created a cirrhosis assessment form that is to be completed by site investigators based on study participants data at the time of their enrollment visit. We have completed cirrhosis assessments for 121 study subjects and are using this to aid data analysis.

Pathology review of the available biopsy specimens: We created a detailed pathology review form that included an in depth and systematic assessment of available study subject liver biopsy specimens. Initially, we used this form to evaluate 5 liver biopsy samples available at the Yale Pathology repository. Currently, we are exploring how to access available samples from other study participants and complete a uniform assessment by our pathologist at Yale, Dr. Ilke Nalbantoglu. We are currently expanding access to this assessment to enrollees at all external sites.

Neurology: modified UWDRS: As a part of the patient evaluation in the study, we video record their neurologic examinations. Twenty-two of these video recordings were shared (after additional consent was obtained) for review and application of the UWDRS and modified UWDRS score by six expert neurologists across the globe in a blinded fashion. Analysis of their assessments will help to develop a more accurate neurological assessment tool for WD. This work in progress is being led by Dr. Amar Patel at Yale.

Pediatric: We enrolled 41 pediatric patients. The age at enrollment varied between 4 months to 17 years. Six of these study subjects reached age 18, their age of consent, and transitioned from the pediatric to the adult cohort. The Pediatric writing group to report on data from this unique cohort had its first meeting on December 6th and will be coordinating their data needs with our statistician at Yale.

Pregnancy: Three patients in the registry became pregnant, and hopefully will be able to report on their outcomes in the near future.

Age 65+: We have 5 patients enrolled at age 65 or older (an additional 4 reached age 65 while in the study).

Scientific Collaboration(s)
Our specimens continue to be used for studies by the Harrington laboratory in Surrey, UK and by the Hahn laboratory in Seattle Children's for ongoing work.
Specimens from the serum repository were sent for study to Clavia Ruth Wooton-Kee, Ph.D., Assistant Professor of Pediatrics-Nutrition, Molecular and Cellular Biology at the Baylor College of Medicine who is studying the protein GDF-15 as a marker of inflammation.

National and international presentation of data from the registry
Our investigators presented our findings at national and international conferences in Europe and the US. Dr. Schilsky presented data on the registry enrollment at a virtual meeting of the British

Association for the Study of Liver. Dr. To presented data on liver tests as an e-poster presentation Available abstracts and publications will be made available to the WDA web site.

Article(s) published in peer-review journal(s):
Christopher J. Collins, Fan Yi, Remwilyn Dayuha, Phi Duong, Simon Horslen, Michelle Camarata, Ayse K. Coskun, Roderick H.J. Houwen, Tudor L. Pop, Heinz Zoller, Han-wook Yoo, Sung Won Jung, Karl H. Weiss, Michael L. Schilsky, Peter Ferenci, Si Houn Hahn, Direct Measurement of ATP7B Peptides Is Highly Effective in the Diagnosis of Wilson Disease, Gastroenterology, Volume 160, Issue 7, 2021, Pages 2367-2382.e1, ISSN 0016-5085, https://doi.org/10.1053/j.gastro.2021.02.052.
(https://www.sciencedirect.com/science/article/pii/S0016508521004571

Camarata MA, Ala A, Coskun AK, Deng Y, Gonzalez-Peralta RP, Maciejewski KR, Patel A, Rubman S, To U, Tomlin R, Schilsky ML, Zimbrean PC. The Effect of Mental Health, Neurological Disease, and Liver Disease on Quality of Life in Patients With Wilson Disease. J Acad Consult Liaison Psychiatry. 2021 Sep-Oct;62(5):528-537. doi: 10.1016/j.jaclp.2021.04.004. Epub 2021 May 25. PMID: 34044196.
Manuscripts in preparation (and investigator lead authors):

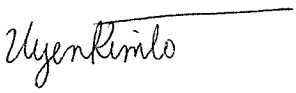
Harington: Accurate NCC and validation studies
Patel: UWDRS and modified UWDRS; interobserver validation
Zimbrean: Major depressive disorder and Wilson disease
Valentino and Gonzalez: Pediatric Wilson disease, characterization of our cohort

Abstract: AASLD meeting November 2021:
Title: Patterns of ALT and AST in adult patients with treated Wilson Disease: Results from a multi-site registry.

Oral presentation: European Association of Psychosomatic Medicine conference in June 2021

Title: Bipolar disorder in patients with Wilson Disease

Michael L. Schilsky. MD
Principal Investigator



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