

August , 2018

Wilson Disease Registry Progress Report

The launch of the Wilson Disease registry began at Yale University in December 2017. Enrollment of both adult and pediatric subjects has been steady and we will be expanding over the next year to become a multi-site international study involving at least four centers in the United States and one in the United Kingdom. We are currently working with colleagues at Michigan, Royal Surrey (UK), Baylor Houston, Seattle Children's Hospital to prepare for their future launches.

Objective of Research:

A registry study is a particularly valuable research tool for rare diseases such as Wilson disease because it pools together patient data from multiple centers and provides the study with a larger number of patients than would otherwise be available from a single site. Larger numbers of patients are required for statistical analysis to achieve meaningful results. In addition to capturing initial information when patients first participate in the registry, we are prospectively collecting data over several years. A prospective ongoing data collection performed in a uniform and pre-prescribed manner will help reduce bias and improve the quality of results.

The aims of our study are as follows:

Aim 1. Study the natural history of a carefully characterized cohort of patients with WD followed longitudinally at Centers of Excellence for WD in the United States and in the UK.

Aim 2. Evaluate parameters for diagnosis and treatment monitoring for patients on chelation therapy and zinc treatment for their WD.

Aim 3. Determine whether a composite index or a biomarker can be used as a surrogate marker for treatment monitoring for current patients on therapy that can be used for future patient treatment trials.

Alongside data collection, blood specimens are being accrued in a repository for genetic studies and copper analysis to aid future investigators with research on Wilson Disease.

Progress Summary/Accomplishments:

- **Design of the OnCore database to host the Wilson Disease Registry study**

We have carefully designed and built the Wilson Disease registry using an online platform called OnCore. In the planning stages we had meetings with a multi-disciplinary team of physicians at Yale— hepatologists, psychiatrists, neurologists as well as pediatric subspecialists to design registry study questions that capture important data elements. We have also selected assessment tools to prospectively evaluate patients including liver scores, neurological scores and psychiatric assessment tools. We have worked closely with an OnCore systems programmer assigned to our project to design and build the database to reflect the information that requires capturing and allow data to be exported to allow future statistical analysis and

evaluation of results. This database has been finetuned throughout the course of the study to ensure data capture is accurate and complete prior to multi-site activation.

- **Design of a Manual of Operations and Procedures to ensure standardized data collection across multiple sites**

To ensure data is collected in a standardized fashion when multiple sites across the United States and in the UK become active we have designed a manual of procedures and operations at the central coordinating site, Yale. The manual includes essential information including, aims and objectives, site activation procedures and training, data collection protocols and methods, monitoring plans, laboratory procedures and protocols and procedures for material collection and shipments. A prospective ongoing data collection performed in a uniform and pre-prescribed manner will help reduce bias and improve the quality of results.

We have continued to update the protocol and manual of procedures and refined the pediatric protocol with support from our pediatric neurologist and pediatric hepatologists to capture assessments using validated measures to target the needs of adolescents and young children. We have included the use CBCL for mental health evaluation, PSOM SNE 0-2 and PSOM SNE >2 for neurological evaluation alongside the UWDRS when able in those age > 6 years of age. We have also included the PEDs-QL for quality of life measurement in children which will be performed alongside the SF-12 when pediatric patients transition into the adult arm of the study.

- **Creation of a Biorepository of Genetic and Copper Specimens**

Alongside data collection, blood specimens are being accrued in a repository for genetic studies and copper analysis to aid future investigators with research on Wilson Disease and lead to more accurate monitoring of treatments.

Samples from patients at the Yale site, with consent, have also been used to prepare blood spots and these have been sent for analysis to the the laboratory of Dr Sihoun Hahn in Seattle who is conducting a study on advanced diagnostic testing for Wilson disease.

To create a bio-repository we have worked with the OnCore team to create specific labels for samples that enable tracking as they are moved into storage and from storage to processing at external sites. DNA from the initial six month sample collection has been extracted locally and stored. We are aiming to batch ship samples to Seattle for mutation analysis and to Surrey, UK for copper analysis by the end of the month once appropriate contracts/material transfer agreements are in place.

- **Recruitment of Wilson Disease patients**

Alongside the development of the registry and biorepository, recruitment of Wilson Disease patients during clinics and through the creation of web/email advertisements has been successful. The registry study has been introduced to patients at Wilson Disease clinics and questions and concerns addressed. Consent forms and study coordinator contact details have been distributed. Patient contact details of interested patients were also collected to facilitate future enrollment. In addition a presentation at the Wilson Disease Association annual conference helped inform patients of the progress of the study and contacts of interested patients were collected as well as information on what site was most local to them.

- **Enrollment to date and preliminary data**

As patients often travel from far and it is important to collect all data on the same day, coordination is key. Evaluation of patients who enter this study is comprehensive and includes a medical history review, a neurological examination, a hepatologic evaluation and psychiatric assessments. The equivalent pediatric specialists are involved in assessing children. We started adult enrollment in December and have enrolled 37 adult patients to date. We have been enrolling pediatric patients since April and have enrolled 4 patients to date (age range 1-16 years).

Recruitment:

Interested participants locally: 83

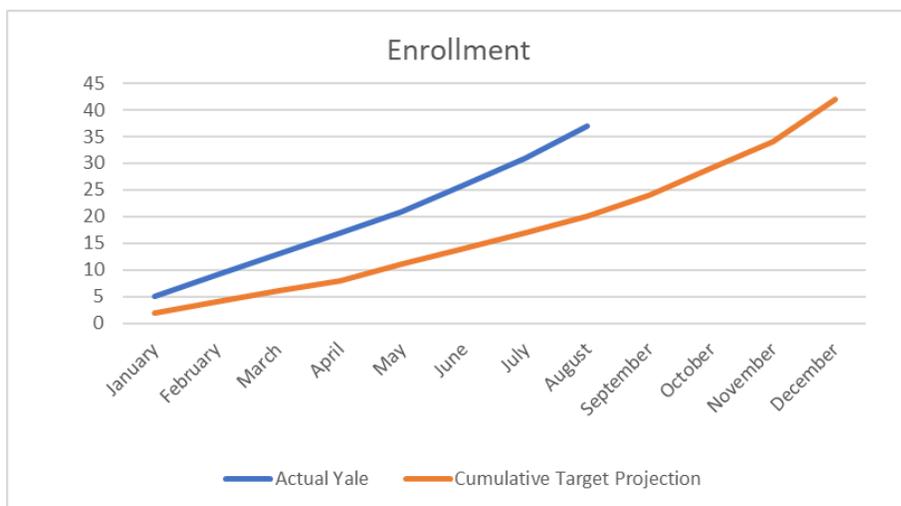
Interested participants other US sites: 41

Interested participants abroad: 9

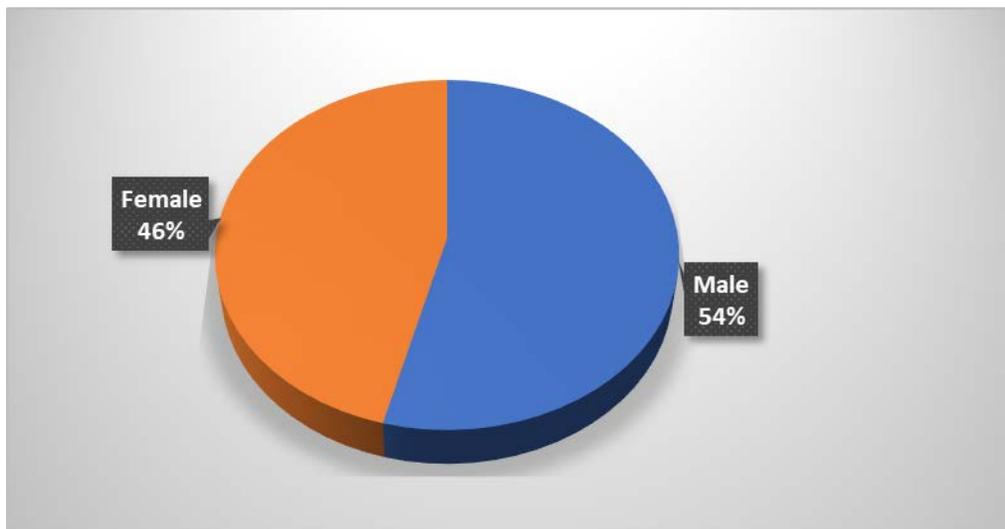
Enrollment:

Adult: 37

Pediatric: 4

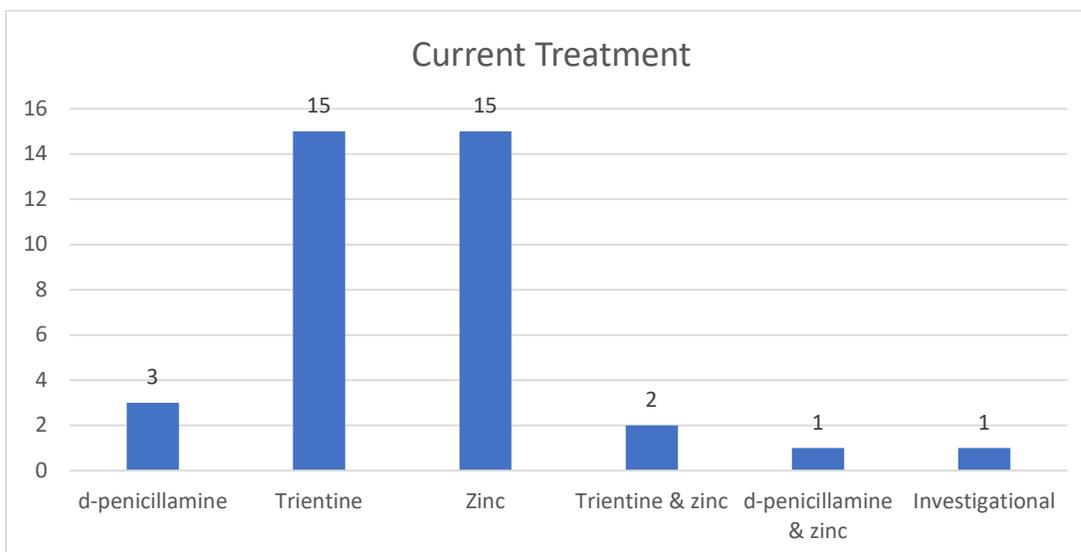


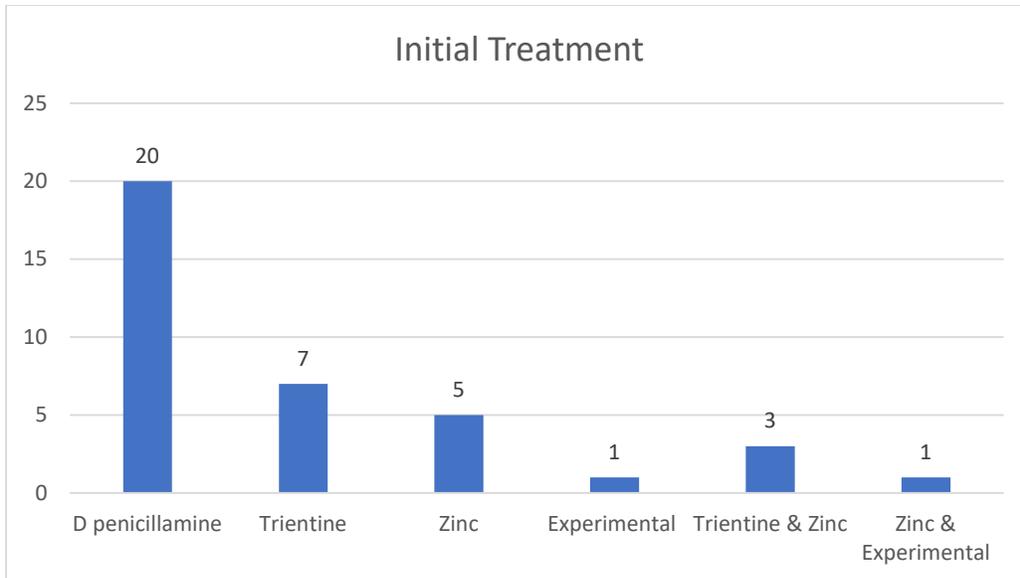
Demographics:



Mean age at enrollment mean 41 (range 1-73)

Age at diagnosis 19 (range 0-59)





- **Training and Support**

In the last month we have had a transition period for me to train the new study coordinator to use the OnCore database, recruit, enroll, process samples and develop an understanding of the sample workflow, tracking and storage space. In addition, I have provided support to other sites who are in the process of becoming active providing our IRB approved study documents, protocols and advertisements for reference and reviewing their IRB study documents and protocol drafts. I have created training materials for use for future study coordinators at the DCC at Yale and training materials to help other sites becoming active to facilitate the onboarding process.

Future Activities:

- **Projected Annual Enrollment:**

Adult: 48 patients

Pediatric: 12 patients

Study Site	Principal Investigator
Yale (site and DCC)	Michael Schilsky MD
University of Michigan	Frederick Askari MD
University of Surrey, UK	Aftab Ala MD PhD
Baylor Houston	Tamir Miloh MD
University of Washington/Seattle Children's Hospital	Sihoun Hahn MD PhD
Florida Hospital	Regino P. Gonzalez-Peralta, MD

- **Timetable for initiation of all sites in 2018/2019**

Site activation	Active	October*	October	October	January	July
						
Study Site	Yale University	University of Michigan	University of Surrey, UK	Baylor Houston	Seattle Children's Hospital	Florida Hospital

* Adjusted from April 2018 to Oct 2018 due to logistical hurdles at the site.

Other work:

- Analysis of acute liver injury and Wilson Disease
- Analysis of zinc treatment for Wilson Disease

Presentations:

- WDA conference, Houston, April 2018: Wilson Disease Registry Update
- BASL Wilson Disease Specialist Interest Group meeting, June 2018: Wilson Disease Registry progress and future targets.

Future Presentations:

- AASLD poster presentation: Outcomes of Acute Liver Injury (ALI) in Adults Due to Wilson Disease: Is Survival without Transplant Possible?
- BASL poster presentation: Outcomes of Acute Liver Injury (ALI) in Adults Due to Wilson Disease: Is Survival without Transplant Possible?
- BASL poster presentation: Maintenance Therapy for Wilson Disease with Zinc: A Comparison between Zinc Acetate and Alternative Zinc Salts

Manuscripts accepted for publication:

- Update on Wilson's disease: focus on WTX-101 – Drugs of the Future
- Prospects for Cure in Wilson Disease

Manuscripts in preparation:

- Maintenance Therapy for Wilson Disease with Zinc: A Comparison between Zinc Acetate and Alternative Zinc Salts
- Outcomes of Acute Liver Injury (ALI) in Adults Due to Wilson Disease: Is Survival without Transplant Possible?

In Press:**Book chapters**

- Michelle Camarata and Michael L. Schilsky (2018); Transplantation considerations in Wilson Disease. In *Wilson Disease: Pathogenesis, Molecular Mechanisms, Diagnosis, Treatment and Monitoring*. Elsevier
- Michelle Camarata, Karl Heinz Weiss and Michael L. Schilsky (2018); Special considerations in Wilson Disease. In *Wilson Disease: Pathogenesis, Molecular Mechanisms, Diagnosis, Treatment and Monitoring*. Elsevier
- Michelle Camarata and Aftab Ala (2018); Diagnostic workup; In *Wilson Disease: Pathogenesis, Molecular Mechanisms, Diagnosis, Treatment and Monitoring*. Elsevier

- Michelle Camarata and Regino P. Gonzalez-Peralta (2018); Unique Pediatric Aspects of Wilson Disease; In Wilson Disease: Management of Wilson Disease: A Pocket Guide. Springer
- Michelle Camarata and Michael L. Schilsky (2018). Treating other Symptoms of Wilson Disease: The Liver. In Management of Wilson Disease: A Pocket Guide. Springer
- Michelle Camarata, Michael L. Schilsky (2018); Wilson disease: Special Circumstances. In Management of Wilson Disease: A Pocket Guide. Springer
- Michelle Camarata and Sihoun Hahn (2018); The Genetics of Wilson disease. In Wilson Disease: Pathogenesis, Molecular Mechanisms, Diagnosis, Treatment and Monitoring. Elsevier