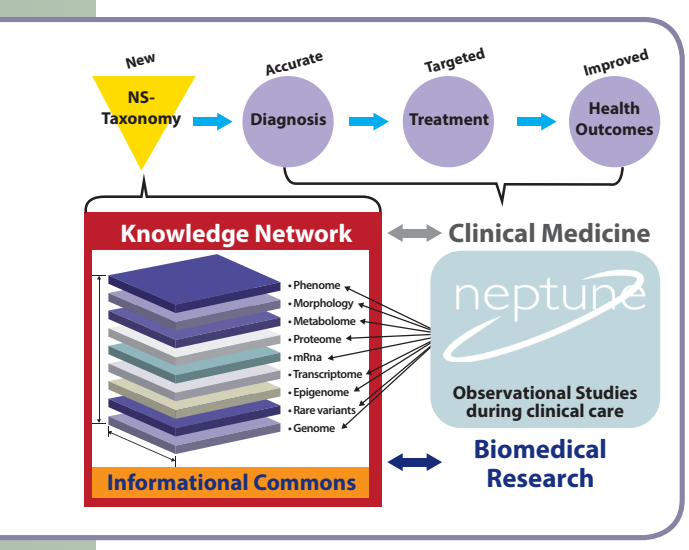
The Nephrotic Syndrome Study Network: A Rare Disease Network for Precision Medicine in Nephrotic Syndrome

By John Sedor, Matthias Kretzler, and Denise L. Taylor-Moon

The main goal of the Nephrotic Syndrome Study Network, NEPTUNE, is to build a translational research infrastructure for diseases manifesting as nephrotic syndrome (NS), which includes focal and segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and membranous nephropathy (MN) (1). The network of investigators from 21 academic centers across the United States and Canada, and two patient interest groups, the NephCure Foundation and the Halpin Foundation, have worked closely together to study these rare glomerular diseases. Despite their rarity, these diseases generate enormous individual, societal, and economic burdens. The current classification of NS fails to capture the molecular bases of these diseases and consequently does not adequately predict either their natural history or their response to therapy. Given our limited understanding of MCD, FSGS, and MN biology and our inadequate classification system, it is not surprising that our therapeutic approach to these diseases is also imperfect. No new therapeutic targets have been validated by clinical trials for two decades, and current therapies rely almost exclusively on immunosuppression, which is used without a clear biological basis, is often not beneficial, and is frequently complicated by significant toxicities (2).

Given these shortcomings, basic science, translational, and clinical studies are needed that address the serious obstacles to providing effective care for the MCD, FSGS, or MN patient. NEPTUNE was funded in 2009 as part of the Rare Disease Clinical Research Networks with support from the National Institutes of Health and the NephCure Foundation to overcome the major barriers impeding the design of NS clinical trials. NEPTUNE is implementing the concept of precision medicine proposed by the Institute of Medicine in 2011 (3) (Figure 1). Precision medicine aims for the development of new disease definitions to be informed by a comprehensive, multilayered analysis of the disease course in observational cohort studies. NEPTUNE is recruiting a core cohort of patients with NS and has generated datasets, which define the underlying genetic architecture and capture environmental exposures, unique molecular phenotypes, histopathology, and prospective clinical outcomes. This disease knowledge along the genotype–phenotype continuum is used by basic and clinical scientists to develop a knowledge network of NS that defines the diseases from molecular pathogenesis rather than from histopathologic patterns. The molecular disease definition (i.e., taxonomy) will allow more accurate diagnosis, which is a prerequisite for targeted treatments that improve health outcomes in NS (Figure 1).

Figure 1. Precision medicine in nephrotic syndrome (mod. National Research Council, 2011).



The NEPTUNE cohort studies were designed to generate multilayered data on the disease course encompassing the genotype–phenotype continuum and generating a NS informational commons as requested by the national academies (1). NEPTUNE has assembled to date more than 450 NS participants with biosamples for the generation of individual catalogues of genomewide variation based on whole genome sequences, renal biopsy sample–derived tissue transcriptomes, and urine and plasma proteomes. These datasets are augmented with digital histopathologic information from renal biopsy specimens (4), longitudinal clinical phenotypes, and patient-reported outcomes, which in aggregate will be used to develop the framework for discovering disease mechanisms, testing biomarkers, and designing trials that integrate outcomes important to patients. In parallel, NEPTUNE is developing innovative tools for collaborations in molecular medicine. A web-based data sharing and analysis platform (Nephromine, www.nephromine.org) will allow the scientific community to link biopsy sample–derived gene expression datasets with predefined clinical parameters. Additional approaches for collaborative data mining and analysis are developed with the aim to establish the informational commons in NS research around the comprehensive clinical and molecular information.

NEPTUNE has extensive pilot, ancillary, and training programs open to the international scientific community to leverage its samples and core data for additional projects that will expand the knowledge base in the NS informational commons. NEPTUNE has supported and is closely linked with parallel efforts in Europe, China, India, and sub-Saharan Africa. Together with its international partners, NEPTUNE has established a joint systems biology core for analyses across disciplines and continents. Additionally, NEPTUNE is facilitating investigator- and industry-led clinical trials of targeted treatments in NS from trial design to implementation, using its clinical research network for effective recruitment of rare glomerular disease (i.e., MENTOR [Membranous Nephropathy Trial of Rituximab] and DUET, clinical trials No. NCT01180036 and No. NCT01613118).

Over the past 4.5 years, NEPTUNE has developed an investigative infrastructure that has established an observational longitudinal cohort of more than 450 incident adult and pediatric patients, allowing for standardized collection of renal biopsy tissues, blood and urine, comprehensive patient history, associated clinical data, and standardized measures of psychosocial well-being. Ongoing recruitment will further grow this unique cohort, and interested patients can be referred to NEPTUNE centers (see https://rarediseasesnetwork.epi.usf.edu/NEPTUNE/centers/index.htm for recruitment centers and investigators). This resource is available to all interested research investigators through ancillary studies to benefit the advancement of care of patients with FSGS, MCD, and MN. It is already used in more than 30 approved ancillary studies ranging from methods development to phase II clinical trials. For further information on available datasets and access, see http://www.neptune-study.org/.

With the joint support and participation of patients, the patient interest group NephCure, clinicians, clinician scientists, and bench researchers from academia and industry, therapeutic targets are now identified and can effectively be moved through a translational research pipeline for evaluation in NS patients.

Please contact the NEPTUNE investigators at neptunearc@umich.edu if you are interested in using or contributing to NEPTUNE.

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