

Rationale and design of the Nephrotic Syndrome Study Network (NEPTUNE) Match in glomerular diseases: designing the right trial for the right patient, today



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Glomerular diseases are classified using a descriptive taxonomy that is not reflective of the heterogeneous underlying molecular drivers. This limits not only diagnostic and therapeutic patient management, but also impacts clinical trials evaluating targeted interventions. The Nephrotic Syndrome Study Network (NEPTUNE) is poised to address these challenges. The study has enrolled >850 pediatric and adult patients with proteinuric glomerular diseases who have contributed to deep clinical, histologic, genetic, and molecular profiles linked to long-term outcomes. The NEPTUNE Knowledge Network, comprising combined, multiscale data sets, captures each participant's molecular disease processes at the time of kidney biopsy. In this editorial, we describe the design and implementation of NEPTUNE Match, which bridges a basic science discovery pipeline with targeted clinical trials. Noninvasive biomarkers have been developed for real-time pathway analyses. A Molecular Nephrology Board reviews the pathway maps together with clinical, laboratory, and histopathologic data assembled for each patient to compile a Match report that estimates the fit between the specific molecular disease pathway(s) identified in an individual patient and proposed clinical trials. The NEPTUNE Match report is communicated using established protocols to the patient and the attending nephrologist for use in their selection of available clinical trials. NEPTUNE Match represents the first application of precision medicine in nephrology with the aim of developing targeted therapies and providing the right medication for each patient with primary glomerular disease.

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KEYWORDS: clinical trials; disease pathway; patient communication

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Nephrotic syndrome (NS) comprises focal segmental glomerular sclerosis (FSGS), minimal change disease, and membranous nephropathy, which are rare glomerular diseases associated with debilitating complications, including possible progression to kidney failure. Despite similar and overlapping symptoms (e.g., edema, proteinuria, and loss of kidney function), individual clinical courses can vary markedly. The only US Food and Drug Administration–approved medical treatments are corticosteroid-based immunosuppressive agents (i.e., prednisone and adrenocorticotropic hormone) that cause severe adverse effects. Off-label use of second-line

immunosuppressive medications is currently part of guideline-based clinical care.

The clinical, histopathology-based taxonomy of NS fails to capture the underlying molecular drivers of these diseases (Figure 1). Consequently, current diagnostic categories have limited use in either predicting the disease course or responding to therapy, frequently putting patients at risk of adverse effects from treatments that prove ineffective. In addition, clinical trials in NS enroll an unstratified, biologically diverse group of individuals. This underlying mechanistic heterogeneity often results in inconclusive trial outcomes, even though the intervention may successfully target a subset of susceptible patients.

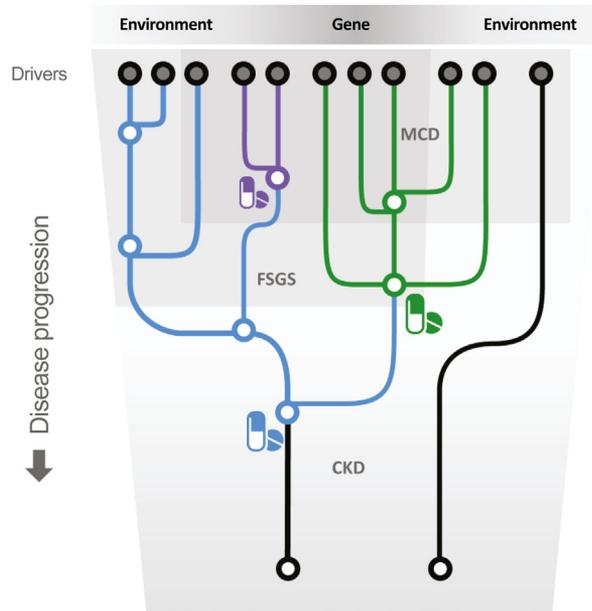


Figure 1 | Nosology of nephrotic syndrome based on an integrative view of disease pathways. Disease initiation by interaction of gene and environmental causal factors (filled circles) combined with disease progression factors (open circles) lead to chronic kidney disease (CKD) via progressive loss of kidney function. The current descriptive diagnostic categories, like focal segmental glomerular sclerosis (FSGS) and minimal change disease (MCD), show significant overlap in underlying mechanism of disease initiation and progression. Current and future therapies can target disease-initiating or progression pathways in glomerular diseases.

NEPTUNE

The Nephrotic Syndrome Study Network (NEPTUNE) was developed to define the molecular mechanism of NS for targeted therapeutic interventions. NEPTUNE follows the natural history of patients and aims to improve the diagnosis, management, and treatment of NS using innovative research strategies¹ (Figure 2). Participants are enrolled into NEPTUNE at the time of a diagnostic kidney biopsy or at initial presentation of disease for pediatric patients for whom a biopsy is usually not clinically indicated. In the

biopsy cohort, an extra core of kidney tissue is obtained during the clinically indicated procedure for research studies. Blood and urine specimens, along with clinical data, are collected prospectively every 4 to 6 months for up to 5 years. NEPTUNE has recruited a prospective longitudinal observational cohort of 861 patients with proteinuric, glomerular diseases who have contributed deep clinical, histologic, genetic, and molecular data as well as profiles of their long-term outcomes under standard care or in independent clinical trials. A key component of NEPTUNE that was

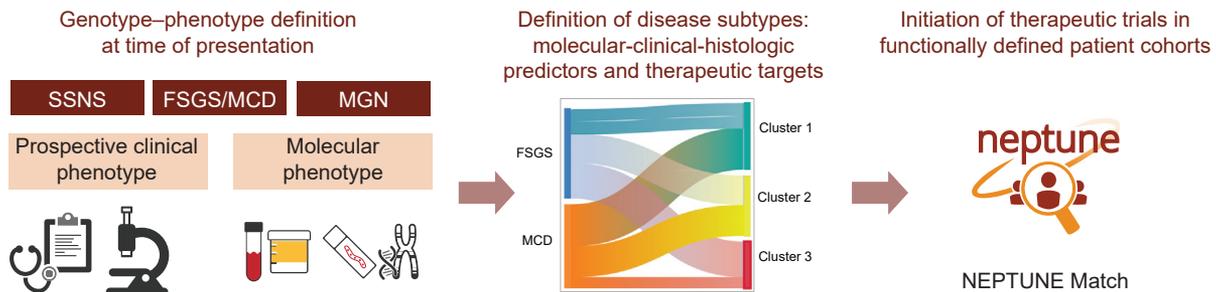


Figure 2 | Three-step approach to developing the Nephrotic Syndrome Study Network (NEPTUNE) framework to test precision medicine in nephrotic syndrome. Step 1: establishment of a knowledge network for comprehensive and prospective disease phenotypes. Step 2: definition of mechanistic disease subtypes using diverse data for patient segmentation via genetic-molecular-clinical-histology data layers. Step 3: mapping pathways targeted in ongoing and future trials to patients’ molecular activation profiles to match patients to trials. FSGS, focal segmental glomerular sclerosis; MCD, minimal change disease; MGN, membranous glomerulonephritis; SSNS, steroid-sensitive nephrotic syndrome.

established at its inception was the creation of a dedicated biorepository for long-term storage of the full range of biospecimens collected from each participant.¹

NEPTUNE has continuously enhanced its ability to derive multiscale data sets robustly and efficiently from the clinical data and biosamples contributed by study participants. This effort has been conducted through approved ancillary studies that leverage the Biorepository and tranSMART database. For example, capture of environmental exposures and socioeconomic status is incorporated into prospective ascertainment of long-term outcomes relevant to glomerular diseases. Kidney biopsy tissue is used for a digital pathology-driven structural definition of the disease state,^{2–9} whole-genome sequencing,^{10–15} gene expression profiles from microdissected glomeruli and tubule-interstitial compartments,¹⁶ and single nuclear RNA sequencing.^{17–19} Blood- and urine-derived noninvasive proteomic and metabolomic biomarker profiles are mapped to transcriptomic signatures in the kidney.^{16,20–23} The heterogeneous information sources are carefully annotated in the NEPTUNE Knowledge Network for comprehensive mechanistic disease definitions. The NEPTUNE Knowledge Network is accessed by the kidney research community via a study-specific NEPTUNE tranSMART instance. Neptune tranSMART allows the user to explore diverse data sets in an intuitive data exploration framework with drag and drop functionality. The knowledge graph of currently 861 study participants includes comprehensive patient demographics, socioeconomic status, clinical disease course, biochemical measurements, glomerular disease-specific end points,¹ genotypes, glomerular and tubular gene expression data sets, blood and urine comprehensive (Somascan) and targeted (Luminex) proteomic data, blood and urine metabolomics profiles, and the NEPTUNE Digital Pathology Scoring System histology descriptors.⁵ Single nuclear gene expression profiles from more than a million nuclei can be mined in a NEPTUNE CellXGene instance, and kidney-specific expression quantitative traits can be obtained in the NephQTL server. More than 200 approved ancillary studies have used the NEPTUNE Knowledge Network in support of the international research efforts in glomerular diseases (for access, see www.neptune-study.org/ancillary-studies). The NEPTUNE research infrastructure has matured sufficiently so that each participant's data can be assessed, and

molecular profiles generated, in a timely manner, to generate a comprehensive molecular nephrology report for each patient that can be effectively communicated to him/her.

RATIONALE FOR MOLECULAR DISEASE DEFINITIONS IN NS

Defining NS in molecular terms is essential in precision medicine to identify appropriate therapeutic targets and improve clinical trial design. NEPTUNE investigators have had early success using multiple data domains to identify disease mechanisms activated in discrete subgroups of NS^{5,16} and in identifying variability in specific molecular pathway signals in patients with FSGS and IgA nephropathy.^{24,25} These have served as starting points for matching patients for targeted therapies and resulted in the first molecular stratified phase 2 trial active in NS (clinicaltrials.gov/NCT04009668).^{2,3}

THE NEPTUNE MATCH PRECISION MEDICINE FRAMEWORK

In recent years, in parallel with an improved understanding of disease pathogenesis, there has been a substantial increase in the number of clinical trials enrolling participants with NS. An evidence-based, scientifically informed clinical trials selection process for patients and providers will enhance the likelihood of successful outcomes across these trials. This requires not only the molecular disease definitions of NS applied to individual therapeutic targets in a given patient, but equally important the development of an effective communication strategy to inform participants of clinical trials that target mechanisms that may match their disease biology. The goal of NEPTUNE Match is to foster the implementation of precision medicine in NS, whereby the right trial is made available to the right patient at the right time.

To test if a precision medicine approach can be offered to patients with NS, the following 4 steps have been developed for NEPTUNE Match (Figure 3):

- Step 1: Generate individual noninvasive molecular disease profiles in NEPTUNE study participants in real time.
- Step 2: Match individual molecular disease profiles in the molecular nephrology board report with targets of ongoing NS trials.
- Step 3: Establish a communication framework to educate study participants of the

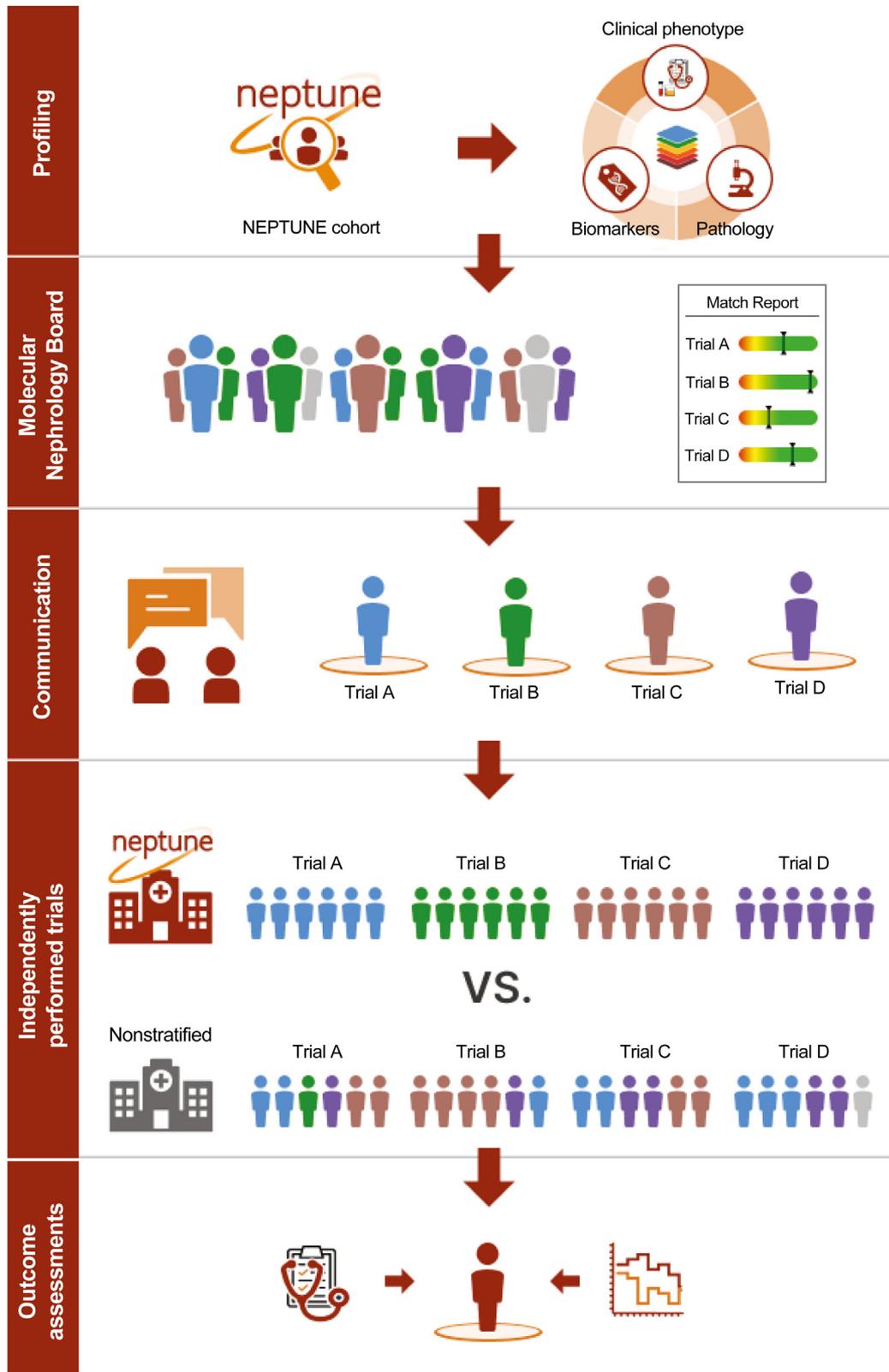


Figure 3 | Flow diagram of Nephrotic Syndrome Study Network (NEPTUNE) Match. The NEPTUNE knowledge network is used to establish a tissue-level target activation signature. Noninvasive biomarkers of the target activation signature are developed and tested in the available NEPTUNE sample repository. NEPTUNE study participants joining Match provide biosamples for biomarker profiling and adjudication of their signature in a trial-specific context. Target activation signatures are adjudicated by the Match Molecular Nephrology Board. Activation signatures for the participating trials are communicated to patients to aid in their selection of nephrotic syndrome trials. Outcomes are reported back by the independently executed trials to test for association with the Match activation signature.

Molecular Nephrology Board recommendation for targeted trial participation.

- Step 4: Compare retrospectively kidney health outcomes in NEPTUNE Match study participants versus trial subjects with misaligned or unknown match alignment.

Therapeutic biomarker identification and Match activity score development

A key prerequisite for NEPTUNE Match is the development of noninvasive predictive biomarkers representative of the activity of the specific disease pathways being targeted by the intervention. Predictive biomarkers can be used to develop trial-specific quantitative Match pathway activity scores. Match disease pathway activity scores can be derived from a spectrum of molecular changes in response to pathway activation or therapeutic intervention. Sources for the treatment response predictive biomarkers include the following: (i) literature-defined molecular pathway signatures linked to cause-and-effect transcriptional target activation¹⁶; (ii) *in silico* modeling of downstream transcriptional targets of a specific pathway²⁴; (iii) experimentally derived molecular signatures reflecting treatment responses in model systems (e.g., kidney, blood, or urine molecular profiles from preclinical murine, rat, cell culture, and organoid models) mapped back to human disease profiles in NEPTUNE; or (iv) molecular profiles from kidney, blood, or urine linked to clinically defined treatment responses obtained in early-stage proof-of-concept trials (phase 1b or phase 2a). The NEPTUNE Knowledge Network has annotated comprehensive clinical and molecular information of all NEPTUNE participants to aid in both target signature identification and noninvasive biomarker development. To date, the most effective strategy to define a target activation signature for Match uses gene expression profiles with a shared regulation between NEPTUNE kidney biopsy profiles and model systems, which are reversed to the healthy state by drug treatment. This target activation signature gene set is then analyzed across the cohort to define further associations with clinical or histologic baseline characteristics and outcomes (see the study by Mariani *et al.*¹⁶ for a representative example).

Transcripts and proteins comprising the target activation signature in kidneys are linked to proteomic and metabolomic profiles from blood and urine samples obtained at the time of kidney biopsy to identify noninvasive

surrogates of the activation signature. In the biomarker assay selection and development workflow, priority is given to candidate protein biomarkers in blood or urine showing robust correlation with the expression of corresponding genes or with the target activation signature in kidneys. Single-cell gene expression profiles provide expression distribution in kidney cells guiding selection of the biofluids for assay development (vascular expression toward plasma, and tubular expression toward urine as biomarker matrix). Biomarker assay selection, feasibility evaluation, validation, and optimization for specific biosamples follow standard protocols.^{26–28} Finally, the biomarker profiles across the NEPTUNE cohort samples are generated and used to build a predicting model of the kidney activity state. Models to date have been mainly composite of baseline clinical characteristics and a combination of urine and/or plasma protein biomarkers (for a representative example, see tumor necrosis factor (TNF) study design described below). Once a prediction model is generated and cross-validated, all baseline biosamples from patients in the cohort undergo retrospective biomarker profiling, and the distribution of the Match activity scores across the cohort is established. Individual patient noninvasive scores are assigned a rank among the pathway activation scores generated across the entire NEPTUNE cohort. The quartile rank of the predicted Match activity profile is then returned to the Molecular Nephrology Board and used to generate NEPTUNE Match reports that display the individual pathway activity level in relationship to the entire NEPTUNE patient population (Figure 3).

In a proof-of-concept study of this strategy, NEPTUNE investigators have studied TNF inhibitors in FSGS. In the FONT (Novel Therapies for Resistant FSGS) trial, a response to adalimumab, a monoclonal antibody to TNF, was observed in a limited subgroup of patients,^{29–31} resulting in an overall negative clinical trial outcome. To test the hypothesis that high kidney TNF activation might be a predictor of a favorable response to TNF inhibition, a TNF activation signature was obtained from NEPTUNE kidney biopsy gene expression profiles using transcripts known to be upregulated on TNF activation. The TNF-dependent differential gene expression of the activation signature was experimentally validated in kidney organoids.¹⁶ Podocyte and tubular cell compartment were identified as a site

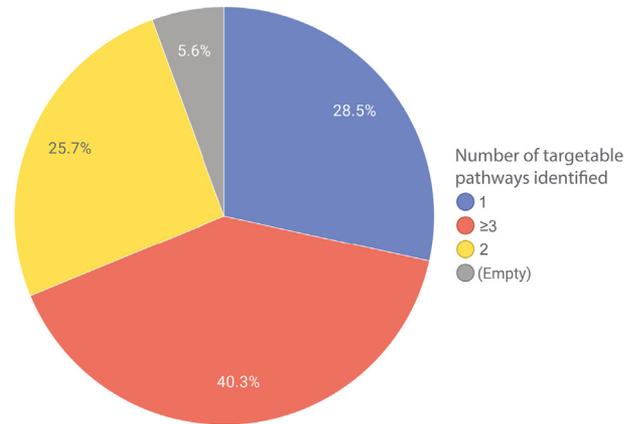


Figure 4 | Example of distribution of activation profiles in Match. Number of targetable mechanisms for a sample of Nephrotic Syndrome Study Network (NEPTUNE) participants (n = 85) with either minimal change disease or focal segmental glomerular sclerosis based on a combination of transcriptional “response” profiles and urine markers.

of differential gene expression of the TNF signature in NEPTUNE single-nucleus RNA-sequencing profiles. Tissue inhibitor of metalloproteinases 1 (TIMP1) and monocyte chemoattractant protein 1 were identified as urinary proteins with tight correlation to their corresponding kidney transcripts (normalized for urinary creatinine). A model using urinary monocyte chemoattractant protein 1 and TIMP1 together with estimated glomerular filtration rate and urine protein/creatinine ratio enabled prediction of TNF activity in kidneys with an area under the curve of 0.92.¹⁶ Elevated TNF activity assessment is being used as the primary inclusion criterion in an ongoing target engagement proof-of-concept trial in patients with FSGS (NCT04009668).

Currently, tissue-derived Match activity scores are linked to ongoing clinical development programs in NS for 4 studies. Each of these has customized Match activity scores and biomarker(s). For example, the combination of transcriptional “response” profiles and urine markers from targetable mechanisms met the criteria for at least 1 of the 4 mechanisms being assessed in 85 participants with either FSGS or minimal change disease (Figure 4).

NEPTUNE Match study design and implementation

Participation in NEPTUNE Match is open to all NEPTUNE participants. The roster of clinical trials included in NEPTUNE Match include investigator- and industry-initiated trials. By partnering with NEPTUNE Match, the investigators commit to returning trial data to NEPTUNE. Only clinical trials that investigate

therapeutic targets that are amenable to target-specific assessment and consistent with the molecular profiling abilities of the NEPTUNE Profiling Units are selected for inclusion.

NEPTUNE Match enrollment commences with informed consent describing risks and benefits of participating in Match. It is based on the following inclusion criteria:

- (i) Willing and able to consent, and as appropriate assent, to participate in NEPTUNE Match.
- (ii) Must be potentially eligible for the NEPTUNE Match partnering trials (e.g., if no trial is enrolling a participant aged <2 years, those aged <2 years are not eligible).

Step 1: generate individual noninvasive molecular disease profiles in NEPTUNE study participants in real time

Comprehensive data assessing the disease state of NEPTUNE participants are needed in real time. NEPTUNE Profiling Units for clinical phenotype and biofluid-based biomarker quantification have been established to rapidly evaluate participant clinical, histologic, and molecular data to generate patient-specific molecular pathway scores for timely review by the Molecular Nephrology Board.

Step 2: match individual disease processes with targeted interventions

The Molecular Nephrology Board reviews the information on the pathway activity scores provided by the NEPTUNE analytical units. Pathway activation of molecules targeted by clinical trials pursued in NS are reviewed for each participant. The proposed strength of the

match of each participant to each open trial is presented to the Molecular Nephrology Board for discussion. The Molecular Nephrology Board aggregates and assesses the participant-specific trial matching and provides input on the final participant-specific Match report.

The participant-specific Match report is then generated, indicating the pathway activation scores of the study participant relative to the overall NEPTUNE population in quartiles. The Match report provides this information for each clinical trial for which the patient qualifies, based on specific biomarkers.

Step 3: establish a communication framework to educate study participants of the Molecular Nephrology Board recommendation for targeted trial participation

Because the information contained in the Match report is experimental and not validated, effective communication tools are essential to inform study participants and NEPTUNE site investigators about the intent of the study and the experimental nature of the integrated analysis and the personalized output. An interdisciplinary team led by experienced health educators and genetic counselors, in collaboration with a patient advisory panel, has developed and implemented a communication strategy that combines tailored educational materials with training of NEPTUNE Match participating clinical site investigators. This strategy supports accurate interpretation and transmission of the NEPTUNE Match report to participants.

Communication content: Neptune Match Report. Key findings from the Molecular Nephrology Board trial matching analyses and deliberations are conveyed to study participants by way of the NEPTUNE Match Report. The report indicates the strength of matching to ongoing clinical trials, but also expresses the uncertainty and research origins of the information in the report. The creation of NEPTUNE Match Reports follows health education principles, including matching of content to patients' informational needs and health literacy levels, use of visual aids to clarify meaning of information, and avoidance of information overload of the participant.

Communication method. Before initiation of the NEPTUNE Match Report sharing, the Communication Team leads a training session for study clinicians-investigators to explain the information provided in the report and its implications for clinical trial decision-making

and patient care. Topics to be addressed in the training include an explanation of how trial matching information is derived, limitations of this information, strategies for effectively reinforcing key points, and guidance on how best to address likely questions from participants regarding the report.

The communication of the Match report may include the local clinician-investigator, study coordinator, and members of the communication team in addition to the adult patient/decision-making proxy for minor participants. This communication includes a review of the trial-matching assessment, patient/caregiver questions, initial teach back, and assessments of psychological distress. A telephone follow-up is scheduled 2 weeks after the initial visit to address any questions or concerns that the participant may have.

Communication assessment. During the communication interactions, participant/decision-making proxy comprehension assessments are performed.

Teach back is an assessment with patient-specific prioritized concepts determined by the Communication Team, which evaluates the participant's understanding of key points during the communication and follow-up visits.^{4–11} Teach back is a method used in research and care delivery environments whereby information is communicated to the patient/family and the patient/family member is asked to summarize what he/she heard/learned. The steps in this method can be summarized as follows:

- (i) Research information is shared using plain language and by means of the physical report with participants.
- (ii) Participants are then asked to explain in their own words how they would explain this information to someone at home.
- (iii) Communicator repeats or corrects for accuracy and gaps.
- (iv) Participants are asked to repeat their explanation. This second explanation is the basis of the teach-back score, rated as no comprehension (0), partial comprehension (1), or full comprehension (2) for each of 3 teach-back concepts. The possible teach-back score ranges from 0 to 6.

The psychological impact of the NEPTUNE match process is monitored using 2 established measures. FACToR-NEPTUNE is a measure that has been modified from the Feelings About Genomic Testing Results (FACToR).³²

FACToR-12 is used to assess the psychosocial impact of returning genomic findings to patients in research and clinical practice, with subscales assessing (i) distress from learning test results, (ii) uncertainty about the meaning and implications of results, and (iii) positive reactions to results. The FACToR-NEPTUNE uses an abbreviated, adapted version of the FACToR-12 measure to evaluate the psychosocial impact of receiving the NEPTUNE Match Report. We selected this instrument because of the similarity of molecular profiling strategy with genetic testing as a means of characterizing patients. Therefore, the potential stress provoked by receiving the Match report may resemble it in kind and degree. State Trait Anxiety Inventory (mini-STAI) scale³³ is a widely used instrument and is being used in our context to assess a participant's general anxiety symptoms overall at both the consent visit and the follow-up visit, allowing for assessment of the potential for increased anxiety levels following results disclosure.

Step 4: retrospective comparison of kidney health outcomes in NEPTUNE Match study participants

Outcome frequencies of participants enrolled in trials with an aligned match versus trial participants with misaligned or unknown match alignment will be compared to assess the impact of Match on treatment responses. NEPTUNE Match does not enroll patients into clinical trials. Rather, its objective is informational (namely, to provide a report that summarizes the degree of consonance between a patient's underlying disease process and the mechanism of action of a therapy under evaluation in a clinical trial). It is intended to establish a framework to share disease activity information to guide patients and nephrologists in their decision-making regarding the optimal trial for them. The ultimate decision about enrolling in a Match trial is made by the patient and his/her attending nephrologist, who may or may not be a NEPTUNE investigator. Once patients select a trial, the patient screening and enrollment for participation are governed by the independently executed trial protocols. The leadership team of the trial will be responsible for reporting the overall and individual NEPTUNE Match trial participant outcomes back to NEPTUNE for analysis on completion of the trial. The efficacy of NEPTUNE Match will be assessed by a pooled analysis of outcomes in all participating trials.

On the basis of several assumptions, we can provide power to assess the comparison of binary treatment responses (e.g., proportion of participants with FSGS partial remission at 4 months, based on proteinuria,³⁴ between trial participants with trial match alignment to those with no match alignment). We assume that all FSGS trials participating in the Match study, regardless of whether phase 2 or phase 3 with long- or short-term primary end points, capture proteinuria and estimated glomerular filtration rate measurements at a common time point, allowing us to pool clinical outcome data. Our current data suggest that a sample size of 300 participants is relatively conservative. With this sample size, assuming a 2-sided type I (false-positive) error of 5%, that 50% of participants are on therapies for which their molecular profile is matched, and that participants are randomized 1:1 to active therapy and placebo, and using a 2-sample Fisher exact test, we would have at least 80% power to detect absolute group differences of 25% between outcome response frequency in patients who are assigned a matching trial treatment to nonmatched treatment responses of 20% to 30%; for example, we have 86% power to detect a difference of 25% treatment response in nonmatched participants versus 50% treatment response in matched participants. Because the pooled effect size will be mitigated by trials with ineffective therapies, we also assessed effect sizes for individual trials involved in the Match study. Taking a 75-patient phase 2 study as an example and using the same assumptions, we would have at least 80% power to detect absolute group differences of 50% with nonmatched treatment response of 20% to 30%; for example, we have 82% power to detect a difference of 25% treatment response for nonmatched participants and 75% treatment response for matched participants in a trial of 75 participants. Our power would likely be considerably greater if we were to compare continuous treatment differences, such as the change from baseline in urine protein/creatinine ratio, that we will be able to assess more completely as we gain more experience with the Match study.

NEPTUNE Match is a dynamic enterprise where partnering trials and associated biomarkers of NS disease mechanisms continue to be developed and will be added to the roster of available clinical trials. To facilitate the interaction between academic and private partners leading the clinical trials in Match, the NEPTUNE Pre-competitive Public-Private

Partnership Platform was established. The NEPTUNE Pre-competitive Public-Private Partnership Platform serves as a framework for precompetitive assessment of pathways targeted in clinical trials, initiated by the private partners or academic investigators with public funding support.

In summary, Match responds to the need to replace the enrollment of a heterogeneous set of patients to clinical trials with an evidence-driven strategy matching the drug mode of action to the disease mechanism(s) active in the individual patient. In parallel, NEPTUNE Match empowers patient participants by providing them with additional state-of-the-art information related specifically to the molecular characteristics of their disease that they can use when evaluating participation in available clinical trials.

PROGRESS AND CHALLENGES

- NEPTUNE has developed a broad multi-omics approach for a mechanism-based categorization of primary glomerular diseases that lends itself to precision medicine therapeutic initiatives, a key advance in nephrology.
- In NEPTUNE Match, noninvasive biomarker profiles have been developed to identify patients with distinct mechanisms of kidney injury based on assessment of the kidney status. This is a key step in translating basic science discoveries about glomerular diseases into practical application for patient care.
- With Match, a framework has been created to evaluate the unique molecular profile in individual patients in a comprehensive and efficient manner.
- In partnership with academic clinical trialists and industry sponsors, molecular targeted therapies are being developed in NEPTUNE to expand the stratification approaches within the Match program.
- The NEPTUNE network has been trained and certified to communicate the state-of-the-art research findings that emerge from the Match evaluation to patients to ensure understanding of the results and thoughtful use as they consider enrollment in prospective clinical trials.

Challenges

- Lack of robust model systems recapitulating human disease processes to evaluate targets in clinical development in NS. We are addressing this problem by incorporating newer technologies, such as organoids to

model nephrotic syndrome *in vitro* and to assess the effects of proposed therapies.^{16,35}

Increased data sharing among clinical investigators will promote better understanding of the natural history of the primary glomerular disorders and complement efforts underway in Match to delineate discrete subtypes of each glomerulopathy.

- Educating the nephrologists in academic centers and community practice about the potential impact of precision medicine initiatives in nephrology in general and glomerular diseases in particular. We plan to establish regional networks of community nephrologists to promote awareness of Match and to facilitate referral of patients to NEPTUNE sites for potential participation in this cutting-edge research activity.
- Creating an infrastructure for outreach to patients to increase their understanding of precision medicine in nephrology and to provide meaningful answers to their key questions, including: What is my disease doing to my kidney? What will happen to my kidney? What can be done to help my kidney disease? Efforts are underway to partner with patient advocacy groups to foster engagement with Match.
- Coordinating preclinical and clinical programs so that Match activity profiles can be generated in advance of clinical trial deployment.

VISION FOR THE FUTURE

NEPTUNE Match represents an organized multidisciplinary effort to apply precision medicine approaches for the prioritization of clinical trials for patients with kidney disease, specifically primary glomerular disorders. It represents the first steps toward the goal of providing the right treatment in the optimal sequence for each individual patient. Match is in the formative stages and has achieved key objectives that are vital for the long-term success of this initiative. Looking to the future, we anticipate further innovation to improve the program and facilitate expansion across nephrology centers with a focus on precision medicine. Harmonization of sample collection, processing, and storage of biospecimens collected during routine medical care and clinical trial visits will ensure that patients can be evaluated for active, precision medicine-based clinical trials in a timely manner. It will enable prospective testing for matching with new trials that will be

implemented in the future. Expanding the scope of collaboration with academic and industry partners will help sustain the discovery pipeline needed to define therapeutic targets and valid biomarker signatures in individual patients. In addition, it will expand the number of therapeutic options available to patients and provide them with additional decision support on potential efficacy, adverse effects, and feasibility of novel therapies being evaluated in clinical trials. NEPTUNE Match offers an opportunity to create an infrastructure of highly qualified sites that have the interest, personnel, institutional resources, and experience required to conduct trials of innovative precision medicine-based therapies. We anticipate that NEPTUNE Match will act as a catalyst for the design and implementation of novel trial designs, such as platform trials, adaptive trials, and SMART and $n + 1$ designs³⁶ that will facilitate the efficient evaluation of emerging therapeutic agents. In collaboration with regulatory agencies, suitable end points may be defined to expedite early-phase assessment of targeted therapies for susceptible patients and advance these agents into successively larger phase 2 and 3 studies. Finally, partnerships with patient support groups and regional and national nephrology societies can help all stakeholders appreciate the promise and limitation of precision medicine therapy for kidney disease. Such a clinical translational program can help roll out precision medicine trials in an ethical manner to meet the needs of the full range of patients, from pediatric to geriatric, affected by primary glomerular diseases. The challenge confronting the nephrology community to bring novel therapeutic modalities to glomerular disease clinics is substantial. Because of the commitment of research participants in our studies, we have a rich resource of samples, data, and knowledge in place to bring novel treatments to our patients.

APPENDIX

Members of the Nephrotic Syndrome Study Network (NEPTUNE)

NEPTUNE collaborating sites. *Atrium Health Levine Children's Hospital, Charlotte, SC:* Susan Massengill*, Layla Lo*
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Children's Mercy Hospital, Kansas City, MO: Tarak Srivastava*, Kelsey Markus*

Cohen Children's Hospital, New Hyde Park, NY: Christine Sethna*, Suzanne Vento*
Columbia University, New York, NY: Pietro Canetta*
Duke University Medical Center, Durham, NC: Opeyemi Olabisi*, Rasheed Gbadegesin**, Maurice Smith*
Emory University, Atlanta, GA: Laurence Greenbaum*, Chia-shi Wang*, Emily Yun*
The Lundquist Institute, Torrance, CA: Sharon Adler*, Janine LaPage*
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Johns Hopkins Medicine, Baltimore, MD: Meredith Atkinson*, Miahje Williams*
Mayo Clinic, Rochester, MN: John Lieske, Marie Hogan, Fernando Fervenza
Medical University of South Carolina, Charleston, SC: David Selewski*, Cheryl Alston*
Montefiore Medical Center, Bronx, NY: Kim Reidy*, Michael Ross*, Frederick Kaskel**, Patricia Flynn*
New York University Medical Center, New York, NY: Laura Malaga-Dieguez*, Olga Zhdanova**, Laura Jane Pehrson*, Melanie Miranda*
The Ohio State University College of Medicine, Columbus, OH: Salem Almaani*, Laci Roberts*
Stanford University, Stanford, CA: Richard Lafayette*, Shiktij Dave*
Temple University, Philadelphia, PA: Iris Lee**
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