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Designing Clinical Trials for the Treatment of Membranous Nephropathy in the Anti-Phospholipase A2 Receptor 1 Era: Results of a NephCure Membranous Nephropathy Workshop

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Abstract
Primary membranous nephropathy is a common cause of adult-onset nephrotic syndrome, with an overall incidence of 12 cases per million per year. Primary membranous nephropathy is an autoimmune kidney disease; however, primary membranous nephropathy autoantigens remained elusive until 2009, when the M-type phospholipase A2 receptor 1 (PLA2R) was identified as a disease autoantigen. This was followed relatively rapidly by the identification of several other autoantigens. Autoantibodies against PLA2R are detectable in ≈75% of patients with primary membranous nephropathy. The discovery of circulating and deposited autoantibodies against PLA2R offers an opportunity in nephrology to personalize disease management. On January 14, 2023, NephCure Kidney International convened a scientific workshop in Arlington, Virginia, to discuss the state of the science on autoantibodies against PLA2R and considerations related to the incorporation of autoantibodies against PLA2R in drug development programs for

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membranous nephropathy. The present report captures the discussion that occurred at the Membranous Nephropathy Scientific Workshop.

Introduction

The identification of autoantibodies to specific glomerular target antigens in membranous nephropathy (MN), beginning with phospholipase A2 receptor 1 (PLA2R) in 2009 [1], has opened a new window on diagnosis and disease monitoring [2]. Similar to the discovery of the transmembrane receptor tyrosine kinase human epidermal growth factor receptor 2 (HER2)/neu in breast cancer, which ultimately led to a more personalized approach to treatment [3, 4], autoantibodies to PLA2R (aPLA2R) represent a circulating biomarker by which to diagnose this major form of MN [5] and potentially allow for individualized treatment decisions via longitudinal monitoring. Since identifying PLA2R as an antigen for MN, the field has blossomed with the description of additional pairs of target antigens and corresponding autoantibodies, such as those to thrombospondin type-1 domain-containing 7A (THSD7A) [6], neural epidermal growth factor-like 1 (NELL1) [7], and high temperature requirement serine peptidase 1 (HTRA1) [8], that additionally may help guide diagnosis and therapy [9].

Observational data have largely supported a paradigm in which the nephrotic state is maintained with the persistence of circulating aPLA2R, whereas disappearance of aPLA2R will ultimately lead to a reduction of proteinuria with a lag time, due to the slower clearance of immune deposits and repair of the glomerular filtration barrier [10]. Change in proteinuria (e.g., complete remission) is accepted as a surrogate end point for approval of novel therapies in MN [11], yet the fact that these clinical responses tend to occur relatively late challenges the design and interpretation of clinical trials. In many patients with primary MN whose disease is associated with aPLA2R, this serologic biomarker could provide a reliable additional indicator of disease remission that would be expected to occur sooner than the proteinuric outcome. It is tempting to hypothesize that the use of aPLA2R, specifically in a disease whose natural history can span several years, might provide clinicians and clinical trialists with a quicker surrogate of disease remission.

In 2014, a commercially available aPLA2R enzyme-linked immunosorbent assay (ELISA) was cleared for sale in the USA by the US Food and Drug Administration (FDA) to aid in the diagnosis of MN. Observational research studies as well as experience with using this ELISA off-label in the clinical setting have led Kidney Disease: Improving Global Outcomes to suggest as a practice point that aPLA2R levels might be followed, in appropriate patients, to monitor the immunologic activity of the disease and its response to therapy [12]. Direct pathogenicity of aPLA2R is suggested by the recurrence of MN when a kidney allograft is transplanted in the presence of circulating aPLA2R [13, 14] as well as a growing body of evidence from animal models [15, 16]. These observations support the biological plausibility of aPLA2R as a likely surrogate marker of proteinuric and clinical outcomes.

Given these advances with aPLA2R, there is significant interest in using aPLA2R levels in drug development programs to support more tailored approaches to administering investigational agents and as an efficacy end point in clinical trials of MN. However, such uses raise additional considerations. On January 14, 2023, NephCure Kidney International convened a scientific workshop in Arlington, Virginia, to discuss the state of the science on aPLA2R and considerations related to the incorporation of aPLA2R in drug development programs for MN. The workshop was organized and funded by NephCure Kidney International, who invited participants from the USA, Europe, and Asia. Stakeholders within the MN community, including nephrologists, scientists, industry representatives, regulatory officials, patient advocates, and patients with MN, attended (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000544808). The workshop aims were to (i) understand the current use and limitations of aPLA2R in clinical trials; (ii) identify the desired use of aPLA2R as a biomarker in the conduct of clinical trials; (iii) understand regulatory needs, pathways, and requirements to support use of aPLA2R in the context of clinical trials; (iv) create a roadmap to facilitate incorporation of aPLA2R into clinical trials; and (v) obtain input from patients with MN about challenges and unmet needs. This report captures the discussion that occurred at the workshop.

Current Understanding, Use, and Limitations of aPLA2R

We will first review selected evidence from the literature that shaped our early understanding of aPLA2R. As a major caveat, our understanding of the relationship between aPLA2R, proteinuria, and clinical course in MN has

been evolving since the first description of autoantibodies to PLA2R, and this body of knowledge remains incomplete but continues to grow. Early investigations were confounded because of an initial lack of awareness of the many other autoantibodies and target antigens that would be discovered after aPLA2R [9, 17]. A flawed initial assumption was that cases of primary MN could be dichotomized into those that were aPLA2R seropositive and aPLA2R seronegative. Thus, early studies likely included in their aPLA2R-seronegative cohort not only those with PLA2R-associated MN with no detectable aPLA2R but also those with other types of MN in whom aPLA2R would have no bearing on disease activity. Staining for PLA2R within immune deposits on kidney biopsy would prove necessary for the identification of seronegative cases of PLA2R-associated MN [18]. A second major flaw was the assumption that the presence and/or titer of aPLA2R in the circulation could be directly correlated with proteinuria at the same time point, without accounting for the time lag that is now known to exist.

Association of Circulating aPLA2R with Overall MN Disease Activity

The earliest studies used Western blotting (a sensitive and specific assay, but impractical for routine clinical use) to detect and measure human aPLA2R. These were followed by the introduction of an immunofluorescence assay in which biochips coated with cells expressing human PLA2R were used to detect and measure aPLA2R in a semi-quantitative manner [19], and finally by several research and commercial ELISAs for aPLA2R, all seeking to establish (and, to some degree, quantify) the presence of aPLA2R in blood. The first description of aPLA2R noted the generalized presence of aPLA2R during periods of clinically significant disease activity [1]. An impactful case series studied 18 individuals with MN, each with a serum sample available during the initial nephrotic state, at clinical remission, and after a subsequent relapse of MN [20]. In the 14 patients with PLA2R-associated MN, aPLA2R levels were high in both the initial nephrotic phase of the disease and again with relapse but were undetectable in most subjects when in clinical remission. Other studies, in cross-sectional analysis, showed higher prevalence and higher ELISA titers of aPLA2R during active disease when compared with those with partial or complete remissions [21].

Baseline aPLA2R Correlates Weakly with Baseline Proteinuria and Has Limited Prognostic Value in MN

ELISAs soon routinely supplanted Western blotting for faster and more quantitative measurements of aPLA2R [22, 23]. An early study demonstrated weak correlation ($r = 0.259$) between baseline aPLA2R titer and baseline proteinuria, which improved ($r = 0.668$) when the IgG4 subclass of aPLA2R was measured or, in a subgroup with the requisite data, when aPLA2R was adjusted for fractional excretion of IgG to account for urinary aPLA2R losses ($r = 0.679$) [22]. A later study confirmed a weak correlation between baseline aPLA2R and proteinuria and demonstrated that the lowest tertile of detectable aPLA2R titer corresponded to the lowest median baseline proteinuria, whereas the highest baseline proteinuria was in the highest tertile [24]. Compared with patients in the lowest tertile of detectable aPLA2R titers, those with the highest titers were less likely to experience spontaneous remission [22, 25].

The aPLA2R Paradigm Develops

A likely explanation for the less-than-perfect correlation between aPLA2R and proteinuria at any 1 time point is that the 2 parameters are more closely related with a time lag. The prediction of clinical outcome or response to treatment based on a single baseline aPLA2R turned out to be less useful than monitoring the longitudinal and directional course of aPLA2R. A decline or disappearance of aPLA2R before full resolution of proteinuria in patients who ultimately achieved clinical remission was already apparent in 2009 [1], and a model that featured immunologic remission (disappearance of aPLA2R) occurring before clinical remission was formally proposed in 2010 [26].

Several studies support the concept that effective treatment of aPLA2R-positive MN necessitates an immunologic response defined as a decline/disappearance of circulating aPLA2R. Retrospective studies in rituximab-treated patients with MN [27] and prospective studies in patients with MN treated with different types of immunosuppression or by supportive care alone [28] demonstrated that aPLA2R decreases first, followed by a more gradual and protracted decline in proteinuria. Thus, declining aPLA2R is an early indicator that proteinuria will improve in the following months, whereas failure to achieve a (significant) decrease in aPLA2R was associated with failure to achieve remission [24, 27]. The reason for this relationship relates to the time needed to clear the immune deposits and restore the glomerular filtration barrier following the elimination of circulating autoantibodies [10]. The cumulative clinical experience soon led to proposals and guidelines for the monitoring of aPLA2R to guide therapy [2, 29], which is now routinely done in clinical practice.

Use of aPLA2R Testing in Clinical Practice

The use of aPLA2R in clinical practice, however, has not yet been systematically studied since the commercial aPLA2R ELISA was cleared by the FDA in 2014. To evaluate how the assay is being used by clinicians, we queried the Labcorp Diagnostics database from 2017 to 2019. Specifically, we determined the following: (i) the number of unique patients in whom aPLA2R was ordered and measured; (ii) the *International Classification of Diseases, Tenth Revision*, codes used for these patients; (iii) the number of "positive" aPLA2R results; and (iv) the frequency of repeat aPLA2R measurements in individual patients.

During this 3-year interval, 14,263 individuals had aPLA2R testing, of whom 1,406 (9.9%) were positive. Overall, this cohort tested positive 2,602 times, indicating that >1 test was ordered in many individuals. The top 5 reported *International Classification of Diseases, Tenth Revision*, codes (an imperfect indicator of actual diagnosis) for all the patients in whom aPLA2R was ordered were proteinuria, unspecified (R80.9); unspecified nephritic syndrome with diffuse membranous glomerulonephritis (N05.2); essential hypertension (I10); nephrotic syndrome with unspecified morphologic changes (N04.9); and recurrent and persistent hematuria with diffuse membranous glomerulonephritis (N02.2). Of those who tested positive, ≈900 patients had aPLA2R concentrations ≥50 relative units/mL. In those patients with proteinuria measured within 30 days of the first positive PLA2R assay, most had urine protein-to-creatinine ratio levels ≥5 g/g. These data indicate clinical uptake of the test. The large number of negative test results suggests the assay is being used as an aid in the diagnosis of MN in those with proteinuria or nephrotic syndrome of unknown cause, with some potential inappropriate use, although this is hard to know without patient-level data. Repeat testing also appears to be common, suggesting the test is also being used to monitor disease activity.

Use of aPLA2R Testing in Clinical Trials

To evaluate how PLA2R is currently being used in clinical trials, a search was conducted on clinicaltrials.gov (last accessed May 4, 2024) and identified 11 phase 2 or 3 interventional trials for MN that were currently recruiting subjects. On the basis of the posted information, aPLA2R will be measured in 8 trials, with 5 trials requiring aPLA2R positivity for inclusion, including 1 that requires an aPLA2R level >50 RU/mL. A total of 5 trials plan to assess aPLA2R as an outcome measure, with 1 trial examining aPLA2R as a primary outcome. Three trial postings did not mention aPLA2R testing.

Challenges Associated with Using aPLA2R in Clinical Trials

Another barrier to incorporating aPLA2R into the design and conduct of clinical trials is how best to measure aPLA2R. Presently, only the Euroimmun aPLA2R assay has been cleared by the FDA, and only for use as an aid in the diagnosis of MN. Although this assay has been adopted in several observational studies and clinical trials in MN, other similarly designed ELISAs, with different threshold values, have also been used [22, 30]. In contrast, some investigators have advocated assessing immunologic remission in MN using indirect immunofluorescence [31], which offers a higher clinical sensitivity for aPLA2R [32], especially at low titers [5]. Additionally, a rapid chemiluminescence assay for aPLA2R has been introduced [33]. Finally, as there is currently no universal standard by which to calibrate different assays, each test may have different analytical and clinical performance characteristics, potentially complicating interpretation of their results.

Further work is also needed to understand what constitutes a clinically meaningful change in aPLA2R levels. The clinical sensitivity and specificity of aPLA2R for diagnosis have been well studied. In contrast, much less is known about what constitutes a meaningful change (magnitude/rate) in aPLA2R level. Although a complete disappearance of aPLA2R from the circulation may be clinically meaningful, it has been challenging to identify an absolute aPLA2R threshold that can be used to assess response [34]. Euroimmun defines a negative test as <14 RU/mL, but others have suggested a lower threshold (<3 RU/mL) to differentiate a negative from a positive result [35, 36]. Several studies using the more sensitive immunofluorescence assay or Western blot test have shown that values <14 RU/mL can still represent the presence of aPLA2R [5].

Desired Use of aPLA2R in Clinical Trials

Several potential applications of aPLA2R measurement to MN clinical trials are envisioned: aPLA2R could be used (i) to identify patients for inclusion in a clinical trial; (ii) for longitudinal patient monitoring; and (iii) as an efficacy end point in registration trials (see Table 1). Regulatory considerations related to these uses are discussed in the subsequent section.

Use as Entry Criteria in Clinical Trials

To date, inclusion criteria for clinical trials in MN have generally required confirmation of the diagnosis. Given the specificity of aPLA2R for MN, it is conceivable that a

Table 1. Proposed uses of aPLA2R in registration trials of aPLA2R-MN

Proposed use	Application	Advantages	Disadvantages/barriers	Caveats and considerations
Trial inclusion	• To establish a diagnosis of aPLA2R-MN (in lieu of kidney biopsy) • To identify immunologically active MN in previously biopsy diagnosed patients	• Less burdensome for patients • Facilitates study recruitment • Two measurements taken at separate times can be used to verify inclusion only of immunologically active patients who are not already improving	• Degree of chronic kidney damage difficult to estimate in absence of a kidney biopsy	• Biopsy results with aPLA2R levels will allow a more informed interpretation of residual proteinuria at the end of a trial (i.e., disease activity vs. chronic damage) • aPLA2R positivity alone may be considered for the few patients who cannot undergo a biopsy
	• Positive aPLA2R status required for trial entry • aPLA2R above a certain level required for trial entry	• Ensure enrolling patients with immunologically active disease • Reduce heterogeneity of trial participants to PLA2R-MN • Stratify patients by disease severity using aPLA2R levels; target patients with specific aPLA2R (e.g., high) levels	• Applicability of drug to non-PLA2R-MN patients will not be determined • aPLA2R would need to be measured by a standardized assay • The relationship of aPLA2R levels to disease severity remains to be determined	• To broaden applicability of trial results, a fixed number (e.g., 20%) of non-aPLA2R PMN patients could be recruited • All PLA2R measurements would have to be done using same assay • The clinical phenotype of different aPLA2R levels will need to be established
Longitudinal patient monitoring	• aPLA2R obtained serially to monitor patients for safety and efficacy	• Provide an early signal of the need for rescue therapy for patients who are not responding • Avoid excessive exposure to a noneffective therapy • Identify patients who may benefit from a second or longer course of treatment because aPLA2R response has been incomplete	• Antibody level thresholds for decision-making not yet determined • Antibody assays are not interchangeable and may not have same analytical and clinical performance	• Define the specific assays to be used for measuring aPLA2R in clinical trials • For specific platforms, establish thresholds of response/nonresponse/remission based on time and antibody level • Develop aPLA2R standards to allow interpretation of data from different platforms
Trial end point	• Surrogate end point (validated or reasonably likely)	• Shorten trial duration, enable earlier access to drug • Evaluate the effects of an intervention on a component of the causal pathway of aPLA2R-MN	• Available data insufficient to support use • Need to establish clinically relevant definitions of immunologic response and immunologic remission based on evidence-based relationship with disease outcome	• Data sharing from recent clinical trials and observational cohorts to support necessary analyses

aPLA2R, autoantibodies against phospholipase A2 receptor 1; MN, membranous nephropathy; PLA2R, phospholipase A2 receptor 1; PMN, primary membranous nephropathy.

positive aPLA2R test could be used as an inclusion criterion in lieu of a kidney biopsy [5, 37]. Although this may spare patients an invasive procedure, this approach also has its drawbacks as other information that is obtained from the biopsy may be important for determining whether patients should qualify for enrollment (see Table 1). Such an approach may best be suited for patients who have contraindications to biopsy. An alternative approach would be to use an aPLA2R status to identify the subset of patients with a biopsy-confirmed diagnosis

of MN to establish that the disease is mediated by aPLA2R and to ensure immunologically active disease at the time of enrollment. This could be accomplished by using the sensitive immunofluorescence assay to establish the presence of aPLA2R [5] in conjunction with quantitation by ELISA to establish a baseline for longitudinal measurements. In principle, requiring aPLA2R positivity or specifying aPLA2R level for inclusion could enhance the homogeneity of the trial population or enrich it in targeting specific MN subpopulations (e.g., patients with high aPLA2R levels).

Use for Longitudinal Patient Monitoring and Guiding Treatment Decisions during a Clinical Trial

aPLA2R may also be useful for patient monitoring during a trial. Evidence from recent randomized controlled trials in MN suggests that an immunologic response usually occurs before a proteinuria response [38–41]. As such, one could envision using aPLA2R to monitor patients during a trial and guide decision-making. For example, lack of a "substantial" decrease in aPLA2R levels after several months of treatment could signal the need to "rescue" the participant (i.e., discontinue study drug and offer the patient an alternative therapy). Alternatively, aPLA2R levels could be used to tailor the dosing regimen to an individual's needs. For example, they could be used to identify the subset of patients who should be given a second course of treatment or a longer course of treatment (e.g., redose patients with an inadequate PLA2R response). Such an approach is particularly attractive if a drug may cause significant toxicities. As an argument for consideration of aPLA2R in a clinical trial, 23 of the 130 subjects enrolled in the pivotal membranous nephropathy trial of rituximab (MENTOR) had to exit the trial at 6 months because they failed to achieve a 25% decline in proteinuria from baseline [39]; it is conceivable that a favorable decline in aPLA2R at the 6-month point (which, in fact, was the case for many, as shown in the supplemental data for this study) might have enabled them to remain in the trial, with an expectation that proteinuria would decline sufficiently at a later time point.

aPLA2R as an Efficacy End Point in Registration Trials

In 2015, members of the FDA and the American Society of Nephrology Glomerular Disease Advisory Group published an article on complete remission and partial remission of proteinuria as surrogate end points for a treatment effect on progression to kidney failure in patients with MN with heavy proteinuria [11]. The authors concluded that the available data supported the use of a complete remission of proteinuria as a surrogate end point in clinical trials of MN. The authors also concluded that the available data supported the use of a partial remission of proteinuria as a "reasonably likely" surrogate end point, but also highlighted gaps in the data as well as challenges associated with using partial remission as an end point for accelerated approval.

Because an immunologic remission is expected to occur before a clinical remission, there is significant interest in whether "immunologic remission" could be used as an efficacy end point in registration trials. Available data described above indicate that aPLA2R antibodies are on the causal pathway of MN, and that the disappearance of aPLA2R is associated with a high likelihood of subsequent proteinuria remission and favorable long-term kidney health. However, further work is needed to support the use of "immunologic remission" (as defined by aPLA2R levels) as a surrogate end point and basis for either accelerated or traditional approval (Table 1). There is also interest in whether a combined end point (i.e., the combination of a sustained "disappearance" of circulating aPLA2R and a clinical partial remission) might have a sufficiently strong relationship with kidney outcomes in MN to support its use as a surrogate. At this point in time, there are not enough data to support the use of aPLA2R as a reasonably likely surrogate end point in clinical trials. However, efforts to collect and assess such data are beginning (see below), and we strongly advocate that all clinical trials measure aPLA2R levels at baseline and at prespecified intervals throughout the trial in aPLA2R-positive individuals.

Regulatory Considerations Related to in vitro Devices and the Use of aPLA2R in Clinical Trials

In the USA, the review and approval of in vitro devices (IVDs) are primarily driven by the potential benefits and risks to the patient based on how the device will be used in clinical practice (i.e., the intended use). For aPLA2R, the current aPLA2R assay is cleared to "aid in the diagnosis of primary membranous glomerulonephritis in conjunction with other laboratory and clinical findings." Because the assay's intended use is only to "aid" in the diagnosis of MN, the potential risk due to an erroneous result is reduced, as an accurate diagnosis is reached from reviewing other findings (e.g., the biopsy) in addition to the aPLA2R result. However, if the intended use of aPLA2R is expanded to other uses, such as monitoring treatment response (for the purpose of adjusting treatment), then the

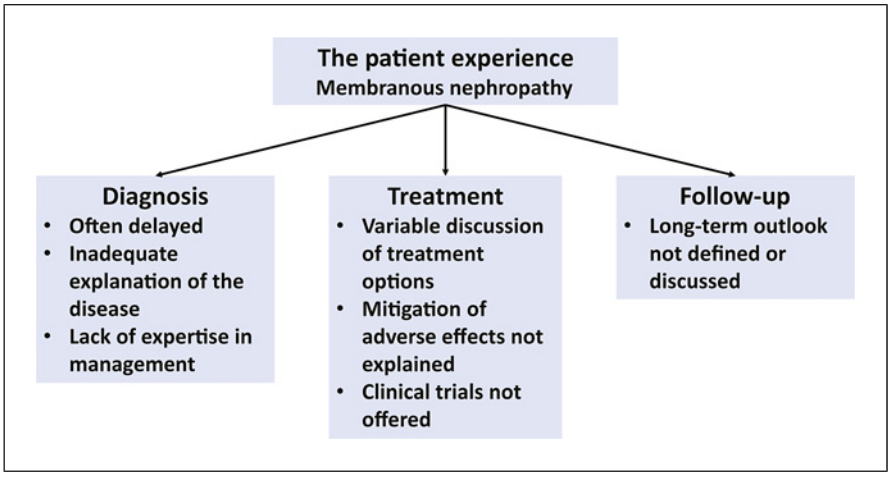

Fig. 1. A distillation of the main areas of management improvement patients brought up during discussion of their personal disease journeys.

expanded intended use now presents new benefit/risk considerations. In this example, an inaccurate IVD result could lead to withholding appropriate therapy or inappropriately administering further therapy. Thus, when the intended use of an IVD is to provide information that is essential for the safe and effective use of a corresponding therapeutic product, it is necessary for that IVD to undergo analytical and clinical performance validation to ensure it performs adequately in the setting of that (new) intended use. When an IVD is used in such a way, it is classified as an in vitro companion diagnostic device (IVD companion diagnostic device). This approach is common in the oncology field, where scientific advances have led to FDA-approved treatments that are tailored to specific tumor characteristics (e.g., specific epidermal growth factor receptor genetic mutations in non-small-cell lung cancer). This shift to a more tailored approach in oncology has required IVD companion diagnostic devices that underwent rigorous analytical and clinical performance validation for that specific use. A more detailed overview of the regulatory considerations for in vitro companion diagnostic devices can be found in the FDA Guidance "In Vitro Companion Diagnostic Device" and FDA Draft Guidance "Principles of Co-development of an In Vitro Companion Diagnostic Device With a Therapeutic Product."

Patient Voice

A highlight of the MN workshop was the perspective of patients at various points in their journey with MN and their candid description of their interactions with the health care system around the time of disease onset. The main themes of the discussion are distilled in Figure 1. The need for good communication throughout the disease journey and an expectation that the treating nephrologists remain well informed of advances in MN research were highlighted. Although these asks seem self-evident, they are often difficult to implement given the time constraints of clinical practice and the rapid pace of new research in MN. Importantly, patients want to participate in finding treatments for MN and are willing to share their own data and participate in clinical investigations. Despite this, many patients are not routinely presented with clinical trial opportunities, something the nephrology community can act on to improve in partnership with patient advocacy organizations and nephrology professional societies.

A Call to Action

aPLA2R is a disease-specific biomarker for MN that reflects the autoimmune pathogenesis of the disease and appears to track closely with disease activity in many patients. Nephrologists are already using aPLA2R to individualize the treatment of MN, and there is significant interest in aPLA2R levels as efficacy end points in registration trials of new therapeutics for MN. Many, but not all, contemporary MN clinical trials do assess aPLA2R levels using currently available assays, and we encourage this for all future trials. However, to realize the full potential of aPLA2R to facilitate drug development, several outstanding questions need to be addressed. These include, but are not limited to, establishing a calibration standard for aPLA2R assays, defining aPLA2R thresholds for immunologic response and immunologic remission,

and understanding how to combine clinical data (e.g., serum albumin, kidney function) with aPLA2R response thresholds to improve prediction of disease outcome. As noted above, patients with MN are eager to participate in clinical trials for the development of new therapeutics and to share their data. The workshop concluded with a consensus that existing MN data sets and biorepositories from academia and pharma, including aPLA2R data from clinical trials, be brought together and leveraged to address these issues, similar to what is currently being done for focal segmental glomerular sclerosis with the Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis (PARASOL) project [42].

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Conflict of Interest Statement

P.H.N. is the protocol chair for the Immune Tolerance Network (NIAID) REBOOT trial. L.H.B. receives patent royalties through Boston University for diagnostics for membranous nephropathy. He also consults for Cerium Pharmaceuticals, CANbridge Pharmaceuticals, and GlycoEraDr. B.H.R. consults for HiBio-Biogen Pharmaceuticals. All the other authors declared no competing interests. The opinions expressed in this article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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Author Contributions

M.P., P.H.N., B.S.G., L.H.B., A.M.T., A.H.H., E.A.S., and B.H.R. contributed to the manuscript similarly: worked on initial draft, were responsible for the specific manuscript sections, contributed to revisions for final draft, and read and approved the manuscript. J.M.T. read and approved the final version of the manuscript.

Supplementary Material

Online supplementary material is available online at www.kidney-international.org.

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