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The investigative burden of membranous nephropathy in the United Kingdom

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ABSTRACT

Background. Membranous nephropathy (MN) represents two distinct disease entities. Primary MN is now recognized as an autoimmune condition associated with the anti-PLA2R antibody and secondary MN occurs in tandem with malignancy, infection, drug therapy and other autoimmune conditions. Prior to the development of accessible enzyme-linked immunosorbent assays, the diagnosis of MN was one of exclusion. We studied whether the introduction of serum anti-PLA2R antibody testing leads to a reduction in the frequency of investigations in MN patients.

Methods. Patients from three UK centres with a diagnosis of MN between 2009 and 2014 were identified. We compared patients who had a positive anti-PLA2R test within 6 months of biopsy with those who had no test or a negative test. Records were reviewed for investigations that took place 6 months prior to and 6 months following the biopsy date to see if these were normal or identified a secondary cause of MN.

Results. In total, 184 patients were included: 80 had no test, 66 had a negative anti-PLA2R test and 38 had a positive test within 6 months of diagnosis. In 2012, 46.5% of patients had an anti-PLA2R test, increasing to 93.3% in 2014. From 2012 to 2014 the number of screening tests dropped from 10.03 to 4.29 and the costs from £497.92 to £132.94.

Conclusions. Since its introduction, a progressively higher proportion of patients diagnosed with MN had an anti-PLA2R test. This has led to a reduction in the number of screening tests and in the cost of investigations carried out. The anti-PLA2R test has the potential to reduce this burden as its use becomes more widespread.

Keywords: biomarkers, kidney biopsy, membranous nephropathy, nephrotic syndrome, proteinuria

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**INTRODUCTION**

Membranous nephropathy (MN) is among the most common causes of nephrotic syndrome in adults worldwide [1–6]. For decades it has been a histological diagnosis with two distinct entities: primary or autoimmune membranous nephropathy (PMN) and secondary MN. Despite their histological similarities, the pathogenesis and treatments differ greatly, meaning that differentiating between the two conditions is essential. Secondary MN is associated with a multitude of conditions such as malignancy, viral infections such as hepatitis B and C, medications and other autoimmune conditions such as lupus and toxins [7–9]. As such, management is aimed at treating the underlying condition.

PMN, originally known as idiopathic MN, has always been considered an autoimmune disease, although the offending antibody remained elusive until the discovery of antibodies to the M-type phospholipase receptor 1 (anti-PLA2R) in 2009 [10–15]. This immunoglobulin G class antibody is found in ~75% of patients with PMN and has high affinity for podocytes [10, 16, 17]. There is now considerable evidence to suggest that not only is it a sensitive biomarker of disease activity, but also pathogenic in its own right. High titres are known to correlate with disease activity, and for patients who go into remission, the anti-PLA2R levels decrease months before clinical signs, such as a reduction in proteinuria. The converse is also true with relapse predicted by an increase in antibody levels [13, 14, 18–21].

The antibody level can also help to provide some level of prognostication, with high titres associated with a worse renal outcome. Regular testing of anti-PLA2R antibodies allows for patients with PMN and has high affinity for podocytes [10–15]. There is now considerable evidence to suggest that not only is it a sensitive biomarker of disease activity, but also pathogenic in its own right. High titres are known to correlate with disease activity, and for patients who go into remission, the anti-PLA2R levels decrease months before clinical signs, such as a reduction in proteinuria. The converse is also true with relapse predicted by an increase in antibody levels [13, 14, 18–21].

The antibody level can also help to provide some level of prognostication, with high titres associated with a worse renal outcome compared with low titres [13]. If treatment does not result in antibody negativity, patients are left with a high risk of relapse. In fact, if treatment does not result in antibody negativity, they are left with a high risk of relapse and a reduction in anti-PLA2R levels decrease months before clinical signs, such as a reduction in proteinuria. The converse is also true with relapse predicted by an increase in antibody levels [13, 14, 18–21].

The benefit of regular anti-PLA2R testing led to the introduction of the first quantitative anti-PLA2R enzyme-linked immunosorbent assay (ELISA) test, which was developed in Manchester and became available across the northwest of England towards the end of 2011 [13]. Since then a commercial anti-PLA2R test has been developed and is now readily available internationally [23]. Prior to the development of these ELISAs, PMN was a diagnosis of exclusion. Given the association of secondary MN with malignancy or identified a secondary cause of MN. Investigations included viral and autoimmune screens, X-rays, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; OGD, oesophagogastroduodenoscopy; USS, ultrasound scan; TFTs, thyroid function tests; TAP, thorax, abdomen and pelvis.

**Hypothesis**

With the anti-PLA2R test becoming more ubiquitous, the introduction of anti-PLA2R antibody testing leads to a reduction in the frequency of investigations for patients with MN.

**MATERIALS AND METHODS**

All adult patients with biopsy-proven MN between 2009 and 2014 from three large teaching hospitals in the northwest of England covering a population of ~7 million were included in the study. Patients were excluded if biopsy was not conclusive of MN. Patients were identified from patient records and histopathology results from each centre.

Day 0 was taken as the date of renal biopsy. Records were reviewed for investigations that took place 6 months prior to and 6 months following the biopsy date to see if these were normal or identified a secondary cause of MN. Investigations included viral and autoimmune screens, X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, ultrasound scans, upper and lower gastrointestinal (GI) endoscopies and cystoscopies. Investigations were excluded if they were not performed in relation to the diagnosis of primary versus secondary MN.

Records were also interrogated to determine if a patient had an anti-PLA2R test and at what date. The result was only included if the sample was also taken within 6 months of the date of biopsy. A positive anti-PLA2R test was taken as >40 U/mL for the ELISA and a titre of >1:10 for the Euroimmun indirect immunofluorescence test (IIFT). A negative ELISA was taken as <40 U/mL and a titre of ≤1:10 for the Euroimmun IIFT [13].

Costs were assigned to each investigation in pounds sterling and taken from the National Health Service (NHS) reference costs for 2015–16 [24]. For chest and abdominal X-rays, the costs were taken from the NHS England National Tariff for 2015–16 [25]. The cost of anti-PLA2R testing was not included (Table 1).

For each patient, a total cost was determined for the frequency of investigations for patients with MN.

| Investigation | Mean value | LQR | UQR | Source         |
|---------------|------------|-----|-----|----------------|
| Hepatitis B   | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| Hepatitis C   | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| HIV           | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| RF            | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| ds-DNA        | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| ANA           | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| Complement    | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| PSA           | 1.18       | 0.78| 1.39| DAP504 NHS ref costs |
| ANCA          | 6.42       | 4.02| 7.65| DAP506 NHS ref costs |
| TFTs          | 1.18       | 0.78| 1.39| DAP504 NHS ref costs |
| Chest X-ray   | 25.00      |     |    | National tariff |
| Abdominal X-ray| 25.00    |     |    | National tariff |
| CT head       | 93.93      | 65.19| 115.59| RD20A NHS ref costs |
| CT thorax     | 102.50     | 70.75| 134.97| RD21A NHS ref costs |
| CT abdomen    | 102.50     | 70.75| 134.97| RD21A NHS ref costs |
| CT TAP        | 120.70     | 88.30| 138.91| RD26Z NHS ref costs |
| MRI           | 145.14     | 113.26| 173.53| RD01A NHS ref costs |
| PET           | 798.20     | 430.64| 1213.54| RN07A NHS ref costs |
| OGD           | 352.21     | 322.20| 432.22| FZ602 NHS ref costs |
| Colonoscopy   | 371.27     | 236.45| 521.90| FZ51Z NHS ref costs |
| Sigmoidoscopy | 207.69     | 152.04| 247.24| FZ54Z NHS ref costs |
| USS abdomen   | 50.62      | 38.54| 60.44| RD402 NHS ref costs |
| Cystoscopy    | 151.71     | 101.68| 175.50| LB72A NHS ref costs |

All costs in British pound sterling. NHS ref costs, National Health Service reference costs 2015–16 [18]; National tariff, National Health Service non-mandatory currencies and prices 2015–16 [19]; LQR, lower quartile range; UQR, upper quartile range, HIV, human immunodeficiency virus; RF, rheumatoid factor, dsDNA, double-stranded deoxyribonucleic acid; ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; PSA, prostate-specific antigen; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; OGD, oesophagogastroduodenoscopy; USS, ultrasound scan; TFTs, thyroid function tests; TAP, thorax, abdomen and pelvis.
| Parameter                         | No anti-PLA2R | Negative anti-PLA2R | Positive anti-PLA2R | Total   |
|----------------------------------|---------------|---------------------|---------------------|---------|
| Patients                         | 80 (43)       | 66 (36)             | 38 (21)             | 184 (100) |
| Age at diagnosis (years), mean (SD) | 59 (15.58)   | 57 (15.64)          | 57 (13.19)          | 58 (15.10) |
| Gender                           |               |                     |                     |         |
| Female                           | 32 (40)       | 24 (36)             | 11 (29)             | 67 (36)  |
| Male                             | 48 (60)       | 42 (64)             | 27 (71)             | 117 (64) |
| Hepatitis B                      |               |                     |                     |         |
| Negative test                    | 38 (48)       | 28 (42)             | 13 (34)             | 78 (43)  |
| No test                          | 42 (52)       | 38 (58)             | 25 (66)             | 105 (57) |
| Hepatitis C                      |               |                     |                     |         |
| Negative test                    | 38 (48)       | 28 (42)             | 12 (32)             | 78 (42)  |
| No test                          | 42 (52)       | 38 (58)             | 26 (68)             | 106 (58) |
| HIV                              |               |                     |                     |         |
| Negative test                    | 17 (21)       | 20 (30)             | 12 (32)             | 49 (27)  |
| No test                          | 63 (79)       | 46 (70)             | 26 (68)             | 135 (73) |
| Rheumatoid factor                |               |                     |                     |         |
| Negative test                    | 31 (39)       | 17 (26)             | 8 (21)              | 56 (30)  |
| No test                          | 48 (60)       | 48 (73)             | 30 (79)             | 126 (68) |
| Positive test                    | 1 (1)         | 1 (2)               | 0 (0)               | 2 (1)    |
| Anti-dsDNA                       |               |                     |                     |         |
| Negative test                    | 44 (55)       | 44 (67)             | 26 (68)             | 114 (62) |
| No test                          | 35 (44)       | 22 (33)             | 12 (32)             | 69 (38)  |
| Positive test                    | 1 (1)         | 0 (0)               | 0 (0)               | 1 (1)    |
| ANA                              |               |                     |                     |         |
| Negative test                    | 61 (76)       | 53 (80)             | 29 (76)             | 143 (78) |
| No test                          | 18 (22)       | 12 (18)             | 9 (24)              | 39 (21)  |
| Positive test                    | 1 (1)         | 1 (2)               | 0 (0)               | 2 (1)    |
| Complement (C3/C4)               |               |                     |                     |         |
| Negative test                    | 60 (75)       | 48 (73)             | 27 (71)             | 135 (73) |
| No test                          | 19 (24)       | 17 (26)             | 11 (29)             | 47 (26)  |
| Positive test                    | 1 (1)         | 1 (2)               | 0 (0)               | 2 (1)    |
| PSA                              |               |                     |                     |         |
| Negative test                    | 11 (14)       | 13 (20)             | 10 (26)             | 34 (18)  |
| No test                          | 68 (85)       | 53 (80)             | 28 (74)             | 149 (81) |
| Positive test                    | 1 (1)         | 0 (0)               | 0 (0)               | 1 (1)    |
| ANCA                             |               |                     |                     |         |
| Negative test                    | 61 (76)       | 50 (76)             | 31 (82)             | 142 (77) |
| No test                          | 19 (24)       | 16 (24)             | 7 (18)              | 42 (23)  |
| TTFs                             |               |                     |                     |         |
| Negative test                    | 30 (38)       | 18 (27)             | 20 (53)             | 68 (37)  |
| No test                          | 50 (62)       | 48 (73)             | 18 (47)             | 116 (63) |
| AXR                              |               |                     |                     |         |
| Positive test                    | 3 (4)         | 1 (2)               | 0 (0)               | 4 (2)    |
| Negative test                    | 39 (49)       | 33 (50)             | 21 (55)             | 93 (51)  |
| No test                          | 38 (48)       | 32 (48)             | 17 (45)             | 87 (47)  |
| AXR                              |               |                     |                     |         |
| Negative test                    | 4 (5)         | 1 (2)               | 1 (3)               | 6 (3)    |
| No test                          | 76 (95)       | 65 (98)             | 37 (97)             | 178 (97) |
| CT head                          |               |                     |                     |         |
| Negative test                    | 3 (4)         | 2 (3)               | 3 (8)               | 8 (4)    |
| No test                          | 77 (96)       | 64 (97)             | 35 (92)             | 176 (96) |
| CT thorax                        |               |                     |                     |         |
| Positive test                    | 0 (0)         | 1 (2)               | 0 (0)               | 1 (1)    |
| Negative test                    | 6 (8)         | 1 (2)               | 5 (13)              | 12 (7)   |
| No test                          | 74 (92)       | 64 (97)             | 33 (87)             | 171 (93) |
| CT abdomen                       |               |                     |                     |         |
| Positive test                    | 0 (0)         | 1 (2)               | 0 (0)               | 1 (1)    |
| Negative test                    | 2 (2)         | 1 (2)               | 1 (3)               | 4 (2)    |
| No test                          | 78 (98)       | 64 (97)             | 37 (97)             | 179 (97) |
| CT TAP                           |               |                     |                     |         |
| Positive test                    | 2 (2)         | 1 (2)               | 0 (0)               | 3 (2)    |
| Negative test                    | 20 (25)       | 15 (23)             | 9 (24)              | 44 (24)  |
| No test                          | 58 (72)       | 50 (76)             | 29 (76)             | 137 (74) |

(continued)
The mean cost and number of investigations with 95% confidence intervals (CIs) were calculated with standard bootstrapping using 10,000 samples with replacement [26, 27].

The number of investigations and the cost of investigations per year were then analysed based on the presence of a positive anti-PLA2R versus a negative test or no sample taken. Significance was calculated using the Student’s t-test and

All values are presented as n (%) unless stated otherwise.
HIV, human immunodeficiency virus; ANA, anti-nuclear antibody; PSA, prostate-specific antigen; ANCA, anti-neutrophil cytoplasmic antibodies; TFTs, thyroid function tests; CXR, chest X-ray; AXR, abdominal X-ray; CT, computed tomography scan; TAP, thorax, abdomen and pelvis; MRI, magnetic resonance imaging; PET, positron emission tomography; OGD, oesophagogastroduodenoscopy; USS, ultrasound scan.

Table 2. Continued

| Parameter         | No anti-PLA2R | Negative anti-PLA2R | Positive anti-PLA2R | Total  |
|-------------------|---------------|---------------------|---------------------|--------|
| MRI               |               |                     |                     |        |
| No test           | 79 (99)       | 65 (98)             | 37 (97)             | 181 (98) |
| Positive test     | 0 (0)         | 1 (2)               | 0 (0)               | 1 (1)  |
| PET               |               |                     |                     |        |
| Positive test     | 0 (0)         | 1 (2)               | 0 (0)               | 1 (1)  |
| Negative test     | 11 (14)       | 8 (12)              | 4 (11)              | 23 (12) |
| No test           | 69 (86)       | 57 (86)             | 34 (89)             | 163 (89) |
| OGD               |               |                     |                     |        |
| Positive test     | 1 (1)         | 0 (0)               | 0 (0)               | 1 (1)  |
| Negative test     | 7 (9)         | 8 (12)              | 5 (13)              | 20 (11) |
| No test           | 72 (90)       | 58 (88)             | 33 (87)             | 163 (89) |
| Colonoscopy       |               |                     |                     |        |
| Positive test     | 0 (0)         | 0 (0)               | 1 (3)               | 1 (1)  |
| Negative test     | 80 (100)      | 66 (100)            | 37 (97)             | 183 (99) |
| No test           |               |                     |                     |        |
| USS abdomen       |               |                     |                     |        |
| Positive test     | 41 (51)       | 33 (50)             | 20 (53)             | 94 (51) |
| Negative test     | 39 (49)       | 33 (50)             | 18 (47)             | 90 (49) |
| No test           | 80 (100)      | 65 (98)             | 35 (92)             | 180 (98) |

FIGURE 1: Proportion of MN patients with anti-PLA2R testing.

FIGURE 2: Proportion of each investigation with no anti-PLA2R testing, a negative anti-PLA2R test and a positive anti-PLA2R test, based on whether the investigation was positive or negative. C3/C4, complement C3/C4; RF, rheumatoid factor; Hep, hepatitis.
defined as <0.05. All analyses were carried out using R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [28].

RESULTS
A total of 184 patients across the three hospitals were included. The mean age of our cohort at diagnosis was 58 years, with a predominance of male patients (64%). A total of 80 (43%) patients did not undergo anti-PLA2R testing within 6 months of the date of biopsy and 104 (57%) patients did have an anti-PLA2R test within 6 months of the date of biopsy; 66 (63% of those tested) had a negative test and 38 (37% of those tested) had a positive test (Table 2 and Figure 2). Of the 184 patients included in the study, 21 (11.4%) were confirmed as secondary MN. Of these 21 patients, 9 were tested for anti-PLA2R and all were negative.

Frequency of anti-PLA2R testing
In 2011, when the anti-PLA2R test became available locally, it was only used in 8 of 20 (40%) patients diagnosed with MN. Since that time there has been a steady increase in the number of patients tested for anti-PLA2R within 6 months of their biopsy, with 93.3% of patients having the test in 2014 (Table 3 and Figure 1).

Table 3. Number of patients per year of biopsy

| Year of biopsy | Number of patients | No anti-PLA2R, n (%) | anti-PLA2R tested, n (%) |
|---------------|-------------------|----------------------|------------------------|
| 2009          | 39                | 39 (100.0)           | 0 (0.0)                |
| 2010          | 28                | 28 (100.0)           | 0 (0.0)                |
| 2011          | 20                | 12 (60.0)            | 8 (40.0)               |
| 2012          | 43                | 23 (53.5)            | 20 (46.5)              |
| 2013          | 39                | 15 (38.5)            | 24 (61.5)              |
| 2014          | 15                | 1 (6.7)              | 14 (93.3)              |

Number of patients who did and did not have an anti-PLA2R test within 6 months of the date of biopsy.

Table 4. Number of tests and cost of tests based on year of biopsy and anti-PLA2R test status

| Year of diagnosis | No test or anti-PLA2R negative | Anti-PLA2R positive | P-value |
|-------------------|--------------------------------|---------------------|---------|
| Cost of tests (£)  |                                |                     |         |
| 2009              | 220.27 (137.93–315.77)         | NA (NA)             | NA      |
| 2010              | 216.93 (120.46–328.56)         | NA (NA)             | NA      |
| 2011              | 227.07 (85.92–392.93)          | 497.92 (89.83–909.00) | 0.563 |
| 2012              | 161.16 (106.45–227.11)         | 226.39 (111.68–369.71) | 0.414 |
| 2013              | 225.64 (107.82–395.67)         | 218.88 (107.62–383.89) | 0.946 |
| 2014              | 244.11 (109.88–429.97)         | 132.94 (29.66–309.44) | 0.405 |

Number of investigations

| Year of diagnosis | No test or anti-PLA2R negative | Anti-PLA2R positive | P-value |
|-------------------|--------------------------------|---------------------|---------|
| 2009              | 6.87 (5.90–7.82)                | NA (NA)             | NA      |
| 2010              | 6.89 (5.57–8.18)                | NA (NA)             | NA      |
| 2011              | 4.57 (2.75–6.62)                | 10.03 (5.00–14.5)   | 0.164   |
| 2012              | 6.85 (5.61–8.09)                | 6.59 (4.90–8.20)    | 0.823   |
| 2013              | 6.44 (5.04–7.88)                | 8.08 (6.21–9.71)    | 0.177   |
| 2014              | 9.01 (6.60–11.2)                | 4.29 (2.60–6.10)    | 0.019   |

Values presented as mean (95% CI). NA, not available.

DISCUSSION
The majority of patients with a histological diagnosis of MN will have primary MN, an autoimmune disease in which 70–80% are anti-PLA2R positive [10]. Since its discovery in 2009, our understanding of the condition has vastly improved, with evidence suggesting the pathogenic nature of the antibody [13, 19–21]. This, coupled with its relative absence in secondary MN [29], makes it a valuable biomarker not only for disease activity, but also for diagnosis.

Prior to the development of the anti-PLA2R blood test, the diagnosis of PMN was one of exclusion at a cost to patients and the healthcare system. In our cohort, the vast majority of
investigations carried out for this reason were negative, a use of resources that is considerable given MN is one of the most common causes of adult nephrotic syndrome worldwide [1–6].

Here we show that use of the test has increased over the years, with a higher proportion of our patients with a tissue diagnosis of MN undergoing concomitant anti-PLA2R testing; 93% of patients in 2014 compared with only 46.5% in 2012. Along with increased use of anti-PLA2R testing, there is a corresponding reduction in the number of other investigations being carried out and a reduction in the cost of investigations.

Approximately one-third of patients with a diagnosis of PMN will go into spontaneous remission, most within the first year [30]. For this reason, and along with the complications associated with immunosuppression, patients have traditionally been treated with supportive care through inhibition of the renin–angiotensin–aldosterone system for 6 months before considering immunosuppression [7]. However, in the anti-PLA2R era, more proactive management may be warranted. It has now been shown that seronegative patients or those with low anti-PLA2R are more likely to go into spontaneous remission and less likely to suffer from renal decline [13, 31]. Conversely, patients with high anti-PLA2R at diagnosis are more likely to have disease progression, worsening renal function and higher levels of proteinuria [13, 21, 31]. The reduction of anti-PLA2R and subsequent reduction in proteinuria has been shown in a number of studies to improve outcomes following treatment [19–21]. It has also been shown that achieving either partial or complete remission leads to better long-term outcomes [32, 33].

There is still some debate, however, around the benefits of early immunosuppression. In a randomly controlled trial, early immunosuppression did appear to lead to remission quicker than postponing immunosuppressive therapy, with a similar chance of disease progression, worsening renal function and higher levels of proteinuria [13, 21, 31]. The reduction of anti-PLA2R and subsequent reduction in proteinuria has been shown in a number of studies to improve outcomes following treatment [19–21]. It has also been shown that achieving either partial or complete remission leads to better long-term outcomes [32, 33].

As use of the anti-PLA2R test becomes more widespread and physician confidence in its ability to differentiate primary from secondary MN and to prognosticate disease progression increases, it has the potential to radically change management practice. As seen in our study, patients traditionally undergo a large number of invasive investigations in order to rule out pathology, and the majority of these understandably come back with nothing abnormal detected. Not only is the cost to the patients’ quality of life a consideration, but also the cost to the health care system, with the use of resources that could be diverted elsewhere. This is especially true given that the cost of the anti-PLA2R test, currently offered in the UK by the Protein Reference Unit in Sheffield, is £25.81 per sample. This makes it cheaper than many of the investigations patients are currently subjected to.

Our study does have a number of limitations, in particular the likely underestimate of investigations carried out. In the Greater Manchester and Preston region, renal medicine operates in a hub-and-spoke manner, with specialist renal departments centralized in large teaching hospitals and patients transferred or referred in from smaller satellite units around the region. This means that some investigations may well have been carried out in the satellite unit before the patients’ transfer of care, and although the majority of these investigations would be expected to be low-cost tests, such as biochemistry, there may be a number of scans and endoscopies that may not have been accounted for. As this was a retrospective analysis based on patient records, another limitation is the unknown societal cost of anti-PLA2R testing, for example, the cost of transport or missed workdays. As there is a general trend towards a reduction in the frequency of investigations in those patients undergoing anti-PLA2R testing, one could expect to see a reduction in the associated costs to society. However, this would need to be confirmed in a prospective trial. As with any retrospective study, there are inherent limitations involved; a randomly controlled trial to investigate the effect of anti-PLA2R testing on the investigative pathway would be ideal. However, given its proven sensitivity and specificity for MN, it would now be unethical to consider the care of a patient with anti-PLA2R positive MN without the use of the antibody level.

The number of positive anti-PLA2R tests in our cohort was lower than reported in other studies, with most reporting in the region of 70–80% of MN patients [10, 14, 19]. There were, however, a large number of patients in the earlier years of its use that were not tested. As the test became more ubiquitous over time, the percentage of positive samples better reflected the literature. For example, in 2014 there were 14 anti-PLA2R tests, of which 10 were positive, representing 71% of patients.

The use of anti-PLA2R is not infallible, with a number of case reports identifying patients with secondary MN and elevated anti-PLA2R [35–38]. Whether this is coincidental, given that patients in the age group most affected by MN are also at risk of malignancy, is yet to be proven conclusively. Each patient still needs a careful and thorough history and examination and investigation as appropriate.

Saying this, as the anti-PLA2R test becomes commonplace in patients with nephrotic syndrome, its use can help to reduce the burden of investigations for both the patient and society and its use should be included in future management guidelines and research.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format.

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