The investigative burden of Membranous Nephropathy in the United Kingdom

Clinical Kidney Journal, 2019, 1–8

doi: 10.1093/ckj/sfz036
Original Article

ORIGINAL ARTICLE

The investigative burden of membranous nephropathy in the United Kingdom

Patrick Hamilton [1,2], Fiona Wilson[1], Rajkumar Chinnadurai [2,3], Smeeta Sinha[2,3], Malinder Singh[4], Arvind Ponnusamy[4], Peter Hall[5], Ajay Dhaygude[4], Durga Kanigicherla[1,2] and Paul Brenchley[1,2]

[1]Manchester Institute of Nephrology and Transplantation, Manchester Royal Infirmary, Manchester, UK, [2]Manchester Academic Health Science Centre, University of Manchester, Manchester, UK, [3]Vascular Research Group, Salford Royal Hospital, Salford, UK, [4]Royal Preston Hospital, Sharoe Green Lane North, Fulwood, Preston, UK and [5]Cancer Research UK Edinburgh Centre, MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, UK

Correspondence and offprint requests to: Patrick Hamilton; E-mail: Patrick.hamilton@mft.nhs.uk

ABSTRACT

Background. Membranous nephropathy (MN) represents two distinct disease entities. Primary MN is now recognized as an autoimmune condition associated with the anti-PLA_2R 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-PLA_2R 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-PLA_2R 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-PLA_2R test and 38 had a positive test within 6 months of diagnosis. In 2012, 46.5% of patients had an anti-PLA_2R 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-PLA_2R test. This has led to a reduction in the number of screening tests and in the cost of investigations carried out. The anti-PLA_2R test has the potential to reduce this burden as its use becomes more widespread.

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

Received: 8.9.2018; Editorial decision: 8.3.2019

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-PLA_2R) 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-PLA_2R levels decrease months before clinical signs, such as a reduction in proteinuria. The converse is also true with relapse predated 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, then they are left with a high risk of relapse and a reduction in anti-PLA_2R level strongly predicts remission [18, 20, 22].

The benefit of regular anti-PLA_2R testing led to the introduction of the first quantitative anti-PLA_2R 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-PLA_2R 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 and given the disease itself is generally a disease of middle age and older, many patients undergo a number of invasive procedures in order to rule out neoplastic disease. At present, there is no universally accepted consensus on the investigative pathway for primary or secondary MN. In patients with PMN, this results in many being procedures performed, with normal findings, at a cost not only to the patient in terms of quality of life, but also a societal cost to health care systems with limited resources.

Hypothesis

With the anti-PLA_2R test becoming more ubiquitous, the introduction of anti-PLA_2R 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.

Table 1. Cost of investigations

Investigation	Mean value	LQR	UQR	Source
Hepatitis B	6.42	4.02	7.65	DAPS06 NHS ref costs
Hepatitis C	6.42	4.02	7.65	DAPS06 NHS ref costs
HIV	6.42	4.02	7.65	DAPS06 NHS ref costs
RF	6.42	4.02	7.65	DAPS06 NHS ref costs
ds-DNA	6.42	4.02	7.65	DAPS06 NHS ref costs
ANA	6.42	4.02	7.65	DAPS06 NHS ref costs
Complement	6.42	4.02	7.65	DAPS06 NHS ref costs
PSA	1.18	0.78	1.39	DAPS04 NHS ref costs
ANCA	6.42	4.02	7.65	DAPS06 NHS ref costs
TFTs	1.18	0.78	1.39	DAPS04 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	FZ60Z 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	RD40Z 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.

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-PLA_2R 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-PLA_2R 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-PLA_2R testing was not included (Table 1).

For each patient, a total cost was determined for the investigations they underwent, using the resource costs as

Table 2. Demographics

Parameter	No anti-PLA_2R	Negative anti-PLA_2R	Positive anti-PLA_2R	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)	79 (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)
TFTs				
Negative test	30 (38)	18 (27)	20 (53)	68 (37)
No test	50 (62)	48 (73)	18 (47)	116 (63)
CXR				
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)

Table 2. Continued

Parameter	No anti-PLA_2R	Negative anti-PLA_2R	Positive anti-PLA_2R	Total
MRI				
Negative test	1 (1)	1 (2)	1 (3)	3 (2)
No test	79 (99)	65 (98)	37 (97)	181 (98)
PET				
Positive test	0 (0)	1 (2)	0 (0)	1 (1)
No test	80 (100)	65 (98)	38 (100)	183 (99)
OGD				
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)	160 (87)
Colonoscopy				
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)
Sigmoidoscopy				
Negative test	0 (0)	0 (0)	1 (3)	1 (1)
No test	80 (100)	66 (100)	37 (97)	183 (99)
USS abdomen				
Negative test	41 (51)	33 (50)	20 (53	94 (51)
No test	39 (49)	33 (50)	18 (47)	90 (49)
Cystoscopy				
Negative test	0 (0)	1 (2)	3 (8)	4 (2)
No test	80 (100)	65 (98)	35 (92)	180 (98)

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.

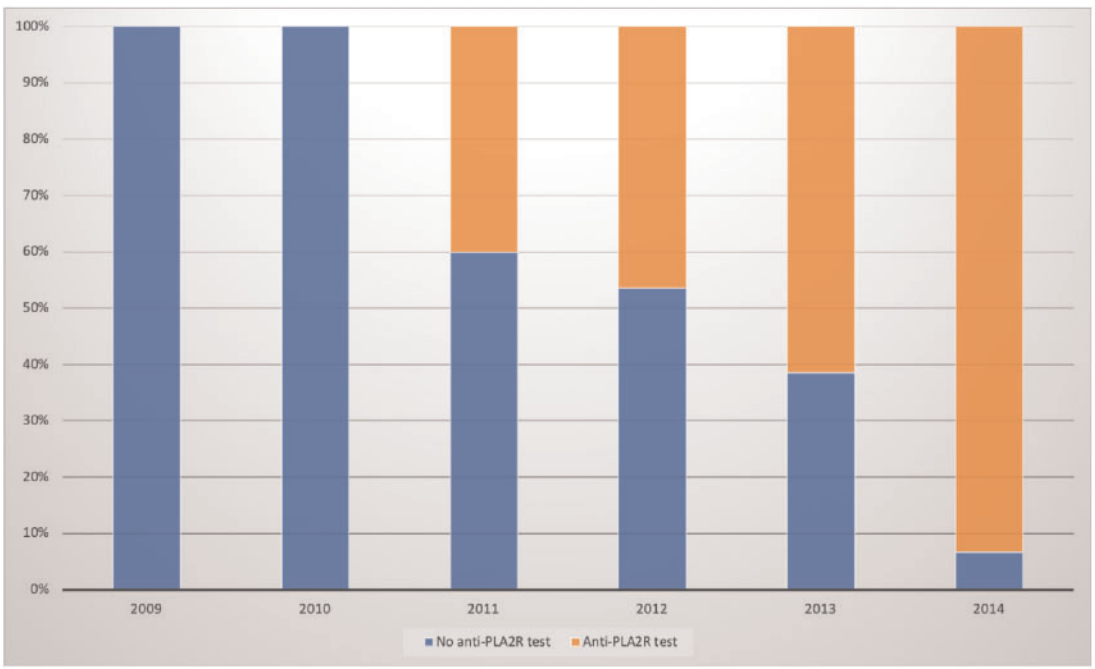

FIGURE 1: Proportion of MN patients with anti-PLA_2R testing.

mentioned above. 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-PLA_2R versus a negative test or no sample taken. Significance was calculated using the Student's *t*-test and

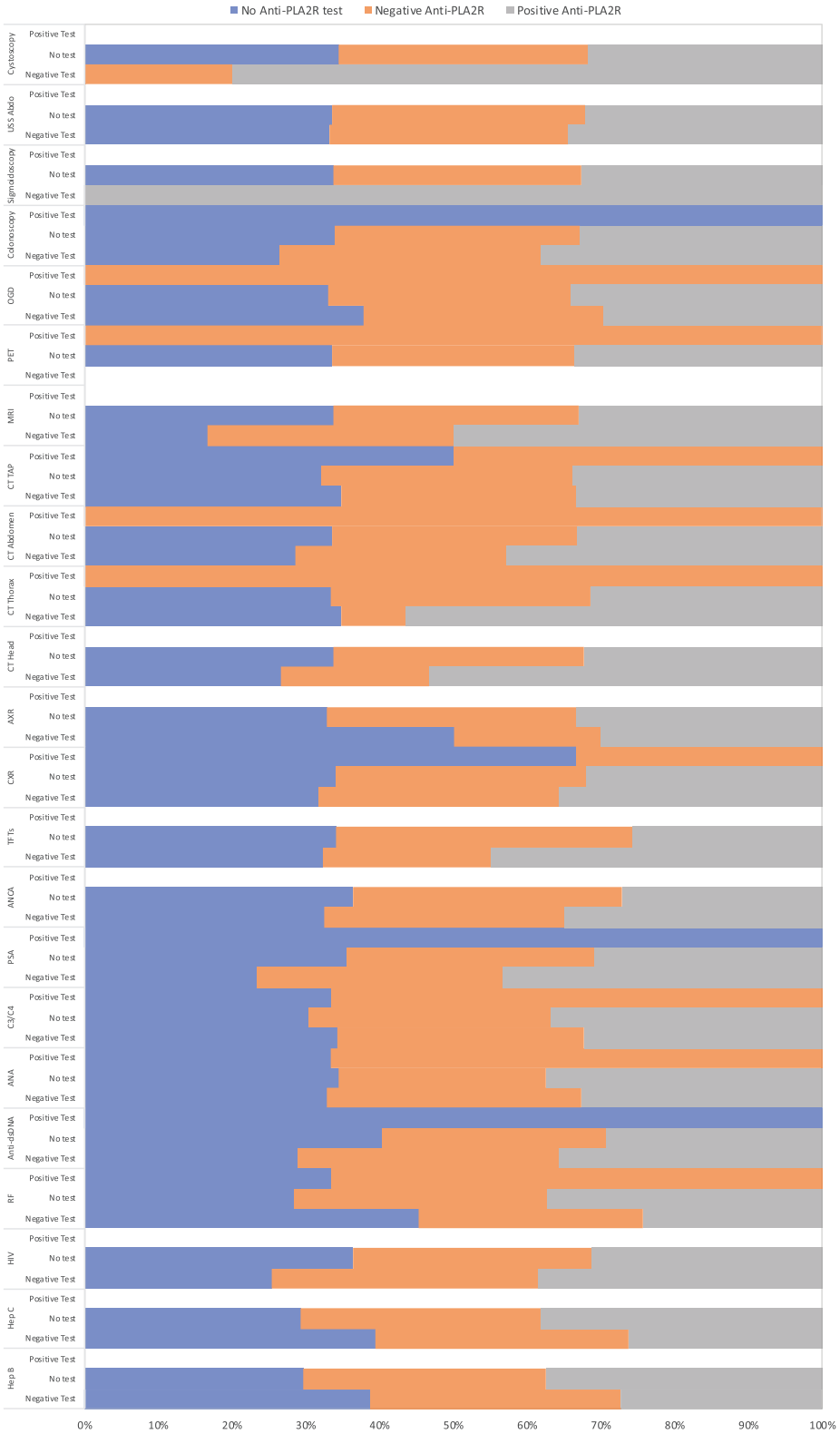

FIGURE 2: Proportion of each investigation with no anti-PLA_2R testing, a negative anti-PLA_2R test and a positive anti-PLA_2R test, based on whether the investigation was positive or negative. C3/C4, complement C3/C4; RF, rheumatoid factor; Hep, hepatitis.

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-PLA_2R testing within 6 months of the date of biopsy and 104 (57%) patients did have an anti-PLA_2R 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-PLA_2R and all were negative.

Frequency of anti-PLA_2R testing

In 2011, when the anti-PLA_2R 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-PLA_2R 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-PLA_2R, *n* (%)	anti-PLA_2R 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-PLA_2R test within 6 months of the date of biopsy.

Number of investigations

There were a total of 1230 investigations performed in all patients, of which only 20 were positive and led to a diagnosis of secondary MN. From 2011 onwards, there is a reduction in the number of investigations performed in anti-PLA_2R seropositive patients. In 2012, the first full year of anti-PLA_2R availability, there was a mean of 6.85 tests (95% CI 5.61–8.09) per patient in those with no anti-PLA_2R testing or a negative test. In the seropositive group, the mean number of tests was 6.59 (95% CI 4.9–8.2). This difference was not statistically significant (P=0.823). In 2014, the mean number of tests performed per patient in the seropositive group decreased to 4.29 tests (95% CI 2.6–6.1) compared with 9.01 in seronegative patients; this represented a significant difference (95% CI 6.6–11.02; P = 0.019; Table 4).

Cost of investigations

The total cost of investigations within 6 months of biopsy for all patients was £39 177.83 and, of this, £5533.04 was spent on investigations with a result leading to a diagnosis of secondary MN. In patients with no anti-PLA_2R testing or a negative result, the cost of investigations remained relatively stable over the years at £220.27 (95% CI 137.93–315.77) in 2009 and £244.11 (95% CI 109.88–429.97) in 2014. In patients with a positive anti-PLA_2R, the cost of investigations decreased each year from its introduction, going from £497.92 (95% CI 89.83–909.00) in 2011 to £132.94 (95% CI 29.66–309.44) in 2014, although the difference in cost per year was not significant between the groups (Table 4).

DISCUSSION

The majority of patients with a histological diagnosis of MN will have primary MN, an autoimmune disease in which 70–80% are anti-PLA_2R 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-PLA_2R blood test, the diagnosis of PMN was one of exclusion at a cost to patients and the health care system. In our cohort, the vast majority of

Table 4. Number of tests and cost of tests based on year of biopsy and anti-PLA_2R test status

Year of diagnosis	No test or anti-PLA_2R negative	Anti-PLA_2R 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)	0.363
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			
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.

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-PLA_2R testing; 93% of patients in 2014 compared with only 46.5% in 2012. Along with increased use of anti-PLA_2R 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-PLA_2R era, more proactive management may be warranted. It has now been shown that seronegative patients or those with low anti-PLA_2R are more likely to go into spontaneous remission and less likely to suffer from renal decline [13, 31]. Conversely, patients with high anti-PLA_2R at diagnosis are more likely to have disease progression, worsening renal function and higher levels of proteinuria [13, 21, 31]. The reduction of anti-PLA_2R and subsequent reduction in proteinuria has been shown in a number of studies to improve outcomes following treatment [19–21]. It has also long 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 adverse event profile. At the end of the 6-year follow-up, 86% of patients in the early immunosuppression group had achieved remission compared with 67% in the late treatment group. However, there was no statistical difference in serum creatinine, albumin or proteinuria [34]. Given the relatively short follow-up time with respect to the long disease course of MN, over time one could speculate that a difference may have been observed. This study was also carried out in the pre-anti-PLA_2R era when disease severity was based on proteinuria. By utilizing the anti-PLA_2R titre, those patients with high levels who are unlikely to go into spontaneous remission and have a higher chance of disease progression could have a shorter time to treatment without the need to wait for unnecessary invasive investigations.

As use of the anti-PLA_2R 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-PLA_2R 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-PLA_2R 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-PLA_2R 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-PLA_2R 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-PLA_2R-positive MN without the use of the antibody level.

The number of positive anti-PLA_2R 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-PLA_2R tests, of which 10 were positive, representing 71% of patients.

The use of anti-PLA_2R is not infallible, with a number of case reports identifying patients with secondary MN and elevated anti-PLA_2R [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-PLA_2R 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.

REFERENCES

1. Rivera F, López-Gómez JM, Pérez-García R *et al*. Frequency of renal pathology in Spain 1994–1999. *Nephrol Dial Transplant* 2002; 17: 1594–1602
2. McGrogan A, Franssen CFM, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. *Nephrol Dial Transplant* 2011; 26: 414–430
3. Braden GL, Mulhern JG, O'Shea MH *et al*. Changing incidence of glomerular diseases in adults. *Am J Kidney Dis* 2000; 35: 878–883
4. Simon P, Ramee M-P, Boulahrouz R *et al*. Epidemiologic data of primary glomerular diseases in western France. *Kidney Int* 2004; 66: 905–908

5. Swaminathan S, Leung N, Lager DJ *et al*. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. *Clin J Am Soc Nephrol* 2006; 1: 483–487
6. Malafronte P, Mastroianni-Kirsztajn G, Betônico GN *et al*. Paulista registry of glomerulonephritis: 5-year data report. *Nephrol Dial Transplant* 2006; 21: 3098–3105
7. Eknoyan G, Eckardt KU, Kasiske BL. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 1–274
8. Lefaucheur C, Stengel B, Nochy D *et al*. Membranous nephropathy and cancer: epidemiologic evidence and determinants of high-risk cancer association. *Kidney Int* 2006; 70: 1510–1517
9. Hofstra JM, Wetzels JFM. Management of patients with membranous nephropathy. *Nephrol Dial Transplant* 2012; 27: 6–9
10. Beck LH, Bonegio RGB, Lambeau G *et al*. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; 361: 11–21
11. Stanescu HC, Arcos-Burgos M, Medlar A *et al*. Risk HLA-DQA1 and PLA_2R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; 364: 616–626
12. Coenen MJH, Hofstra JM, Debiec H *et al*. Phospholipase A2 receptor (*PLA2R1*) sequence variants in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2013; 24: 677–683
13. Kanigicherla D, Gummadova J, McKenzie EA *et al*. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. *Kidney Int* 2013; 83: 940–948
14. Hofstra JM, Beck LH, Beck DM *et al*. Anti-phospholipase A2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2011; 6: 1286–1291
15. Hofstra JM, Debiec H, Short CD *et al*. Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; 23: 1735–1743
16. Fresquet M, Jowitt TA, Gummadova J *et al*. Identification of a major epitope recognized by PLA2R autoantibodies in primary membranous nephropathy. *J Am Soc Nephrol* 2015; 26: 302–313
17. Oliveira DB. Membranous nephropathy: an IgG4-mediated disease. *Lancet* 1998; 351: 670–671
18. Bech AP, Hofstra JM, Brenchley PE *et al*. Association of anti-PLA2R antibodies with outcomes after immunosuppressive therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2014; 9: 1386–1392
19. Beck LH, Fervenza FC, Beck DM *et al*. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. *J Am Soc Nephrol* 2011; 22: 1543–1550
20. Ruggenenti P, Debiec H, Ruggiero B *et al*. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. *J Am Soc Nephrol* 2015; 26: 2545–2558
21. Hoxha E, Thiele I, Zahner G *et al*. Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. *J Am Soc Nephrol*; 2014; 25: 1357–1366
22. Herrmann SMS, Sethi S, Fervenza FC. Membranous nephropathy. *Curr Opin Nephrol Hypertens* 2012; 21: 203–210
23. Anti-Phospholipase A2 Receptor IIFT (IgG). https://www.euroimmun.com/documents/Indications/Autoimmunity/Nephrology/PLA2R/FA_1254_D_UK_A.pdf (25 May 2018, date last accessed)
24. NHS Reference Costs 2015-2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/ attachment_data/file/577084/National_schedule_of_reference_costs_-_main_schedule.xlsx (25 May 2018, date last accessed)
25. NHS England National Tariff for 2015 to 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/331887/15-16_Non-Mandatory_model_16072014.xlsx (25 May 2018, date last accessed)
26. DiCiccio TJ, Efron B. Bootstrap confidence intervals. *Stat Sci* 1996; 11: 189–228
27. Efron B, Tibshirani RJ. Introduction. In: *An Introduction to the Bootstrap*. Boston: Springer, 1993, 1–9
28. R Core Team R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2018; https://www.R-project.org/
29. Hofstra JM, Wetzels JF. Anti-PLA2r antibodies in membranous nephropathy: ready for routine clinical practice? *Neth J Med* 2012; 70: 109–113
30. Polanco N, Gutiérrez E, Covarsí A *et al*. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2010; 21: 697–704
31. Hoxha E, Harendza S, Pinnschmidt H *et al*. M-type phospholipase A2 receptor autoantibodies and renal function in patients with primary membranous nephropathy. *Clin J Am Soc Nephrol* 2014; 9: 1883–1890.
32. Kanigicherla DAK, Short CD, Roberts SA *et al*. Long-term outcomes of persistent disease and relapse in primary membranous nephropathy. *Nephrol Dial Transplant* 2016; 31: gfv435–2114
33. Troyanov S, Wall CA, Miller JA *et al*. Idiopathic membranous nephropathy: definition and relevance of a partial remission. *Kidney Int* 2004; 66: 1199–1205
34. Hofstra JM, Branten AJW, Wirtz JJJM *et al*. Early versus late start of immunosuppressive therapy in idiopathic membranous nephropathy: a randomized controlled trial. *Nephrol Dial Transplant* 2010; 25: 129–136
35. Timmermans SAMEG, Ayalon R, van Paassen P *et al*. Anti–phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. *Am J Kidney Dis* 2013; 62: 1223–1225
36. Xie Q, Li Y, Xue J *et al*. Renal phospholipase A2 receptor in hepatitis B virus-associated membranous nephropathy. *Am J Nephrol* 2015; 41: 345–353
37. Qin W, Beck LH, Zeng C *et al*. Anti-phospholipase A2 receptor antibody in membranous nephropathy. *J Am Soc Nephrol* 2011; 22: 1137–1143
38. Stehlé T, Audard V, Ronco P *et al*. Phospholipase A2 receptor and sarcoidosis-associated membranous nephropathy. *Nephrol Dial Transplant* 2015; 30: 1047–1050