

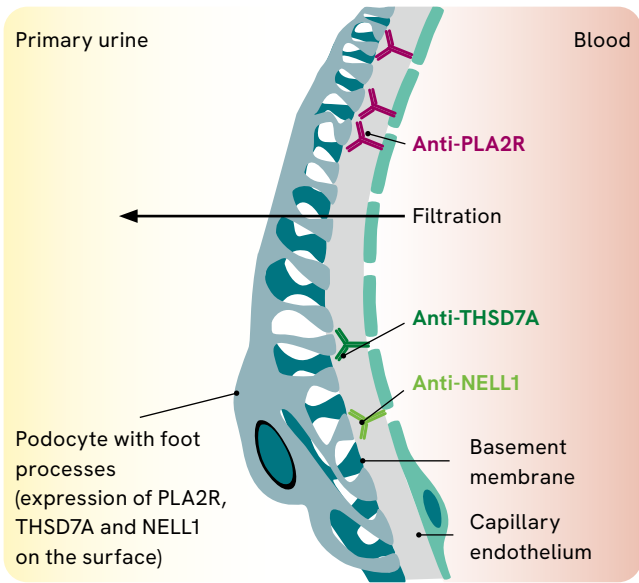
Biomarkers in primary membranous nephropathy.



Primary membranous nephropathy (pMN)

Primary membranous nephropathy (pMN) is a chronic inflammatory disease of the renal corpuscles (glomeruli), which can take very different courses.

A third of patients have no major kidney function impairment and experience spontaneous remission without medication, a third show no symptomatic changes



Filtration barrier of the kidney

Serological markers for pMN

- Anti-PLA2R autoantibodies: marker with the highest specificity and sensitivity
- Anti-THSD7A autoantibodies: supplementary marker especially in anti-PLA2R-negative patients
- Worldwide exclusive qualitative and quantitative test systems (ELISA, ChLIA and IIFT) for determination of the two markers

and have persistent proteinuria, and another third have severe worsening of symptoms, developing nephrotic syndrome and requiring a kidney transplant.

The gold standard for the diagnosis of MN is usually kidney biopsy. However, the invasive method is very stressful for patients and does not allow differential diagnosis between primary (pMN) and secondary (sMN) membranous nephropathy (MN resulting from an underlying disease).

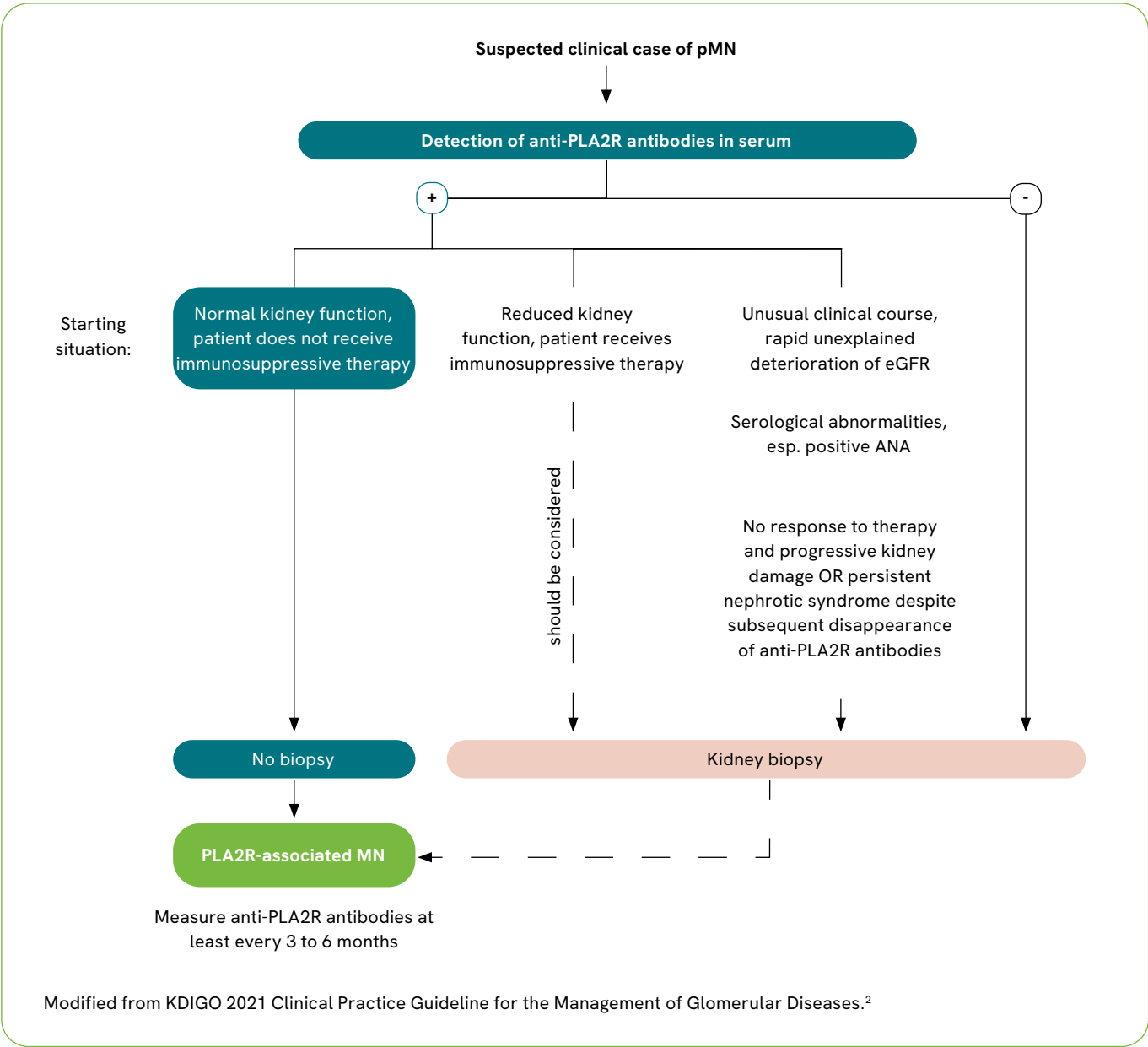
In 2009, Beck et al. identified the **phospholipase A2 receptor (PLA2R)**, which is expressed in the cell membrane of podocytes of healthy glomeruli, as a specific target antigen for autoantibodies in pMN.¹ By detecting anti-PLA2R antibodies, the diagnosis of pMN can be made with high accuracy – in some cases even without a biopsy (see figure page 3).²

In 2014, Tomas et al. described another target antigen of autoantibodies in patients with pMN: **THSD7A (thrombospondin type-1 domain-containing 7A)**.³

In 2020, Sethi et al. discovered a third target antigen for pMN-associated autoantibodies: **NELL1 (neural epidermal growth factor-like 1 protein)**.⁴



Diagnostic guideline for suspected pMN²



Anti-PLA2R autoantibodies

Since the discovery of anti-PLA2R antibodies as highly specific marker of pMN and the development of serological test systems, the antibodies have become the subject of numerous research projects.

These show that the serum antibodies have a specificity of almost 100 % and a prevalence of 70 % to 80 % in pMN.⁵

Sensitivities differ depending on the detection method and are slightly higher for the indirect immunofluorescence test (IIFT; 83.2%) and chemiluminescence immunoassay (ChLIA; 83.9%) than for ELISA (73.5%). ELISA and ChLIA enable quantitative determination of the antibody concentration, as is required for monitoring of the disease course and therapy.^{6,7}



Anti-PLA2R autoantibodies

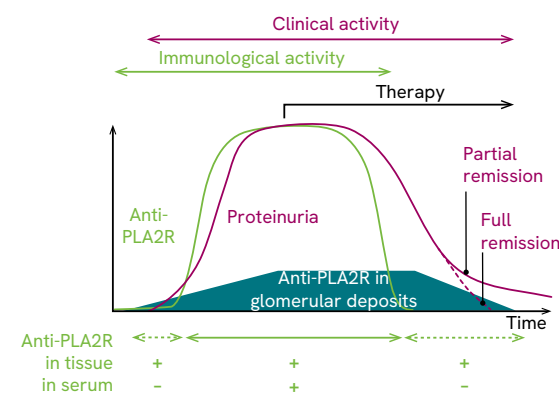
- Most important serological marker for pMN
- Specificity of over 99 % and prevalence of approx. 80 %
- The serological determination of anti-PLA2R enables differential diagnosis, monitoring of the disease course and therapy, prognosis and risk assessment after transplantation.

Monitoring of the disease course and therapy

Today, it is known that the anti-PLA2R antibody titer correlates with the clinical activity of the disease.

With successful immunosuppressive therapy, the titer decreases within a short time, accompanied by a delayed reduction of clinical symptoms (proteinuria).

The determination of the antibody titer is therefore a suitable tool for monitoring the disease status and the patient's response to therapy.^{8,9}



Modified from Francis JM, et al.¹⁰

Making a prognosis

High anti-PLA2R antibody levels are also a risk factor for an unfavourable outcome of the disease (no remission) or the need for a longer treatment duration until clinical remission. Presumably due to the associated pronounced proteinuria, high antibody levels are also associated with a rapid loss of kidney function.

In addition, the probability of spontaneous remission seems to be smaller for patients with high antibody titers than for those with relatively low titers.

Thanks to its predictive value, the marker can significantly support the doctor's therapy decision.¹¹⁻¹³

Risk assessment after transplantation

Furthermore, regular determination of the anti-PLA2R antibody titer in pMN patients with kidney transplants can help to predict possible relapses.

There is evidence that high titers are associated with an increased risk of disease recurrence both before and after transplantation.^{14, 15}

Anti-THSD7A autoantibodies

The prevalence of anti-THSD7A antibodies is given with values of up to 10%. Although antibodies against PLA2R and THSD7A can occur in parallel in rare cases, anti-THSD7A antibodies have been found predominantly in anti-PLA2R-seronegative pMN patients.

A study by Hoxha et al. (2016) suggests that the clinical picture of anti-PLA2R- and anti-THSD7A-positive pMN patients differs in that malignant tumours were found more frequently in anti-THSD7A-positive patients.

As a supplement to anti-PLA2R antibodies, anti-THSD7A antibodies are therefore another marker in serological pMN diagnostics.

Due to their high specificity, they are equally suited for differentiation from secondary MN as anti-PLA2R antibodies.

Moreover, simultaneous determination of anti-PLA2R and THSD7A antibodies increases the serological detection rate.^{3, 16-18}



Anti-THSD7A autoantibodies

- Supplementary serological marker
- Up to 10% of anti-PLA2R-seronegative pMN patients are anti-THSD7A positive.
- Anti-THSD7A autoantibodies can be associated with malignant tumours.

Anti-NELL1 autoantibodies

Anti-NELL1 antibodies have been detected in anti-PLA2R-negative and biopsy-confirmed cases of pMN.

In a study of over 800 cases, the prevalence was 2%. Very rarely, anti-NELL1 antibodies also occurred in

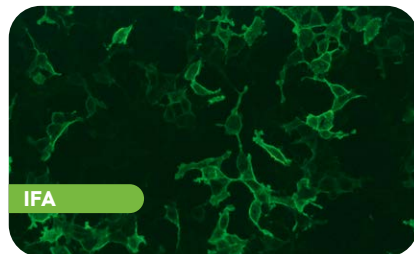
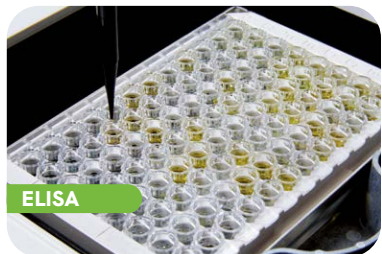
parallel with anti-PLA2R and anti-THSD7A antibodies.

In terms of clinical and pathological appearance, anti-NELL1-positive pMN does not differ from anti-PLA2R-positive pMN. However, women were more frequently affected.^{4, 19}

Worldwide exclusive test systems from Euroimmun for the detection of anti-PLA2R and anti-THSD7A autoantibodies



ChLIA: Anti-PLA2R ChLIA (IgG) for IDS-i10* and IDS-iSYS Multi-Discipline Automated System* **ELISA:** Anti-PLA2R ELISA (IgG) for manual and automated processing **IFA:** with transfected cells (Anti-PLA2R IIFT and Anti-THSD7A IIFT) for manual and automated processing and microscopy as well as computer-assisted result proposals



Order

Test system	Testname	Substrate	Order number
ChLIA	Anti-PLA2R ChLIA (IgG)	Recombinant antigen	LA 1254 G
ELISA	Anti-PLA2R ELISA (IgG)	Recombinant antigen	EA 1254 G
IFA	Anti-PLA2R IIFT	Transfected cells	FA 1254-50-R
	Anti-THSD7A IIFT	Transfected cells	FA 1254-51-R
	Membranous Nephropathy Mosaic 1 IIFT	Transfected cells	FA 1254-1-R

Parameters for research use only**

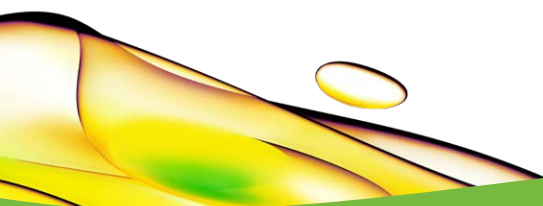
Test system	Testname	Substrate	Order number
IIFT	Anti-NELL1 IIFT	Transfected cells	FA 1254-52
	IIFT: Membranous Nephropathy Mosaic 2	Transfected cells	FA 1254-2

*Product manufactured by Immunodiagnostic Systems Limited (IDS); available to ordner from your local Euroimmun contact
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**For research use only, not for in vitro diagnostic use.

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