بسم الله الرحمن الرحيم

Glomerulonephritis And Malignancy

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Overview & Objectives

- Epidemiology of Cancer-associated glomerulopathy (CAG)
- Mechanisms of CAG
- Which cancer ...association… which GN?
- How should we screen for CAG?
- treatment of CAG?

Epidemiology

- Cancer ……three times greater in GN patients > 50 years.
- MN: 10% risk of CAG.
- In a Danish registry study, 911 cancers in 5594 patients. Prevalence at biopsy was **5.5%** (expected 3.1% in the general population),
- incidence was not increased < 1 year before biopsy. Increased cancer rates were seen for lung, prostate, renal, non-Hodgkin lymphoma, myeloma, leukaemia and skin.

Leeaphorn N , et al., Am J Nephrol. 2014
Heaf, J.G., Hansen, A. & Laier, G.H. Quantification of cancer risk in glomerulonephritis. *BMC Nephrol* 19, 27 (2018).

Heaf *et al. BMC Nephrology* (2018) 19:27
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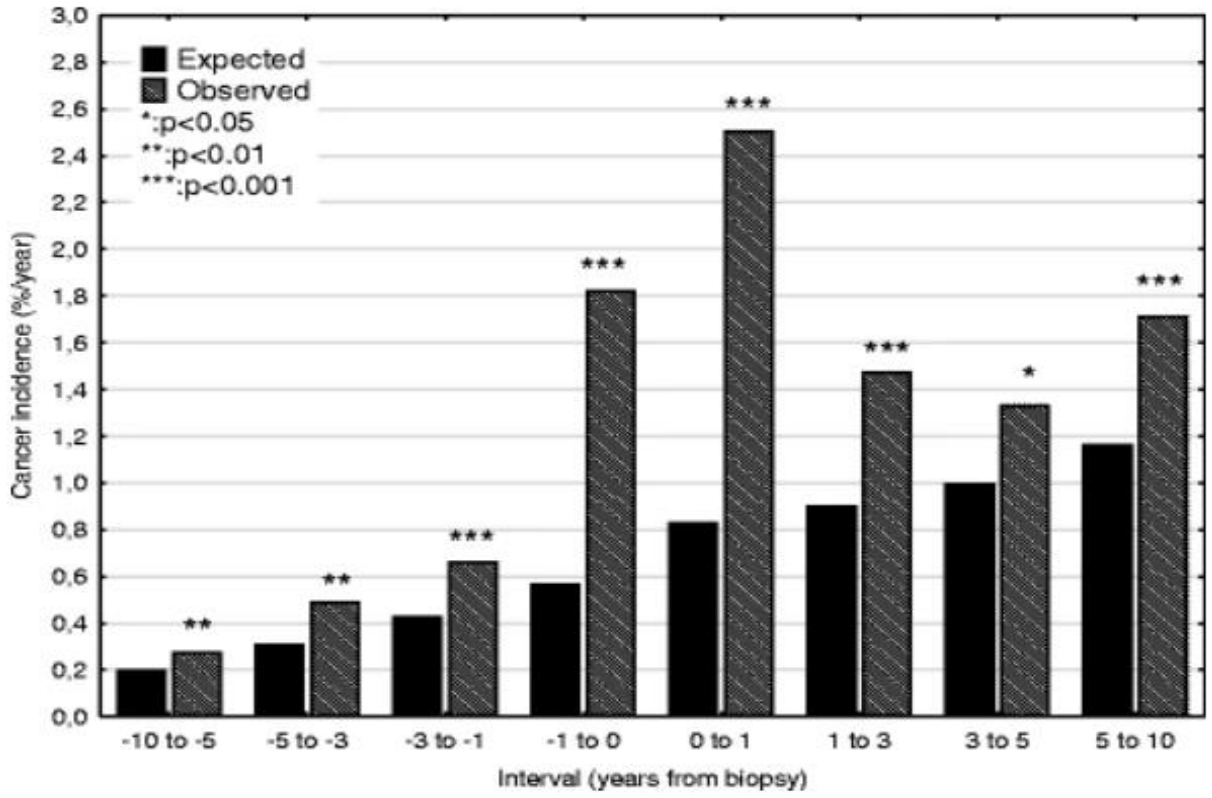
BMC Nephrology

RESEARCH ARTICLE Open Access

Quantification of cancer risk in glomerulonephritis

James Goya Heaf[1*], Alastair Hansen[2] and Gunnar Hellmund Laier[3]

Fig. 1



Observed and expected any cancer incidences for all biopsied

Table 1 Patient age, sex, and cancer prevalence at diagnosis (observed vs. expected)

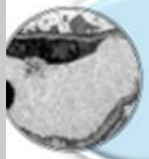
	No. patients	Age (yrs)	Female (%)	Patients with Cancer	Prevalence (%)	Expected prevalence (%)	Risk Ratio
Minimal change	428	43,3 ± 19	46	19	4,4	1.9	**2.4 (1.4–3.7)[c]**
Endocapillary	137	43,4 ± 18	53	7	5,1	1.7	**3.0 (1.2–6.2)[a]**
Focal segmental glomerulosclerosis	408	49,0 ± 17	34	27	6,6	2.7	**2.4 (1.6–3.5)[c]**
Mesangioproliferative	1185	42,2 ± 17	36	36	3,0	1.7	**1,8 (1.2–2.5)[b]**
Membranous	741	52,3 ± 17	41	37	5,0	3.2	**1.5 (1.1–2.1)[a]**
Membranoproliferative	298	49,2 ± 17	50	22	7,4	2.4	**3.1 (1.9–4.7)[c]**
Proliferative	113	43,4 ± 19	46	7	6,2	2.1	**2.9 (1.2–6.0)[a]**
Focal segmental proliferative	507	47,3 ± 19	36	15	3,0	2.3	1,3 (0.7–2.1)
Focal	146	56,1 ± 17	41	6	4,1	3.1	1.3 (0.5–1.8)
Crescentic	610	58,4 ± 16	39	27	4,4	3.9	1.1 (0.7–1.6)
Unclassified	552	55,4 ± 18	41	82	14,9	3.0	**4.9 (3.9–6.1)[c]**
Anti-GBMGN	92	55,5 ± 22	53	1	1,1	4.4	0.2 (0–1.4)
ANCA associated vasculitis	278	59,1 ± 16	38	21	7,6	4.2	**1,8 (1.1–2.5)[a]**
Lupus nephritis unspecified	99	38,1 ± 17	77	1	1,0	1.5	0,7 (0–3.8)
Lupus nephritis all	422	36.4 ± 15	77	7	1.7	0.7	1.2 (0.5–2.5)
Any	5594	49.4 ± 18	41	330	5.5	3.1	**1,8 (1.4–2.1)[c]**

Significant risk ratios in bold type
[a]:< 0.05; [b]:< 0.01; [c]:< 0.001

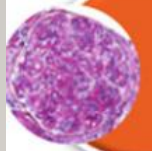
Heaf, J.G., Hansen, A. & Laier, G.H. Quantification of cancer risk in glomerulonephritis. *BMC Nephrol* 19, 27 (2018).

Paraneoplastic Glomerular Diseases

ACKD
Advances in Chronic Kidney Disease



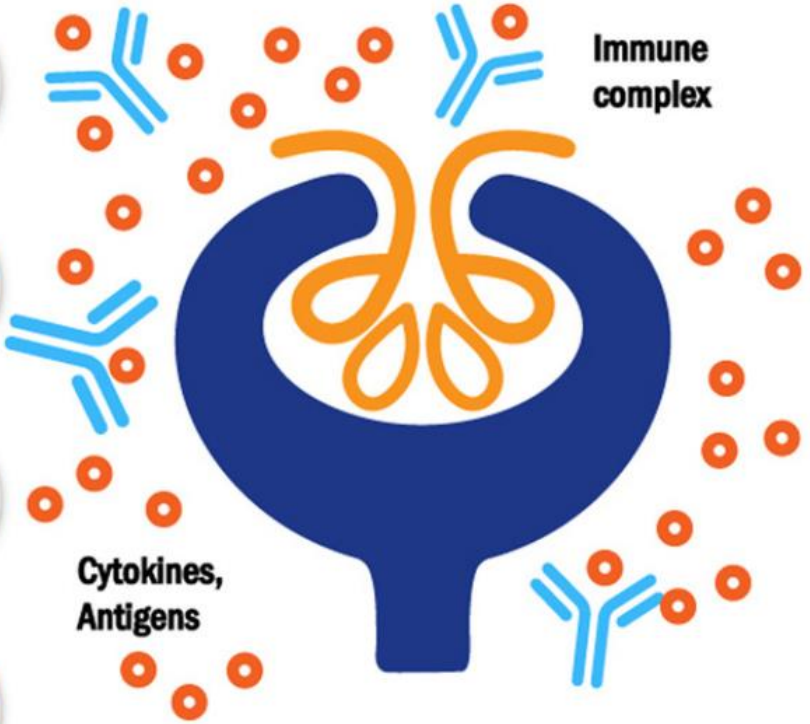
MCD/FSGS
Hodgkin's lymphoma, leukemia, GI Cancer (Ca)



MPGN
Lung, renal, GI cancer
Leukemia, Lymphoma

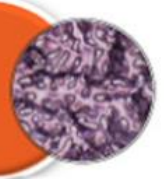
AA Amyloidosis
Hodgkins lymphoma
Renal Cancer

Immunotactoid Glomerulopathy
Lymphoproliferative Ca

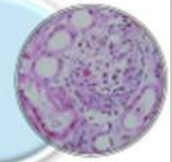


MPGN-Membranoproliferative glomerulonephritis, MCD- minimal change disease, FSGS-Focal segmental glomerulosclerosis, TMA -Thrombotic microangiopathy, MN-Membranous nephropathy

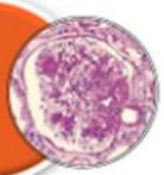
MN
Lung, GI, renal, breast Ca
prostate, hematological Ca



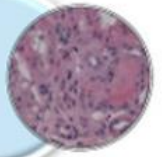
ANCA Vasculitis
Renal, GI Cancer
Thymoma



IgA Nephropathy
Renal, Lung Cancer
Cutaneous lymphoma



TMA
GI, Breast Cancer
Myeloproliferative Ca



Reference: Jeyabalan and Trivedi. ACKD.2022
VA by Mythri Shankar, MD, DNB

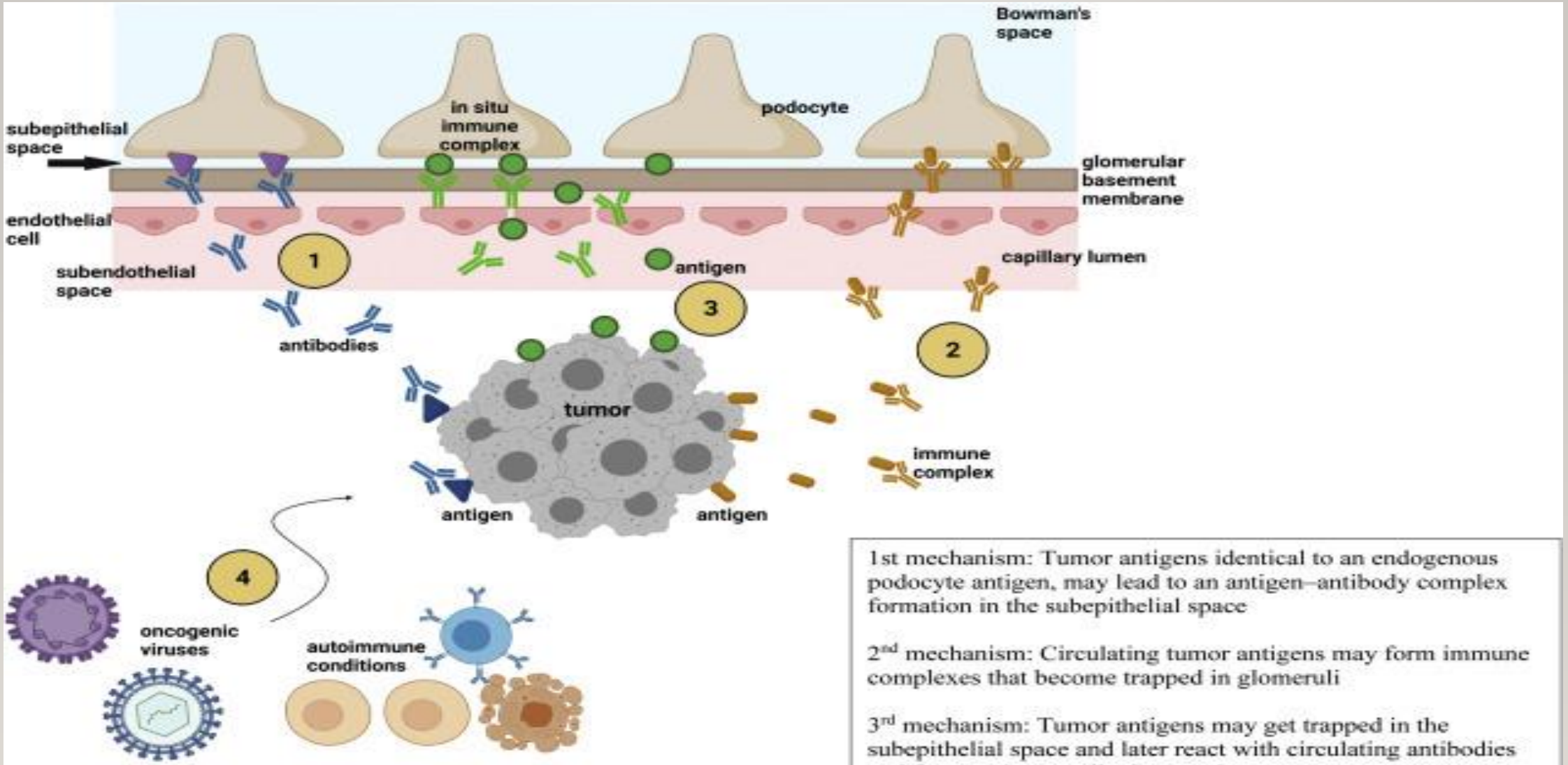
Conclusion: Most of our recent understanding of paraneoplastic GNs has emerged from the discovery of target antigens in membranous. Treatment of paraneoplastic GNs is usually directed at the underlying malignancy.

Jeyabalan A, Trivedi M. Paraneoplastic Glomerular Diseases. *Adv Chronic Kidney Dis*. 2022;

Mechanism Of CAG

- Cancer → paraneoplastic GN
  - hormones, growth factors, cytokines (IL-6, TNF-α, …), tumor antigens ….disrupt the normal immune response and lead to immune dysregulation.
- Drugs……..
- infection and environmental issue….

Murt, Ahmet et al. "Malignancies and glomerulonephritis: when to suspect and when to screen?." *Clinical kidney journal* vol. 18,5 sfaf101. 10 Apr. 2025



1st mechanism: Tumor antigens identical to an endogenous podocyte antigen, may lead to an antigen–antibody complex formation in the subepithelial space

2nd mechanism: Circulating tumor antigens may form immune complexes that become trapped in glomeruli

3rd mechanism: Tumor antigens may get trapped in the subepithelial space and later react with circulating antibodies and form antigen-antibody complexes

4th mechanism: An extrinsic trigger, such as infection or altered immune system may have direct contributory effects on the development of both cancer and MN

Membranous Nephropathy

- 42 malignancy-associated MN ….14 before the diagnosis of MN .
- The median time to detect malignancies: 14 month
- CAG + Immunosuppressive therapy :no Remission in > 50%
- 6 /10 patients remission of cancer …..remission of MN,
  - delay of cancer diagnosis: malignancies after MN; malignancies occult; no screening
  - malignancies within the first year ….related to the onset of GN.
  - later : *de novo* cancer .
  - Recurrence of disease… screening for malignancy and, PLA2R and THSD7A

Murt, Ahmet et al. "Malignancies and glomerulonephritis: when to suspect and when to screen?." *Clinical kidney journal* vol. 18,5 sfaf101. 10 Apr. 2025

Membranous Nephropathy (Biomarkers)

Table 2: The rate of malignancy as reported in studies with proposed antigens implicated in MN.

Antigen	Rate of positivity in primary membranous nephropathy	Approximate incidence of MN antigens [13]	Rate of underlying malignancy when reported positive
PLA2R [13, 34]	70%–80%	55%	Up to 5%[a]
THSD7A [8, 34]	3%	2%	6%–25%
NELL-1 [9, 10]	1%–2%	10%	10%–30%
PCDH7 [12]	2%	2%	20%

PCDH7, Protocadherin 7; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type-1 domain-containing 7A; NELL-1, neural epidermal growth factor-like 1.

Murt A, Berke I, Bruchfeld A, et al. Malignancies and glomerulonephritis: when to suspect and when to screen?. *Clin Kidney J*. 2025

Membranous Nephropathy(CAG)

- **Pathology:** additional subendothelial deposits
  - dominant IgG1 and IgG2 .
  - more inflammatory cells (8 inflammatory cells per glomerulus, 75 % sensitivity and 92 % specificity)
- Thromboembolic disease.
- Cancer treatment is the main strategy
- No remission of MN after resolution of cancer (or when the tumor cannot be identified during relapses of GN):immunosuppressive therapy (particular if PLA2R ab positive).
- **Rituximab** is the most reasonable option for the treatment of MN patients who have concomitant malignancies and PLA2R positivity.

Murt A, Berke I, Bruchfeld A, et al. Malignancies and glomerulonephritis: when to suspect and when to screen?. *Clin Kidney J*. 2025

MCD/IgAN

- **MCD**…..Hodgkin's disease, other lymphomas, solid organ malignancies (thymoma, kidney, lung, GI).
- pathophysiological :viral involvement(EBV), HHV8
- constitutional symptoms OR steroid-resistant or relapsing MCD…Hodgkin's disease…. lymph node examination.
- high frequency of kidney replacement therapy requirement.
- malignancies in **IgA nephropathy**: buccal cavity, nasopharynx, respiratory tract (mucosal immune dysregulation) . RCC(> 50 years)

Jhaveri KD, et al., Glomerular diseases associated with cancer, chemotherapy, and hematopoietic stem cell transplantation. *Adv Chronic Kidney Dis*. 2014;

MPGN/ FSGS/ TMA

- **MPGN** : most common GN in patients with CLL.
    - lung, kidney, stomach cancers.
    - Non-Hodgkin's lymphoma, hairy cell leukemia,
- **FSGS**: RCC, thymoma, Hematologic Malignancy.
- Cancer-Associated **TMA**: Mucin-producing gastric, lung, and breast cancers . poorer response to plasmapheresis (because of the activity of ADAMTS13)

Jhaveri KD, et al., Glomerular diseases associated with cancer, chemotherapy, and hematopoietic stem cell transplantation. *Adv Chronic Kidney Dis*. 2014;

Oncogenic Role Of Immunosuppressive Therapy

- **Glucocorticoids**: state of immunodeficiency,
- **cyclophosphamide**: bladder cancer (mucosal inflammation / direct oncogenic
- effect). Prevention: fluid intake and MESNA.
- lymphoma in SLE, AML in granulomatosis with polyangiitis.
- **Cumulative dose** < 360 mg/kg, i.e., 2 mg/kg/day for 6 months or 1 mg/kg/day for 12 months.
- long-term **chlorambucil** in polycythemia vera or ovarian cancer: acute leukemia.
- daily doses <0.1–0.2 mg/kg and not prolonging treatment for more than 3 months.

Pani, Antonello et al. "Glomerular diseases and cancer: evaluation of underlying malignancy." *Journal of nephrology* vol. 29,2 (2016)

Oncogenic Role Of Immunosuppressive Therapy

- Azathioprine: in organ transplant recipients
  - ✓Multiple sclerosis: duration of 10 years and accumulative dose above 600 g.
  - ✓Data from a Danish registry (IBD) :lymphoid tissue and urinary tract cancer,
- Mycophenolic acid : impairment in the immune surveillance,

✓ antiproliferative activity against leukemia and lymphoma

✓ anti-tumor effect against colon and prostate cancer.

- Calcineurin inhibitors (CNI) : lymphoproliferative disorders and Kaposi sarcoma in TX Pt. (dosage and duration)

✓ patients with GN: short duration and low dose

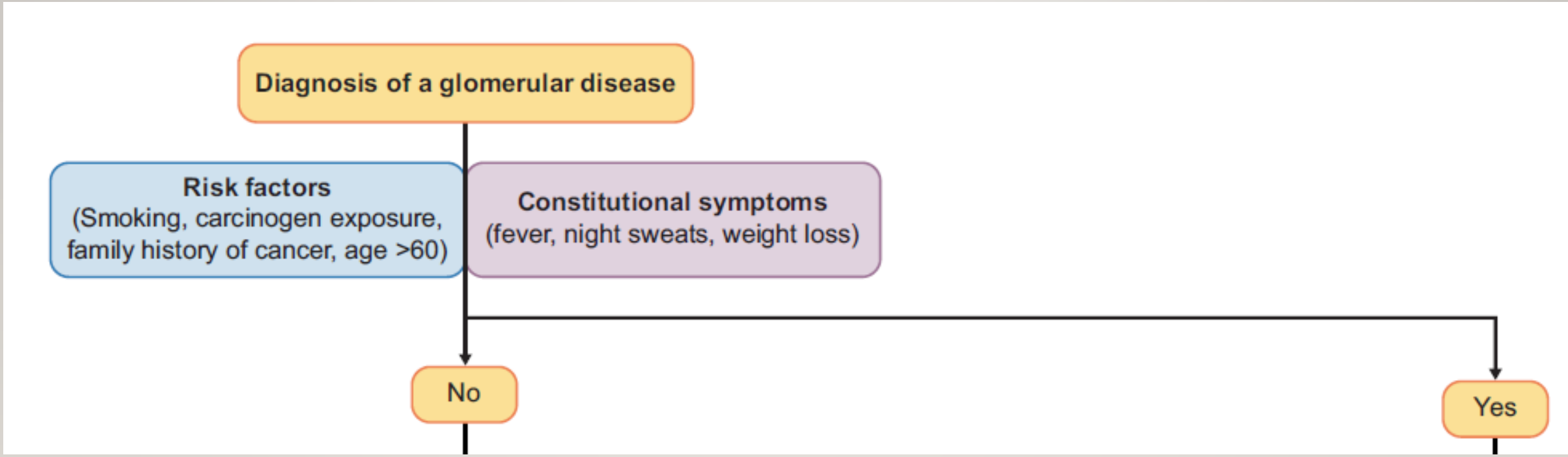
Pani A, Porta C, Cosmai L, et al. Glomerular diseases and cancer: evaluation of underlying malignancy. *J Nephrol*. 2016;

Table 2. Chemotherapy-Associated Glomerular Diseases

Kidney Biopsy Findings	Chemotherapy Agents
TMA	Mitomycin C, gemcitabine, Anti-VEGF therapies (bevacizumab, sunitinib, sorafenib, pazopanib, axitinib, imatinib) CNI (tacrolimus, cyclosporine) mTOR inhibitors (sirolimus, temsirolimus, everolimus) radiation therapy Inteferons Anthracyclines (doxorubicin, daunorubicin)
MPGN	Gemcitabine, mTOR inhibitors
FSGS NOS	mTOR inhibitors Anthracyclines (doxorubicin, daunorubicin)
MCD	Interferons Lenalidomide Pamidronate Anthracyclines mTOR inhibitors
Collapsing glomerulopathy	Interferons Pamidronate, EGFR antagonist mTOR inhibitors Anthracyclines
MN	mTOR inhibitors
CGN	Filgrastim
Lupus-like nephritis	Ipilimumab
IgA nephropathy	mTOR inhibitors

Jhaveri KD, et al. Glomerular diseases associated with cancer, chemotherapy, and hematopoietic stem cell transplantation. *Adv Chronic Kidney Dis*. 2014

When Should We Screen For CAG?



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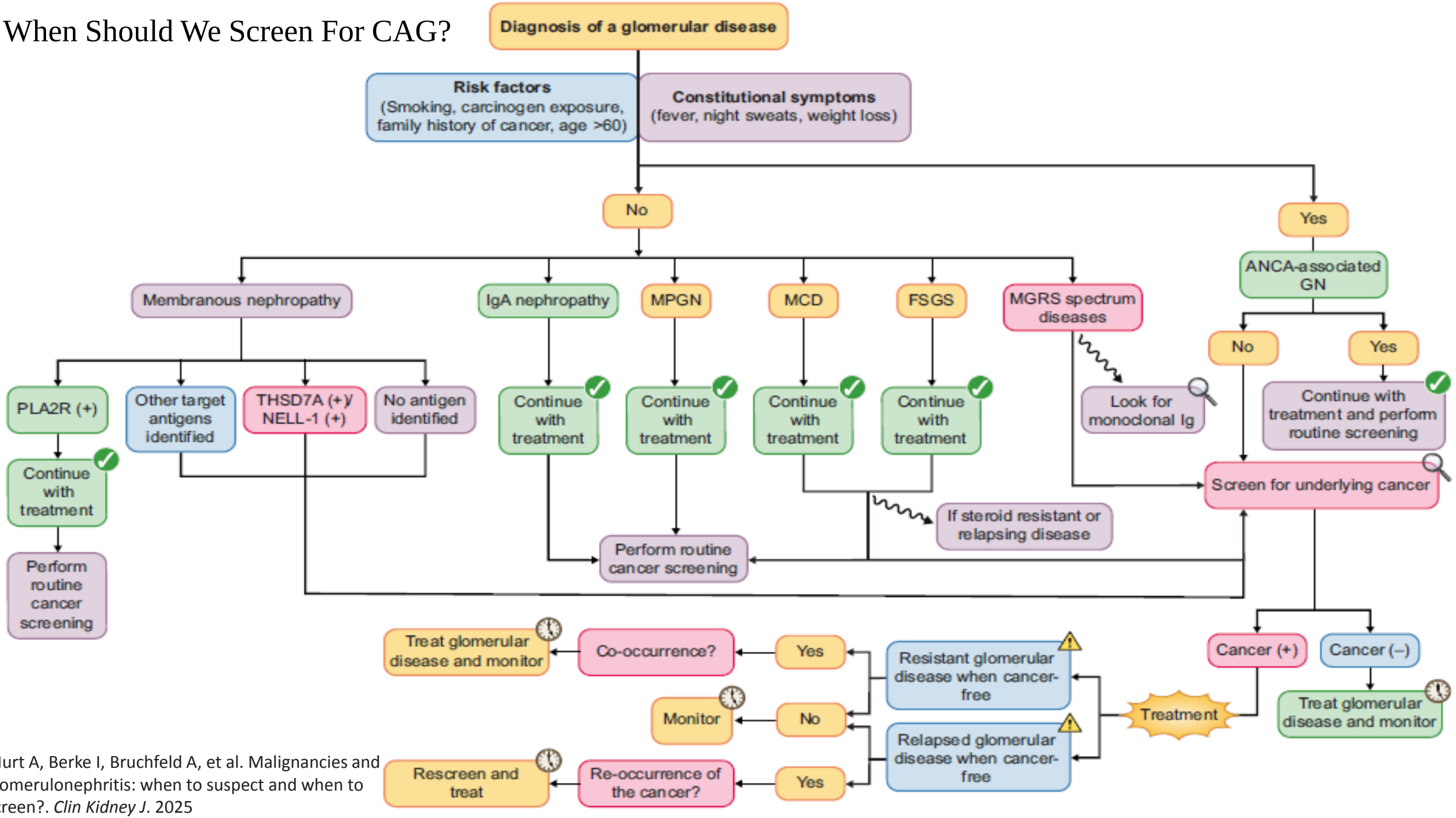
When Should We Screen For CAG?



Murt A, Berke I, Bruchfeld A, et al. Malignancies and glomerulonephritis: when to suspect and when to screen?. *Clin Kidney J*. 2025

Key Routine Screenings by Cancer Type, USPSTF (updated 2024-2025) and ACS

Cancer Type	Population (Average Risk)	Recommended Screening Method	Frequency/Interval	Notes/Updates (as of 2025)
Breast	Women aged 40-74 years	Screening mammography	Every 1-2 years (biennial preferred by USPSTF; annual by ACS)	
Cervical	Women aged 21-65 years	- Ages 21-29: Pap test (cytology) - Ages 30-65: Primary HPV test, Pap alone, or co-test (HPV + Pap)	- Every 3 years (Pap alone, 21-29) - Every 5 years (HPV or co-test, 30-65) - Every 3 years (Pap alone, 30-65)	HPV vaccination reduces need.
Colorectal	Adults aged 45-75 years	- Stool-based tests (e.g., FIT, FIT-DNA) - Visual exams (e.g., colonoscopy, CT colonography, sigmoidoscopy)	- FIT: Annually - FIT-DNA: Every 3 years - Colonoscopy: Every 10 years - CT colonography or sigmoidoscopy: Every 5 years (with FIT every 3 years for sigmoidoscopy)	Earlier if family history.
Lung	Adults aged 50-80 years with ≥20 pack-year smoking history (current or	Annual low-dose CT (LDCT) scan	Annually	

Prostate Cancer: USPSTF gives a C grade for men aged 55-69 (PSA)

Screening

Table 1: A proposed screening strategy for patients with glomerular diseases and suspected underlying malignancy.

History, signs/symptoms	Ask for constitutional symptoms; family history; thorough physical examination, especially for palpable lymph nodes, hepatomegaly, or splenomegaly; ask for symptoms of prostate enlargement
Laboratory tests	Complete blood count, lactate dehydrogenase, liver and kidney function tests
Viral serology	Hepatitis B and C, human immunodeficiency virus, EBV, human papillomavirus
Tumor markers[a]	Carcinoembryonic Antigen, CA 125, CA 19–9, CA 15–3, Alpha Fetoprotein, Prostate-specific Antigen
Initial imaging	Chest X-ray, abdominal ultrasound
Step-up imaging techniques upon indication	CT of the chest, abdomen, and pelvis; consider PET/CT scan when there are signs of unexplainable inflammation
Routine age-specific screening	Fecal occult blood test, PAP smear, mammography, gastroscopy, colonoscopy
More specific tests	Urine cytology or cystoscopy for patients with risk factors and ongoing and unexplainable hematuria (especially when exposed to alkylating agents) Bone marrow biopsy when hematologic malignancy is suspected

Murt A, Berke I, Bruchfeld A, et al. Malignancies and glomerulonephritis: when to suspect and when to screen?. *Clin Kidney J*. 2025

Screening1

Table 4 Proposed oncological screening of patients with nephrotic syndrome and of patients undergoing long-term immunosuppressive therapy

Screening levels	Proposed procedures
First level analyses	Collection of family and patient's complete clinical history
	Careful physical examination including:
	Skin examination → if suspicious, dermatoscopy
	Testicular palpation in young males → if positive, testicular US
	Breast palpation in women → if suspicious, move to a second level test
	Routine investigations:
	Complete blood count, PT, PTT, electrolytes, uric acid, and renal and liver function tests, baseline viral titers
	Chest x-ray
	Neck US + full abdomen (including renal and urinary tract) US
	Fecal occult blood search → if positive, gastroscopy ± colonoscopy

Pani A, Porta C, Cosmai L, et al. Glomerular diseases and cancer: evaluation of underlying malignancy. *J Nephrol*. 2016;

Screening 2

Second level analyses (if first level analyses are negative)

Women

- Gynecological examination → if suspicious, transvaginal US
- Pap test
- Breast US ± mammography
- If unexpected monomorphic hematuria → cystoscopy

Men

- Urological examination (including digital rectal examination)
- PSA dosage and, if one or both suspicious → trans-rectal prostate US and biopsy
- If unexpected monomorphic hematuria → cystoscopy

Pani A, Porta C, Cosmai L, et al. Glomerular diseases and cancer: evaluation of underlying malignancy. *J Nephrol*. 2016;

Screening 3

Third level analyses (if first and second level analyses are negative), only in high risk patients (one or more of the following): 1) Heavy smokers 2) Alcohol abusers 3) Older than 60 years/old 4) Thromboembolic events 5) Long term immunosuppressive therapy 6) HBV and/or HCV and/or HIV infection	Colonoscopy Computed tomography of the chest Search for malignant cells in urine and cystoscopy Contrast-enhanced liver US in cirrhotic patients ENT examination ± upper respiratory tract fibroendoscopy Consider cautiously a few specific tumor markers (e.g., alpha$_1$-fetoprotein in HBV and/or HCV-positive patients)
Renal pathology clues (only for MN)	High suspicion of secondary MN in case of: Detection of mesangial or sub-endothelial electron dense deposits More than eight leukocytes per glomerulus Prevalence of IgG1, IgG2 or IgG3 deposits at immunofluorescence Absence of anti PLA2R1 antibodies

Pani A, Porta C, Cosmai L, et al. Glomerular diseases and cancer: evaluation of underlying malignancy. *J Nephrol*. 2016;

Treatment Of CAG?

- treatment of cancer…….. Co-occurrance….. treatment of GN

Table 5 Distribution of observed minus expected cases between –1 and 10 years after biopsy according to GN diagnosis (%)

From: Quantification of cancer risk in glomerulonephritis

Renal Diagnosis	Number	Lung	Melanoma	Breast	Gynaecologic	Prostate	Renal	Bladder	Non-Hodgkin	Myeloma	Leukaemia	Unclassified	Skin	Typical cancers in the literature
Minimal change	27	11			6				13	10		7	41	Renal, lung, colorectal, thymoma, Hodgkin's
Endocapillary	6	37			11	24			14	15				
FSGS	28	21	10			5				6		21	31	Renal, thymoma
Mesangio-proliferative	53	12					9			12		21	45	Renal, lung, unclassified
Membranous	51	17	6			10					5	21	36	Renal, gastric, prostate, lung, unclassified
Membrano-proliferative	33	12							20	9	10	8	37	Renal, lung, leukaemia, unclassified
Proliferative	9	6		7				8	10			24	45	
Focal segmental proliferative	29				9	23						11	51	
ANCA vasculitis	26	6				10			5		11	7	61	Skin, leukaemia, bladder
Lupus (all)	17			9						11		21	58	Hodgkin, non-Hodgkin, myeloma, lung, leukaemia
Unclassified	92					5	25		9	23		16	17	

GN diagnoses with significantly raised incidence only. Negative figures excluded for this analysis. Only figures > 5% shown

Heaf, J.G., Hansen, A. & Laier, G.H. Quantification of cancer risk in glomerulonephritis. *BMC Nephrol* 19, 27 (2018).

THANK YOU