IgAN

Potential drivers of kidney damage in IgA nephropathy[1]

Recognizing the heterogeneous presentation of IgA nephropathy (IgAN) is key to understanding your patient's disease[2]

IgAN, immunoglobulin A nephropathy.

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IgAN: THE MOST COMMON PRIMARY GLOMERULONEPHRITIS WITH BOTH PHYSICAL AND EMOTIONAL BURDENS[2,3]

PATIENTS WITH IgAN FACE CHALLENGING SIGNS AND SYMPTOMS[4]

Patients with IgAN may continue to face burdensome symptoms despite optimized supportive care[2,*]

Symptoms may include[3,†]:

✓ Fatigue ✓ Edema ✓ Insomnia ✓ Hypertension

Laboratory findings may include[2,5]:

✓ Proteinuria ✓ Hematuria ✓ Declining eGFR

HETEROGENOUS PRESENTATION

The diverse clinical and pathological features, coupled with potentially unpredictable disease progression, can call for an understanding of each patient's disease based on symptoms[2]

"I can't stress enough the toll this disease takes on my life. EVERYTHING changed."

-Real patient with IgAN[3]

Patient portrayal.

*Supportive care defined by KDIGO guidelines as ACEi/ARB.[2]
†Based on patient insights.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

THE HETEROGENOUS NATURE OF IgAN REQUIRES YOU TO UNDERSTAND EACH PATIENT'S DISEASE[2]

PATIENTS MAY PRESENT WITH VARIOUS CLINICAL SIGNS[2]

Some patients will still have persistent proteinuria despite optimized supportive care[2,*]

Some patients may experience signs of active inflammation along with proteinuria, including[2,6,7]:

- Persistent hematuria *or*
- Different rates of eGFR decline *or*
- MEST-C scores that may vary depending on severity

IMPLICATIONS FOR DISEASE MANAGEMENT

A multifaceted approach is key to developing a management plan for your patients[2]

You may see varying amounts of C3 and IgA deposition in your patients' biopsies[8]

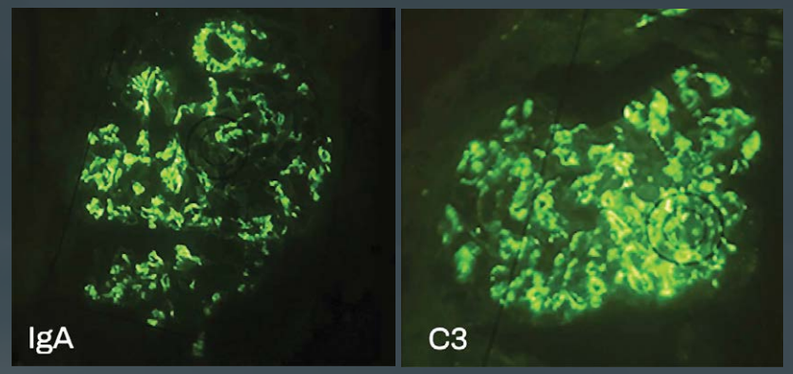


Image showing colocalization of C3 and IgA in a kidney biopsy

Image adapted from: Mastrangelo A, Serafinelli J, Giani M, Montini G. Clinical and pathophysiological insights into immunological mediated glomerular diseases in childhood. *Front Pediatr*. 2020;8:205. Published 2020 May 12. doi:10.3389/fped.2020.00205. License: https://creativecommons.org/licenses/by/4.0/

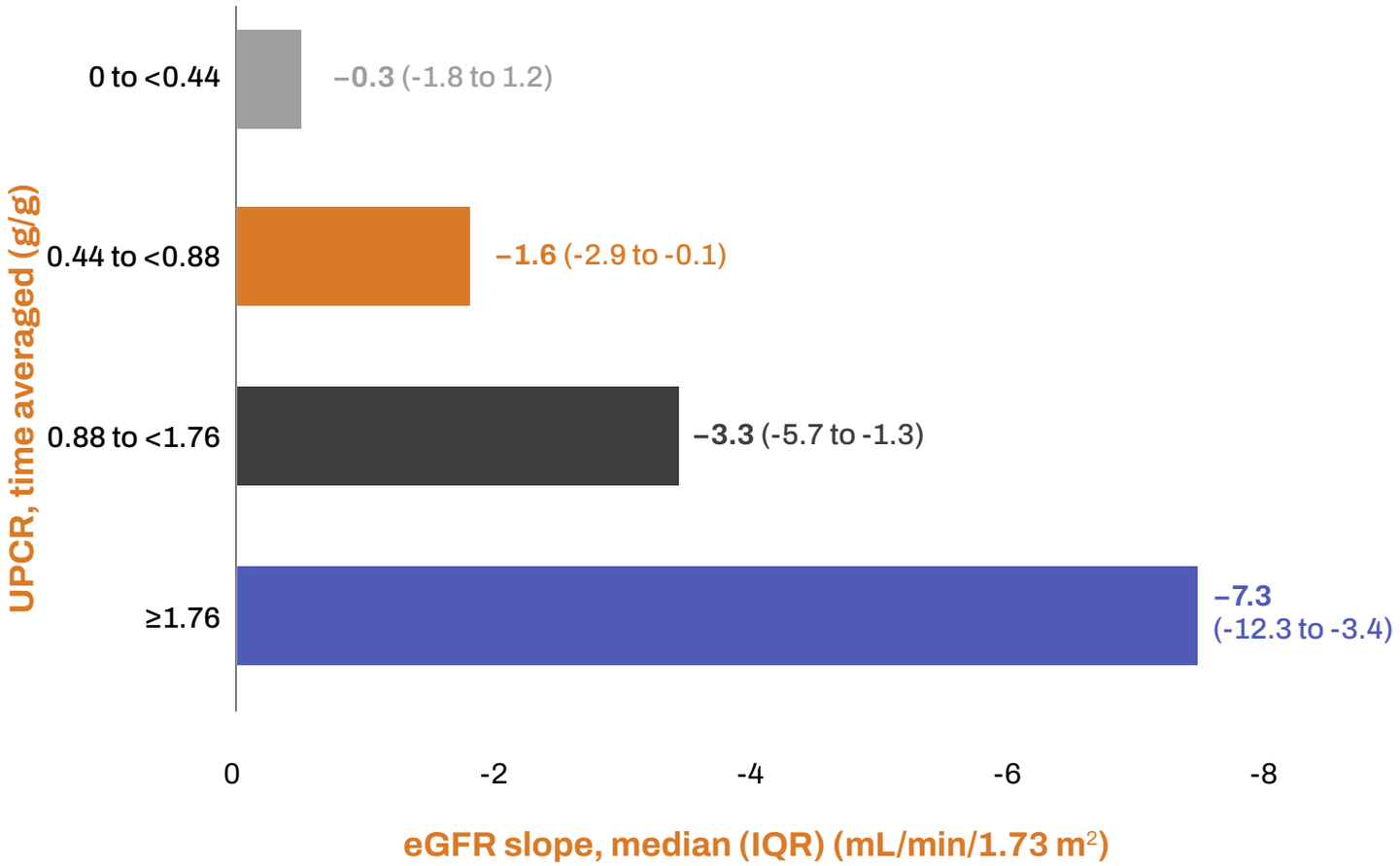
Identifying symptoms as soon as they worsen may help you manage your patients' kidney function[2]

*Supportive care defined by KDIGO guidelines as ACEi/ARB.[2]

C3, complement 3; IgA, immunoglobulin A; MEST-C, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy (T), and crescents (C).

A UK RETROSPECTIVE COHORT FOUND THAT PATIENTS WITH HIGHER LEVELS OF TIME-AVERAGED PROTEINURIA HAD MORE RAPID *e*GFR LOSS[6,*,†]

*e*GFR SLOPE FROM A UK RETROSPECTIVE COHORT[6,*,†]



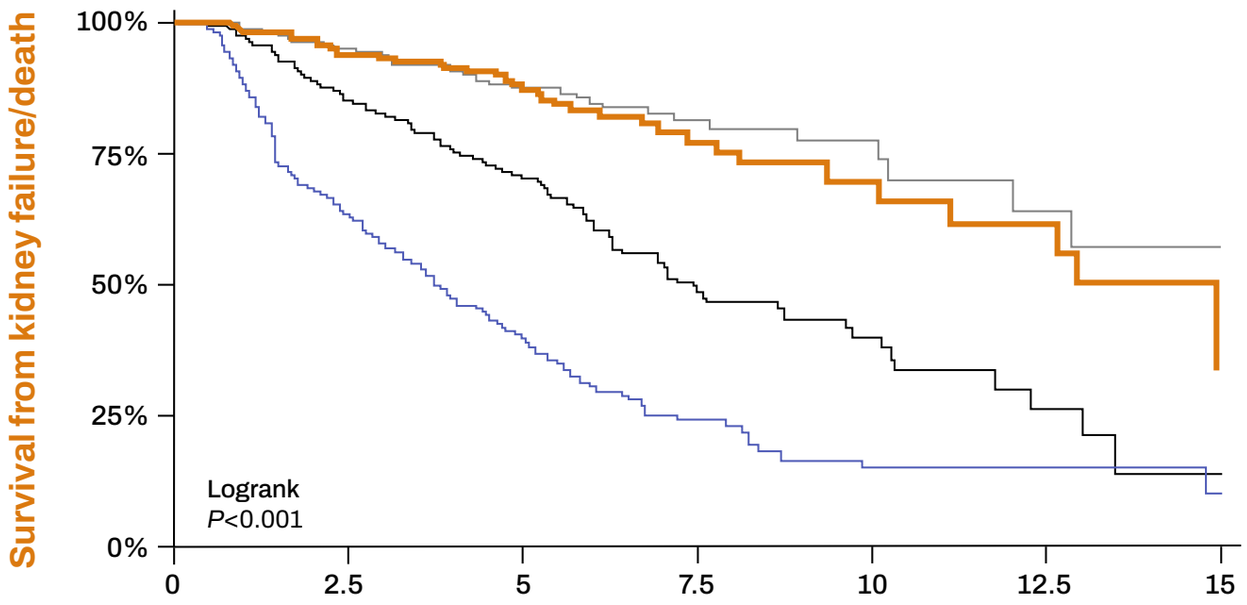
*Data from retrospective cohort of 2299 adults and 140 children with IgAN of the UK National Registry of Rare Kidney Diseases (RaDaR). Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m² at any time in their history of their disease. Analyses of annualized eGFR slopes were calculated using linear regression to fit a straight line through patients' mean eGFR values for each 3-month period of follow-up. Analyses of kidney survival were conducted using Kaplan–Meier and Cox regression. Recruitment into RaDaR was initiated in 2013. Availability of patient medication and blood pressure data was a limiting factor in this study.[6]

†<0.88 g/g is approximately equivalent to <1 g/day.[6]

Image adapted from: Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135

eGFR, estimated glomerular filtration rate; IQR, interquartile range; UK, United Kingdom; UPCR, urine protein-creatinine ratio.

A UK RETROSPECTIVE COHORT FOUND THAT 30% OF PATIENTS WITH A TIME-AVERAGED PROTEINURIA RANGE OF 0.44 TO <0.88 g/g* REACHED KIDNEY FAILURE WITHIN 10 YEARS[6,†]



0 to <0.44 g/g	215	176	114	57	22	10	6
0.44 to <0.88 g/g	175	147	94	40	20	11	1
0.88 to <1.76 g/g	251	195	120	51	20	7	1
≥1.76 g/g	246	142	66	24	10	5	2

Total time-averaged proteinuria

— 0 to <0.44 g/g
— 0.44 to <0.88 g/g
— 0.88 to <1.76 g/g
— ≥1.76 g/g

In all age groups, the majority of patients developed kidney failure in 10 to 15 years[6]

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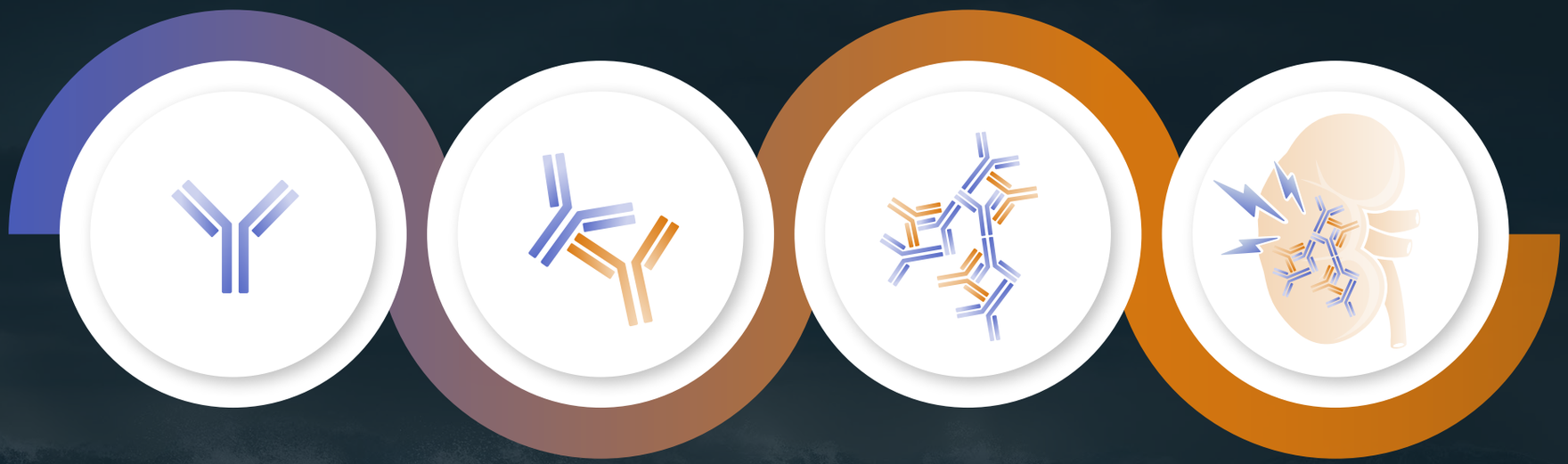
IgAN IS AN AUTOIMMUNE GLOMERULOPATHY CHARACTERIZED BY A MULTI-HIT DISEASE PATHOGENESIS[1]

THE MULTI-HIT MODEL[1,9,10]



HIT 1

Increase in galactose-deficient IgA1 antibodies

HIT 2

Induction of autoantibody production

HIT 3

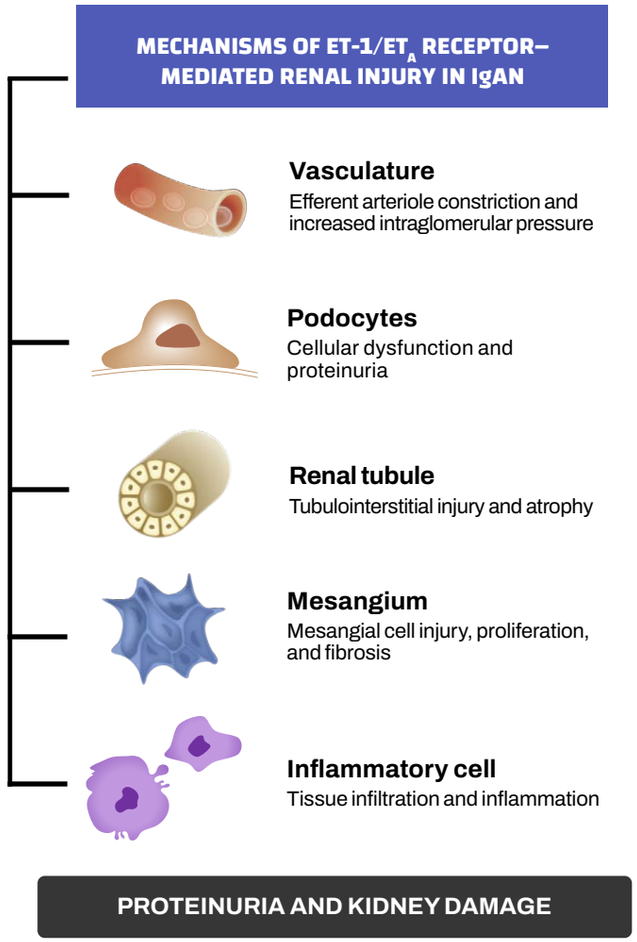
Autoantibodies and antibodies bind to form immune complexes

HIT 4

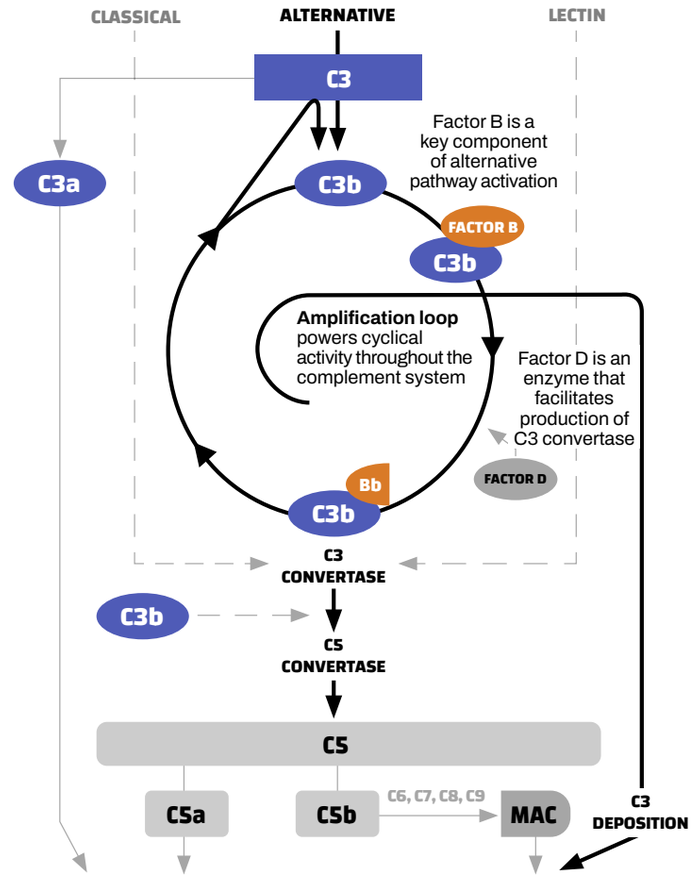
Immune complex deposition in the mesangium activates multiple pathways, which can include the endothelin and complement systems, that may lead to kidney damage, disease progression, and kidney failure

IN HIT 4, OVERACTIVATION OF THE ENDOTHELIN AND COMPLEMENT SYSTEMS CONTRIBUTES TO THE PROGRESSION OF IgAN[1]

INCREASED ET_A RECEPTOR SIGNALING IN THE KIDNEY IS ASSOCIATED WITH PROGRESSION OF IgAN[1]



COMPLEMENT, A KEY PART OF THE IMMUNE SYSTEM, IS ACTIVATED THROUGH THE ALTERNATIVE PATHWAY, AND TO A LESSER EXTENT THE LECTIN PATHWAY[1,11,12]



These processes may lead to proteinuria, inflammation, and fibrosis, which can cause progressive kidney damage[1]

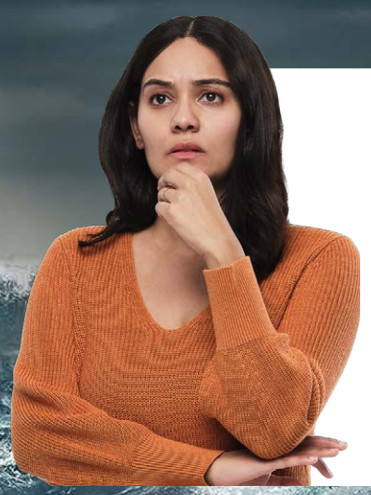
ET-1, endothelin-1; ET_A, endothelin A; MAC, membrane attack complex.

IgAN

PATIENTS WITH IgAN CAN FACE CLINICAL PROGRESSION AND EMOTIONAL BURDENS[2,3,*]

Patients with IgAN may present with various signs and symptoms, highlighting an opportunity to understand each patient's disease[2]

In IgAN pathogenesis, immune complex deposition in the mesangium activates multiple pathways, which can include the endothelin and complement systems, that may lead to kidney damage, disease progression, and kidney failure[1]



A retrospective cohort found that

30% **of patients experience kidney failure**

within 10 years when their time-averaged proteinuria ranges from 0.44 to <0.88 g/g.[6,†,‡]

The heterogeneity of IgAN calls for you to understand each patient's disease[2]

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References

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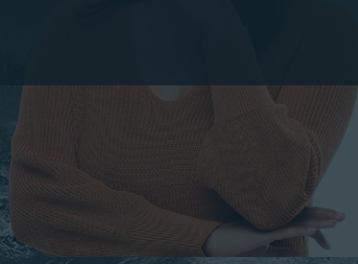
References: 1. Kohan DE, Barratt J, Heerspink HJL, et al. Targeting the endothelin A receptor in IgA nephropathy. *Kidney Int Rep*. 2023;8(11):2198-2210. doi:10.1016/j.ekir.2023.07.023 **2.** Rovin BH, Adler SG, Barratt J, et al; Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(suppl 4):S1-S276. doi:10.1016/j.kint.2021.05.021 **3.** Feldman DL, White EM, Julian B, et al. *The Voice of the Patient: Externally Led Patient-Focused Drug Development Meeting on IgA Nephropathy*. National Kidney Foundation; 2020:1-87. **4.** Carter SA, Gutman T, Logeman C, et al; SONG-GD Investigators. Identifying outcomes important to patients with glomerular disease and their caregivers. *Clin J Am Soc Nephrol*. 2020;15(5):673-684. doi:10.2215/CJN.13101019 **5.** Rajasekaran A, Julian BA, Rizk DV. IgA nephropathy: an interesting autoimmune kidney disease. *Am J Med Sci*. 2021;361(2):176-194. doi:10.1016/j.amjms.2020.10.003 **6.** Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135 **7.** El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA nephropathy: a rapidly evolving field. *J Am Soc Nephrol*. 2024;35(1):103-116. doi:10.1681/ASN.0000000000000242 **8.** Mastrangelo A, Serafinelli J, Giani M, Montini G. Clinical and pathophysiological insights into immunological mediated glomerular diseases in childhood. *Front Pediatr*. 2020;8:205. doi:10.3389/fped.2020.00205 **9.** Rizk DV, Maillard N, Julian BA, et al. The emerging role of complement proteins as a target for therapy of IgA nephropathy. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504 **10.** Lai KN, Tang SCW, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2016;2:16001. doi:10.1038/nrdp.2016.1 **11.** Harris CL. Expanding horizons in complement drug discovery: challenges and emerging strategies. *Semin Immunopathol*. 2018;40(1):125-140. doi:10.1007/s00281-017-0655-8 **12.** Harris CL, Pouw RB, Kavanagh D, Sun R, Ricklin D. Developments in anti-complement therapy; from disease to clinical trial. *Mol Immunol*. 2018;102:89-119. doi:10.1016/j.molimm.2018.06.008



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