The clinical spectrum of C3G and IC-MPGN

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My disclosures

Site investigator in clinical trials sponsored by Novartis, Apellis, Alexion, Vera Therapeutics, Biogen, Boehringer Ingelheim, ADARAx Pharmaceuticals, Astrazeneca.
Travel support by Novartis.
Consultant for Alexion.

Outline

- C3G/IC-MPGN histopathological classification
- Complement system dysregulation in C3G/IC-MPGN (briefly)
- Natural history of C3G/IC-MPGN
- Post transplant recurrence
- Treatment (briefly)
- Summary

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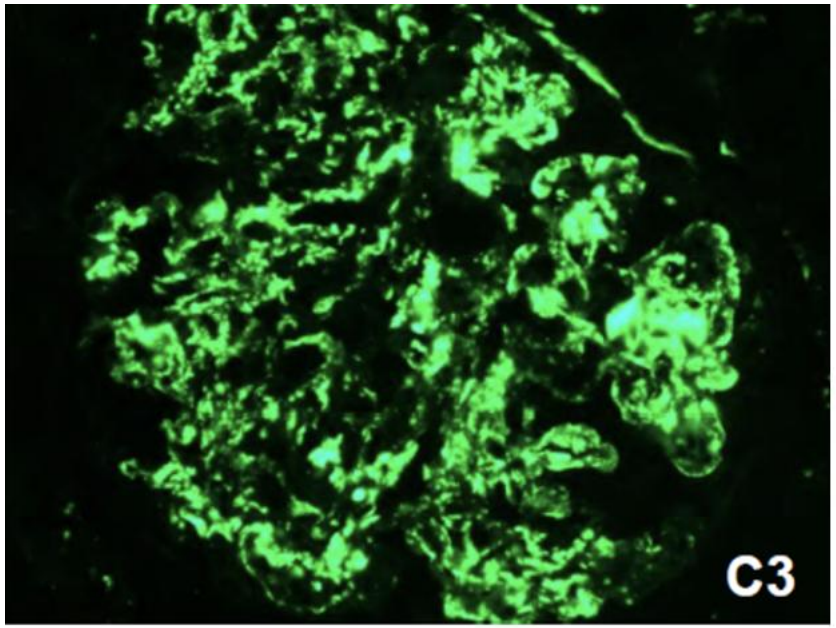
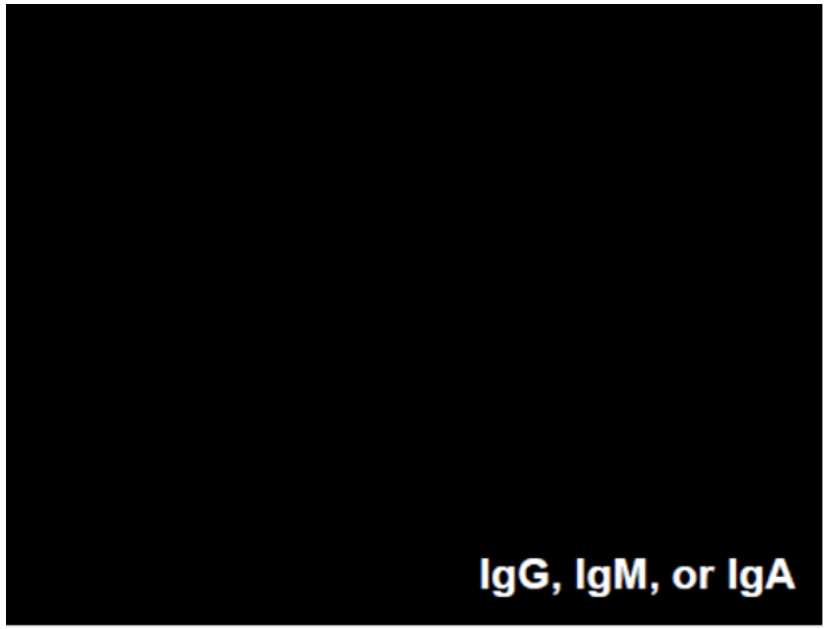
C3 Glomerulopathy



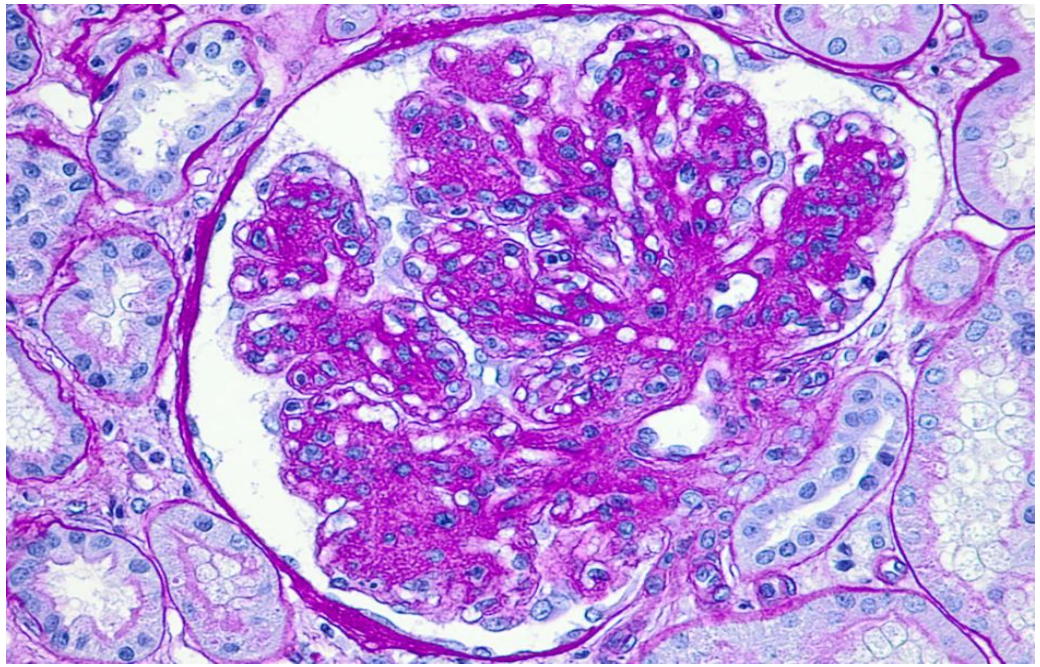


“C3 dominance”

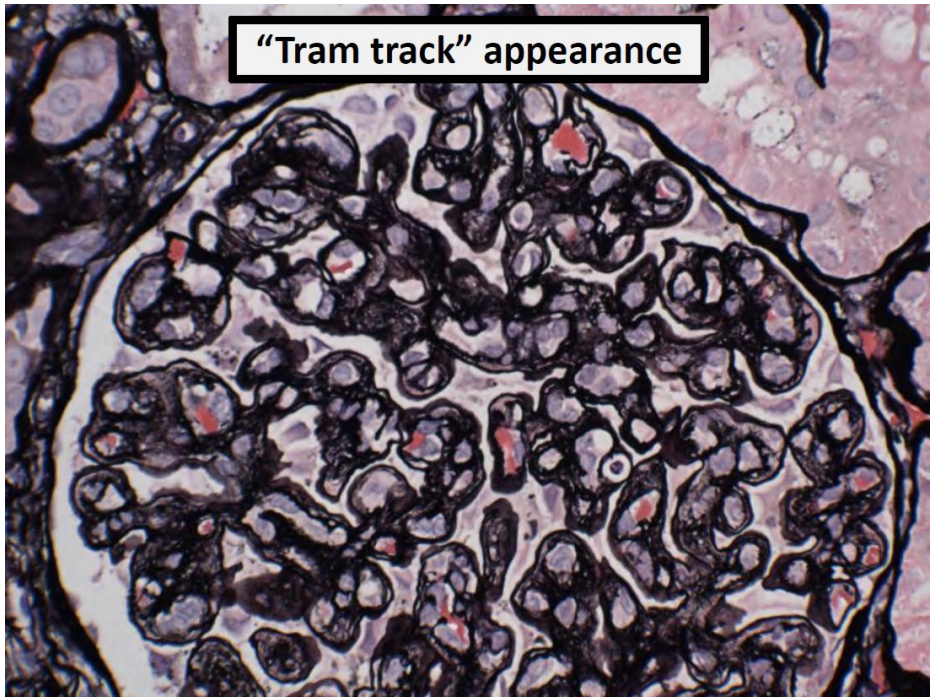
C3 glomerulopathies are characterized by ***uncontrolled activation of the alternative complement pathway****.*

As a consequence, ***continuos deposition of C3 and complement activation products within the glomerulus*** *causing glomerular injury and an inflammatory proliferative response.*

Membranoproliferative glomerulonephritis (MPGN) pattern

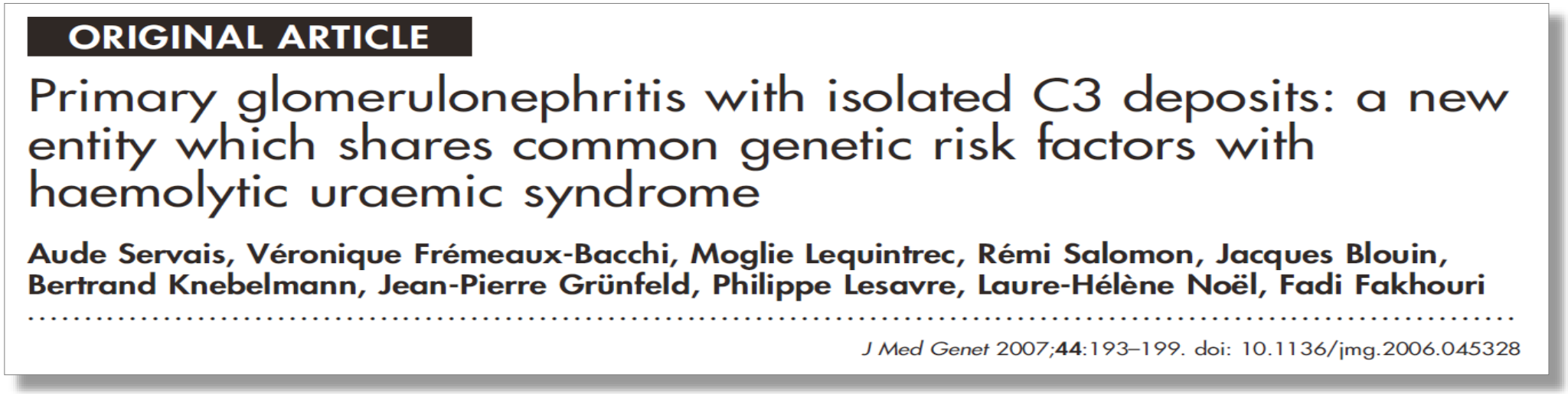


- Endocapillary and mesangial proliferation
- Glomerular lobulation
- Possible necrotizing and crescentic features



- Sub epithelial, sub endothelial and mesangial deposits

C3G: a new disease entity



ORIGINAL ARTICLE

Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome

Aude Servais, Véronique Frémeaux-Bacchi, Moglie Lequintrec, Rémi Salomon, Jacques Blouin, Bertrand Knebelmann, Jean-Pierre Grünfeld, Philippe Lesavre, Laure-Hélène Noël, Fadi Fakhouri

J Med Genet 2007;**44**:193–199. doi: 10.1136/jmg.2006.045328

- **19 patients with bright C3 only glomerular staining**
  - No immunoglobulin deposition
  - No intramembranous highly dense deposits (no DDD)

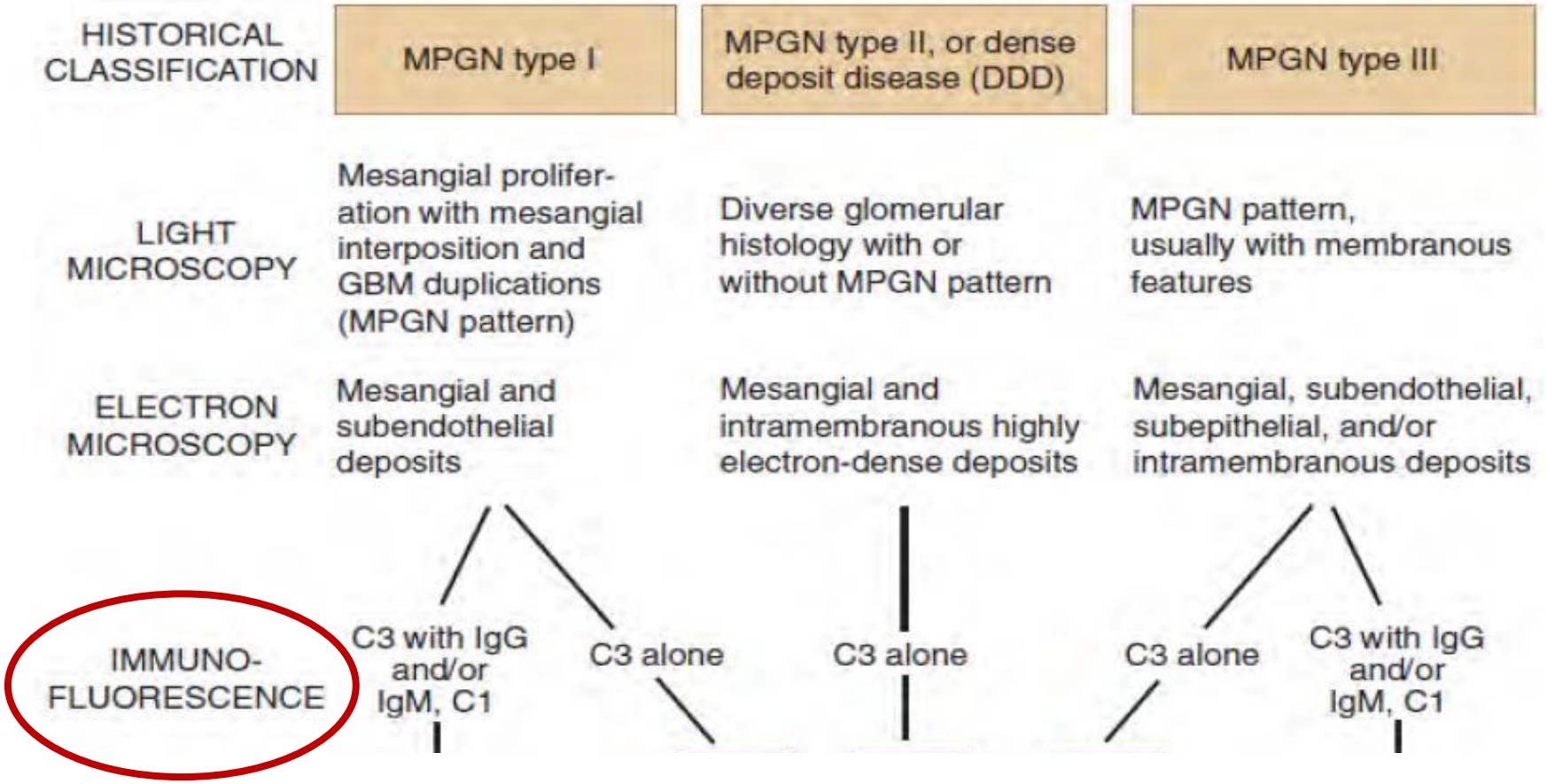
- **Alternative Pathway abnormalities (12/19)**
  - C3NeF positivity (n=7)
  - Mutations in CFH (n=3), CFI (n=2) and MCP/CD46 (n=1)

Evolving MPGN classification

HISTORICAL CLASSIFICATION	MPGN type I	MPGN type II, or dense deposit disease (DDD)	MPGN type III
LIGHT MICROSCOPY	Mesangial proliferation with mesangial interposition and GBM duplications (MPGN pattern)	Diverse glomerular histology with or without MPGN pattern	MPGN pattern, usually with membranous features
ELECTRON MICROSCOPY	Mesangial and subendothelial deposits	Mesangial and intramembranous highly electron-dense deposits	Mesangial, subendothelial, subepithelial, and/or intramembranous deposits

Adapted from D'Agati VD and Bomback AS *Kidney Int* 2012

Evolving MPGN classification



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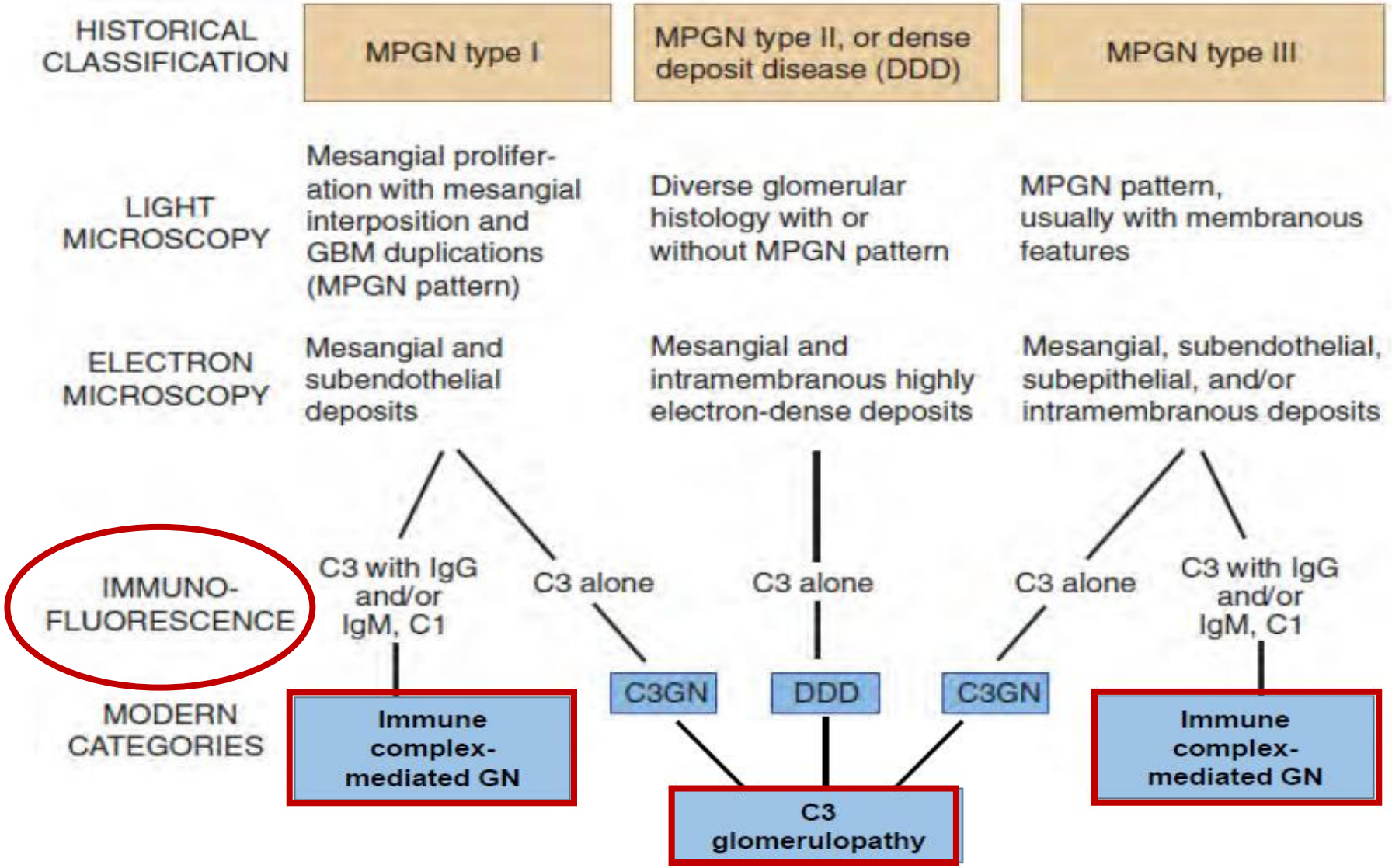
Evolving MPGN classification



Adapted from D'Agati VD and Bomback AS *Kidney Int* 2012

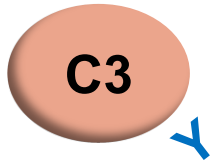
MPGN

IC-mediated MPGN
Ig positive
No C3 dominant

- Infections diseases
- Autoimmune diseases
- Monoclonal gammopathies, Dysproteinemia

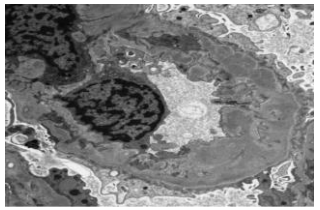
20-30%
No underlying condition
(primary MPGN)

C3 glomerulopathies
C3 dominant*
No or few Ig

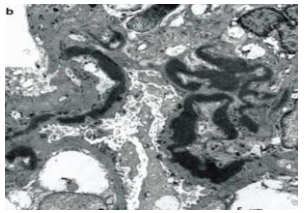


Electron microscopy

- **C3GN**



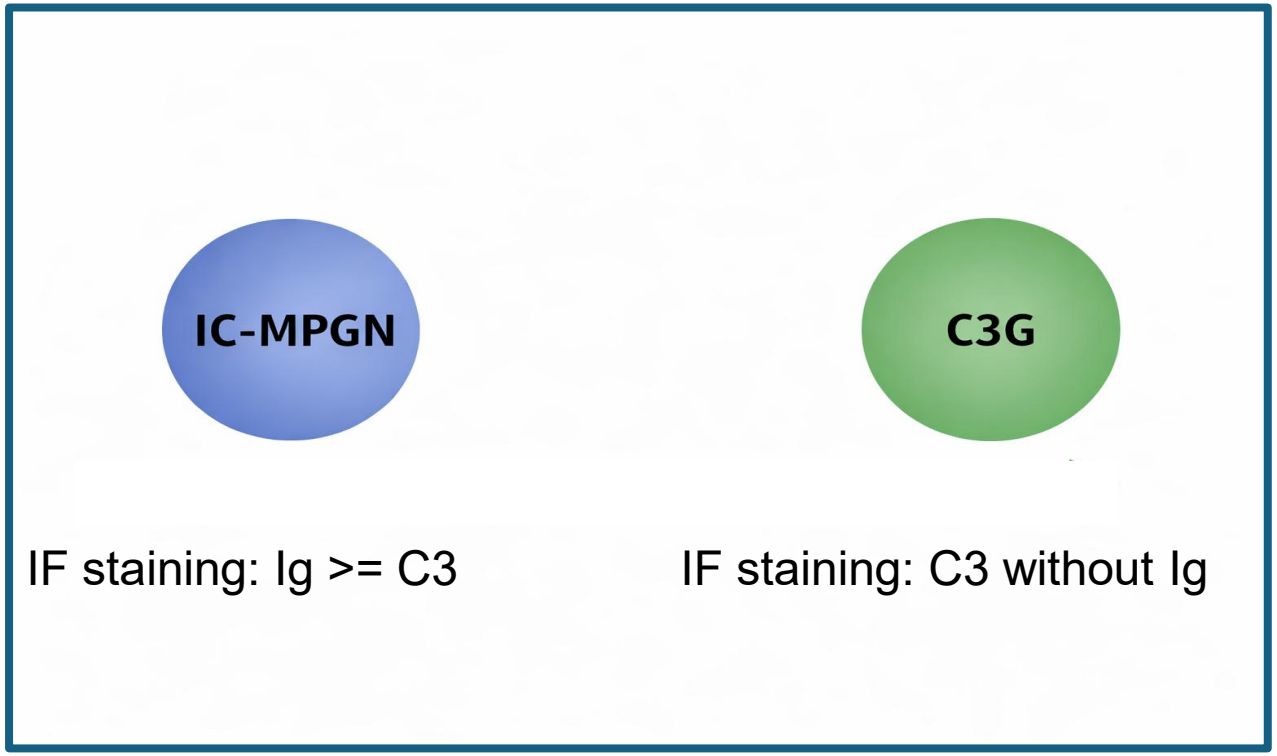
- **DDD**

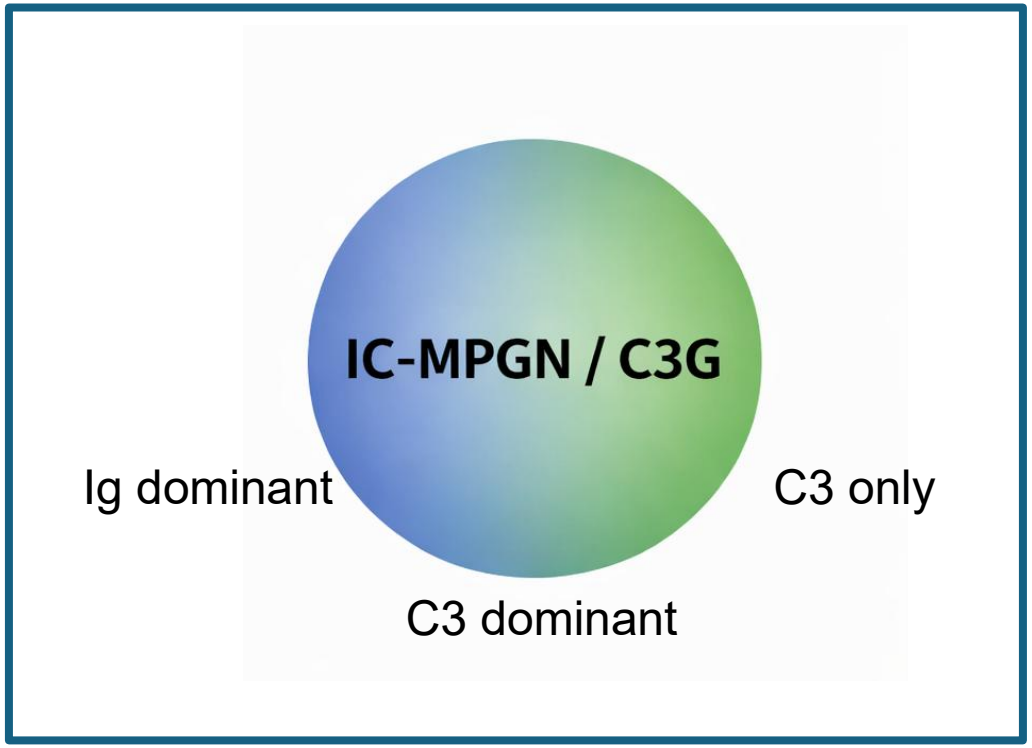


*C3 dominant: C3 staining at least two orders of magnitude stronger than any other common immune reactant

Sethi et al., *N Engl J Med,* 2012
Pickering et al., *Kidney Int*, 2013
Hou et al., *Kidney Int* 2013

IC-MPGN & C3G: two separate entities or the same condition with different manifestations?





Caveats of the C3G/IC-MPGN classification

- **Borderline cases with overlapping features.**
- **Up to 20% of cases of DDD,** the prototype of AP dysregulation, would not be classified as C3G.
- **Up to 17% of patients shift** from IC-MPGN to C3G and vice versa when a kidney biopsy is repeated.
- **Genetic and acquired alternative pathway abnormalities are equally present** both in C3G and IC-MPGN.
- The prevalence of patients with **low C3 (70-90%) and low C4 levels (25-35%) does not differ** across the three histology groups.

Nanchen G, Marasà M et al, cJASN 2026
Iatropoulos P et al, *JASN,* 2018
Bomback AS et al, *Kidney Int* 2018
Hou J et al, *Kidney Int,* 2014
Pickering M et al., *Kidney Int, 2013*
Licht C et al, *Kidney Int, 2006*
Habbig S et al., *Kidney Int 2009*

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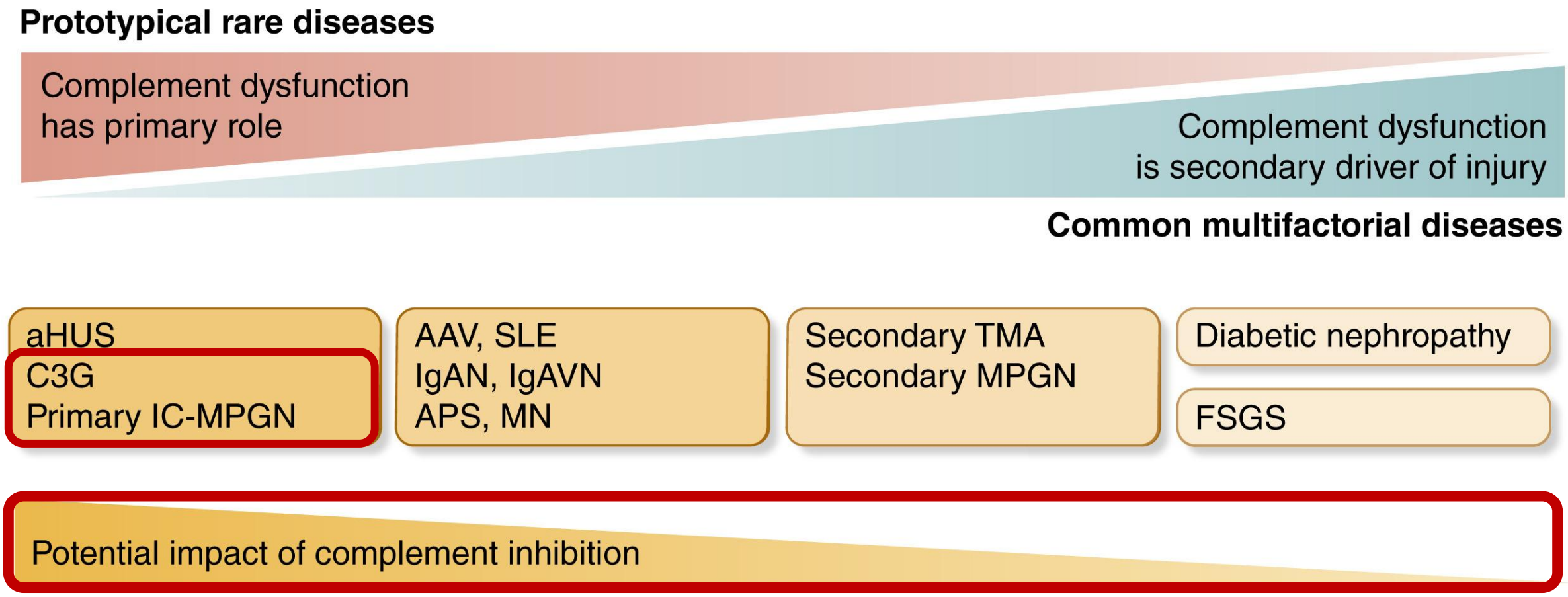
Complement involvement in kidney diseases

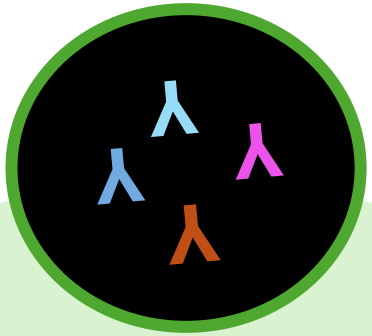


M Vivarelli et al. The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2024

C3G/IC-MPGN Pathophysiology

Mutations in complement genes

CFH	7%
CFI	1%
C3	6.1%
CFB	1.8%
CD46	1%
CFH	3.6%



Antibodies

C3NeF / ***C5NeF***	40-80%
Anti-CFH	4-12%
Anti-C3b	2-3%
Anti-FB	2-3%

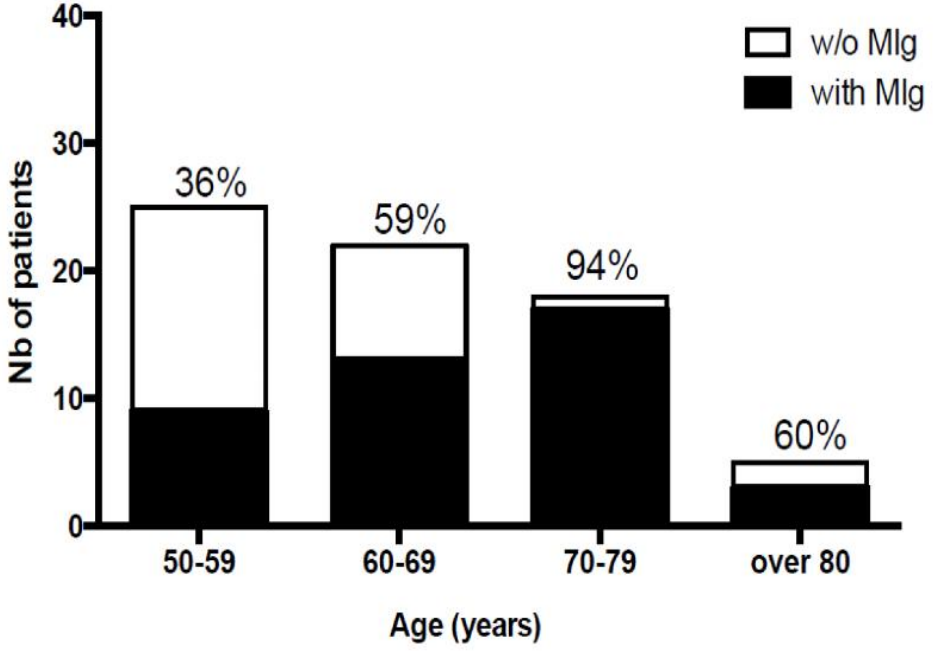
Trigger factors

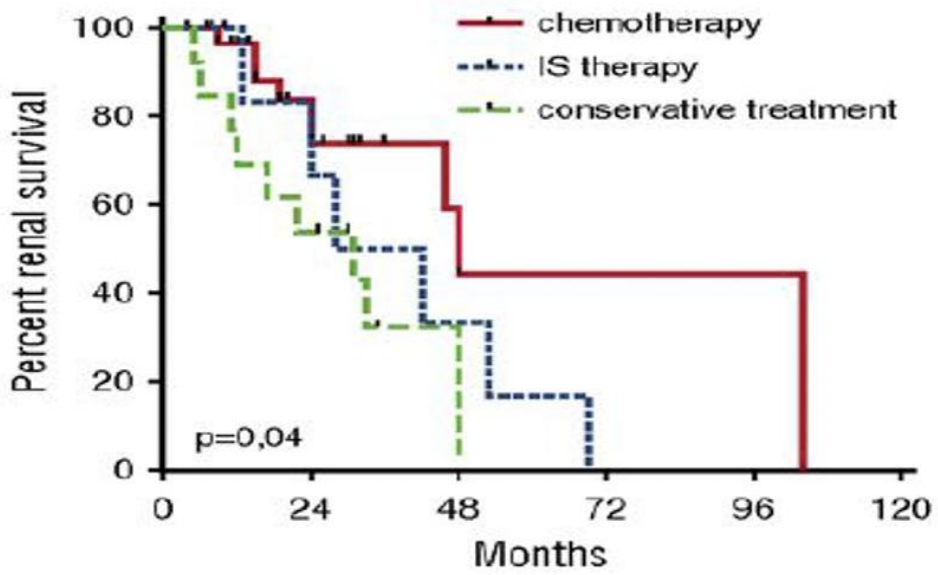
infections
drugs
tumors
Transplant
systemic diseases

Complement AP dysregulation usually leading to low serum C3 levels and normal serum C4 levels

Sethi S, N Engl J Med 2012
Piras R et al., Front Genet 2021
Fakhouri et al., 2020.
Marinozzi MC et al, *JASN* 2017

Monoclonal gammopathy frequency in C3G is age-associated





chemotherapy	29	16	5	2	2	0
IS therapy	8	5	3	0	0	0
Conservative treatment	13	8	2	0	0	0

Chauvet S, et al, *Blood* 2017

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C3G/IC-MPGN: natural history

- Primary forms are ultra-rare
- Predominantly children and young adults
- Variable clinical presentation, ranging from asymptomatic urine abnormalities to RPGN
- Poor overall prognosis: 40% progression to ESKD in 5-10 yrs
- High rate of post transplant recurrence and graft loss

Sethi S and Fervenza F, *N Engl J Med* 2012
Bomback AS et al, *Kidney Int* 2018
Caravaca-Fontan F et al, *Kidney Int Rep* 2025

Natural History and Clinical Associations with Long-Term Outcomes in Primary C3 Glomerulopathy and Immune Complex-Mediated Membranoproliferative Glomerulonephritis.

CJASN®
Clinical Journal of the American Society of Nephrology

Retrospective study

Italian Registry of MPGN

Subjects with biopsy-proven primary C3G/IC-MPGN (n=349)

Median follow-up from biopsy: 5 years

Composite endpoint:

- ESKD
- Doubling of serum creatinine
- Death from kidney causes

Conclusions: Results from a large and well-characterized cohort of individuals with primary C3G/IC-MPGN identify age at onset and proteinuria levels as key predictors of kidney survival.

Giliane Nanchen, Maddalena Marasà, Matteo Breno, et al. **Natural History and Clinical Associations with Long-Term Outcomes in Primary C3 Glomerulopathy and Immune Complex-Mediated Membranoproliferative Glomerulonephritis.** CJASN, DOI: DOI: 10.2215/CJN.0000000953. **Visual Abstract by Maria Fernanda Zavala, MD, MSc**

Table 1. Full cohort description

Cohort Characteristics	Patients with Available Data, *n* (%)	Primary MPGN, all (*n*=349)	IC-MPGN (*n*=141)	C3G[a] (*n*=208)	DDD (*n*=40)	C3GN (*n*=140)
Females, *n* (%)	349 (100)	143 (41)	61 (43)	82 (39)	15 (38)	57 (41)
Age at onset, yr	346 (99)	15 (10–25)	16 (10–33)	14 (10–22)	13 (10–22)	15 (9–22)
Children younger than 12 yr, *n* (%)		108 (31)	41 (29)	67 (32)	16 (40)	45 (32)
Adolescents 12–17 yr, *n* (%)		85 (24)	30 (21)	55 (26)	10 (25)	34 (24)
Age at baseline (biopsy), yr	349 (100)	17 (1128)	18 (11–36)	16 (11–25)	14 (10–22)	16 (11–27)
Interval onset—baseline (biopsy), mo	346 (99)	5.6 (1.4–24)	4.7 (0.8–20.7)	6.5 (1.8–24.1)	7.1 (1.7–33.4)	7.3 (2–26.8)
Clinical presentation at onset, *n* (%)						
Hematuria	340 (97)	288 (85)	110 (82)	178 (87)	33 (85)	121 (88)
Nephrotic-range proteinuria	279 (80)	125 (45)	63 (58)	62 (37)[b]	16 (46)	38 (35)
eGFR (ml/min per 1.73m^2)	217 (62)	83 (61–103)	83 (58–103)	81 (61–102)	93 (67–113)	81 (57–102)
Arterial hypertension	339 (97)	141 (42)	65 (48)	76 (37)	14 (36)	52 (38)
Edema	342 (98)	133 (39)	74 (53)	59 (29)[b]	15 (39)	38 (28)
Complement biochemical and genetic profile, *n* (%)						
Low serum C3 at first measurement	347 (99)	293 (84)	114 (81)	179 (87)	37 (93)	119 (86)
Low serum C4 at first measurement	333 (95)	99 (30)	49 (36)	50 (25)	14 (35)	33 (25)
sC5b-9 at first measurement (ng/ml)	323 (93)	377 (224.5–1394)	358.5 (248.2–1441.2)	396 (209–1357)	286 (199.5–622.2)	490 (209–1604.2)[c]
Positive C3NeFs at first measurement	335 (96)	130 (39)	58 (41)	72 (37)	30 (75)	38 (28)[c]
Rare functional variant in complement gene	346 (99)	53 (15)	18 (13)	35 (17)	5 (13)	26 (19)
Rare variant gene, *n* (%)						
CFH		17 (32)	6 (33)	11 (31)	2 (40)	8 (31)
CFI		6 (11)	0	6 (17)	1 (20)	4 (15)
C3		17 (32)	5 (28)	12 (34)	1 (20)	11 (42)
CFB		4 (8)	44 (22)	0	0	0
THBD		6 (11)	1 (6)	5 (14)	1 (20)	2 (8)
MCP		2 (2)	1 (6)	0	0	0
Structural variant		2 (4)	1 (6)	1 (3)	0	1 (4)
Clinical parameters at baseline (biopsy)						
Proteinuria (g/24 h)	313 (90)	3 (1.1–5.3)	4 (1.9–7.2)	2.3 (0.8–4.6)[b]	2.9 (1.2–6.1)	2.2 (0.7–4.3)
eGFR (ml/min per 1.73 m^2)	317 (91)	84 (57–109)	77 (54–106)	92 (62–111)	102 (71–120)	93 (63–108.9)
Serum albumin (g/dl)	254 (73)	3.3 (2.6–3.9)	2.9 (2.3–3.6)	3.5 (2.9–4)[b]	3.1 (2.2–3.8)	3.6 (3–4.1)[c]
Histological parameters						
Fraction of sclerotic glomeruli, mean (±SD)	337 (97)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Fraction of crescents, mean (±SD)	334 (96)	0.1 (0.2)	0.1 (0.2)	0 (0.1)	0.1 (0.2)	0 (0.1)
Degree of mesangial proliferation (0–3)	339 (97)	2 (1–3)	2 (2–3)	2 (1–2.6)[b]	2 (1–2.5)	2 (1–3)
Degree of endocapillary proliferation (0–3)	333 (95)	1 (0–2)	1.5 (0–2)	1 (0–2)	0.3 (0–2)	1 (0–2)
Degree of interstitial inflammation (0–3)	339 (97)	0.5 (0–1)	1 (0–1)	0.1 (0–1)	0.3 (0–1.1)	0 (0–1)
Degree of interstitial fibrosis (0–3)	335 (96)	0 (0–1)	0.1 (0–1)	0 (0–1)	0 (0–0.1)	0 (0–1)
Degree of arteriolar sclerosis (0–3)	330 (95)	0 (0–0.1)	0 (0–0.2)	0 (0–0.1)	0 (0–0)	0 (0–0.1)
Clinical parameters at 1 yr from baseline						
Proteinuria at 1 yr (g/24 h)	220 (63)	0.9 (0.3–2.6)	1.3 (0.4–4)	0.7 (0.2–1.9)[b]	1.6 (0.2–2.7)	0.6 (0.2–1.6)[c]
Delta proteinuria at 1 yr	208 (60)	−0.6 (−0.8 to −0.2)	−0.6 (−0.8 to −0.1)	−0.6 (−0.8 to −0.2)	−0.6 (−0.8 to −0.3)	−0.6 (−0.8 to −0.2)
eGFR at 1 yr (ml/min per 1.73 m^2)	217 (62)	97 (73–113)	91 (67–110)	101 (80–119)	104 (86–119)	102 (83–121)
Outcome						
eGFR at last follow-up (ml/min per 1.73 m^2)	246 (70)	99 (70–118)	97 (64–114)	100 (72–121)	103 (84–123)	100 (72–121)

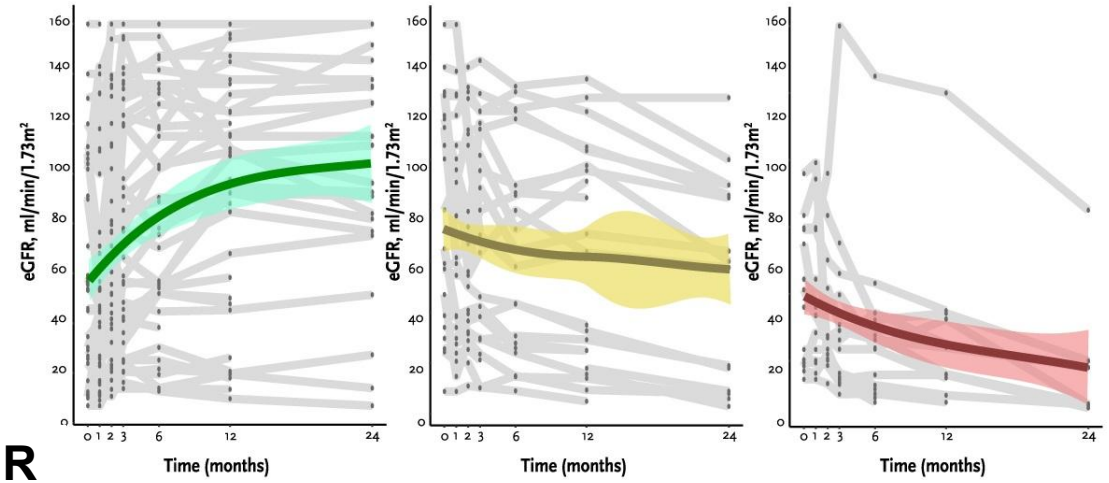
- **31% < 12 years old at diagnosis**
- **>80% had hematuria and nearly 50% had nephrotic proteinuria at presentation**
- Evidences of **complement hyperactivation**:
  - Low C3 in 84%
  - elevated plasma sC5b-9
  - 39% C3Nef-positive (75% DDD)
- Rare functional variant in a complement gene in ~ 15%
- **~ 30% of patients progressed to ESKD**

Nanchen G, Marasa' M et al *CJASN* 2026

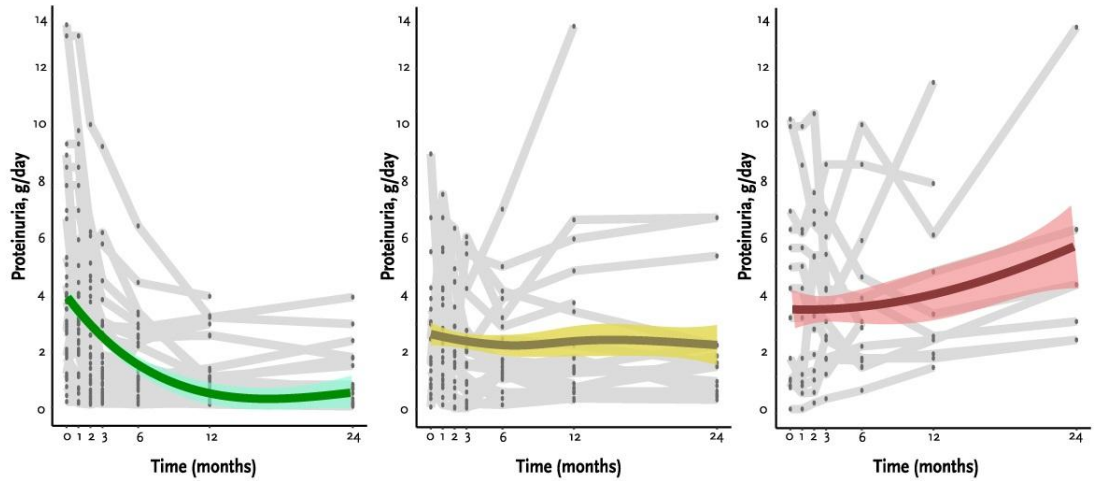
Patterns of eGFR and proteinuria change over time in C3G

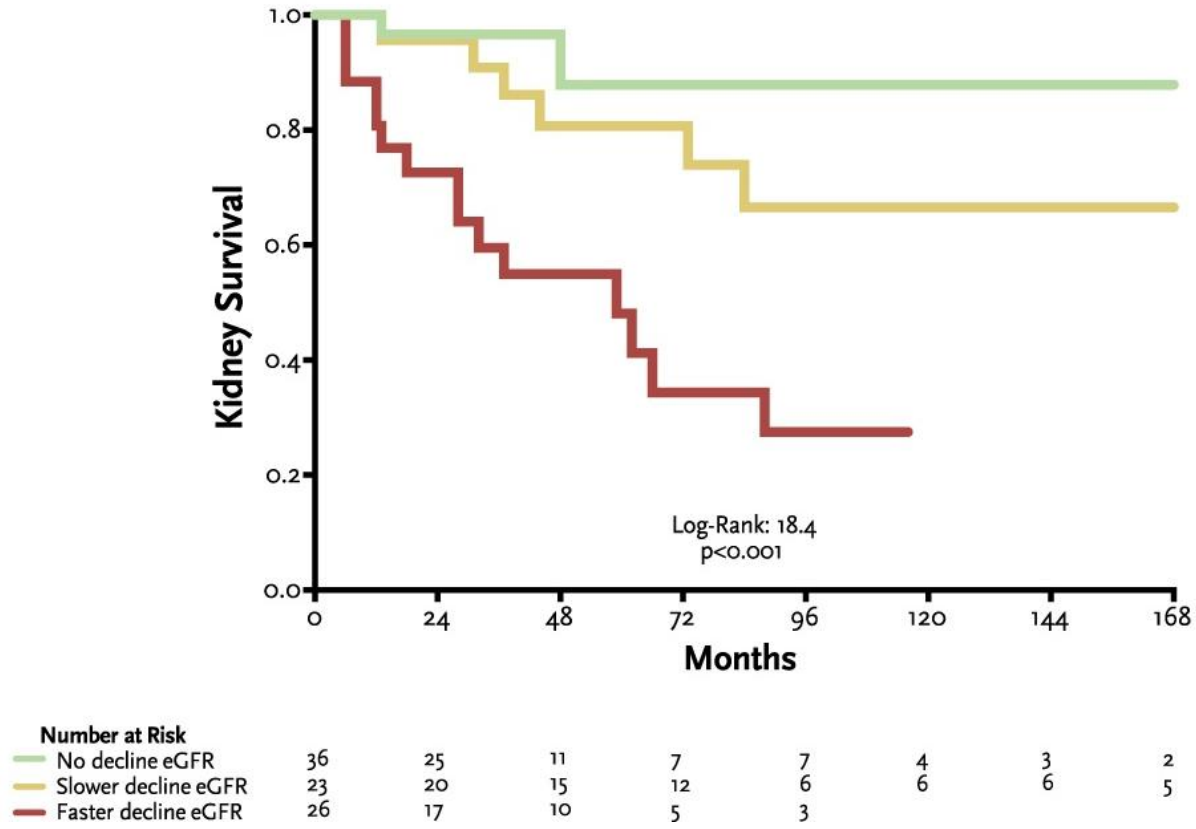
115 C3G patients from 1995 to 2020 in 35 centers

eGFR



uPCR



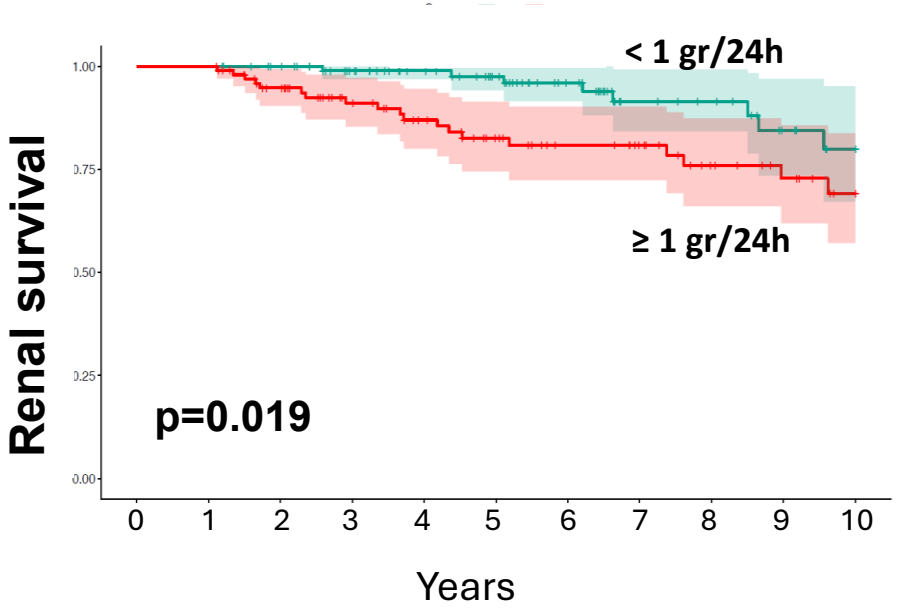


Caravaca-Fontán et al, *Kidney 360* 2023

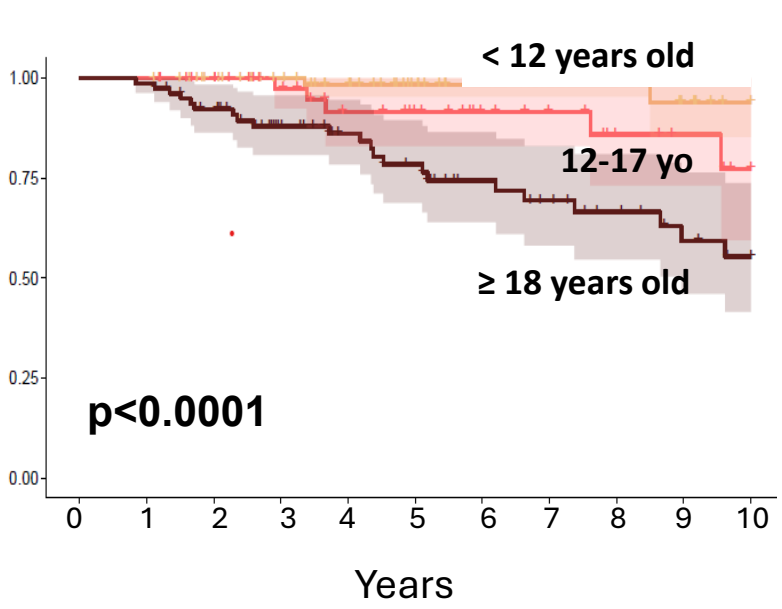
Renal survival at 10 years by different parameters

208 patients with C3G and 141 IC-MPGN

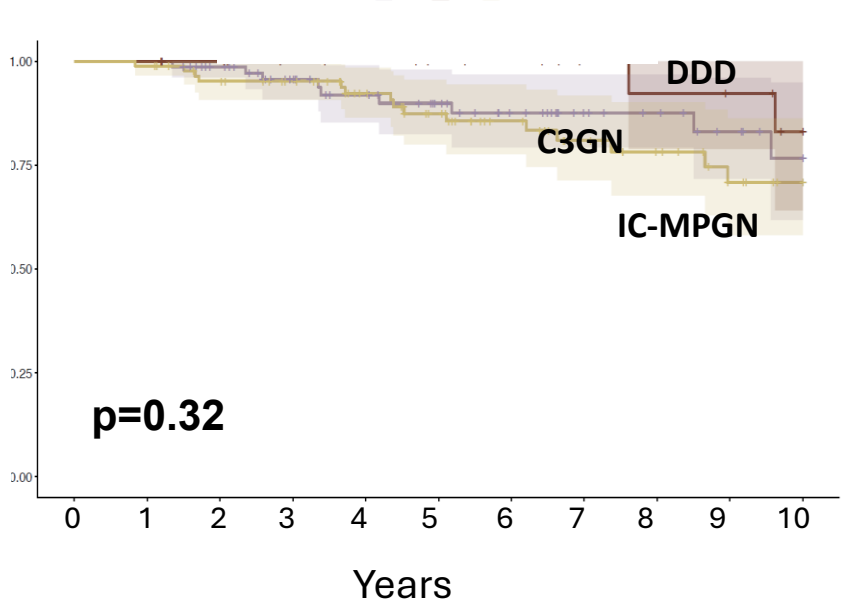
By 1-year proteinuria



By onset age

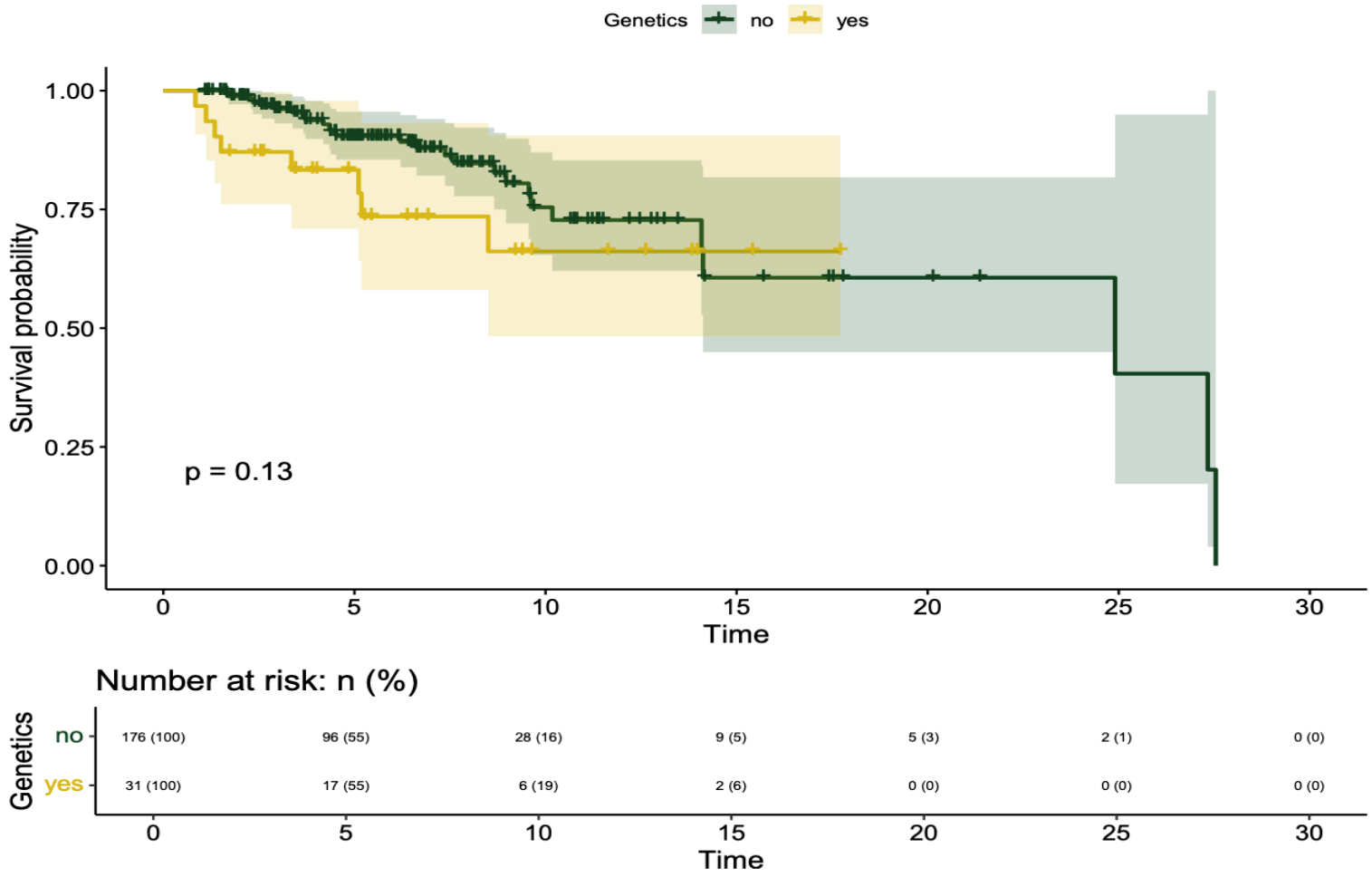


By histological subtype



Nanchen G, Marasa' M et al *CJASN* 2026

No difference in 10-year renal survival by genetic predisposition



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Kidney transplantation in children and adolescents with C3G or IC-MPGN: A natural history study within the CERTAIN research network

AIM: To describe and compare the long-term outcome of children with C3G or IC-MPGN after kidney transplantation

DESIGN:

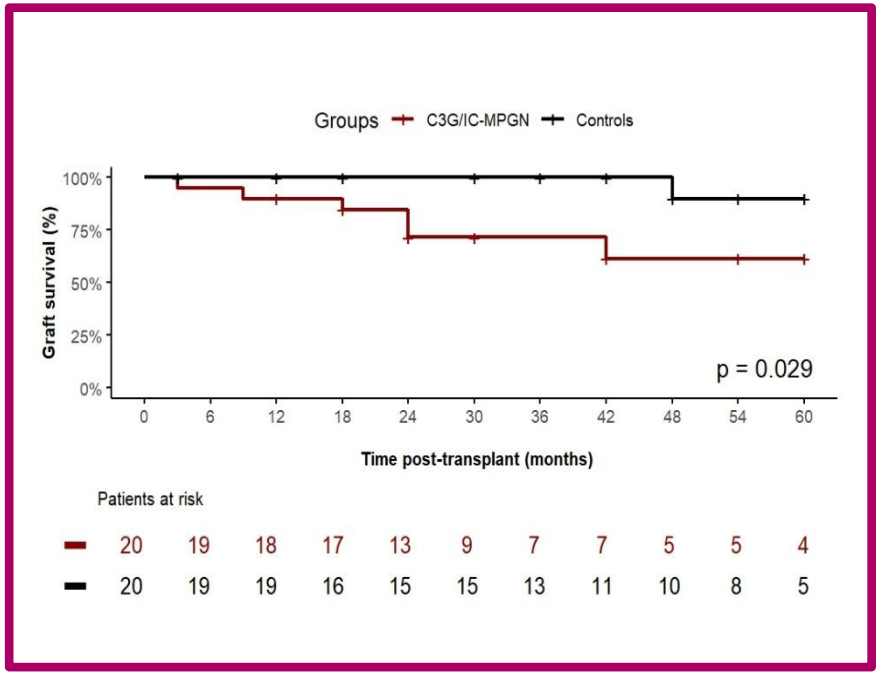
CERTAIN Registry data assessment of children with MPGN

- C3GN (n=12)
- DDD (n=5)
- IC-MPGN (n=3)
- Matched controls (n=20)

OUTCOME at 5 yrs:

Recurrence Rate: 55%

Reduced graft survival in C3G and IC-MPGN (61% vs 90%)

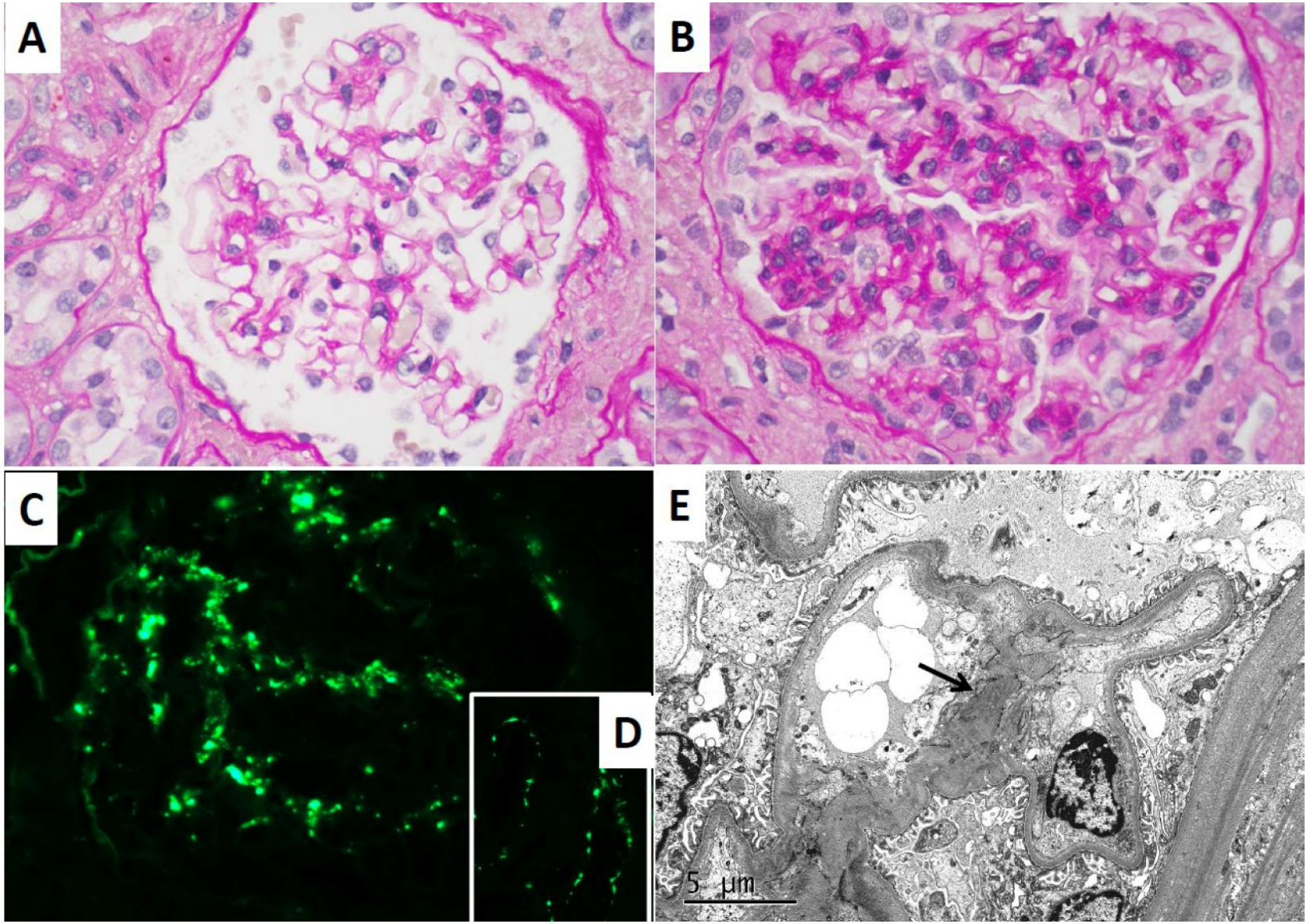


Patry et al. 2024

Published studies on C3G recurrence

Study	Andresdottir et al. 1999	Zand et al. 2014	Regunathan-Shenk et al. 2019	Kumar et al. 2021	Caravaca-Fontán et al. 2023	Tarragon et al. 2024
Total N	13 DDD	21 C3GN	12 C3GN 7 DDD	12 C3GN 9 DDD	31 C3GN 3 DDD	12 C3GN 6 DDD
Study design	Retrospective single-center	Retrospective single-center	Retrospective single-center	Retrospective single-center	Retrospective multicenter	Retrospective single-center
Tx Year	1983–1994	1996–2010	1999–2016	2012–2017	1981–2021	2016–2023
Recurrence %	62%	67%	83% C3GN 86% DDD	67% DDD 42% C3GN	42% C3GN 100% DDD	92% C3GN 83% DDD
Graft failure C3G recurrence	62%	50%	47%	38% in C3GN 56% in DDD	57%	0%
Anti-complement therapy	None	None	37%	None	43%	25% in C3GN 17% in DDD

C3G recurs early after kidney transplantation



- **18 kidney tx recipients** (12 C3GN and 6 DDD on native kidneys)
- **89% recurrence rate at 33 days (13, 141) after tx**
- IF and EM crucial to identify early recurrence
- **No graft loss after a 37-month median follow-up**

Tarragon B et al *cJASN* 2024

How to identify at diagnosis patients at risk of progression/post tx recurrence?

- Histology? 🚫
- Complement markers? 🚫
- Genetics? 🚫

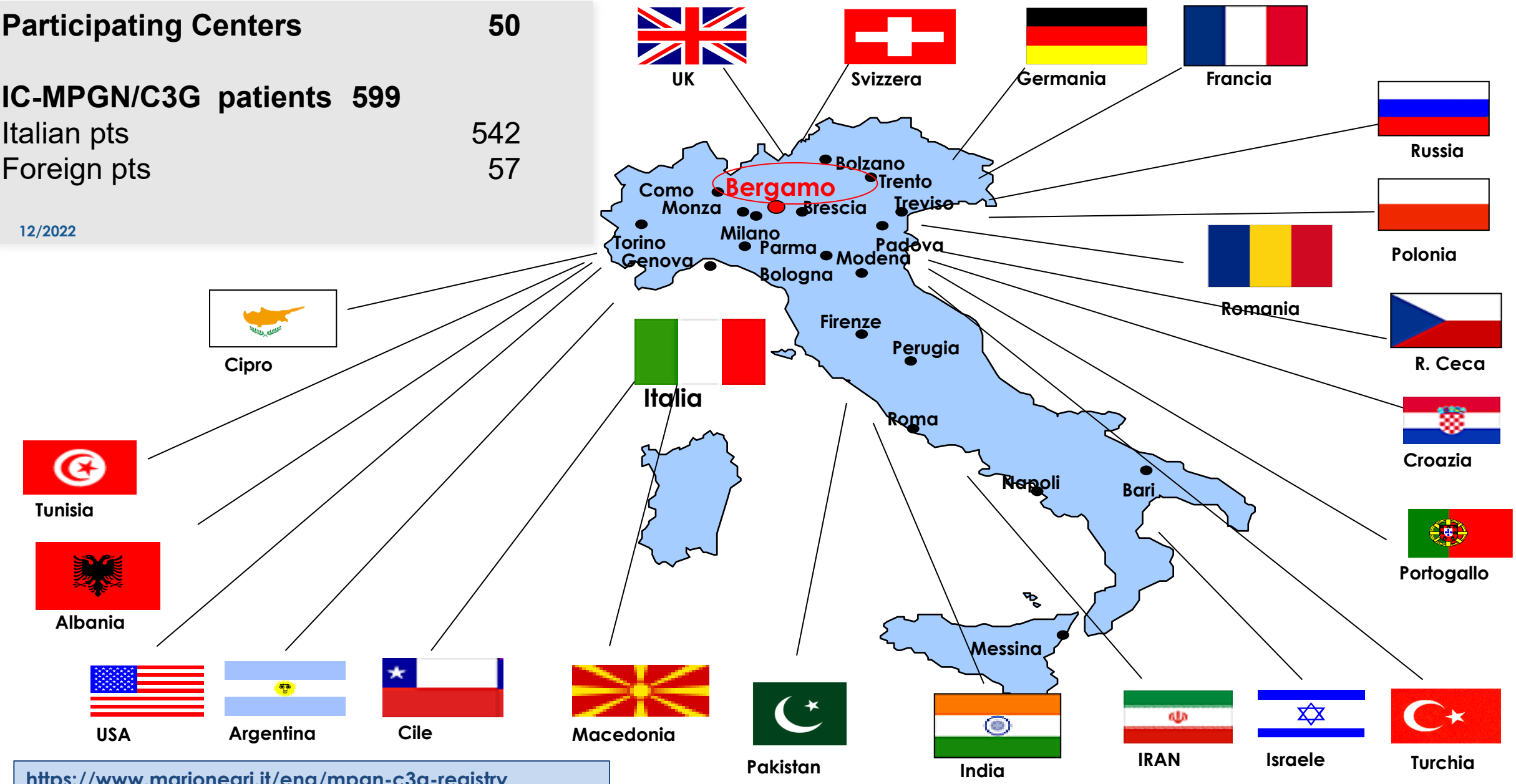
Is it possible to subdivide patients in groups that better reflect pathogenesis?

Aim: *to develop diagnostic tools to identify clinically meaningful subcategories and guide tailored treatments to improve clinical outcomes.*

Italian Registry of MPGN/C3G

Participating Centers	**50**
IC-MPGN/C3G patients	**599**
Italian pts	542
Foreign pts	57

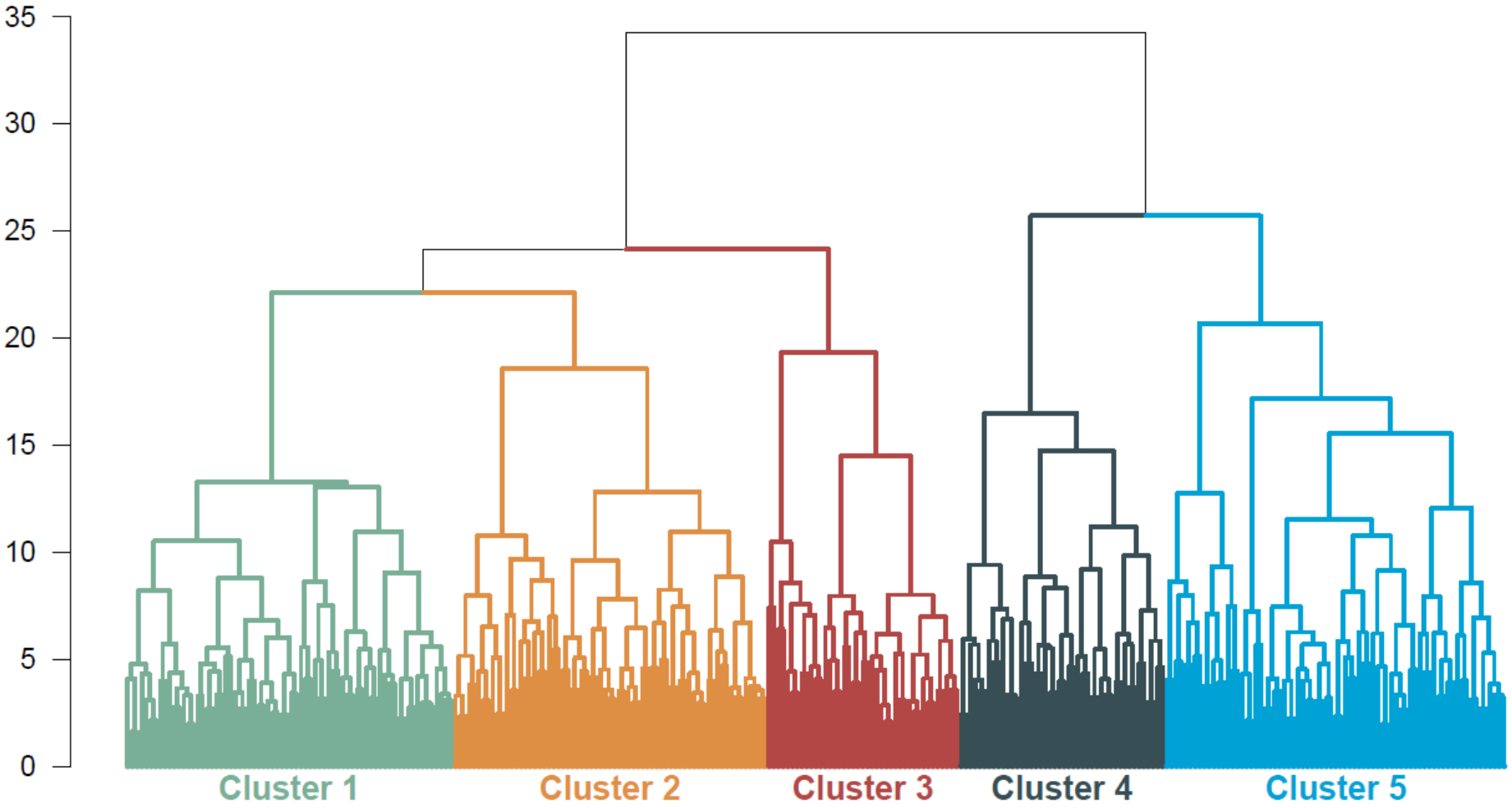
12/2022



https://www.marionegri.it/eng/mpgn-c3g-registry

Cluster analysis in 295 patients with primary IC-MPGN and C3G identified 5 distinct groups

Patient histology: *135 (46%) had IC-MPGN, 125 patients (42%) had C3GN and 35 (12%) had DDD*



Variables included (29)

- ❑ **Clinical**
- ❑ **Histological**
- ❑ **Biochemical**
- ❑ **Genetic**

Benigni et al, *Kidney Int,* 2025

5 cluster differentiates for complement profiles

***Clusters 1-3**:*
Fluid–phase complement activation

Cluster 1
Low serum C3 and high plasma sC5b-9 levels
Fluid-phase AP C3 and C5 convertase activation

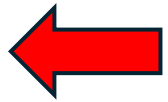
Cluster 2:
Low serum C3 and high plasma sC5b-9 levels
Ig and C1q staining on IF
Fluid-phase AP C3 and C5 convertase activation + classical pathway activation

Cluster 3:
Low serum C3 and mostly normal plasma sC5b-9 levels
Very dense deposits on EM
Fluid-phase AP C3 convertase activation only

Cluster 4 and 5:
Solid–phase AP complement activation
Normal serum C3 levels, normal plasma C5b-9 , Intense C3 staining on IF

Cluster 4
No genetic abnormalities, late onset

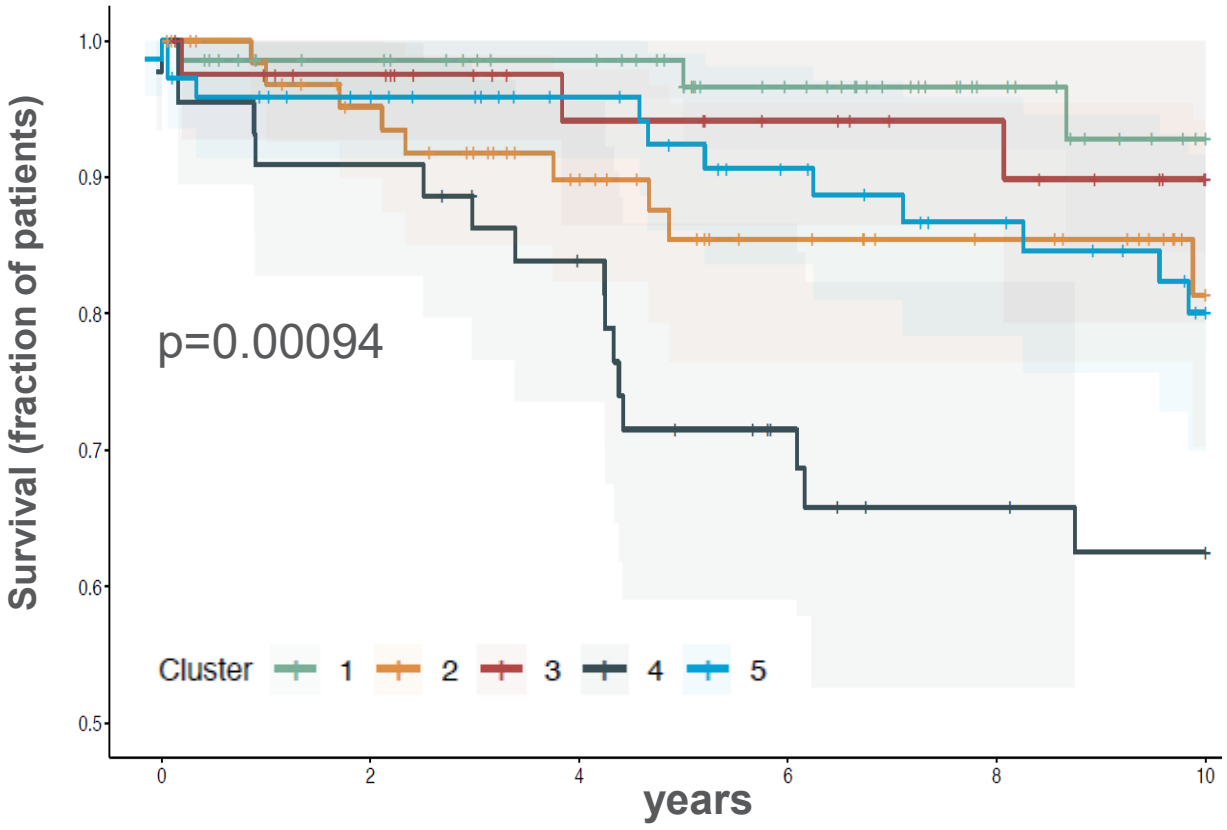
Cluster 5
Complement gene abnormalities, early onset



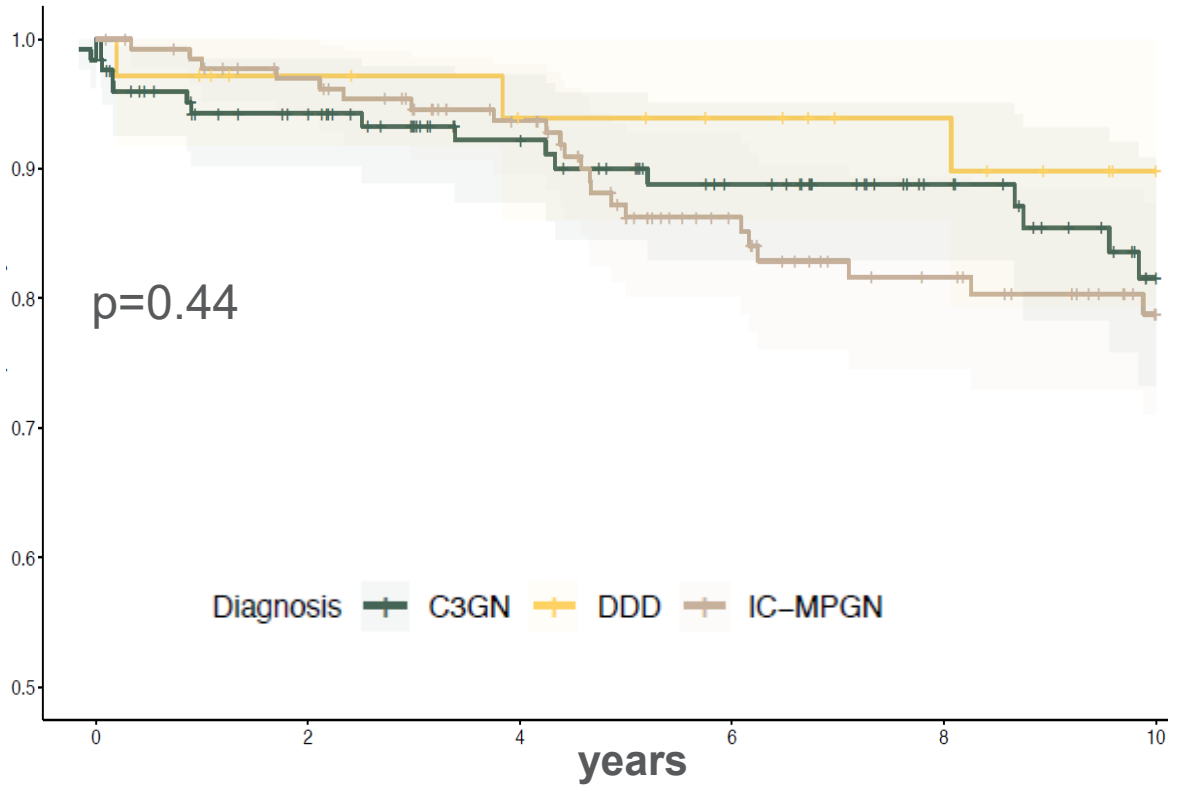
Benigni et al, *Kidney Int,* 2025

Clusters have prognostic value whereas histology do not

ESKD by cluster

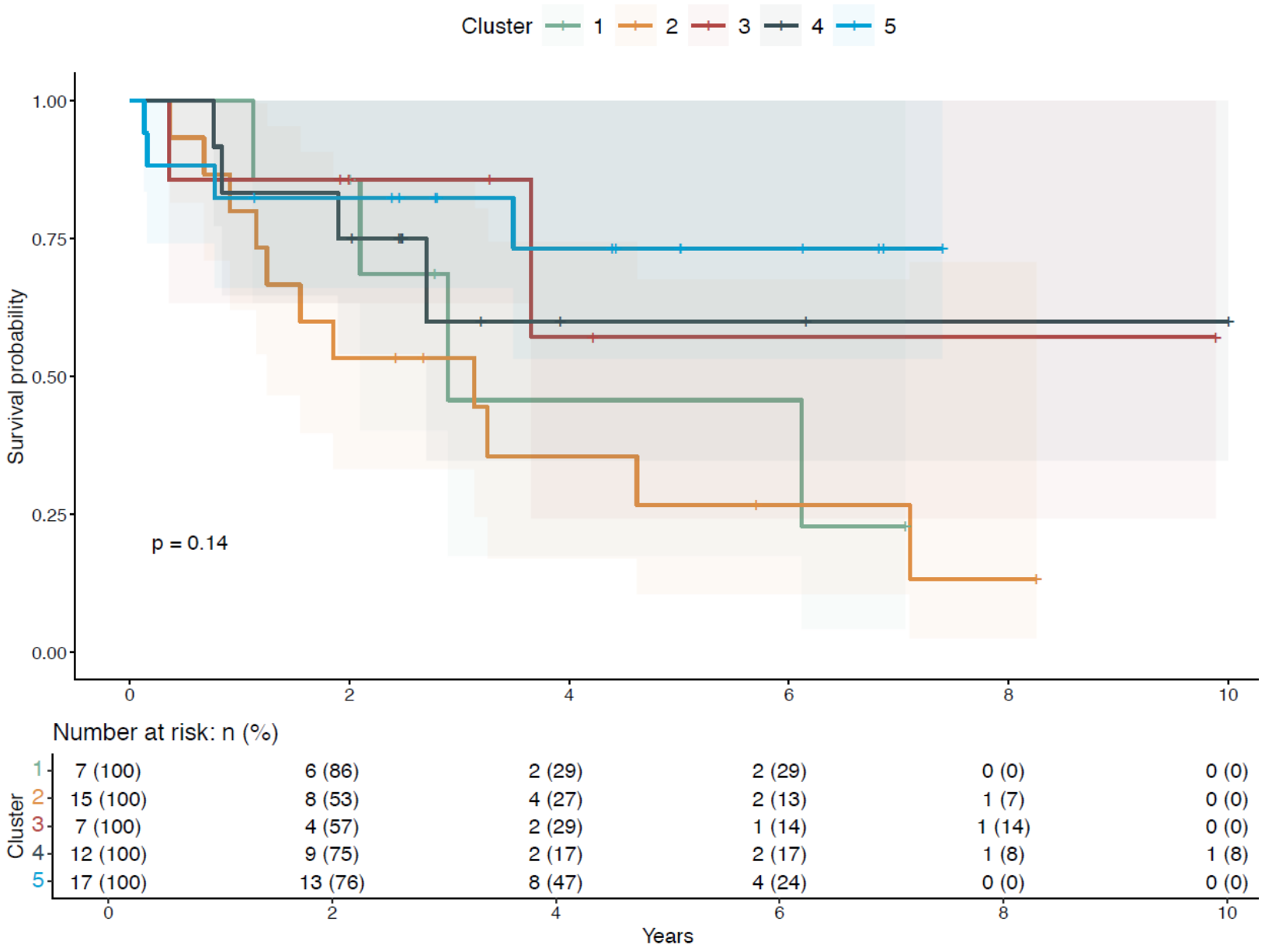


ESKD by histologic group



Benigni et al, *Kidney Int,* 2025

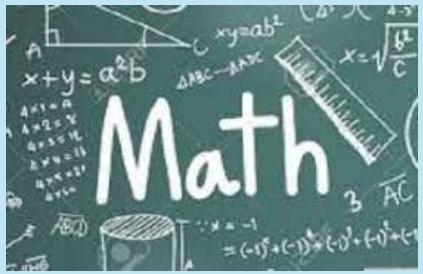
Clusters 1 and 2 showed high risk of post-transplant recurrence



Benigni et al, *Kidney Int,* 2025

Will the clusters lead to patient-tailored therapies and precision medicine?

TOWARD PRECISION MEDICINE FOR C3G AND IC-MPGN



Cluster 1
Fluid-phase AP C3 and C5 convertase activation

Pegcetacoplan
Blocks C3 activation

Iptacopan, NM8074
FB inhibitor

Avacopan
C5aR1 inhibitor

Eculizumab
Anti-C5 ab

Cluster 2
Fluid-phase C3 and C5 convertase activation + classical pathway activation

Pegcetacoplan
Blocks C3 activation

ARO-C3
Liver-targeting C3 silencing

Eculizumab
Anti-C5 ab

Cluster 3
Fluid-phase AP C3 convertase activation only

Pegcetacoplan
Blocks C3 activation

Iptacopan, NM8074
FB inhibitor

Clusters 4 and 5
Solid-phase complement activation

ADX-097
Anti C3d mAb-FH

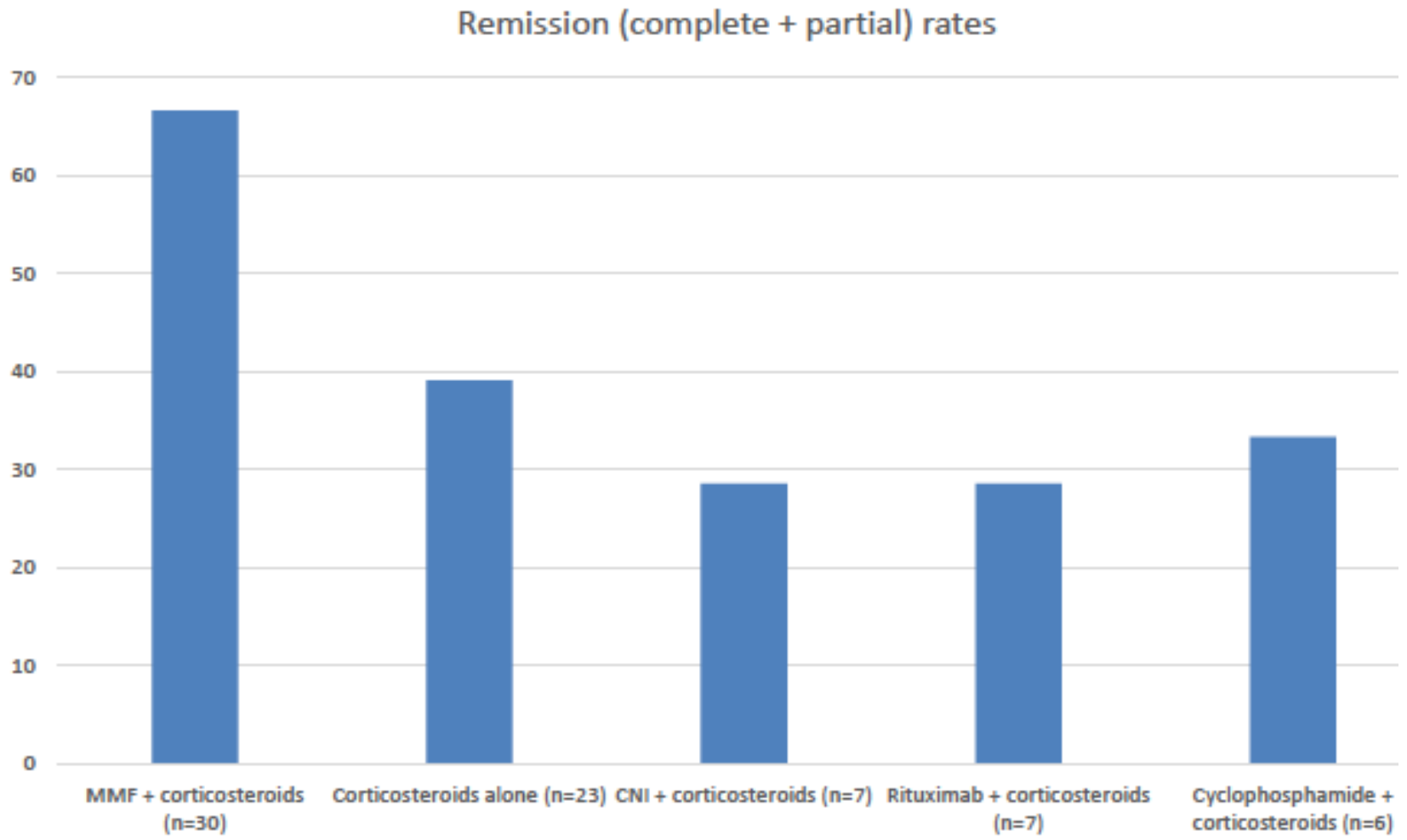
CPV-104
Moss–derived CFH

Outline

- C3G/IC-MPGN histopathological classification
- Complement system dysregulation in C3G/IC-MPGN (briefly)
- Natural history of C3G/IC-MPGN
- Post transplant recurrence
- Treatment (briefly)
- Summary

Non-specific Immunosuppression

73 Patients with G3G (Columbia cohort)



Avasare, et al., *CJASN,* 2018

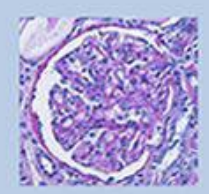
Efficacy of Mycophenolate Mofetil (MMF) in C3 Glomerulopathy - does it depend upon pathogenic drivers?

CJASN
Clinical Journal of the American Society of Nephrology

Retrospective
Multicenter
Observational

n = 97

C3 Glomerulopathy



n = 84

C3 glomerulo nephritis

n = 16

Dense deposit disease

Outcomes IS = Immunosuppression		Remission (Complete + Partial)	Kidney failure (eGFR<15 ml/min)
MMF + Steroids	n = 42	79%	14%
Other IS	n = 38	26%	60%
No IS	n = 17	17%	65%

Pathogenic drivers	Complete remission (n = 18)		Partial remission (n = 28)
Pathogenic genetic variants	0%	P = 0.03	21%
C3 Nephritic factor	44%	P = 0.01	11%

Proteinuria (>3.5 g/day)

Predictor of no response to MMF + Steroids

Conclusions: MMF plus corticosteroids was associated with a higher probability of remission and lower probability of kidney failure. Patients with genetic mutations were more likely to achieve partial remission, whereas complete remissions were common in antibody-mediated forms.

Fernando Caravaca-Fontán, Montserrat Díaz-Encarnación, Laura Lucientes, Teresa Cavero, et al. ***Mycophenolate Mofetil In C3 Glomerulopathy and Pathogenic Drivers of the Disease.*** CJASN doi: 10.2215/CJN.15241219.
Visual Abstract by Divya Bajpai, MD, PhD

Caravaca-Fontan F, *CJASN* 2020

The NEW ENGLAND JOURNAL of MEDICINE March 22, 2012

Eculizumab in a Patient with Dense-Deposit Disease

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Eculizumab for the Treatment of Dense-Deposit Disease

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COMPLEMENT INHIBITORS IN CLINICAL DEVELOPMENT FOR KIDNEY DISEASES

Table 1 | Complement i

Target of inhibition	Drug
C1	ANX009
C3, C3b	Pegcetacoplan
C3	AMY101
C3	ARO-C3
C3b, C5	KP104
C5	Cemdisiran
C5	Crovalimab
C5	Eculizumab
C5	Gefurulimab (ALXN1720)
C5	Ravulizumab

Table 1 | (Continued) **Complement inhibitors in clinical development[a] for kidney diseases**

Target of inhibition	Drug	Inhibitor type	Mechanism	Route	Clinical trials
C5	Nomacopan or coversin (rVA576)	Small protein	Inhibits terminal complement activation by tightly binding to C5 and preventing C5a release and C5b-9 formation, and inhibits leukotriene B4 by capturing the fatty acid within the body of the nomacopan protein	SC	NCT04784455 (pediatric post-BMT HUS, phase 3, recruiting)
C5a	Vilobelimab (IFX-1)	Antibody	Selectively inhibits C5a activity leaving the MAC intact	IV	NCT03712345 (GPA and MPA, phase 2, terminated) NCT03895801 (GPA and MPA, phase 2, completed)
C5aR1	Avacopan	Small molecule	Blocks the binding of the anaphylatoxin C5a with the C5aR1 receptor	Oral twice daily	NCT02464891 (aHUS on dialysis, phase 2, terminated) NCT03301467 (C3G, phase 2, completed) NCT02384317 (IgAN, phase 2, completed)[7] NCT02994927 (AAV, phase 3, completed)[8] NCT01363388 (AAV, phase 2, completed) NCT02222155 (AAV, phase 2, completed)
Factor B	IONIS-FB-LRx	Antisense oligonucleotide	Inhibits liver synthesis of factor B	SC	NCT04014335 (IgAN, phase 2, active not recruiting, ASN poster SA-PO926)[8a] NCT05797610 (IgAN, phase 3 recruiting)
Factor B	Iptacopan (LNP023)	Small molecule	Prevents activity of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT04889430 (aHUS, phase 3, recruiting) NCT03832114 (C3G, phase 2, adults with native or transplanted kidney,[9] extension NCT03955445) NCT04817618 (C3G, phase 3, adults and adolescents >12 years, recruiting, for adults interim results reported)
Factor Bb					
Factor D					
Factor D	Danicopan (ALXN2040, ACH-4471)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT03124368 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03369236 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03459443 (C3G or IC-MPGN, phase 2, terminated)
Factor D	Vemircopan (ALXN2050, ACH-0145228)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral	NCT05097989 (IgAN or LN, phase 2, recruiting)
MASP-2	CM338	Monoclonal antibody	Blocks initiation of the lectin pathway	SC	NCT05775042 (IgAN, phase 2, recruiting)
MASP-2	Narsoplimab (OMS721)	Antibody	Blocks initiation of the lectin pathway	IV	NCT05855083 (pediatric post-BMT HUS, phase 2, recruiting) NCT03205995 (aHUS, phase 3, status unknown) NCT02682407 (C3G, IgAN, LN, MN, phase 2, status unknown) NCT03608033 (IgAN, phase 3, terminated)
MASP-3	OMS906	Antibody	Blocks initiation of the lectin pathway	IV	NCT06209736 (C3G, IC-MPGN, phase 2, not yet recruiting)
Renin[b]	Aliskiren	Small molecule	Blocks renin-mediated C3 cleavage	Oral	NCT04183101 (C3G, phase 2, recruiting)

M Vivarelli et al., *Kidney Int* 2024

IC-MPGN & C3G: two separate entities or the same condition with different manifestations?

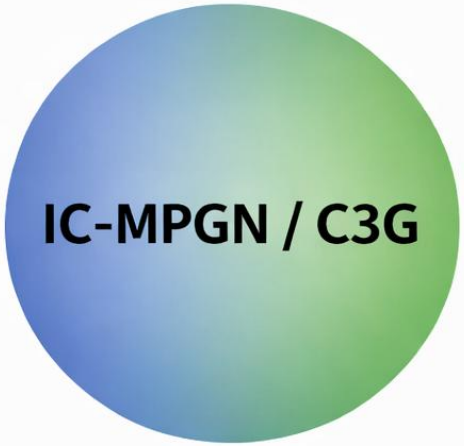
Iptacopan

APPARENT
- ongoing in adults
- ongoing in 12-17 yo

APPEAR-C3G
- completed in adults
- ongoing in 12-17 yo

Approved in:
- ✓ C3G
- ✓ Adults only

Pegcetacoplan



NOBLE: completed (post tx)
VALIANT: completed in adults and 12-17 yo

Approved in:
- ✓ C3G and IC-MPGN
- ✓ Adults and 12-17 yo

Summary

- C3G/IC-MPGN are **ultra-rare complement-mediated** kidney diseases mainly affecting **children and young adults** and characterized by a variable but more frequently **poor prognosis** leading to ESKD and with high post transplant recurrence rate.
- **1-year proteinuria levels >=1 g/24h and younger age at diagnosis** are associated with better prognosis.
- Circulating complement levels, genetic defects, and histological diagnosis do not correlate with patients' outcomes.
- A **cluster-based classification** may provide better prognostic value than current approaches and potentially guide clinical management.
- As complement dysregulation has a central role in the disease pathogenesis, novel recently approved **complement-target therapies will dramatically change the natural history of this disease**.

Thank you!

Acknowledgments

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

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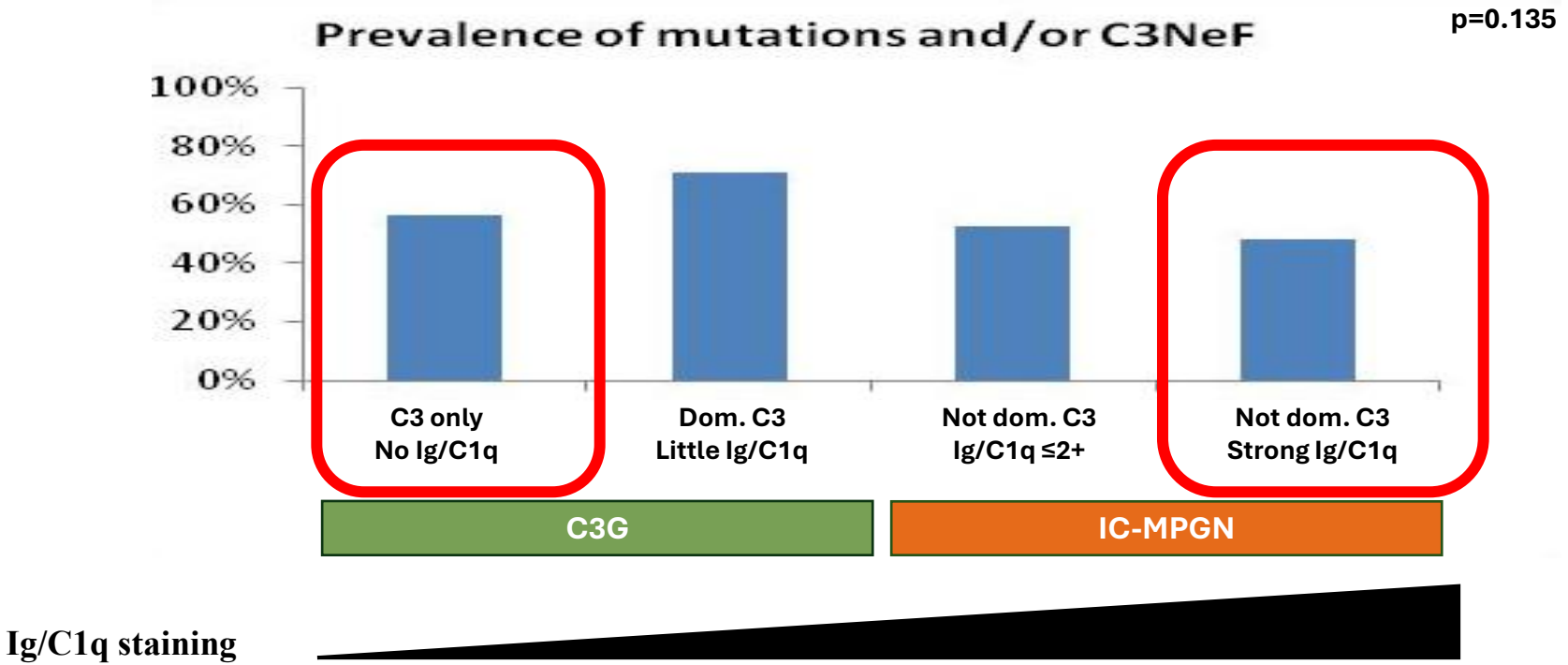
Camillo Carrara
Alessia Gennarini
Valentina Leone

Nephrologists and patients contributing to the Italian Registry of MPGN

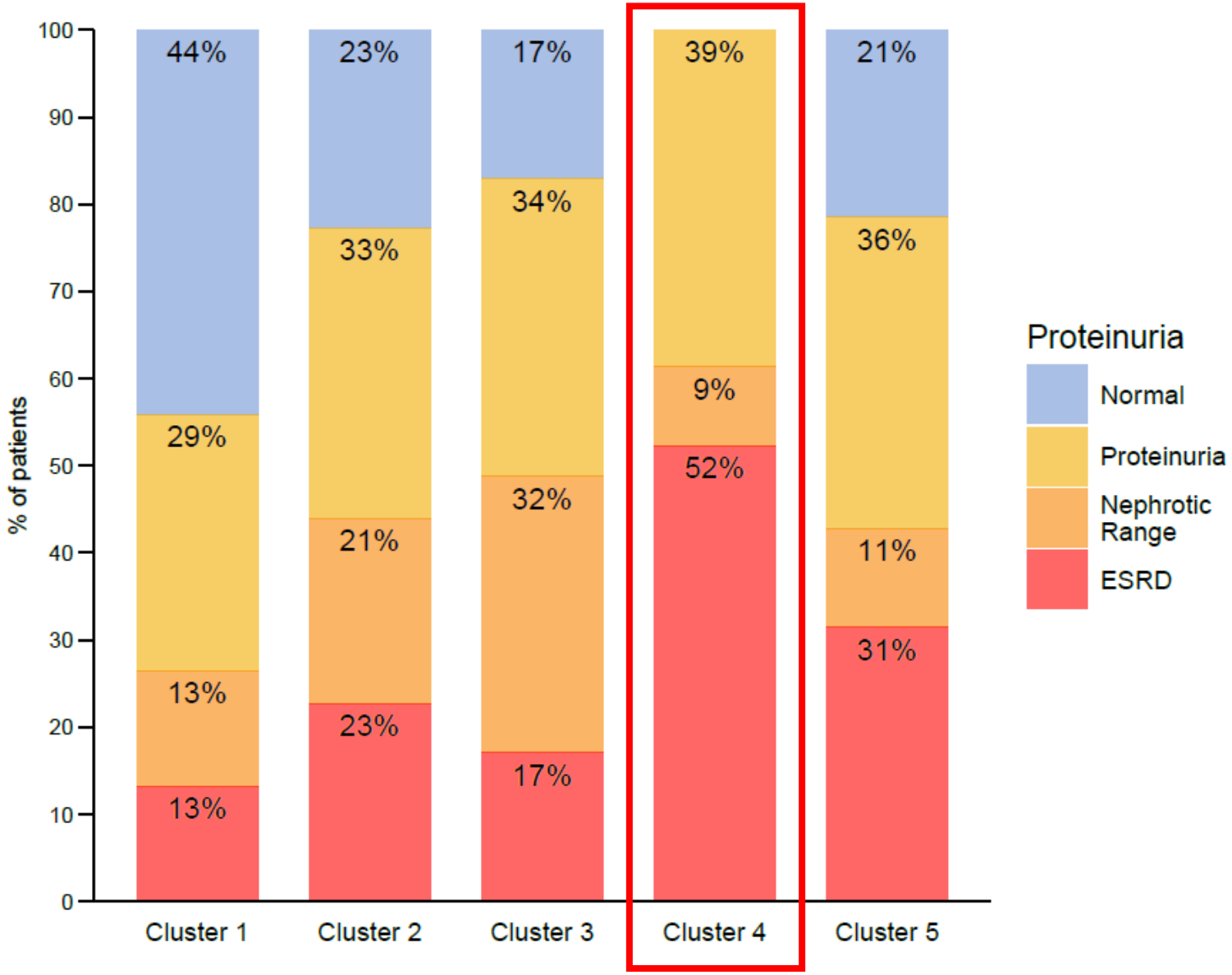
Extra Slides

Genetic and acquired alternative pathway abnormalities are equally prevalent in C3G and IC-MPGN



Even when we compare glomerular bright C3 only vs. strong (3+) Ig and/or C1q cases, we find **no statistically significant difference (57% vs 49%, p=0.4).**

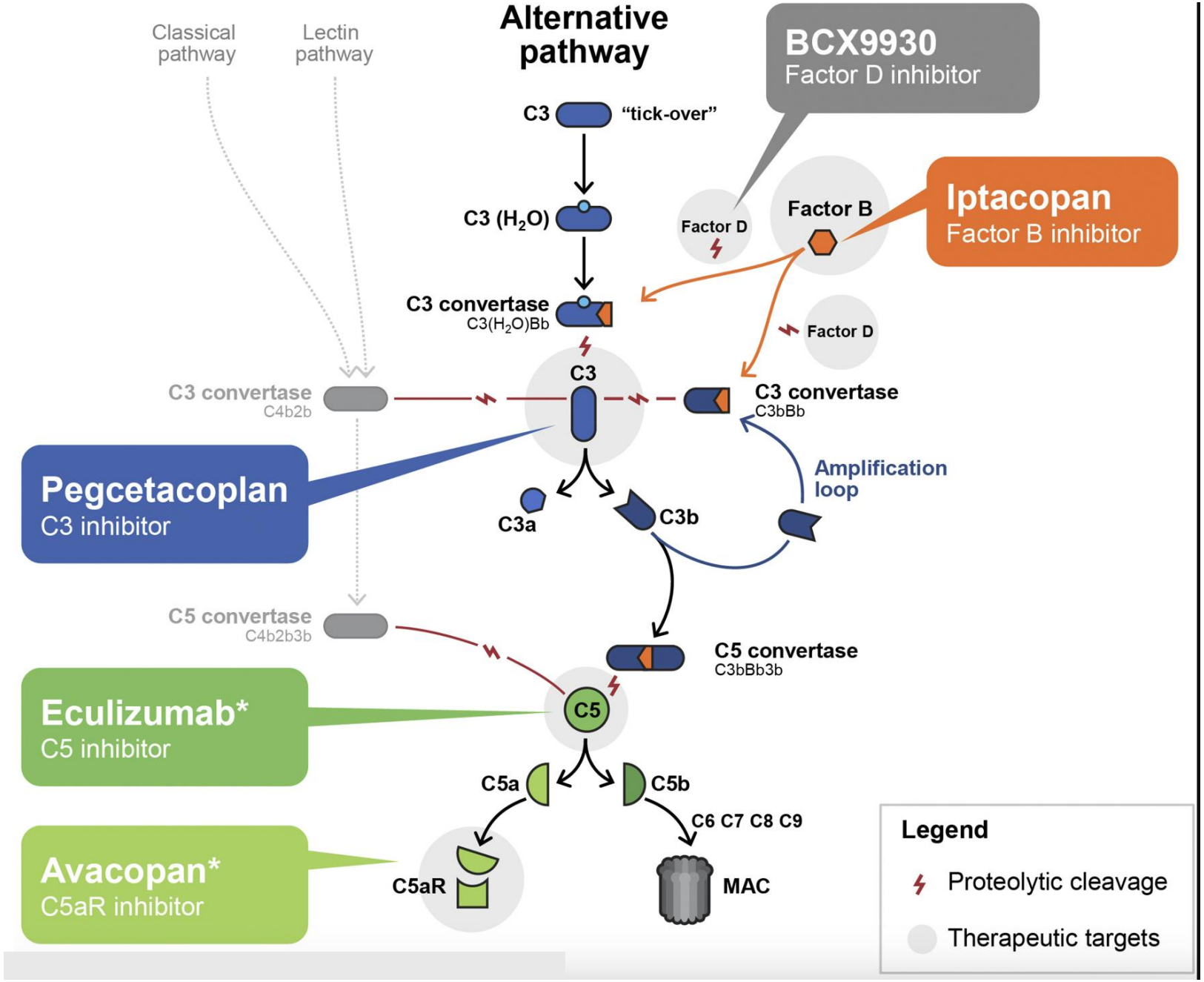
Iatropoulos P et al., *JASN* 2018



At the last available follow-up:

- 52% of patients in cluster 4 had developed ESKD
- 44% of patients in cluster 1 had normal range proteinuria compared with 0% in cluster 4 (74% maintained a normal renal function)

Benigni et al, *Kidney Int,* 2025


Classical pathway
Lectin pathway
Alternative pathway
BCX9930
Factor D inhibitor
C3
"tick-over"
C3 (H2O)
Factor D
Factor B
Iptacopan
Factor B inhibitor
C3 convertase
C3(H2O)Bb
Factor D
C3
C3 convertase
C4b2b
C3 convertase
C3bBb
Amplification loop
Pegcetacoplan
C3 inhibitor
C3a
C3b
C5 convertase
C4b2b3b
C5 convertase
C3bBb3b
Eculizumab*
C5 inhibitor
C5
C5a
C5b
C6 C7 C8 C9
Avacopan*
C5aR inhibitor
C5aR
MAC
Legend
Proteolytic cleavage
Therapeutic targets

These slides belong to Maddalena Marasà, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy

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