CLINICAL PHENOTYPE & ASSESSMENT

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Disclosure of Interests

In the last 12 months I have received unrestricted research grants/support from

- Genentech Inc
- Biogen Idec
- Mallinckrodt Pharmaceuticals
- Sanofi Pharmaceuticals

Honorarium

- Up-To-Date
- American Board of Internal Medicine
- Journal of the American Society of Nephrology

Clinical Phenotype & Assessment

1. What tests are required to diagnose C3G?
2. How should these patients be followed?
3. Can we predict disease course?
4. How does pathology correlate with phenotype?

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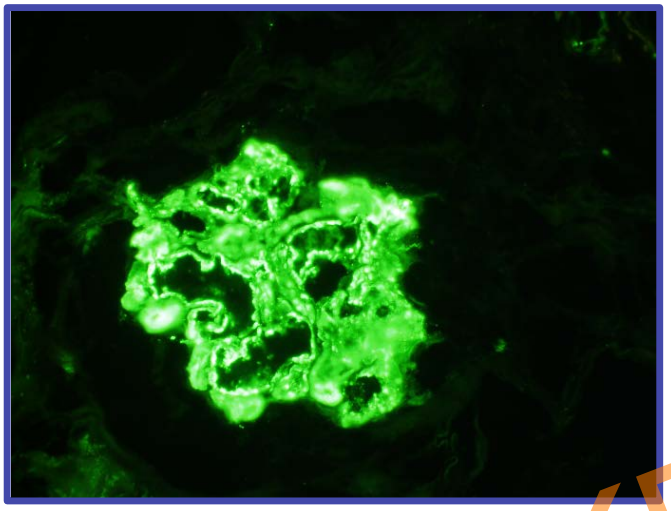
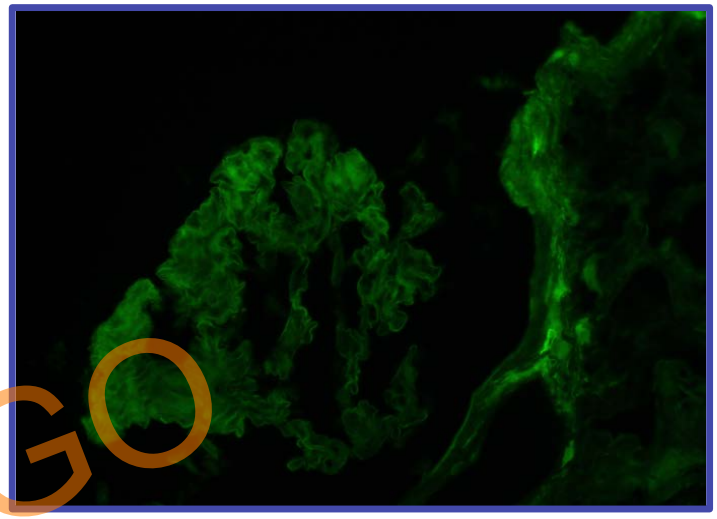
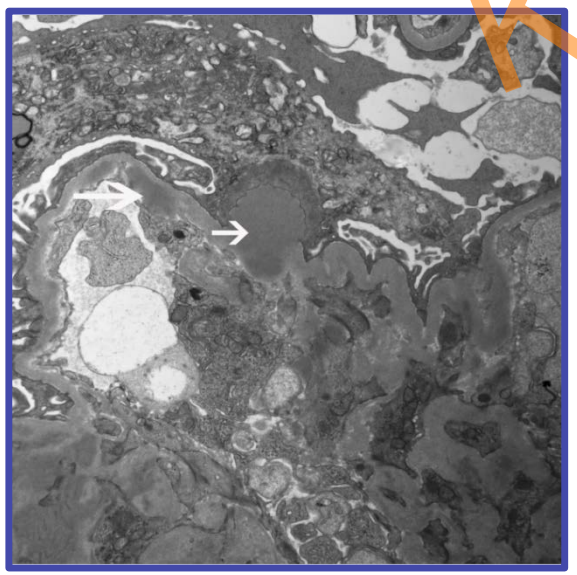
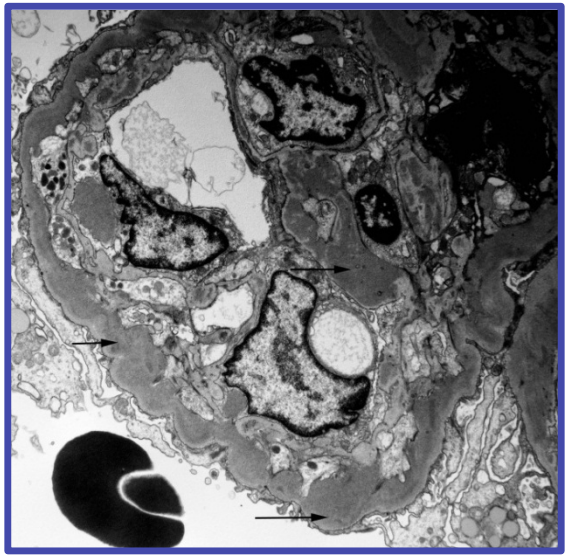
C3 Glomerulopathy









see commentary on page 379

Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies

Aude Servais[1,2], Laure-Hélène Noël[3,4], Lubka T. Roumenina[5], Moglie Le Quintrec[5], Stephanie Ngo[6], Marie-Agnès Dragon-Durey[5,7], Marie-Alice Macher[8], Julien Zuber[2,9], Alexandre Karras[10], François Provot[11], Bruno Moulin[12], Jean-Pierre Grünfeld[1,2], Patrick Niaudet[2,7], Philippe Lesavre[1,2] and Véronique Frémeaux-Bacchi[5,6]

http://www.kidney-international.org original article
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see commentary on page 379

C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up

Sanjeev Sethi[1,6], Fernando C. Fervenza[2,6], Yuzhou Zhang[3], Ladan Zand[2], Julie A. Vrana[1], Samih H. Nasr[1], Jason D. Theis[1], Ahmet Dogan[1] and Richard J.H. Smith[3,4,5]

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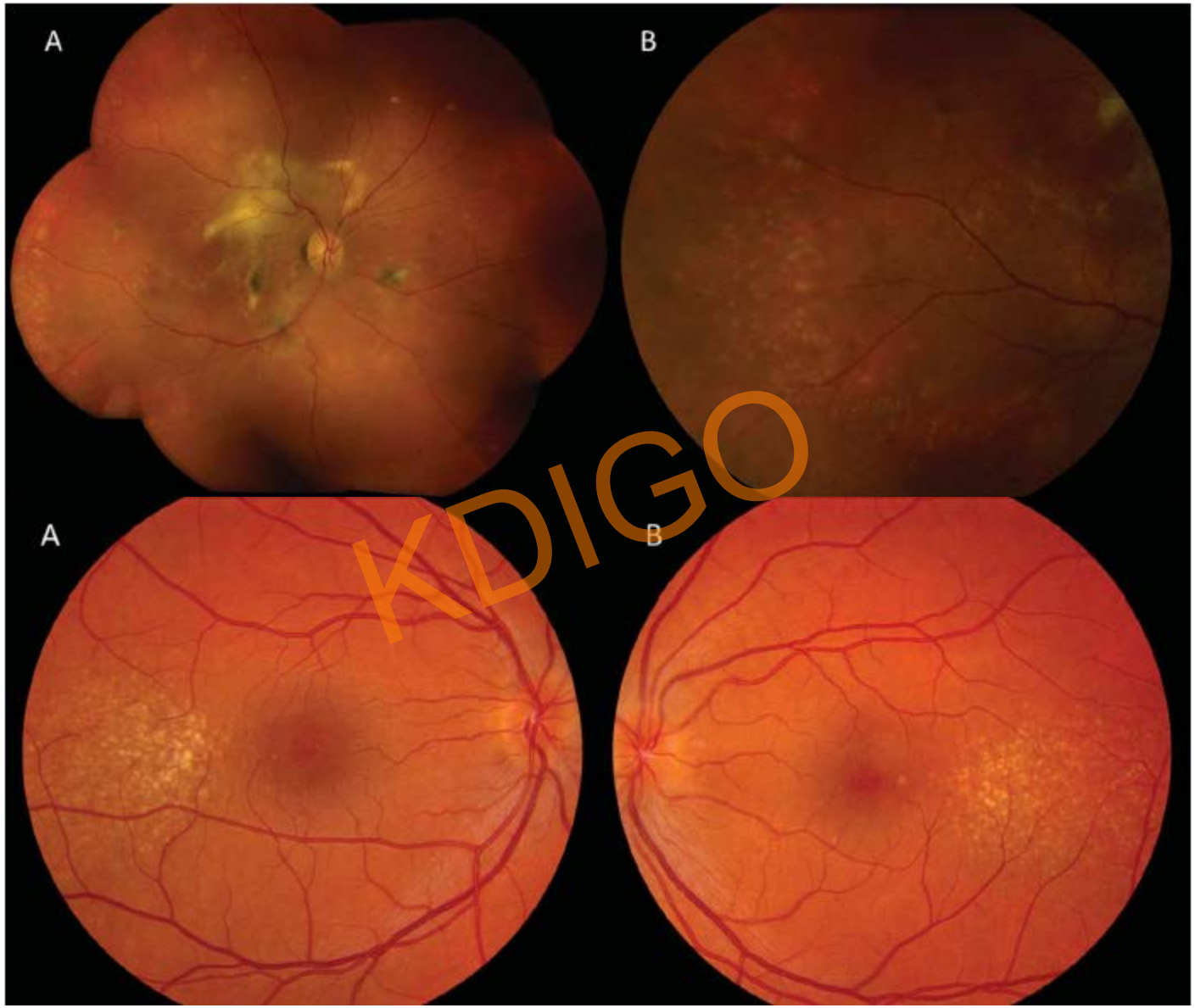
Complement component assessment according to histological type

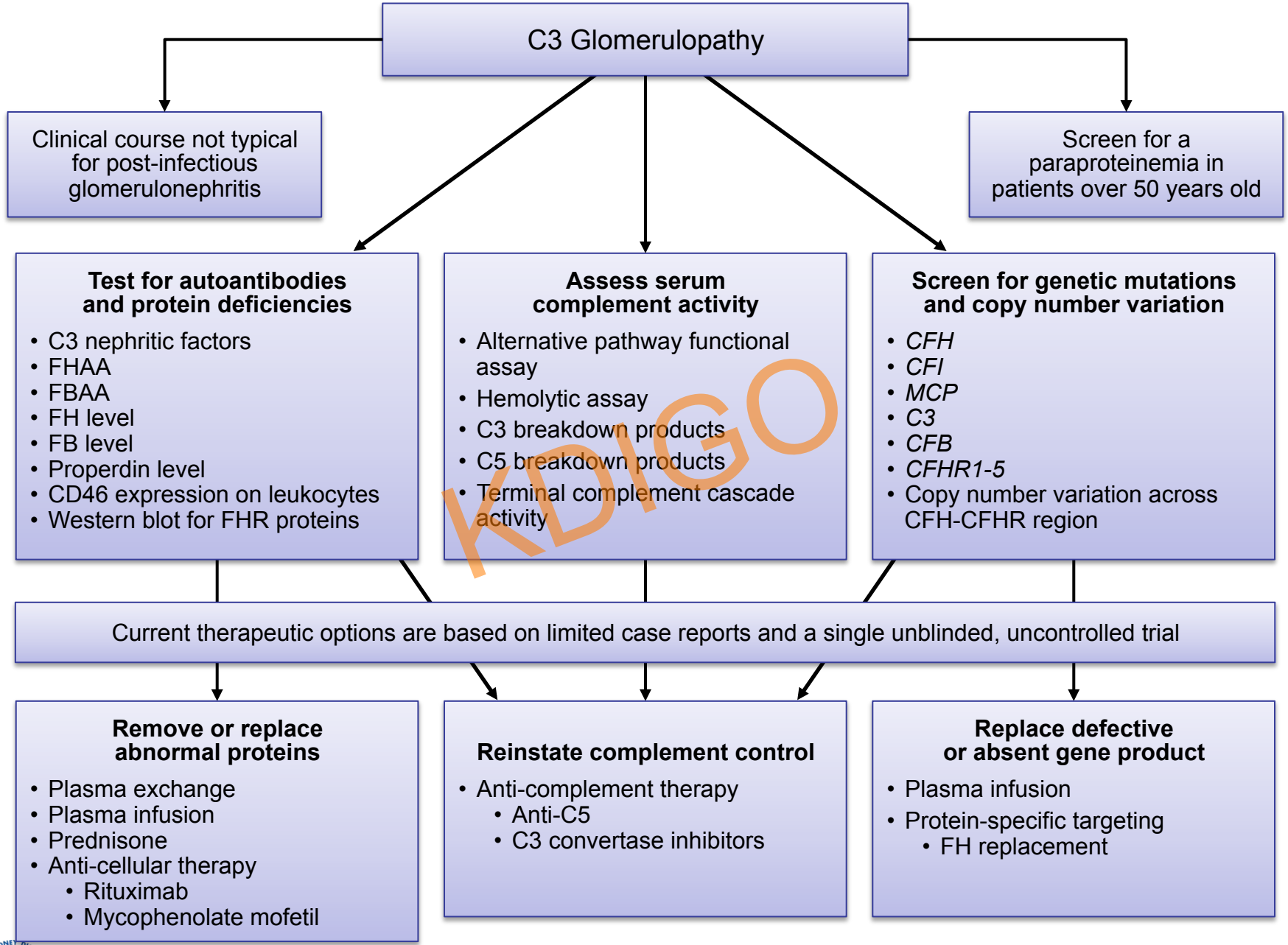
	All	MPGN 1	DDD	GNC3
N	115	41	22	53
C3[a] (660 to 1250 mg/l)	621.91 ± 339.5	583.1 ± 360.7	492.8 ± 337.7	705.4 ± 305.2
Low C3 (<660 mg/l)	53 (46.1%)	19 (46.3%)	13 (59.1%)	21 (39.6%)
C4[a] (93 to 380 mg/l)	227.9 ± 86.3	198.4 ± 65.7	204.8 ± 88.9	260.8 ± 89.3
Low C4 (<93 mg/l)	2 (1.7%)	1 (2.4%)	1 (4.5%)	0
Factor B[a] (90 to 320 mg/l)	116.4 ± 49.3	110.9 ± 42.2	112.6 ± 39.9	122.2 ± 57.7
Low factor B (<90 mg/l)	34 (29.6%)	14 (34.1%)	6 (27.3%)	14 (26.4%)
Low factor H (<338 mg/l)	8 (6.9%)	2 (4.9%)	4 (18.2%)	2 (3.8%)
Low factor I (<42 mg/l)	3 (2.6%)	3 (7.3%)	0	0
C3NeF	65 (58.6%)[b]	22 (53.6%)	19 (86.4%)	24 (45.3%)
Unexplained C3 <660 mg/l	6 (5.2%)	1 (2.4%)	0	5 (9.4%)

Abbreviations: C3NeF, C3 nephritic factor; DDD, dense deposit disease; GNC3, glomerulonephritis with isolated C3 deposits; MPGN, membranoproliferative glomerulonephritis.
[a]Normal values are indicated in brackets.
[b]C3NeF determination was not available in four patients.
Patients under immunosuppressive therapy at the time of complement assessment were excluded from this analysis (*N*=19). Mean ± s.d., number (percentage).

Servais et al., Kidney Int 2012



Dalvin et al. Retinal Cases Brief Reports 2015



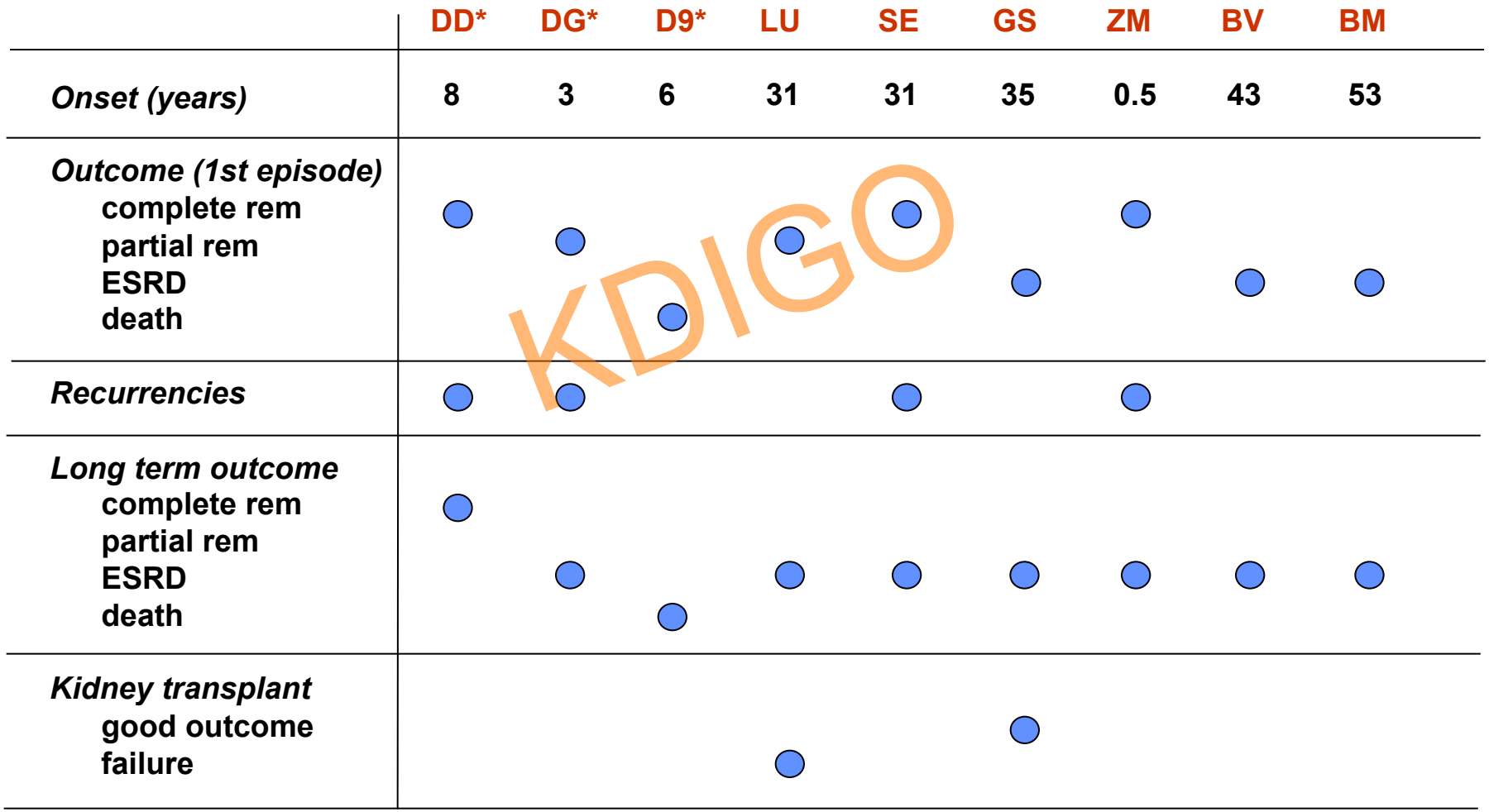
Smith et al 2014

	aHUS	C3 glomerulopathy
Functional assays	CH50, AP50, FH function	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, MCP	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation markers	C3d, Bb, sMAC	C3d, Bb, sMAC
Autoantibodies	anti-FH	C3Nef, anti-FH, anti-FB
Genetic testing	C3, CFH, CFI, CFB, MCP, CFHR1-5, THBD, DGKE	C3, CFH, CFI, CFB, CFHR1-5
Plasma cell disorder		Serum free light chains, serum and urine electrophoresis and immunofixation
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda (usually all negative, with thrombi positive for fibrinogen)	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Angioi, Smith…De Vriese - Kidney Int (in press)

DO THE SAME MUTATION TRANSLATES TO THE SAME PHENOTYPE?

THE R1210C CFH MUTATION: ONSET AND OUTCOME



*these patients also carry mutations in MCP

Caprioli J. et al., 2006

Clinical Phenotype & Assessment

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Clinical Phenotype & Assessment

Will depend on:

a. Renal function

b. Proteinuria

c. Hypertension

d. Laboratory markers?

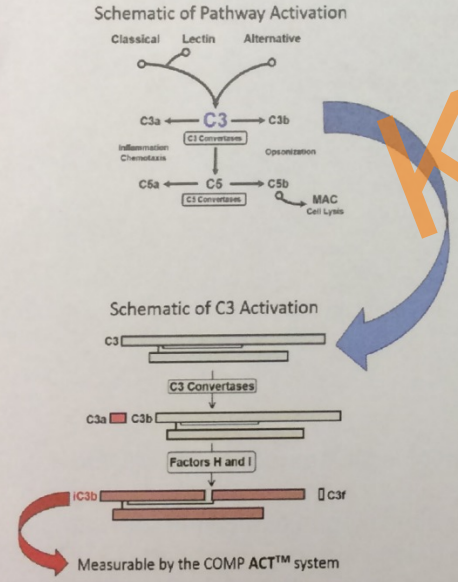
e. Others?

KYPHA

Making sense of inflammation: *with rapid quantification of complement split products*

Complement activation pathways converge on C3/iC3b

Complement is a major mediator of the body's inflammatory response to infection, tissue injury, or autoimmune disease[1-3]. There are three complement activation pathways, the classical, lectin, and alternative pathways which are activated by a variety of substances including antigen-antibody complexes, subcellular and nuclear components of damaged cells and pathogen associated macromolecules [2]. All three complement pathways converge to cleave C3, the central component of the system. C3 is cleaved into several proteolytic activation fragments including iC3b. As a reliable and time-sensitive marker of complement activation, iC3b[4,5] represents a valuable biomarker for complement-mediated inflammation. Furthermore, iC3b is a potent inflammatory modulator itself[6]. C3 is an acute phase protein whose production increases during inflammation, but its measurement in blood may remain low depending on the relative levels of production and consumption. Monitoring both C3 and iC3b simultaneously provides an iC3b/C3 ratio that may help differentiate changes in C3 metabolism due to complement activation.



Complement autoactivation *in vitro*

Complement split product measurements have been plagued by inconsistency due to *in vitro* autoactivation of complement[8-10]. Complement can also be activated by common materials used in sample collection and storage[11,12] making it difficult to obtain reliable data. As a result, the clinical utility of complement-based diagnostics has not been fully realized.

Kypha's lateral flow assay (LFA)*

Kypha's C3 and iC3b tests solve this problem by bringing complement diagnostics to a point-of-care platform[13]. Almost any biofluid sample (blood, plasma, serum, cerebrospinal fluid, etc.) is first diluted in a proprietary buffer that prevents complement activation during the assay**. The sample is then transferred to the test cartridge and placed into the reader for analysis. The results are available just minutes after sample preparation and can be exported in a variety of easily usable formats.

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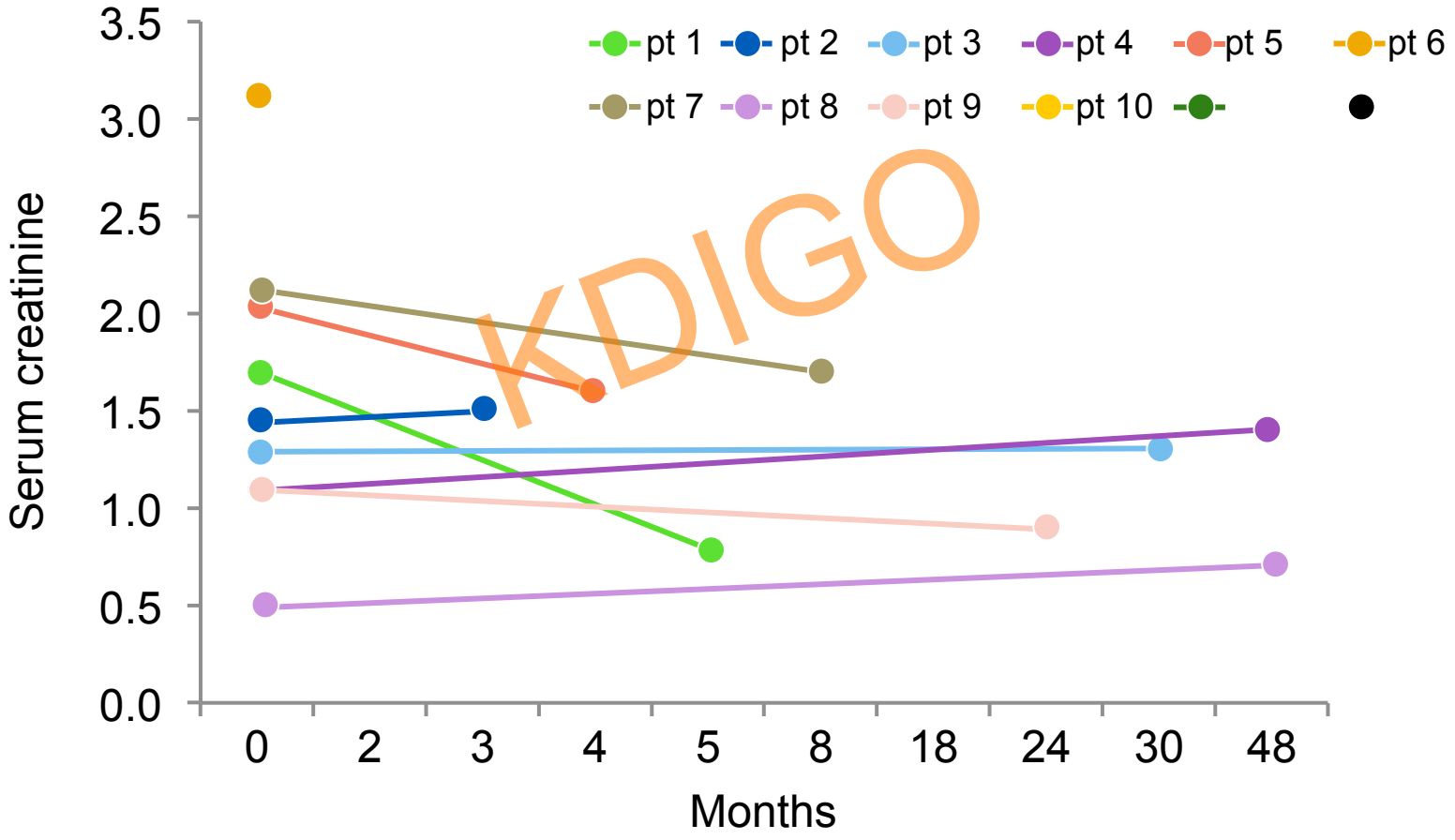
Serum Creatinine at Presentation and Follow-up (in months) of All Patients



Sethi et al. Kidney Int 2012

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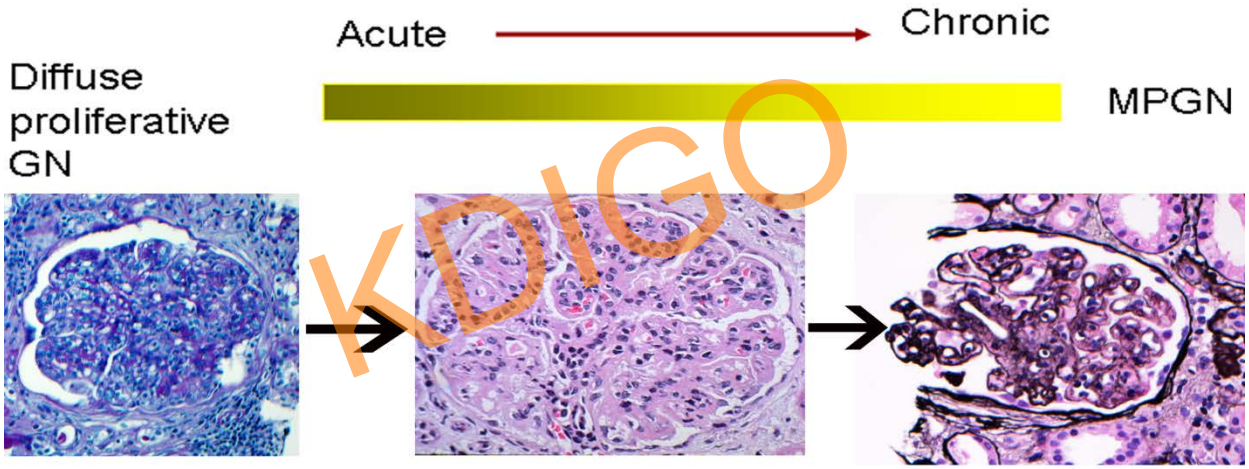
Spectrum of proliferative GN



KDIGO Controversies Conference on Complement-Mediated Kidney Diseases
November 19-21, 2015 | Barcelona, Spain

Questions & Discussion