aHUS: What are the challenges in short-term and long-term patient management?

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Disclosure of Interests

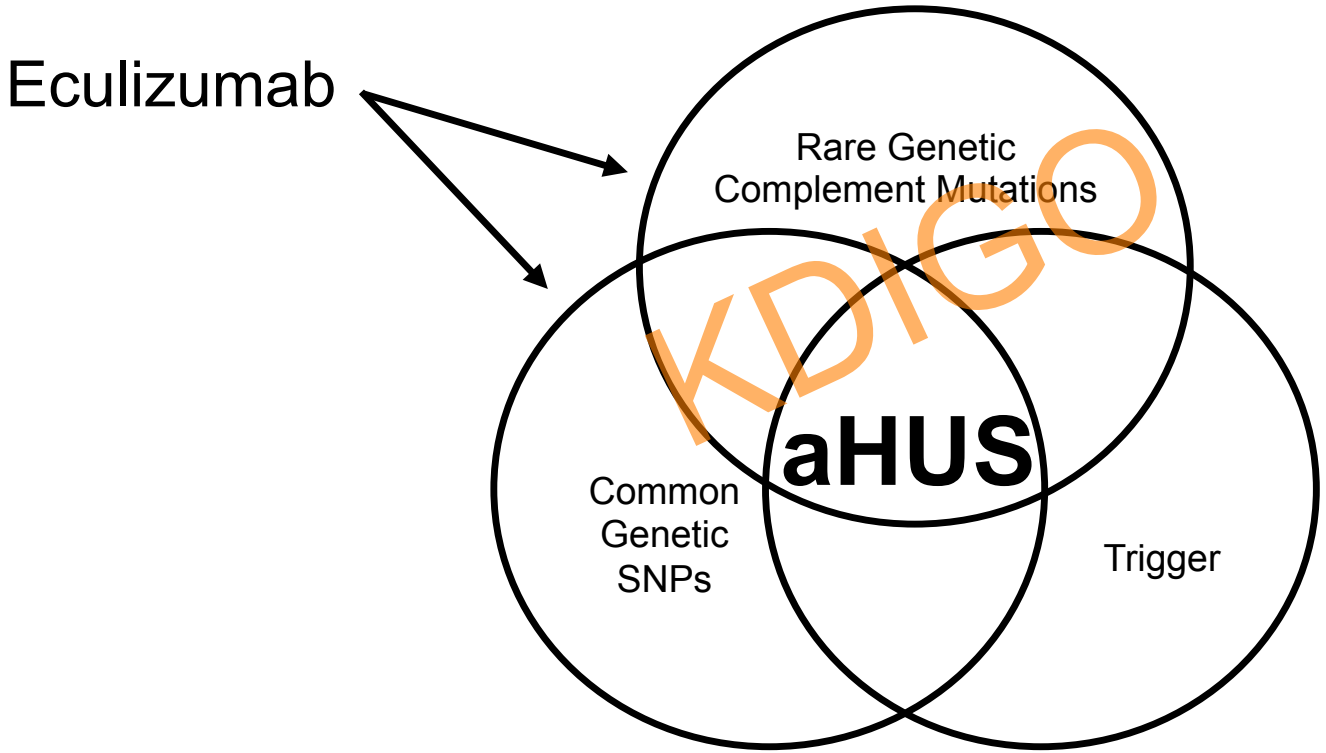
Research Grants

Wellcome Trust, Medical Research Council; Kidney Research UK, Northern Counties Kidney Research Fund; Fight for Sight, Macular Disease Society,

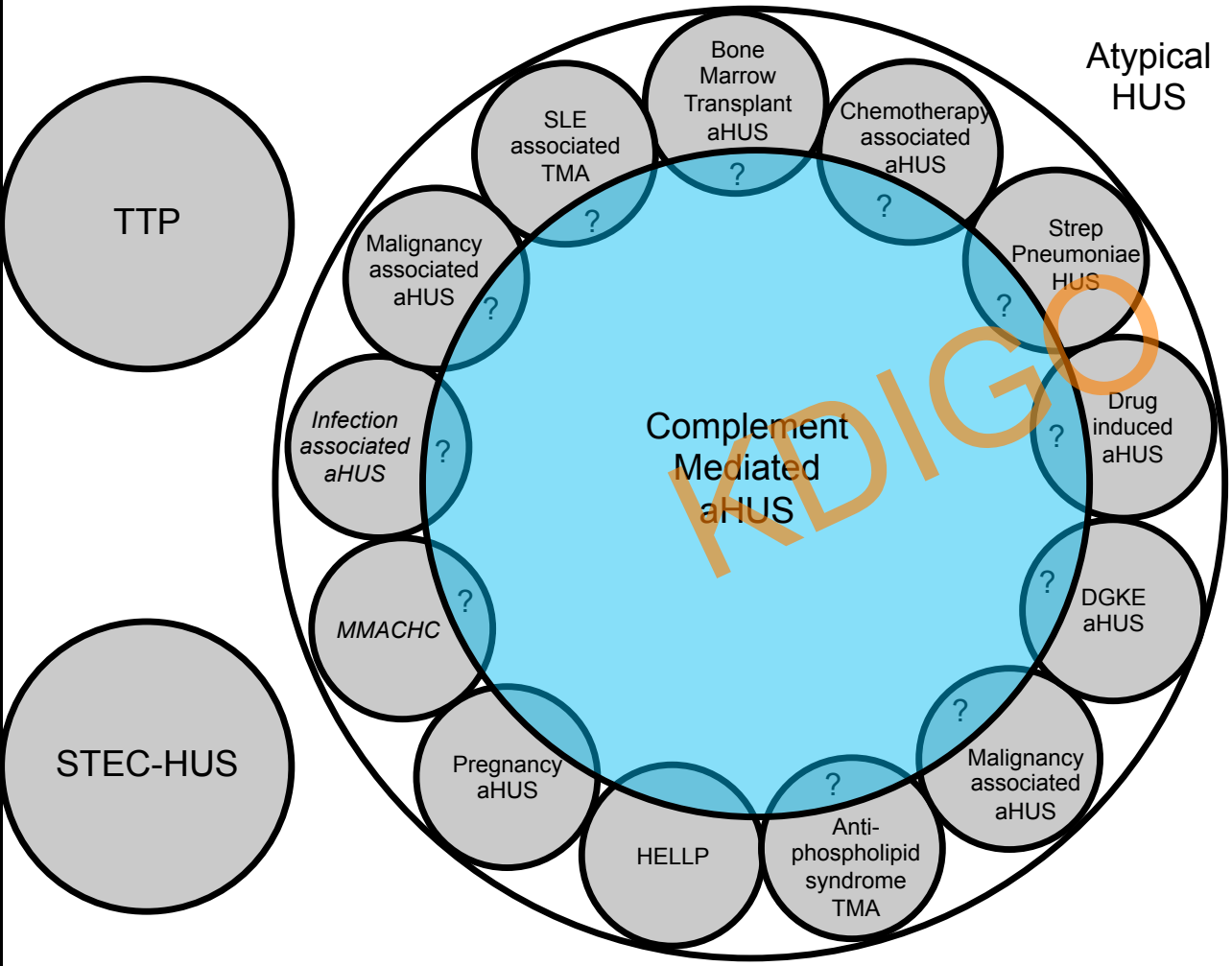
Consultancy

Syncona, Gemini, Biomarin, Alexion

Pathogenesis of aHUS



Short term- making the diagnosis



Multiple associations

Unmasking latent complement defect

Or

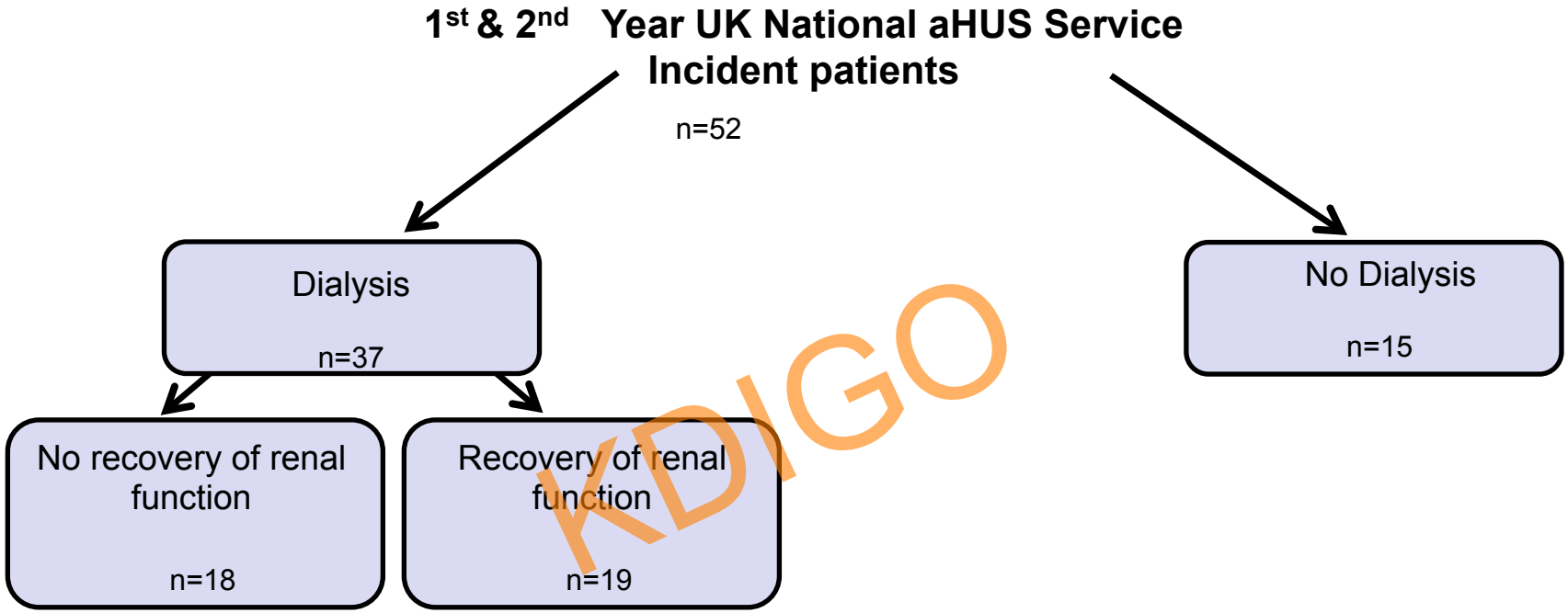
Direct effect

Short Term Management Challenges

Making the diagnosis

- Currently diagnosis of exclusion
- Clinical exclusion difficult
  - e.g. malignant hypertension vs chronic TMA
    - HELLP vs pregnancy associated aHUS
- Currently no biomarker for disease
- Genetics not immediately available
  - Absence of a mutation not necessarily guide to treatment outcome
- What subtypes should we currently be treating

How do we assess response

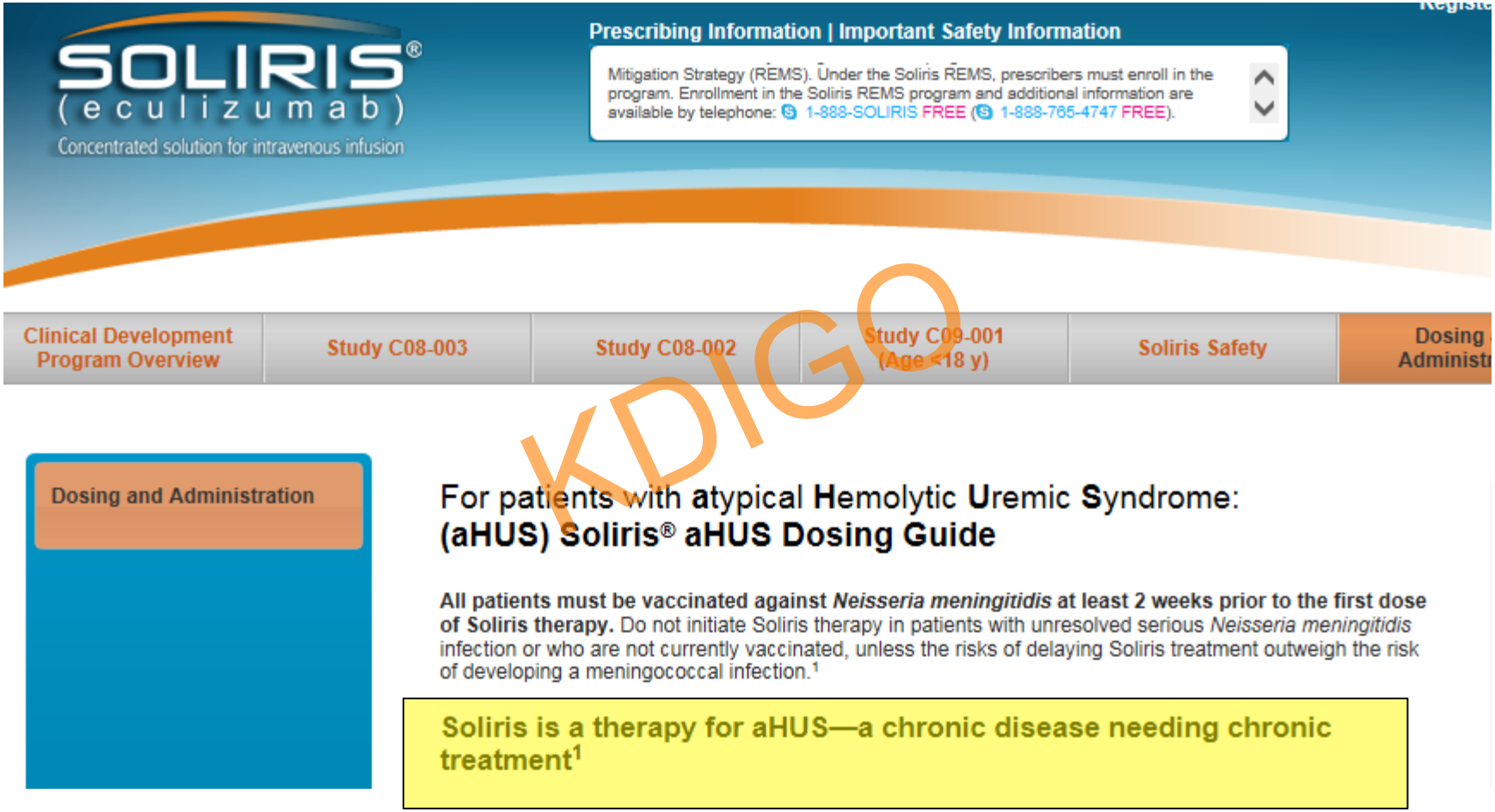


Non Responders vs Late presenters

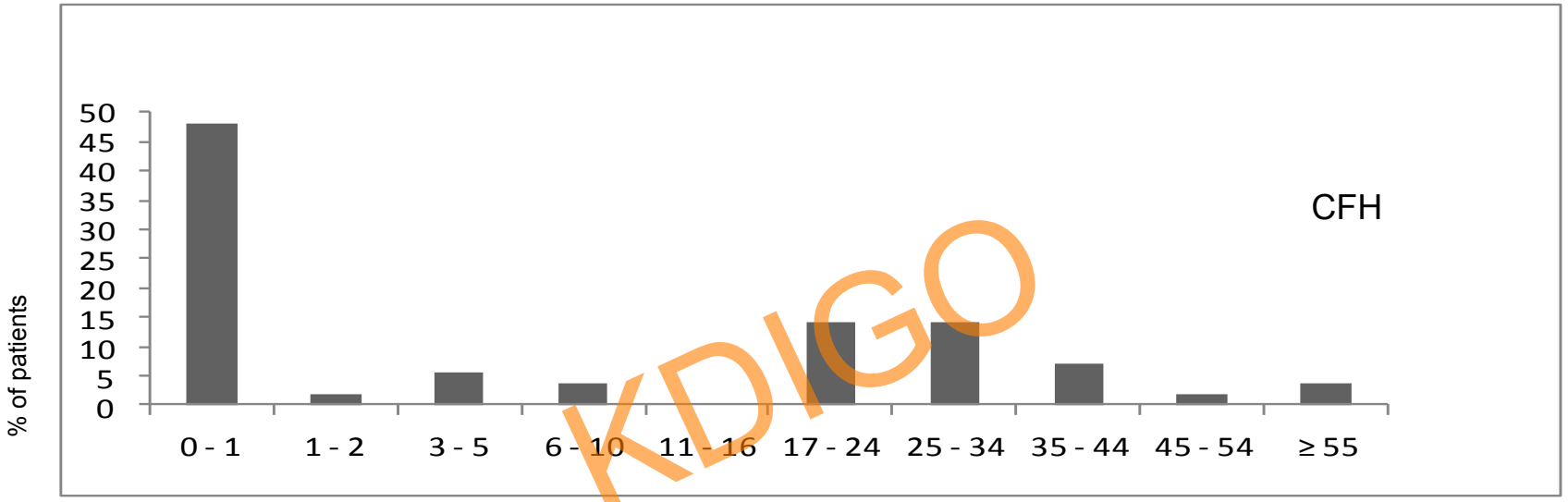
e.g. Polymorphism in *C5* (p.R885H), *DGKE*

Monitoring eculizumab levels /complement blockade

Long Term Management Challenges



Long Term Management Challenges



What is the evidence that aHUS is a chronic disorder requiring long term treatment?

Penetrance is low

Age of onset variable

Normal renal function until presentation with aHUS.

CJASN 5:1844

Long Term Management Challenges

Can Eculizumab be stopped?

AJKD

Case Report

Discontinuation of Eculizumab Maintenance Treatment for Atypical Hemolytic Uremic Syndrome: A Report of 10 Cases

Gianluigi Ardissino, MD, PhD, Sara Testa, MD, Ilaria Possenti, MD, Francesca Tel, MD, Fabio Paglialonga, MD, Stefania Salardi, BS, Silvana Tedeschi, MD, Mirco Belingheri, MD, and Massimo Cugno, MD

ORIGINAL PAPER

A national specialized service in England for atypical haemolytic uraemic syndrome—the first year's experience

N.S. Sheerin[1,3,*], D. Kavanagh[2,3,*], T.H.J. Goodship[2,3,*] and S. Johnson[3,*]

From the [1]Institute of Cellular Medicine, [2]the Institute of Genetic Medicine Newcastle University and [3]the Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK

Long Term Management Strategies

When to stop

- If ESRF
- If dialysis independent

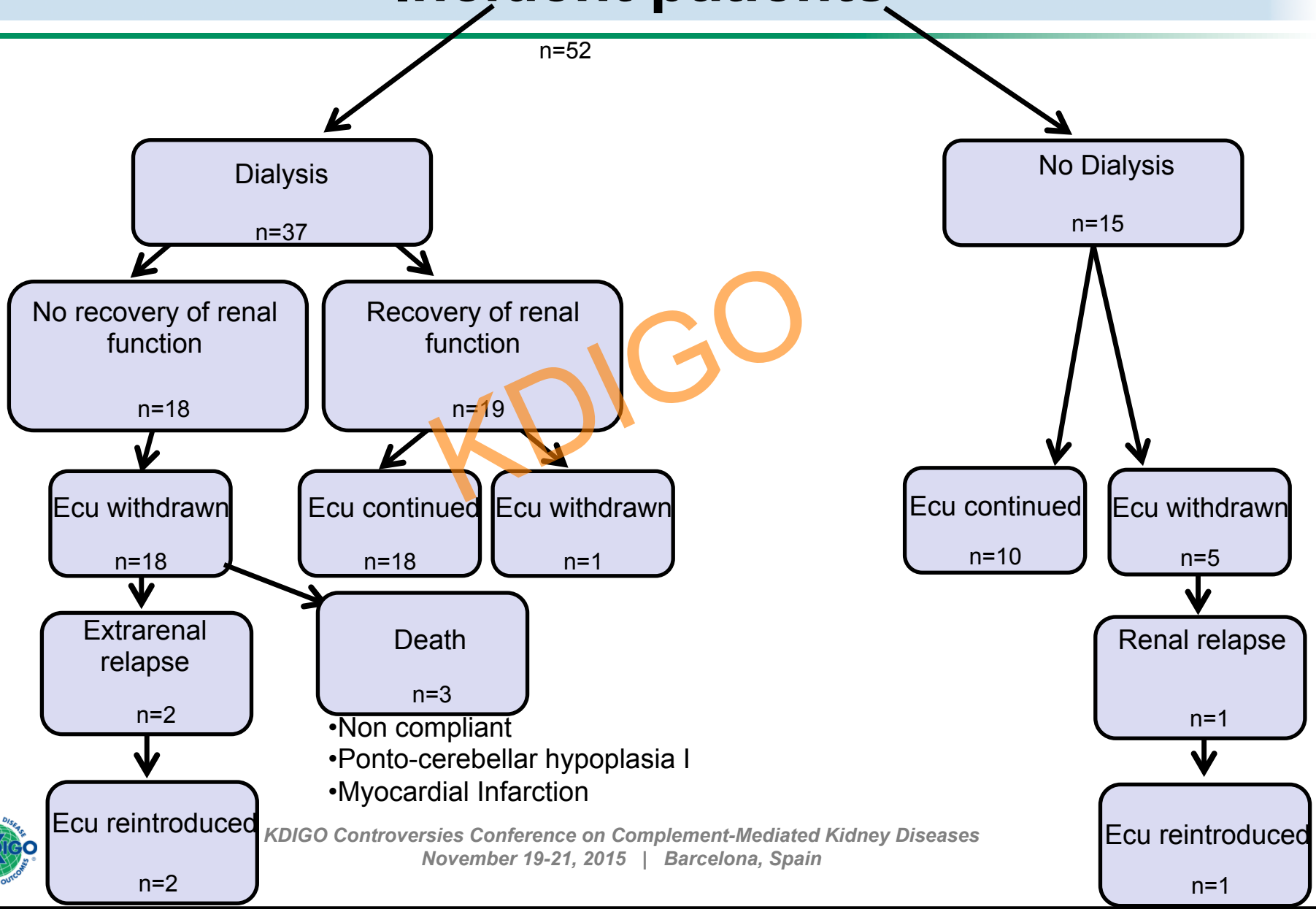
How do we monitor disease driven treatment

- LDH
- Platelets
- Hb
- Urinalysis
- What else

How Frequently?

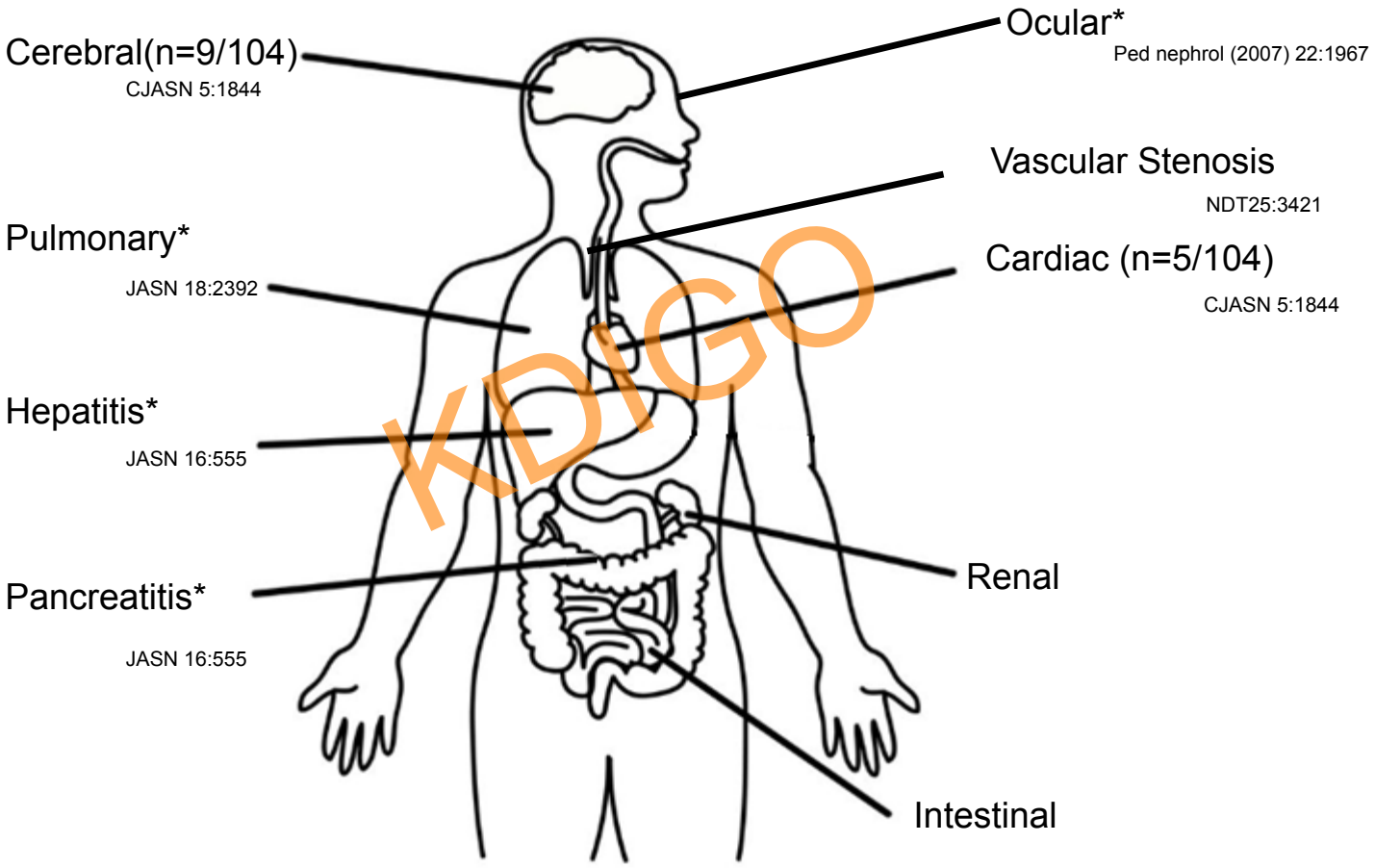
Monitoring extra-renal manifestations

1st & 2nd Year UK National aHUS Service Incident patients



- Non compliant
- Ponto-cerebellar hypoplasia I
- Myocardial Infarction

Extra-renal manifestations



Extra-renal manifestations

Are the acute extra-renal manifestations secondary tp

1) the thrombotic microangiopathy

2) complement activation

3) uraemia and hypertension

Are the chronic extra-renal manifestations caused by

1) long term renal failure / dialysis access

2) complement activation

If it is a consequence of complement activation how many of the sequelae will be treated by blockade at the level of C5

Is retinal screening required

Human Molecular Genetics, 2014, Vol. 23, No. 19 **5283–5293**
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Whole-exome sequencing identifies rare, functional *CFH* variants in families with macular degeneration

Yi Yu[1,†], Michael P. Triebwasser[2,†], Edwin K. S. Wong[3,†], Elizabeth C. Schramm[2,†], Brett Thomas[4], Robyn Reynolds[1], Elaine R. Mardis[5], John P. Atkinson[2], Mark Daly[4,6], Soumya Raychaudhuri[6,7,8,9,10], David Kavanagh[3] and Johanna M. Seddon[1,11,12,*]

ORIGINAL ARTICLE

Rare genetic variants in the *CFI* gene are associated with advanced age-related macular degeneration and commonly result in reduced serum factor I levels

David Kavanagh[1], Yi Yu[2], Elizabeth C. Schramm[3], Michael Triebwasser[3], Erin K. Wagner[2], Soumya Raychaudhuri[4,5,6,7], Mark J. Daly[4,5,8], John P. Atkinson[3] and Johanna M. Seddon[2,9,10,*]

Molecular Basis of Factor H R1210C Association with Ocular and Renal Diseases

Sergio Recalde,* Agustin Tortajada,† Marta Subias,† Jaouad Anter,† Miquel Blasco,‡ Ramona Maranta,§ Rosa Coco,‖ Sheila Pinto,† Marina Noris,§ Alfredo García-Layana,* and Santiago Rodríguez de Córdoba†

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Discussion points

- Short Term Management
  - Making the diagnosis
    - What tests are required
    - In a multiple hit model how can we be sure we are not undertreating
  - Can the classification of TMAs reflect treatment pathways
  - Identifying non responders
- Long Term Management
  - What is the evidence for chronic complement activation in aHUS?
  - What is the evidence for long term eculizumab treatment?
  - When should Eculizumab be stopped?
  - Should withdrawal be stratified
    - By genetics/autoantibodies
  - How should disease driven treatment be monitored
- Extra-renal manifestations
  - What symptoms are a direct effect of a TMA and what are a secondary effect of CRF/ dialysis
  - In ESRF what symptoms require treatment
  - How do we monitor patients for extra-renal manifestations