Eurordis aHUS Webinar

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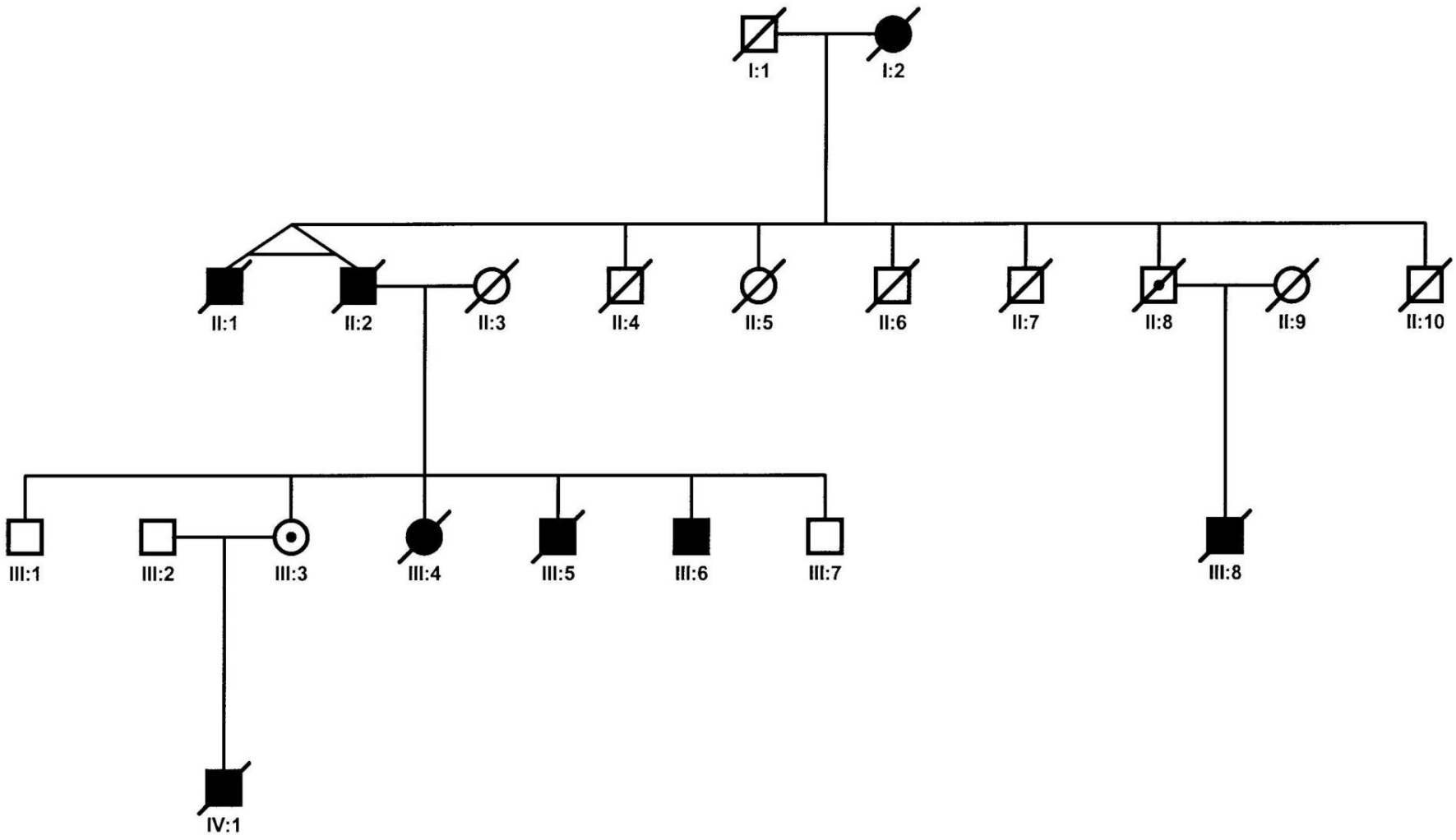
Newcastle family 2014

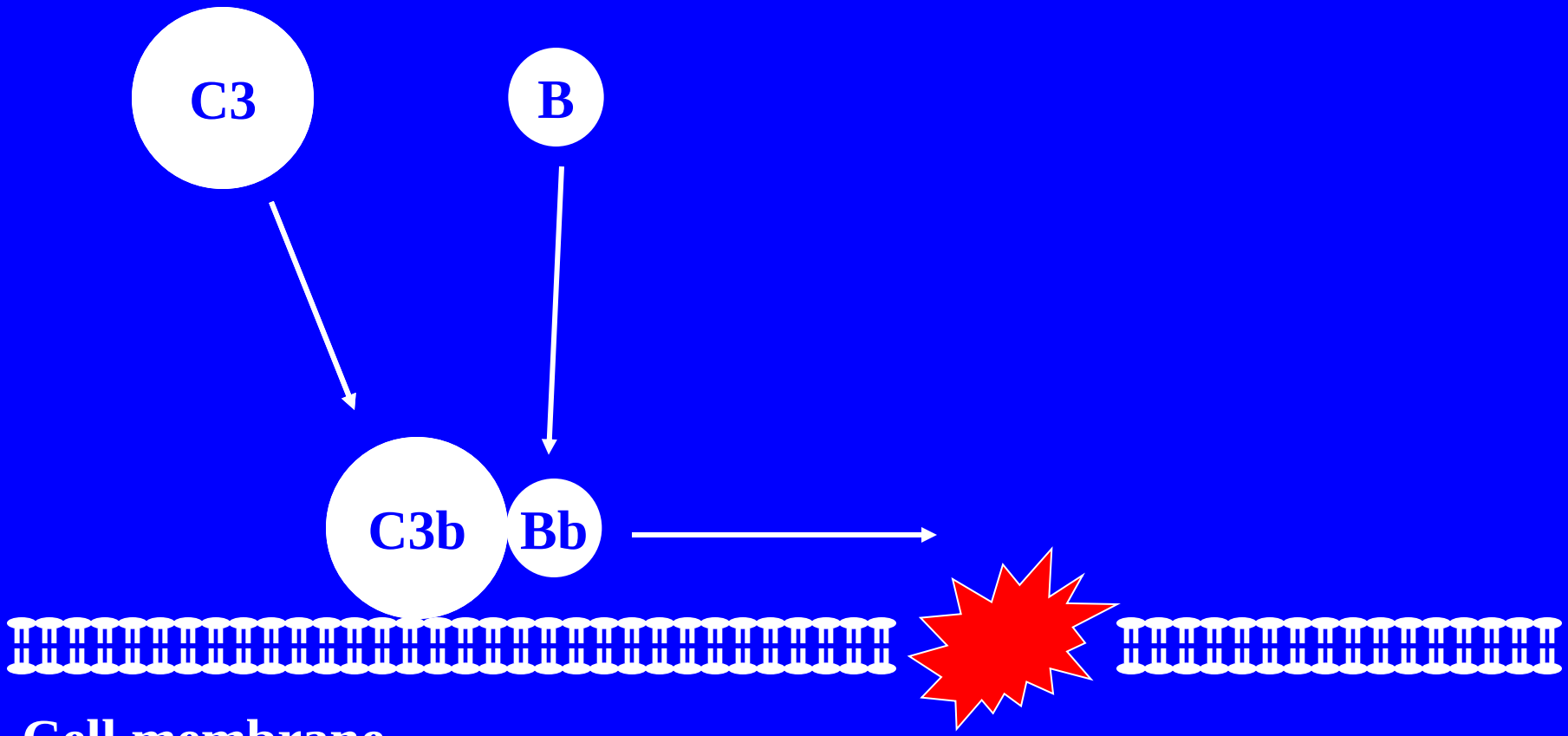


Rare condition strikes eight family members

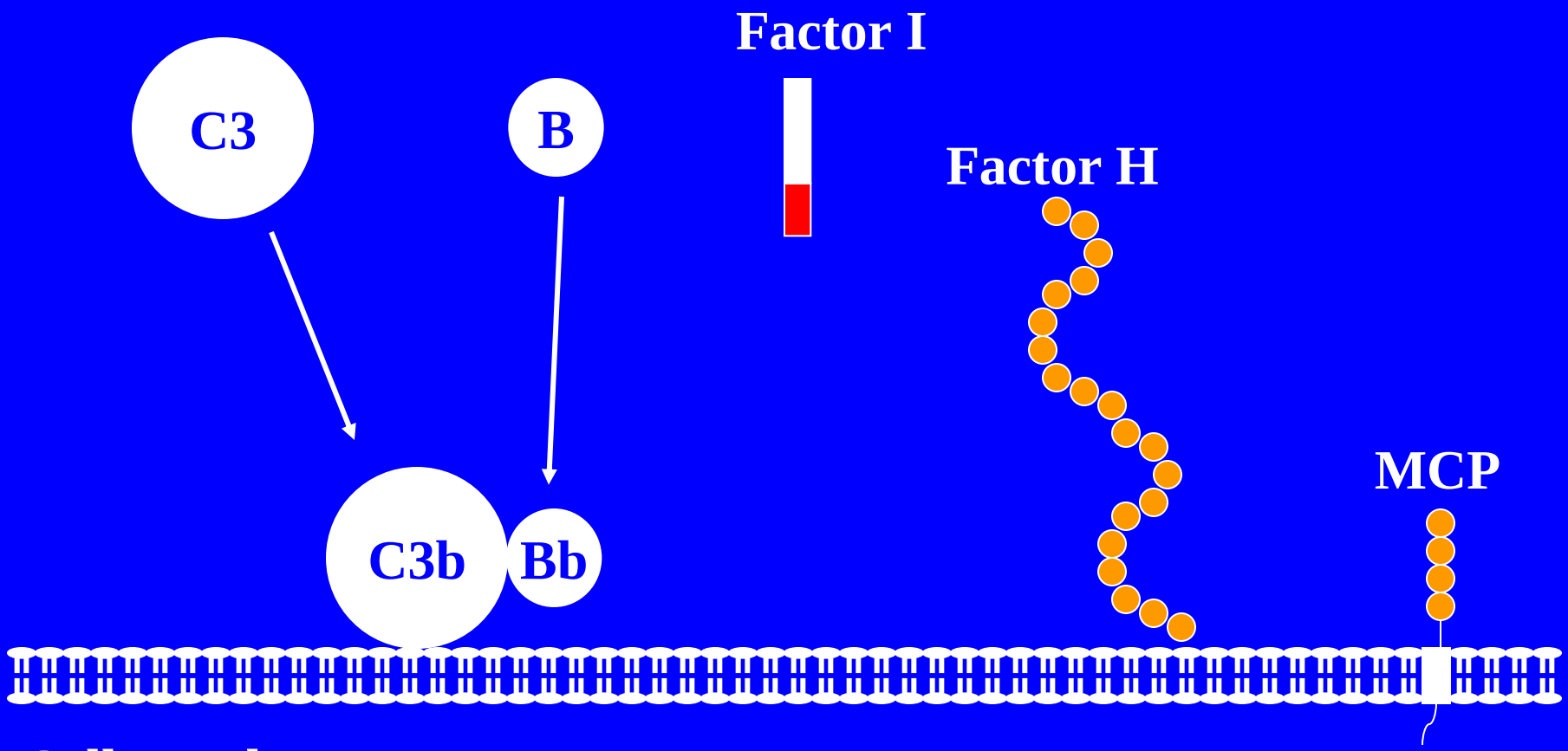
Helen Rae, *Evening Chronicle*, July 23rd 2009

“Dad Shaun McCowie is living with a rare genetic condition that has killed seven members of his family. The 47-year-old has atypical hemolytic uremic syndrome (HUS), a form of kidney failure, and the genetic defect his family has been plagued with is believed to be one of only 10 cases in the world……. “

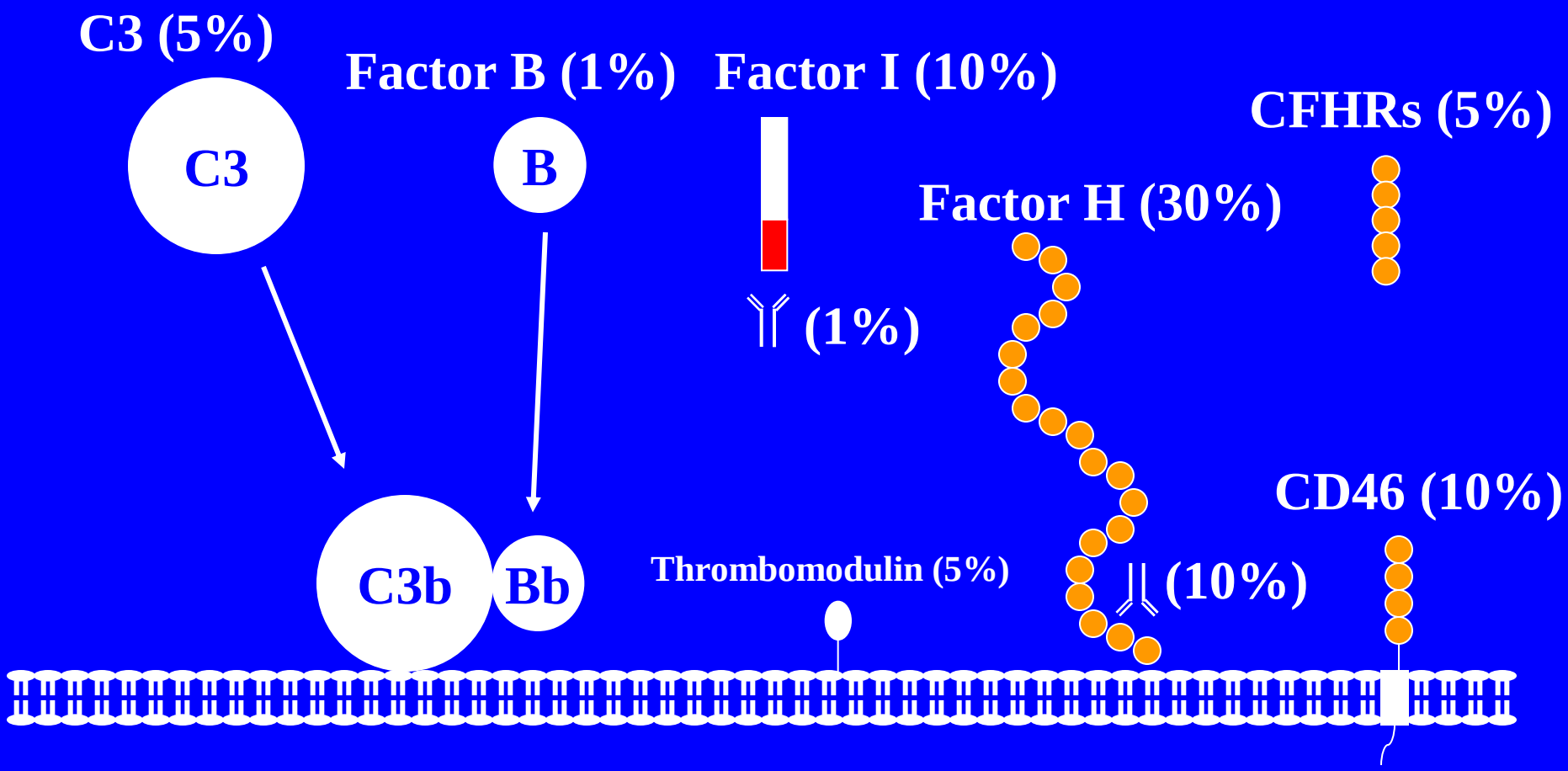
Complement activation

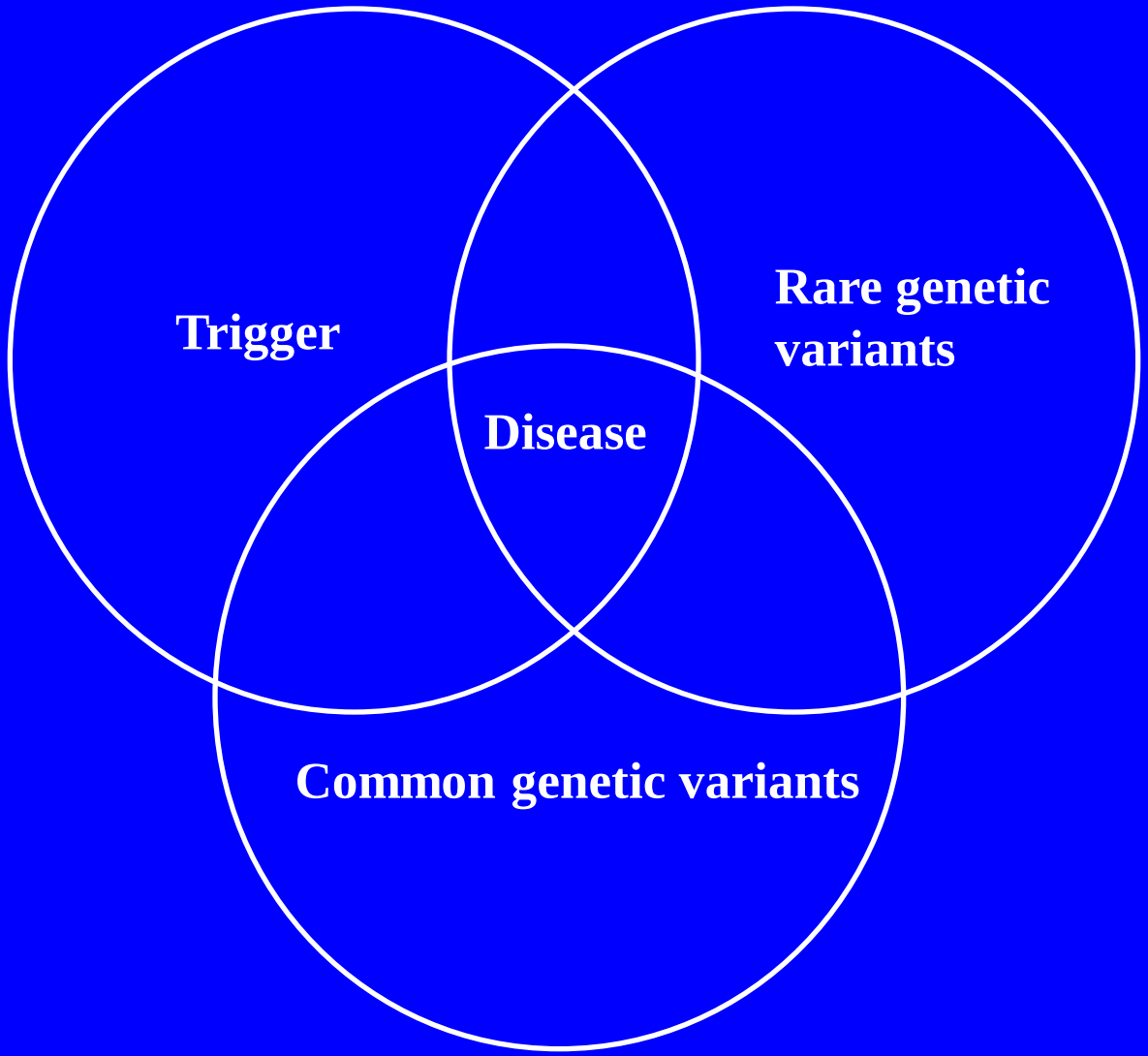


Complement regulation



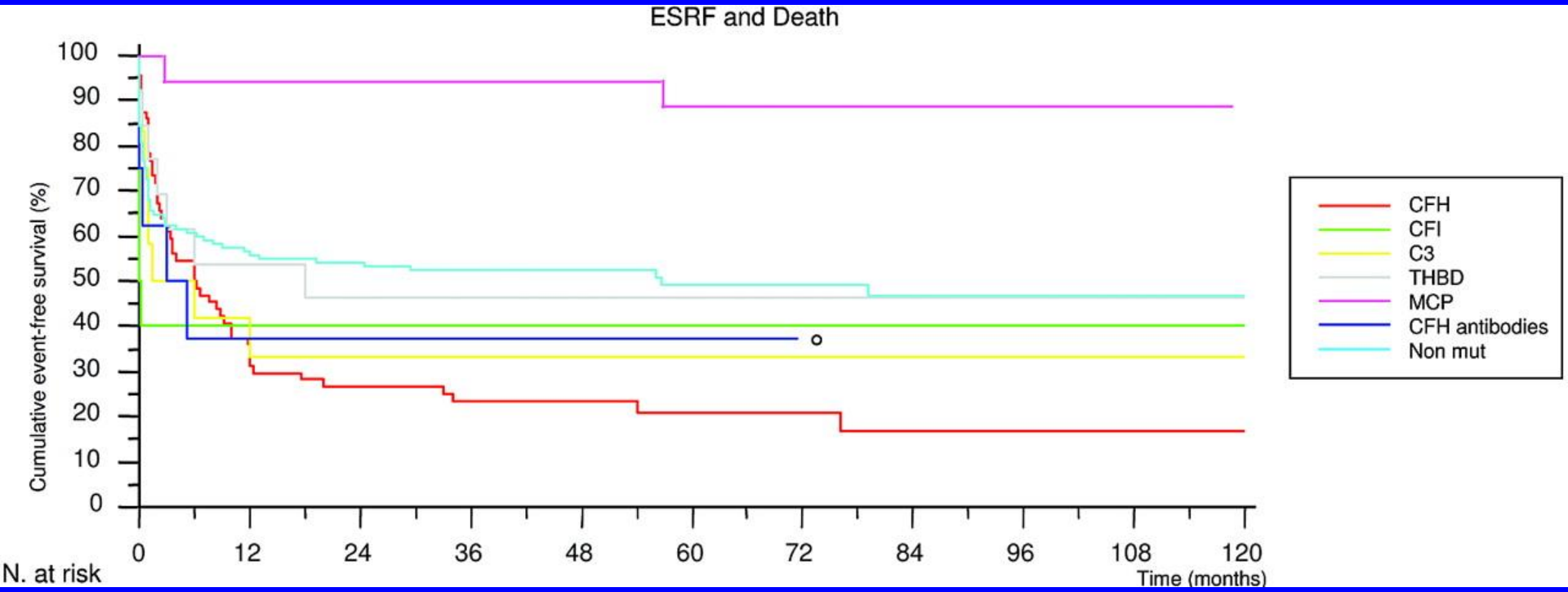
Inherited and acquired abnormalities of complement are found in up to 70% of aHUS patients




Trigger
Rare genetic variants
Disease
Common genetic variants

Initial management

"Recommendations. All patients presenting with aHUS should be offered a trial of plasma exchange and/or plasma infusions. **(weak, low)"**

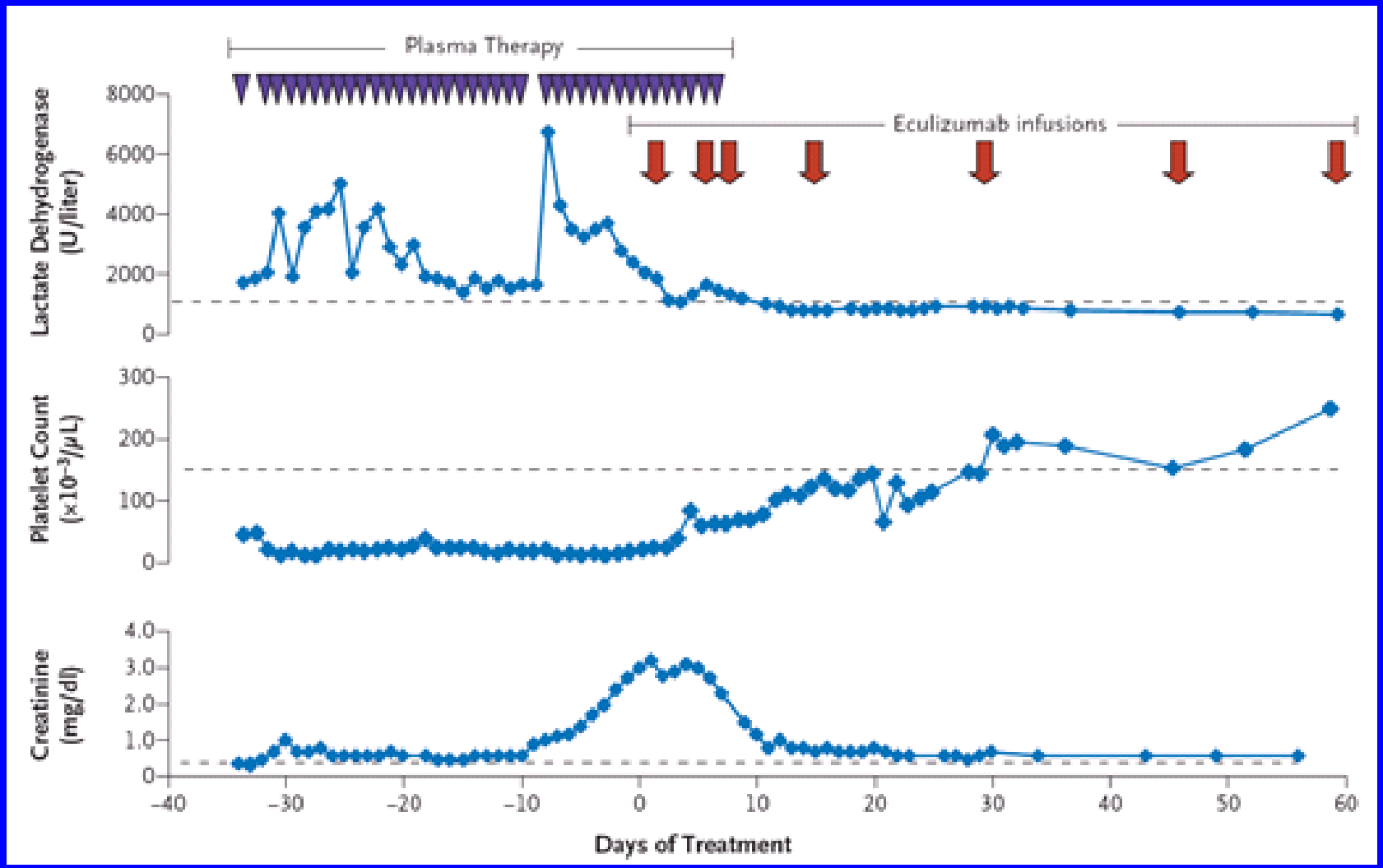


Noris et al, CJASN 2010

Recurrence post transplant according to underlying gene

Mutation	Recurrence rate	Loss of graft
CFH	75-90%	60-90%
CFI	45-80%	90%
C3	40-70%	60%
CFB	100%	100%
CD46	<20%	30%

Gruppo RA, et al. *N Engl J Med.* 2009;360(5):544-6.

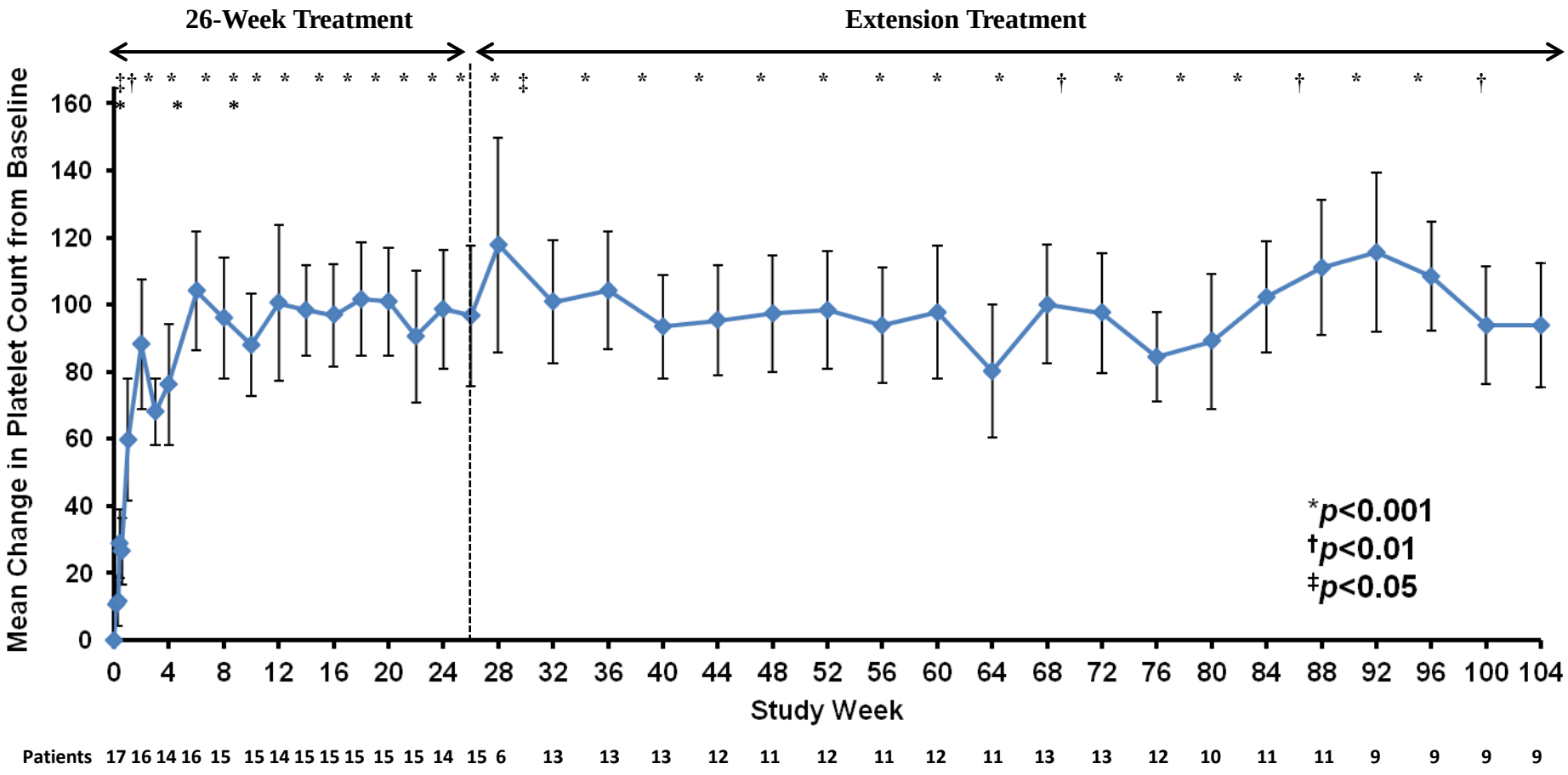


Patient continues to do well at home (and school) on chronic eculizumab (34 months)

Primary endpoint in the resistant study

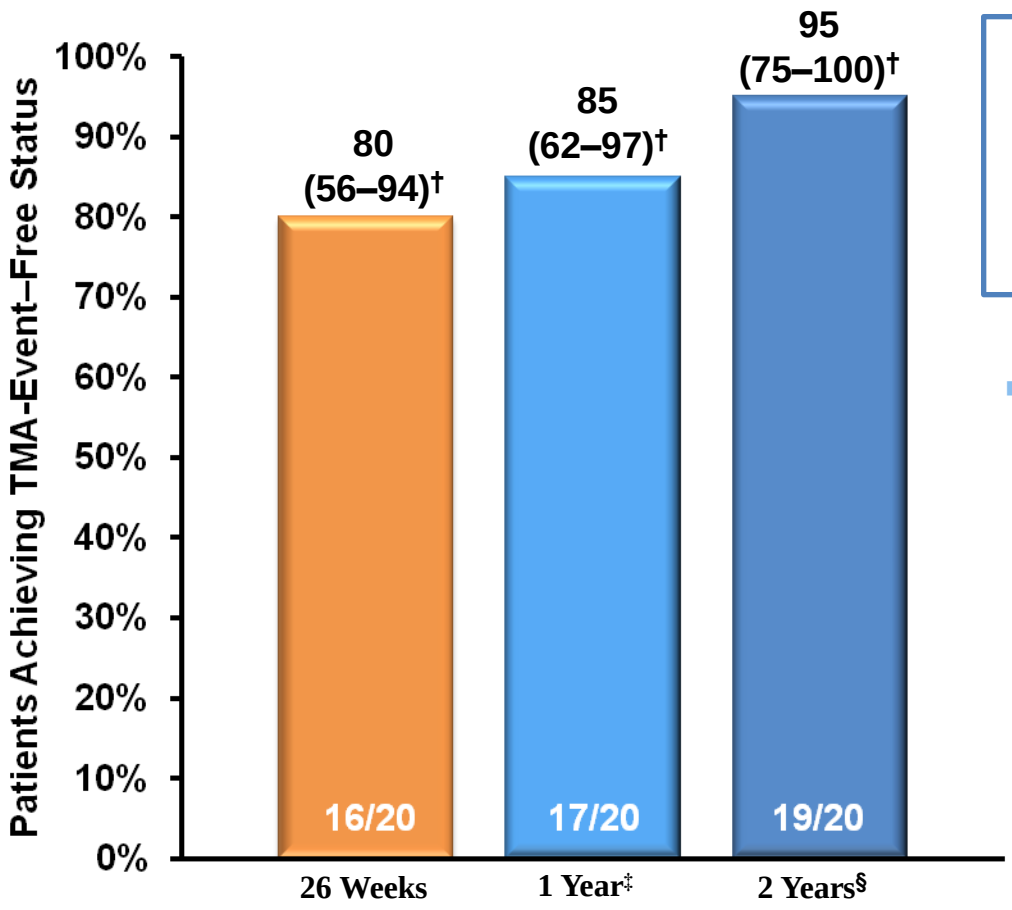
- **Platelet normalization (≥150x10^9/L) was achieved by 26 weeks in 13 of 15 patients (87%) who had low platelets at baseline, and was maintained through two years in 12 of the 13 responders.**

Platelet Count Change from Baseline Through 2 Years of Eculizumab



Bars represent 95% confidence interval (CI).

Patients Achieving TMA Event-Free Status Achieved and Maintained* Through 2 Years with Ongoing Eculizumab



TMA event-free status:
For 12 consecutive weeks, no decrease in platelet count >25% from baseline, and no PE/PI, and no new dialysis

- **Patients achieved and maintained TMA event-free status regardless of the identification of a genetic complement mutation[1]**
  - **14/14 (100%) of patients with known complement mutation**
  - **5/6 (83%) of patients without known complement mutation**

NHS England

Clinical Commissioning Policy Statement: Eculizumab for atypical haemolytic uraemic syndrome

September 2013

Reference: E03/PS(HSS)/a

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the NHS belongs to us all

7. Criteria for commissioning

Eculizumab has been referred to NICE by Ministers of Health as the first topic for evaluation in their new Highly Specialised Technologies Programme. This review will be undertaken during 2013/14.

In the interim, given the serious nature of the disease, NHS England will fund Eculizumab in patients outlined below.

Eculizumab for the treatment of aHUS is not routinely commissioned for patients currently diagnosed with aHUS who have not received approval for Eculizumab from an existing commissioning body.

NHS England will commission eculizumab for new patients with atypical haemolytic syndrome (defined to include those with a functioning kidney) and for existing patients who are on dialysis and are suitable for a kidney transplant. A commissioning for evaluation scheme will be developed for patients who are not suitable for transplant.

8. Patient pathway

It is proposed to deliver the service locally to patients but with co-ordination from the expert centre in Newcastle.

9. Governance arrangements

Diagnosis will be through the Newcastle Centre and in accordance with the pathway described in this policy.

10. Mechanism for funding

A national aHUS service for England

- Very rare diseases in England are managed through a National Specialised Service
- Application considered by the Advisory Group for National Specialised Services (AGNSS) in June 2012 .
- “Ministers agreed with AGNSS that there is evidence for the clinical effectiveness of Eculizumab for the treatment of atypical haemolytic uraemic syndrome but wanted further advice on the affordability of the drug”– referred to NICE

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation
Evaluation Consultation Document (25th February 2014)

1 Evaluation Committee's preliminary recommendations

1.1 Eculizumab is an effective treatment for patients with atypical haemolytic uraemic syndrome (aHUS) and represents a significant development in the management of a serious condition. However, the Evaluation Committee has not yet been presented with an adequate explanation for its considerable cost.

1.2 The Committee is therefore currently unable to prepare a recommendation on the use eculizumab for the treatment of aHUS and has asked for further information from the company to enable it to do so (section 5.8). It has also asked for advice from NHS England on what considerations relating to the management of its specialised commissioning budget it considers should be taken into account in formulating a recommendation.

aHUS treatment in England -patient groups

- **Incident patients**
- Prevalent patients on plasma therapy
- Prevalent patients on dialysis - transplant
- Prevalent patients with infrequent relapses
- Prevalent patients in remission
- Prevalent patients with a functioning transplant
- Unaffected carriers

How do we diagnose aHUS?

aHUS diagnostic criteria established by the aHUS RDG

Exclusion

Shiga toxin associated HUS

Secondary causes – drugs, infection (HIV, Streptococcus pneumonia),

transplantation (bone marrow, liver, lung, cardiac),cobalamin deficiency, SLE, APL Ab syndrome, scleroderma, ADAMTS13 antibodies or deficiency

Inclusion

Renal biopsy showing a TMA

and/or

The classic triad of microangiopathic haemolytic anaemia, thrombocytopenia, renal failure.

How do we diagnose aHUS?

Application for eculizumab to treat aHUS
Clinical and Diagnostic Check List

Patient Name: **DOB:**
NHS Number:

Initiating trigger

- Non-shiga toxin diarrhoea ☐
- Respiratory tract infections ☐
- Other infection ☐
- Malignancy ☐
- Bone marrow transplantation ☐
- New medication (see list) ☐
  detail _____

Extra-renal manifestations

- Neurological involvement ☐
- Pancreatic Involvement ☐
- Ocular involvement ☐
- Digital gangrene ☐
- Other ☐
  _____

Family member also affected ☐

Pregnancy associated ☐

The patient is on

- Haemodialysis ☐
- Plasma Exchange ☐

Date of Presentation :

Full Clinical History (must be completed)

Drugs associated with aHUS
Cisplatin ; Gemcitabine ; Mitomycin ; Clopidogrel ; Quinine; Interferon α,β; Anti-vascular endothelial growth factor; Campath; Cyclosporin tacrolimus ; Ciprofloxacin; Oral contraceptives Illicit drugs [e.g. cocaine, heroin, ecstasy]

Results of investigations confirming a thrombotic microangiopathy and AKI

Test	Date	Result
Platelet count		
Blood film		
LDH		
Haptoglobins		
Prothrombin time		
Creatinine		
Renal biopsy		

Results of investigations confirming a diagnosis of aHUS

Differential Diagnosis	Test	Date Sent	Result
TTP	ADAMTS13 activity		
STEC HUS	Stool culture		
STEC HUS	*E.coli* endotoxin antibodies (IgM)		
APL Antibody syndrome	APL antibody		
SLE	DsDNA		
HIV	HIV test		
Scleroderma	ANA		
Scleroderma	Anticentromere antibodies		
Scleroderma	Anti-acl-70		
Cobalamin C disease	Plasma homocysteine levels		
Cobalamin C disease	Plasma and urine methylmalonic acid levels		
aHUS	C3		
aHUS	C4		
aHUS	CH50		
aHUS	Complement genetics		
aHUS	Factor H autoantibodies		

The results of all these need not be back before you send this form but the result of the ADAMTS13 activity must be available.

Then

- Eculizumab is first line therapy
- Approval sought from NHS England
- Vaccinate with tetravalent meningococcal vaccine and Bexsero
- Antibiotics – ciprofloxacin for two weeks then penicillin/erythromycin
- Start eculizumab
- Genetics available after 8 weeks
- Continue for at least 6 months

aHUS treatment in the future -patient groups

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Liver* and Liver/kidney Tx in aHUS

Age	Reference	1 year survival
2 years	Remuzzi, Lancet 2002	Alive
3 months*	Cheong, Ped Nephrol 2004	Deceased
2 years	Remuzzi, Am J Transplant 2005	Deceased
5 years	Saland, Am J Transplant 2006	Alive
1 year	Jalanko, Am J Transplant 2007	Alive
16 year	Jalanko, Am J Transplant 2007	Alive
4 years	Saland, CJASN 2009	Alive
Adult	Jalanko, Personal communication	Alive
Adult	Sanchez-Corral, Br J Haematol 2010	Alive
4 years*	Haller, Am J Transplant 2010	Alive
5 years	Milner, Personal communication	Alive
12 years	Saland, Personal communication	Deceased
8 years	Saland, Personal communication	Deceased
Child	Cohn, Personal communication	Alive
64 years	Wilson, Am J Kidney Dis 2011	Alive

1 year patient survival of 74% (88%) cf. primary hyperoxaluria 86% (Jamieson, Am J Nephrol 2005)

Treatment of prevalent patients on dialysis in England - transplant with eculizumab

- 40 patients (1 child, 39 adults)
  - 16 lost transplant to recurrent disease
  - 27 with mutations (*CFH* 10, *C3* 7, *CFI* 4, *CFB* 2, *CFH/CFHR1* 2, *CFHR1/CFH* 2)
  - 13 without mutations (5 lost transplant to recurrent disease)
- 11 patients transplanted (4 living donors)
  - 10 prophylactic eculizumab, 1 given eculizumab for early recurrence
- Standard protocol. Transplantation without eculizumab only recommended in previous factor H antibody positive and *CD46* alone. No day 1 dose of eculizumab

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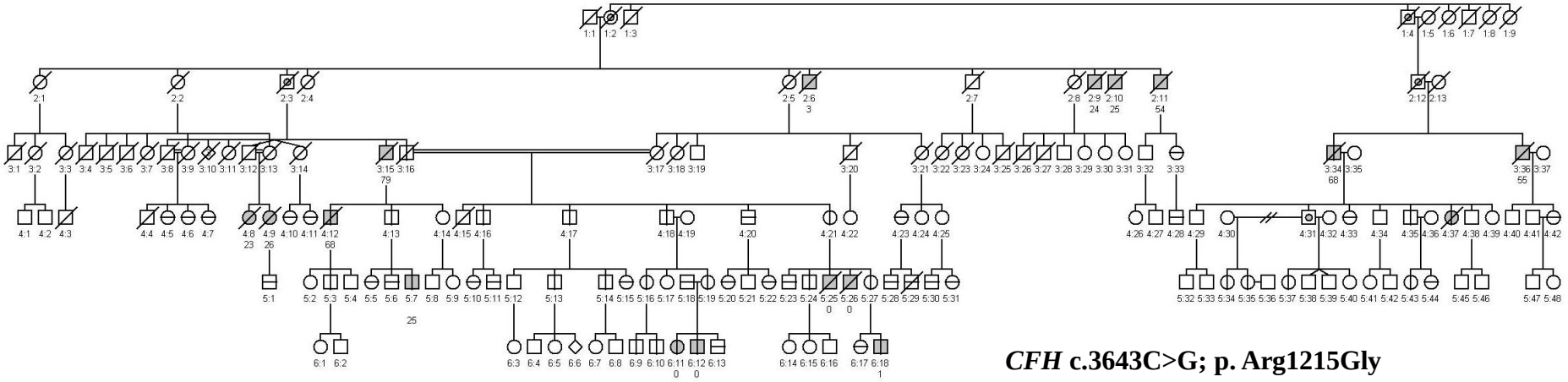
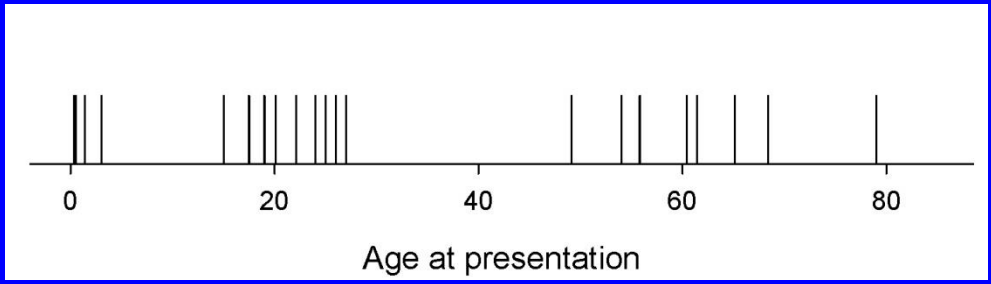
- **Unaffected carriers**

Unaffected carriers



***CFH* c.3643C>G; p. Arg1215Gly**

25 affected individuals
18 unaffected carriers



Penetrance of 64% by the age of 70

Patients funded by NHS England 1/4/2013- 31/3/2014

Total of 44 patients treated with eculizumab

15 children (11M/4F), 29 adults (9M/20F)

23 incident (3 familial)

21 prevalent

Patients funded by NHS England 1/4/2013- 31/3/2014 – Incident patients

	Adults	Children
Dialysis started	12	4
Not on dialysis	2	5

16 patients had started dialysis by the time that eculizumab was given

5 adults and 3 children have stopped dialysis

7 adults who have not stopped dialysis – eculizumab withdrawn in 6

Patients funded by NHS England 1/4/2013- 31/3/2014 – Prevalent patients

11 Transplant patients

	Adults	Children
Recurrent disease	2	1
Prospective	7	1

10 non -transplant patients (6 adults/4 children)

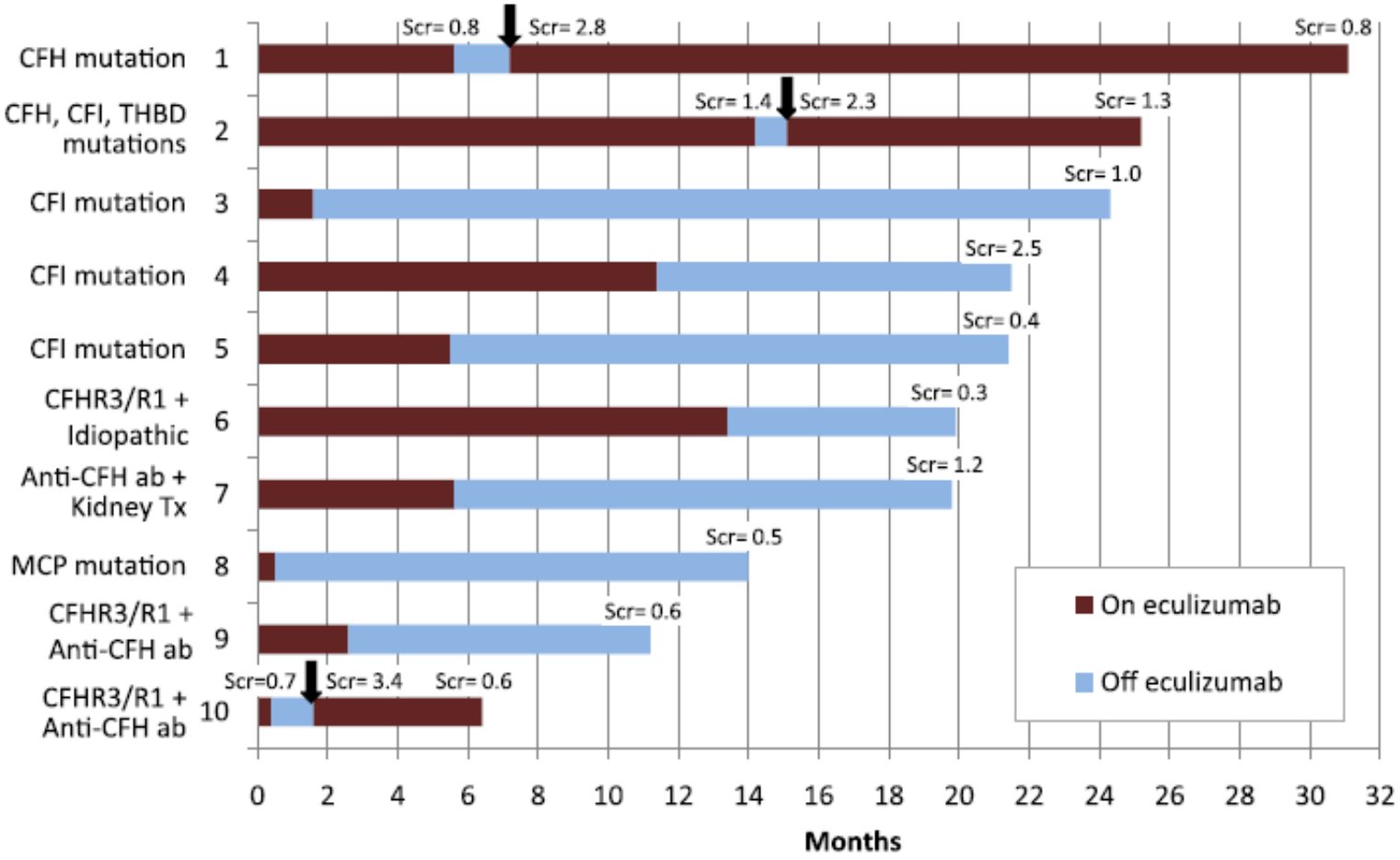
What are the risks of discontinuing eculizumab?

- Patients who have not recovered renal function
  - 6 in the UK, ?1 recurrence
- Patients who have recovered renal function
  - 3 in the UK, no recurrence
- Transplanted patients
  - Nil
- Patients in the Alexion registry
  - 17 discontinued (3 relapsed)

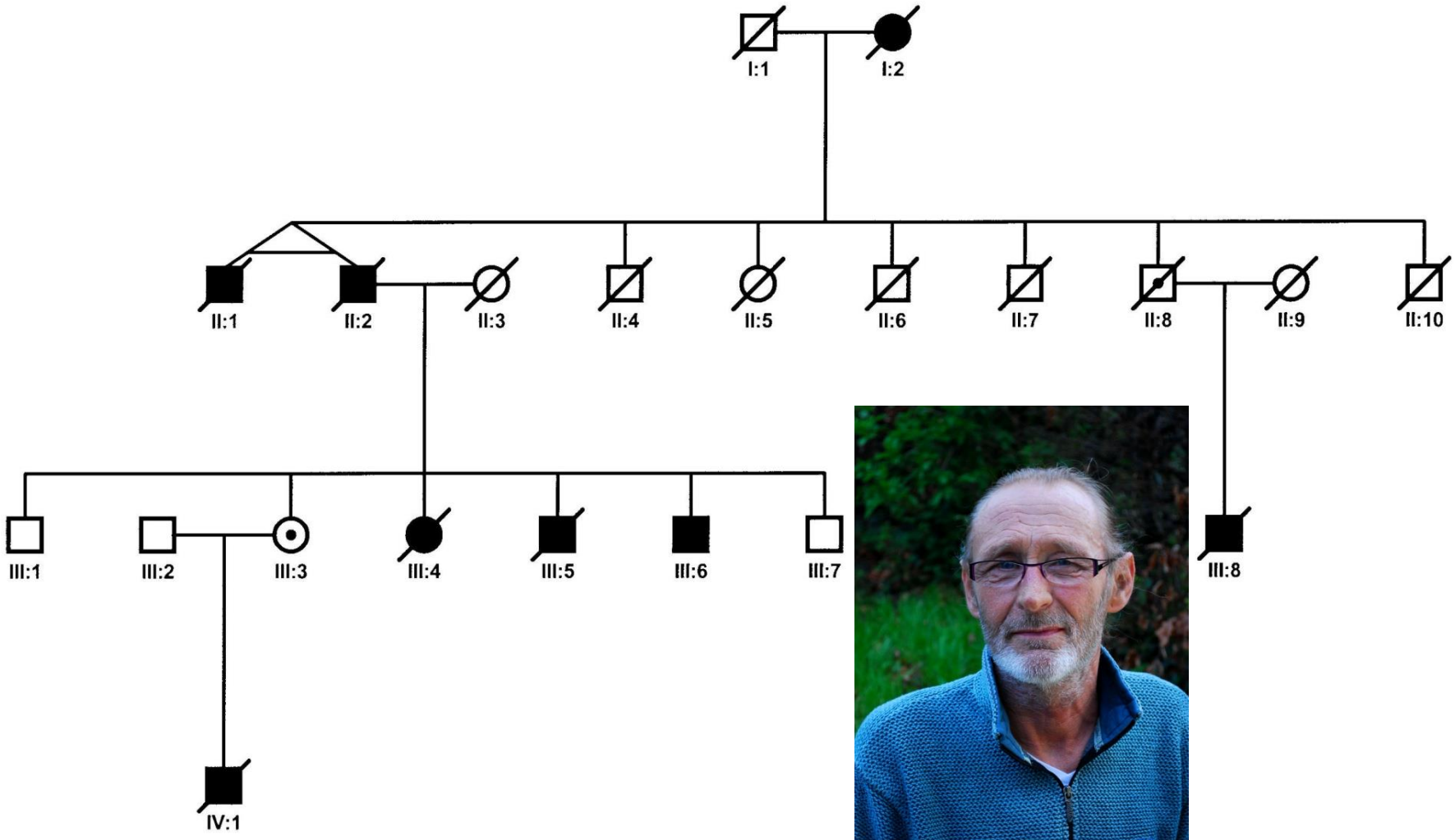
AJKD
Case Report

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



Newcastle family 2014



Comments on the aHUS Global Poll

- Gender
- Time to diagnosis
- Genetic screening
- Treatment
- Research and registries
- Countries involved and participants