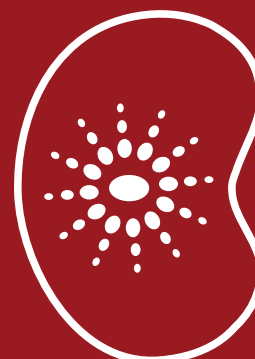
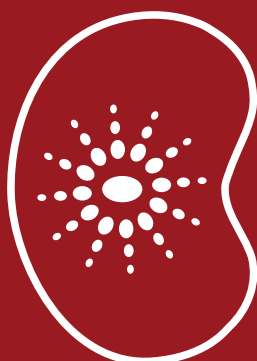
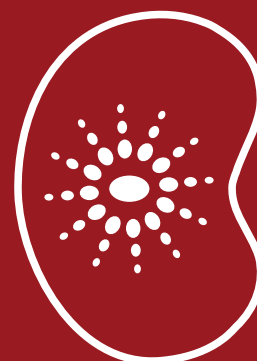
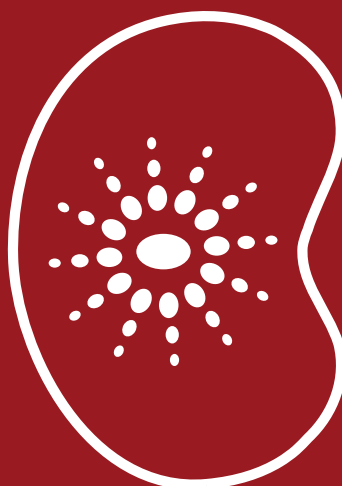
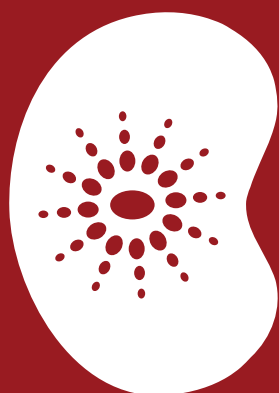
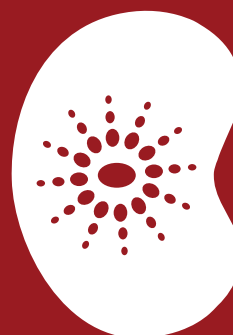
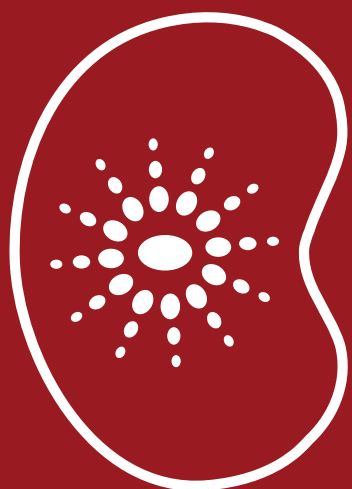


# The Annual Report of the National Renal Complement Therapeutics Centre 2019/20





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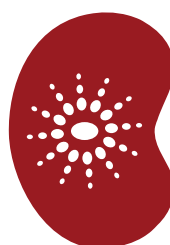
All photographs used in this report were taken before government guidance on social distancing measures for COVID-19 were in place.

# The Annual Report of the **National Renal Complement Therapeutics Centre** 2019/20

**aHUS**  
ATYPICAL HAEMOLYTIC URAEMIC SYNDROME



**NATIONAL  
RENAL  
COMPLEMENT  
THERAPEUTICS  
CENTRE**



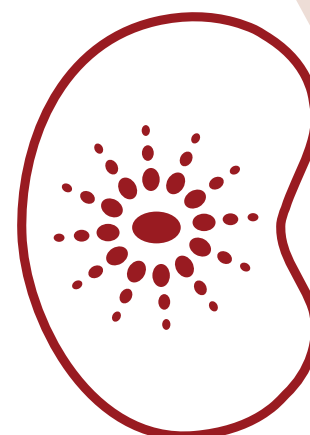
**C3G**  
C3 Glomerulopathy





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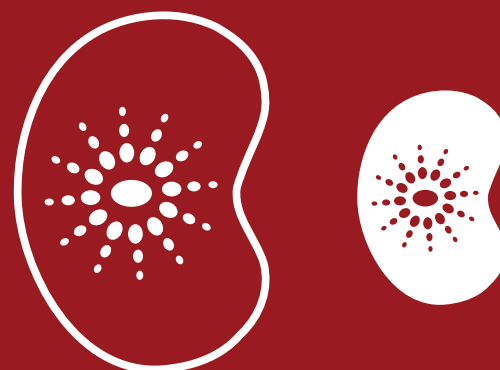
# 1. Service Overview

## 1.1 The National Service

The National Renal Complement Therapeutics Centre is a highly specialised multidisciplinary service focused on complement mediated kidney disease. Our expertise spans adult, paediatric and transitional nephrology; genetics, diagnostics; treatment and basic science, translational and clinical research. The National Atypical Haemolytic Uraemic Syndrome (aHUS) Service co-ordinates the management of patients with aHUS and other thrombotic microangiopathies and was commissioned in May 2016 by NHS England. The National C3G/MPGN service manages the investigation and treatment of these diseases recurring after kidney transplantation and was added to our portfolio in February 2017. Our service delivers a fully integrated care pathway to expedite optimal management of patients referred to us on a shared-care basis with the referring clinicians.

Our core team currently comprises five consultant nephrologists (3 adult and 2 paediatric), two nurse specialists and an administration team who are part of the Newcastle upon Tyne Hospitals NHS Trust. We also have seven dedicated clinical scientists and two consultants working across genetics, haematology and immunology that help us deliver our cutting edge diagnostics. Our consultants also work at the renal units at the Freeman Hospital and the Great North Children's Hospital. The NRCTC is also fully integrated with the Newcastle University Complement Therapeutics Research Group who were responsible for the discovery of the role of complement in aHUS, which ultimately led to the successful treatment of our patients with Eculizumab.





## 1.2 Our Vision and Values

Our vision is to be a centre of clinical excellence for patients with complement-mediated renal diseases, including aHUS and C3G, at the forefront of international research. Our primary core value aligns with that of Newcastle upon Tyne Hospitals NHS Foundation Trust, "achieving local excellence and global reach through compassionate and innovative healthcare, education and research." We wish to empower our patients to be knowledgeable about the care they require and receive. Our aspiration is to encourage our patients to influence the care we deliver, enabling personalised management.

### Our Vision

"a centre of clinical excellence for patients with complement mediated renal disease, including aHUS and C3G at the forefront of international research."

### Our Core Values

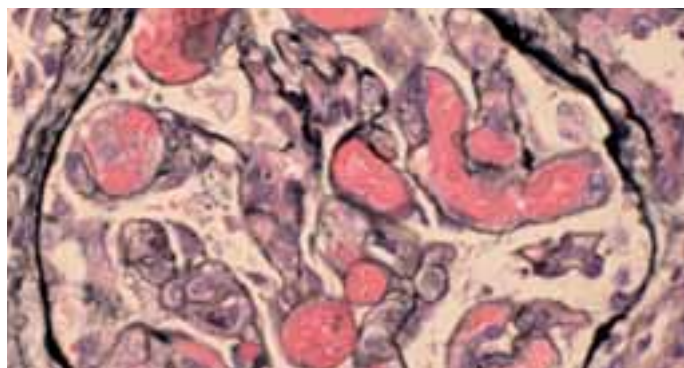
"putting patients at the heart of everything we do"

## 1.3 Disease Context

### 1.3.1 What is aHUS?

Atypical haemolytic uraemic syndrome is a rare disease with an incidence in the UK of 0.4-0.5 per million population. It presents with thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury. Without treatment the prognosis for patients was poor with 50% of patients developing renal failure or dying in the first year after presentation.

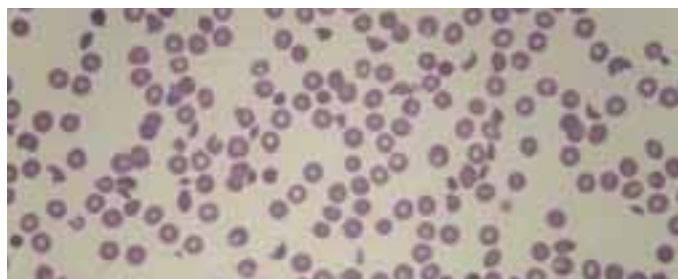
There is no rapidly available test to confirm the diagnosis of complement mediated aHUS and the initial diagnosis is based on clinical, laboratory and pathological findings and the exclusion of other pathologies; in particular, infection related Shiga Toxin (STEC)-HUS and Thrombotic Thrombocytopenic Purpura (TTP).



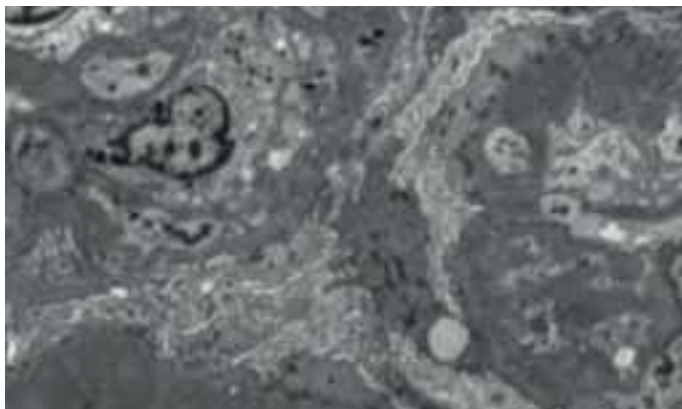
**Renal biopsy showing thrombus formation in aHUS**

Ecuzumab was licenced for the treatment of aHUS in 2011 having been shown to be effective in non-randomised, single arm open label studies. After initial review, preliminary interim funding for the use of Ecuzumab to treat patients with aHUS in England was approved in 2013 whilst the National Institute for Health and Care Excellence (NICE) undertook further review. NICE published its guidance in 2015 recommending that Ecuzumab was commissioned for the treatment of aHUS. However, reflecting the high cost of Ecuzumab, NICE recommended that treatment of patients was co-ordinated through an expert centre.

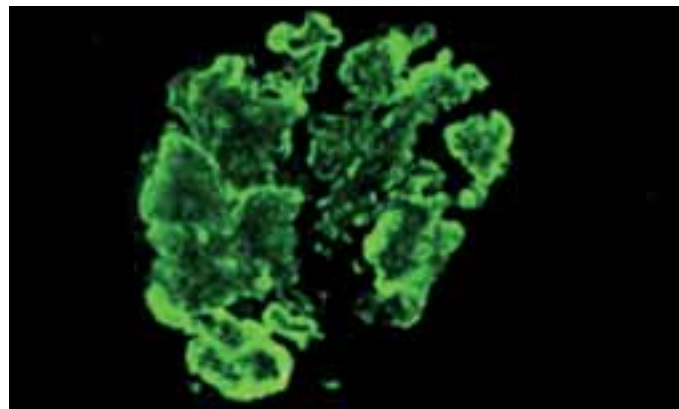
Since 2016, the National aHUS Service has been available 7 days a week 24 hours a day to provide advice on diagnosis and management from Consultants experienced in the management of aHUS. We also provide rapid diagnostic testing and support for clinicians to exclude other forms of Thrombotic Microangiopathy (TMA).



**Blood film from aHUS patient showing schistocytes**



**Sub-endothelial deposits in C3GN seen on electron microscopy**



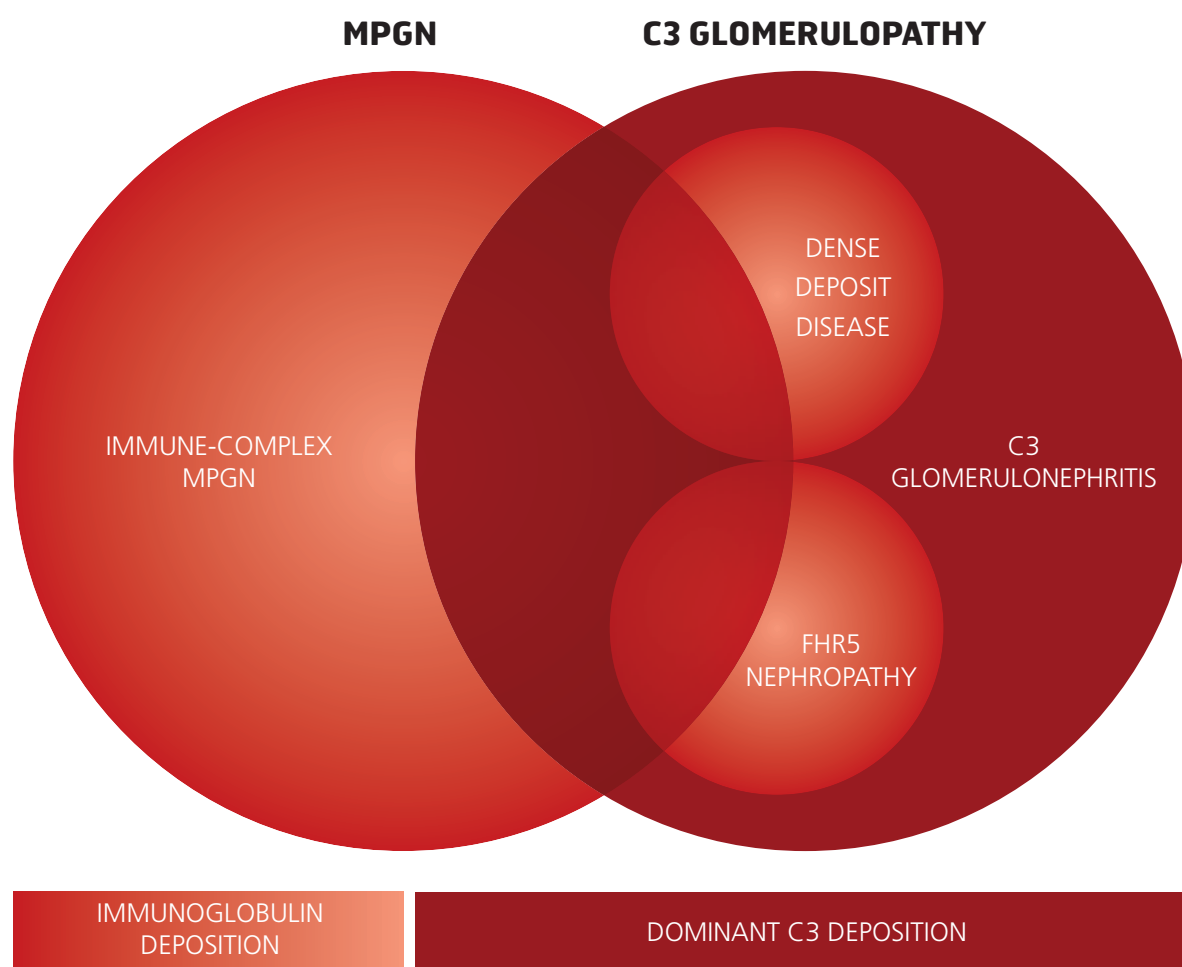
**Strong C3 staining in C3GN**

### 1.3.2 What is C3G?

C3 Glomerulopathy is a rare disease with an estimated incidence of 1-2 per million worldwide. The clinical presentation is variable, ranging from an acute rapid progression of renal failure to a more indolent presentation of chronic kidney disease. On average, patients progress to endstage renal failure within 10 years and most patients who are subsequently transplanted develop recurrent disease, with approximately half of patients losing their kidney transplant to disease recurrence.

The diagnosis of C3G is made on renal biopsy and based on the presence of dominant C3 deposition on immunofluorescence. Sub-classification of C3G into Dense Deposit Disease and C3 Glomerulonephritis is then based on the appearances on electron microscopy.

Eculizumab is not licensed for treatment of C3G but a review of the available evidence of its use in C3G led to approval for use in a Clinical Commissioning Policy (NHSE 16054/P) published in February 2017. The implementation of this policy is co-ordinated through an expert C3G panel comprising the National Renal Complement Therapeutics Centre and the Imperial C3G Service.



**Overlap of MPGN and C3 Glomerulopathy**

## 1.4 Service Development

The NRCTC strives to improve its service year on year. Patients currently benefit from the following services provided by the NRCTC:

- Defined pathways for access to optimal diagnostics and treatments of aHUS and C3G
- Shared care between the NRCTC and an increasing number of clinical teams nationwide
- Consultations with patients and their families using remote technologies (Attend Anywhere), telephone clinics and face-to-face
- Access to disease specific information via our website and virtual live webinars
- Direct input to service development through patient engagement
- An active research programme comprising basic science and clinical studies, including clinical trials in aHUS and C3G

## 1.5 Our Strategy

Our six service strategic objectives reflect how we wish to meet our vision, focusing on where we are now and what we want to achieve in the future.



### Providing exceptional shared care today

- Advice/care will be offered in a timely manner to every person contacting the NRCTC.
- Every person requiring advice/care from the NRCTC will be provided with safe and high quality advice/care. Patients and their families engaging with the NRCTC will receive an excellent patient experience.



### Striving to improve our service

- Each member of the NRCTC team will be exploring ways to improve the delivery of care and advice we offer to clinicians, patients and their families.
- Each member of the NRCTC team will be an advocate for patients and their families.



### Advancing care for tomorrow

- We will enhance the reputation of the Newcastle upon Tyne Hospitals as the provider of a Highly Specialised Service, for the UK and the world.
- We will continue to be the world leaders in complement research with our partners Newcastle University and Newcastle upon Tyne Hospitals.



*Focus group February 2020*

## 1.6 Patient Engagement

The NRCTC actively elicits the views of our patients and their family whilst keeping them informed of our service developments. This year we held our third patient focus group, with representation from all regions of England. This was an opportunity to discuss the changes that were implemented since the initial focus groups. Patient information remained a key theme amongst the focus group, and they remained keen to get updates about the National aHUS service and to consider ways for patients with aHUS and their families to interact, in order to overcome patient isolation and provide support to each other. We are currently pursuing options that include setting up a closed facebook account. The focus group agreed to meet annually.



## 1.7 Working in Partnership and Offering Seamless Care

In order for patients with aHUS to receive excellent care, it is essential that the local clinical team and National aHUS Service each understand their roles and responsibilities in delivering that care. This was mandated in the service specification: namely to facilitate optimal patient management on a shared care basis with referring clinicians. The shared care protocol was initially rolled out to all incident patients commenced on Eculizumab in the new National aHUS Service with subsequent enrolment of the prevalent patients that were already receiving Eculizumab. This protocol is now embedded into our referral pathway.

As part of this pathway, we have a system in place to ensure precious patient samples are couriered to our specialist laboratories in Newcastle (section 1.8.1) including those that require shipping on dry ice. We continue to work closely with the public health england laboratories in Colindale and Manchester (section 1.8.7 ).

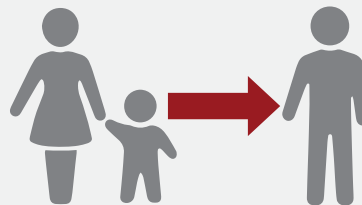
Once a diagnosis has been confirmed, all patients are allocated a named consultant who are then responsible for coordinating their care and liaising with their local team. Paediatric patients will have their ongoing care coordinated by one of our paediatric nephrologists. Transition to adult services will be managed primarily by the local team but at the appropriate time their care will also be transferred to one of our adult nephrologists at the National aHUS Service. Within our trust we also have a dedicated renal young adult care coordinator and our shared care model allows us to utilise her expertise if required.

Patients are also provided with alert cards and wristbands with disease specific information and contact details.

The NRCTC provides its patients with:



**Named  
consultant (adult  
or paediatric)**



**Access to services to  
help transition from  
paediatric to adult care**



**Alert cards and  
wristbands**



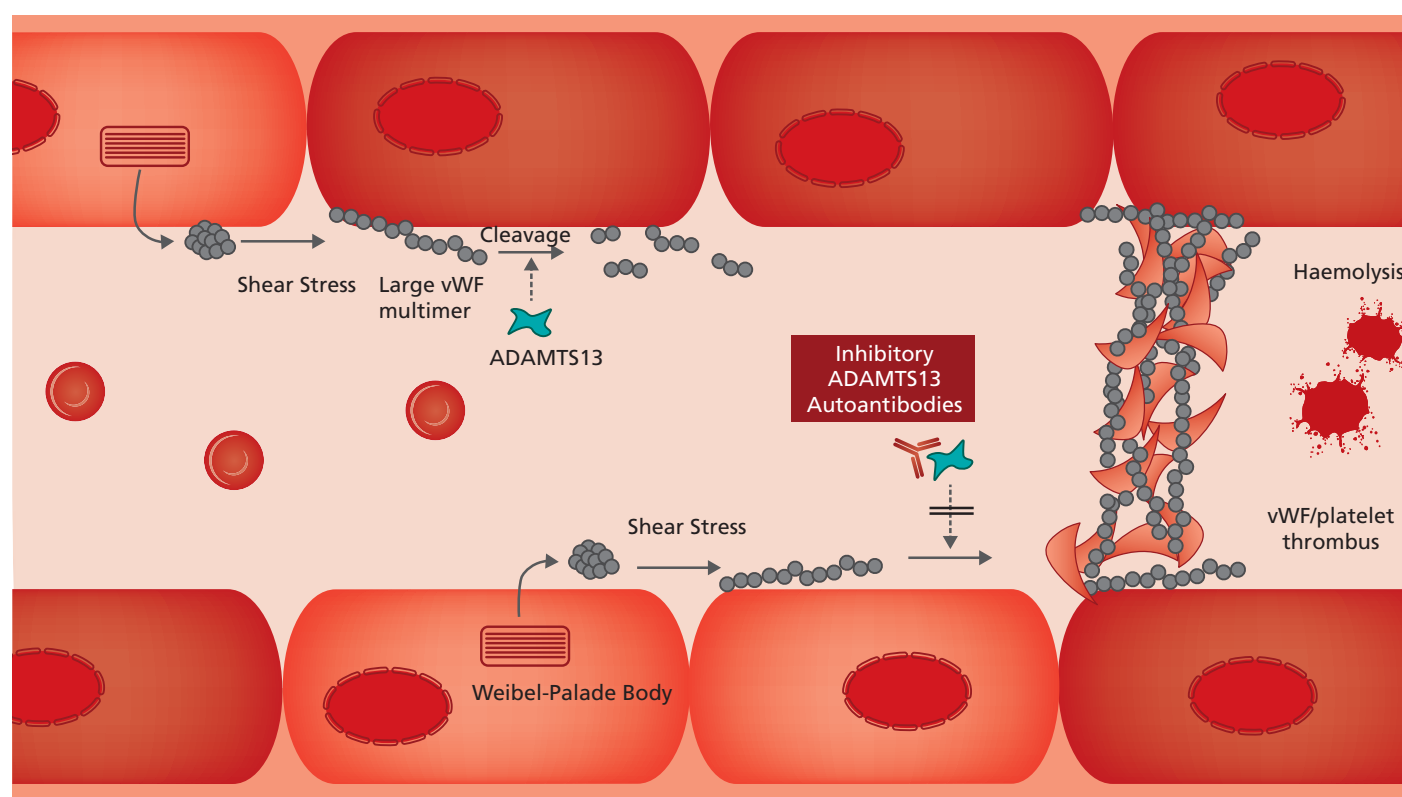
## 1.8 Ensuring High Quality Care that Delivers Optimal Use of Eculizumab

### 1.8.1 Combined aHUS & C3G Lab Diagnostics

To ensure optimal personalised care for our patients, the NRCTC has developed a combined biochemical, haematological, immunological and genetic diagnostic tool kit for aHUS and C3G. This allows for the rapid diagnosis of: atypical HUS; secondary thrombotic microangiopathies; C3 Glomerulopathies (including dense deposit disease, C3 glomerulonephritis and factor H related 5 nephropathy) and membranoproliferative glomerulonephritis. These assays also allow for therapeutic profiling to tailor the management of these diseases.

### 1.8.2 Measurement of ADAMTS13 Activity

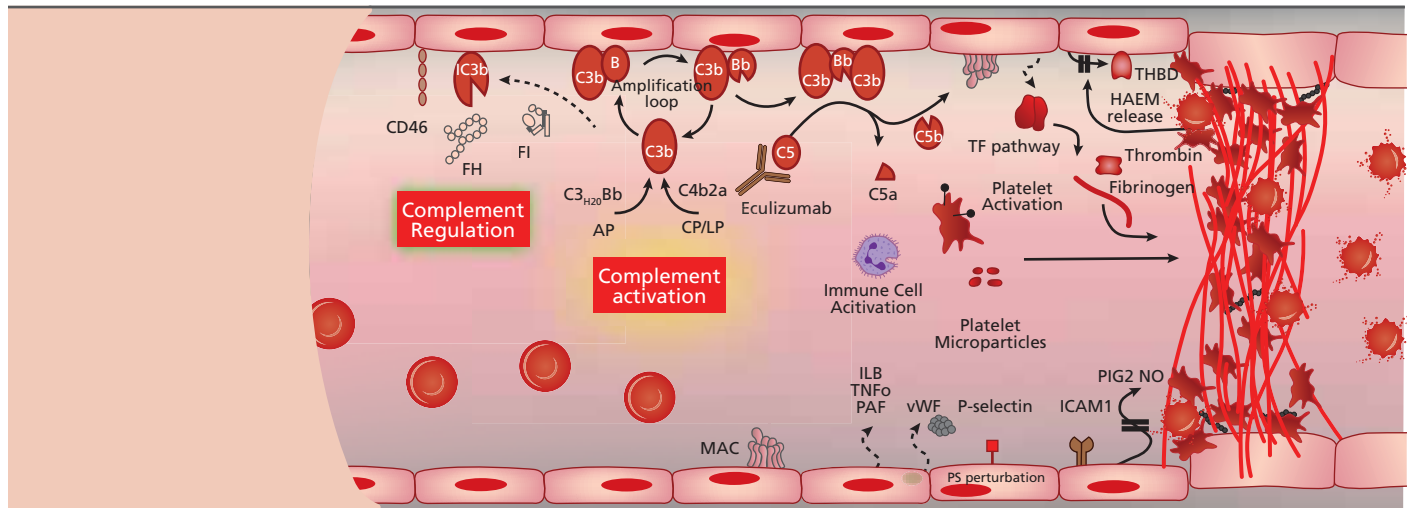
Urgent measurement of ADAMTS13 is the essential initial test in the management of thrombotic microangiopathies as it determines divergent treatment strategies. A very low ADAMTS13 activity is diagnostic of thrombotic thrombocytopenic purpura (TTP). Von Willebrand Factor (vWF) is a large protein that promotes blood clotting by adhering to platelets. Under normal conditions vWF is cleaved by ADAMTS13 to regulate platelet adherence and stop excessive blood clot formation. In TTP, ADAMTS13 deficiency, either acquired (ADAMTS13 autoantibodies) or inherited (recessive mutations in ADAMTS13) results in reduced cleavage of vWF. Platelets bind to vWF forming thrombi resulting in tissue ischemia, platelet consumption, and microangiopathic haemolytic anaemia. The initial management of both TTP and aHUS is plasma exchange except in children (KDIGO 2016) until the ADAMTS13 activity is available. Eculizumab is ineffective in the management of TTP therefore only once it has been excluded can Eculizumab be commenced for aHUS. To facilitate rapid management the NRCTC have a 7 days/week, same day service for ADAMTS13 measurements at the Newcastle Haematology laboratory led by Paul Murphy. Where testing cannot be carried out locally we provide this urgent analysis, including transport of specimens to the Newcastle laboratory.



**Thrombus formation in TTP**

### 1.8.3. Genetics

Since the initial description of mutations in the complement system in aHUS in Newcastle in 1998, genetic analysis has proved a key tool in the diagnosis of aHUS. The Northern Genetics Service (NGS) under Dr David Bourne has long provided complement genetic testing for both atypical HUS and C3G both nationally and globally. The NRCTC provides a fully integrated care pathway with genetics at its core to expedite optimal personalised patient care.



**Thrombus formation in patients with aHUS**

#### Complement Genetics

Standard sequencing of the complement genes factor H, factor I, CD46, C3 and factor B is undertaken on all patients referred to the National aHUS Service. Many complement genes are found on chromosome 1 in a region called The Regulators of Complement Activation (RCA) gene cluster. This region is thought to have arisen from several large genomic duplications. The genetic architecture of this region predisposes to gene conversions and genomic rearrangements and therefore copy number variation analysis is critical to detect them.

#### Complement pharmacogenetics

In addition to providing definitive confirmation of complement mediated aHUS, the next-generation sequencing lab also provides urgent complement pharmacogenetics analysis. A rare genetic polymorphism in the C5 gene (c.2654G>A) predicts Eculizumab non-response. The consequent amino acid alteration prevent Eculizumab binding and thus complement activation is not inhibited. This analysis is immediately performed to identify patients who will not respond to Eculizumab allowing plasma exchange to be rapidly resumed.

#### Eculizumab non response

In addition to complement mediated aHUS, there are other genetic causes of thrombotic microangiopathies that are not complement mediated: *DGKE*; *MMACHC*; and *INF2*. Routine sequencing of the genes *DGKE* and *MMACHC* and bespoke analysis for *INF2* is undertaken to avoid ineffective treatment with Eculizumab and to allow other effective treatments to be instituted (e.g hydroxycobalamin in patients with *MMACHC* associated TMA).



**A polymorphism (red sphere) in the C5 protein (white) prevents Eculizumab (magenta) binding to C5 (protein database identification code:515k)**

#### 1.8.4 Genetic research

The NRCTC University complement genetics group under Professor Kavanagh and the Northern Genetics Service are now fully integrated to provide rapid translational benefits to patients. The use of next generation sequencing technology either locally or via the 100,000 genome project allows the discovery of novel genes that predispose to aHUS. This combined entity is utilizing these cutting edge technologies to personalise management of our patients.

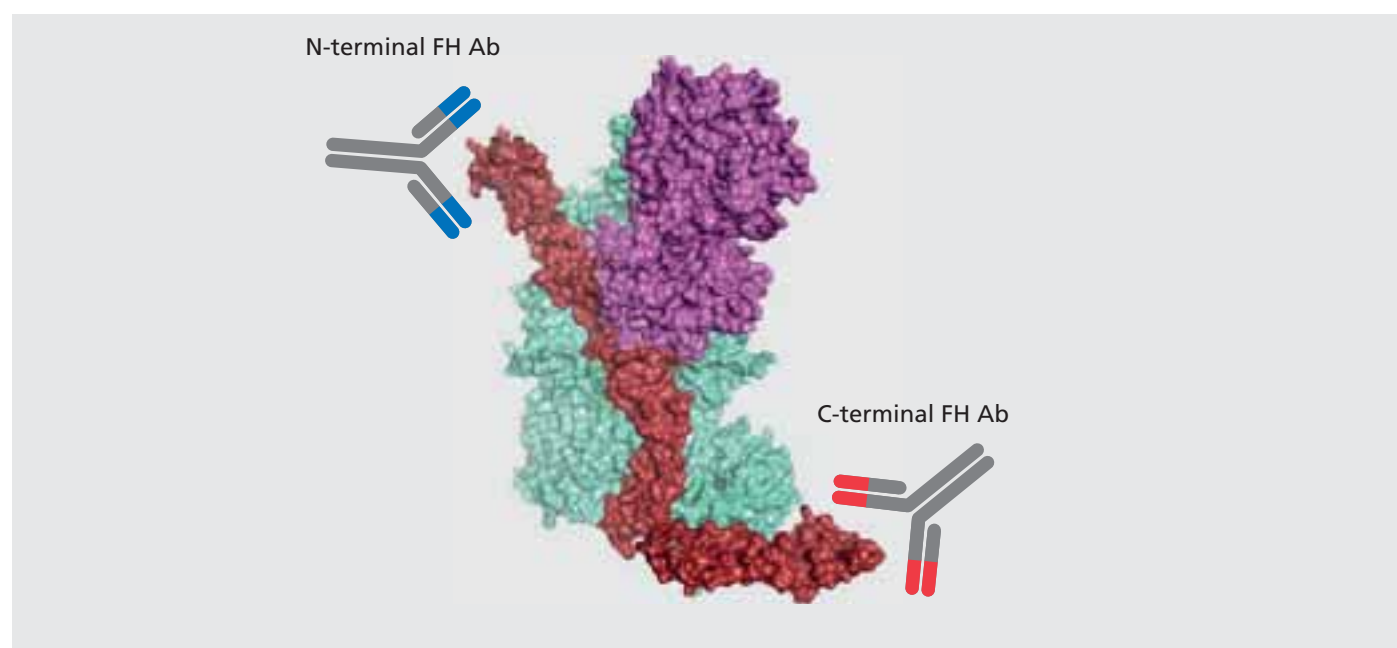
#### 1.8.5 Complement Analysis in aHUS & C3G

Complement assays are a key part of the diagnostic toolkit, providing evidence of complement activation, validation of genetic findings and allowing therapeutic profiling. The Newcastle upon Tyne Hospitals Blood Sciences' Complement Immunology laboratory overseen by Dr Suzie Elcombe and Professor Claire Harris' Complement Therapeutics Research Group at the NRCTC collaborate closely to develop and validate a broad range of assays. All patients referred to the service will have C3, C4, FB, sC5b9, FH, FI, CH100, AH100 and CD46 measurements. In addition bespoke analysis can be undertaken in the university laboratories including complement activation products (C3, C5 and FB split products) and detection of very low levels of other complement proteins. Measurement of both complement proteins and their split products accurately profiles complement activation status and improves diagnostic potential.

#### 1.8.6 Autoimmune Complement Mediated aHUS & C3G

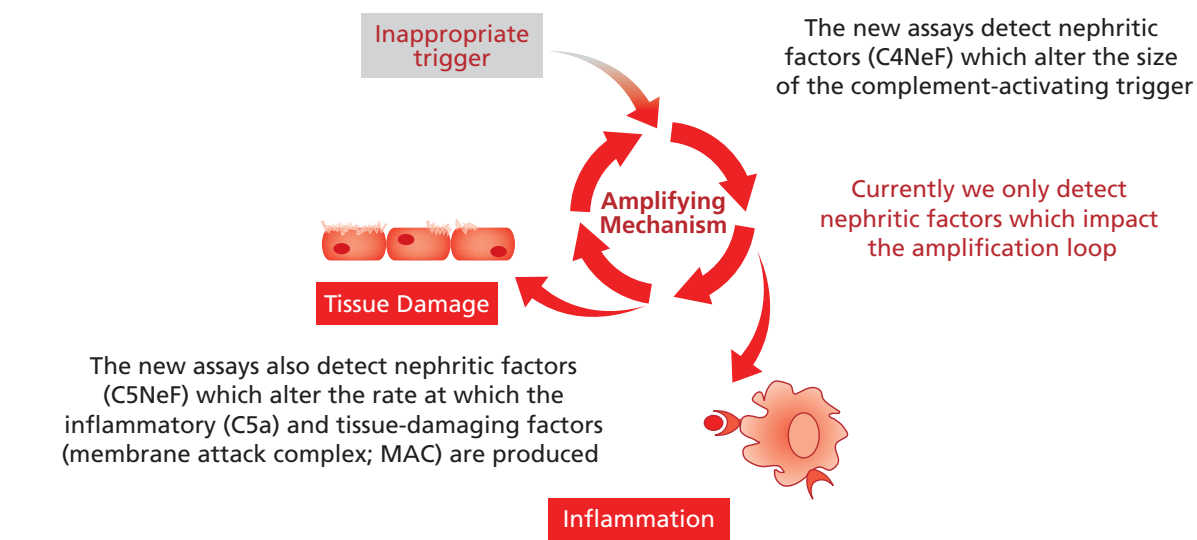
Professor Kevin Marchbank, head of autoimmune aHUS analytics, leads the complement autoantibody service. Autoantibodies to complement factor H are one of the commonest causes of complement mediated aHUS and are also found in C3G.

In addition to the detection of FH antibodies, an epitope mapping service is available to determine the likely functional consequences of these autoantibodies. C-terminal FH epitopes are most commonly detected in aHUS while N-terminal epitopes are usually detected in C3G. Tailored analysis of autoantibodies to other complement protein is available where appropriate. Furthermore, the autoantibody team continues to work with other reference centres around the world to unify analysis and standardise read outs from complement autoantibody tests providing increasing clarity regarding the importance of a given level of a detected autoantibody.

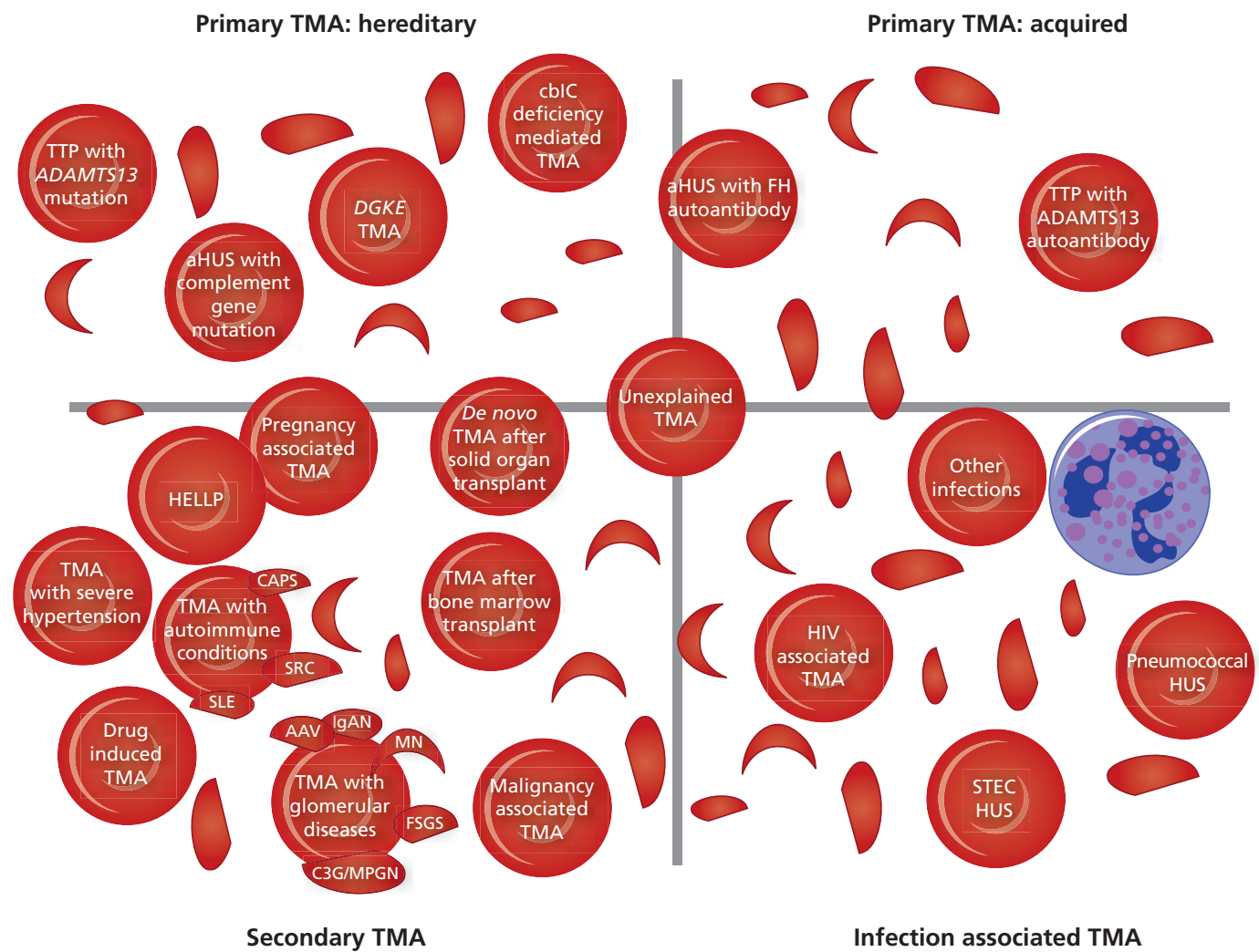


**Epitope mapping of FH autoantibodies.** The kidney is normally protected from damage by complement activation when C3b (cyan) is degraded by the enzyme factor I (purple) and the cofactor factor H (red) (protein database identification:5O35). The location of the autoantibody binding to factor H determines the nature of the disease with C-terminal autoantibodies predisposing to aHUS and N-terminal autoantibodies predisposing to C3G.

In C3G, C3 Nephritic factors are routinely measured and C4 and C5 Nephritic factor assays are under development in Professor Claire Harris' group. These autoantibodies are historically difficult to identify and analyse. The research group is working towards a set of simplified and streamlined assays to enable rapid and semi-automated detection of nephritic factors.



Identifying nephritic factors in C3G



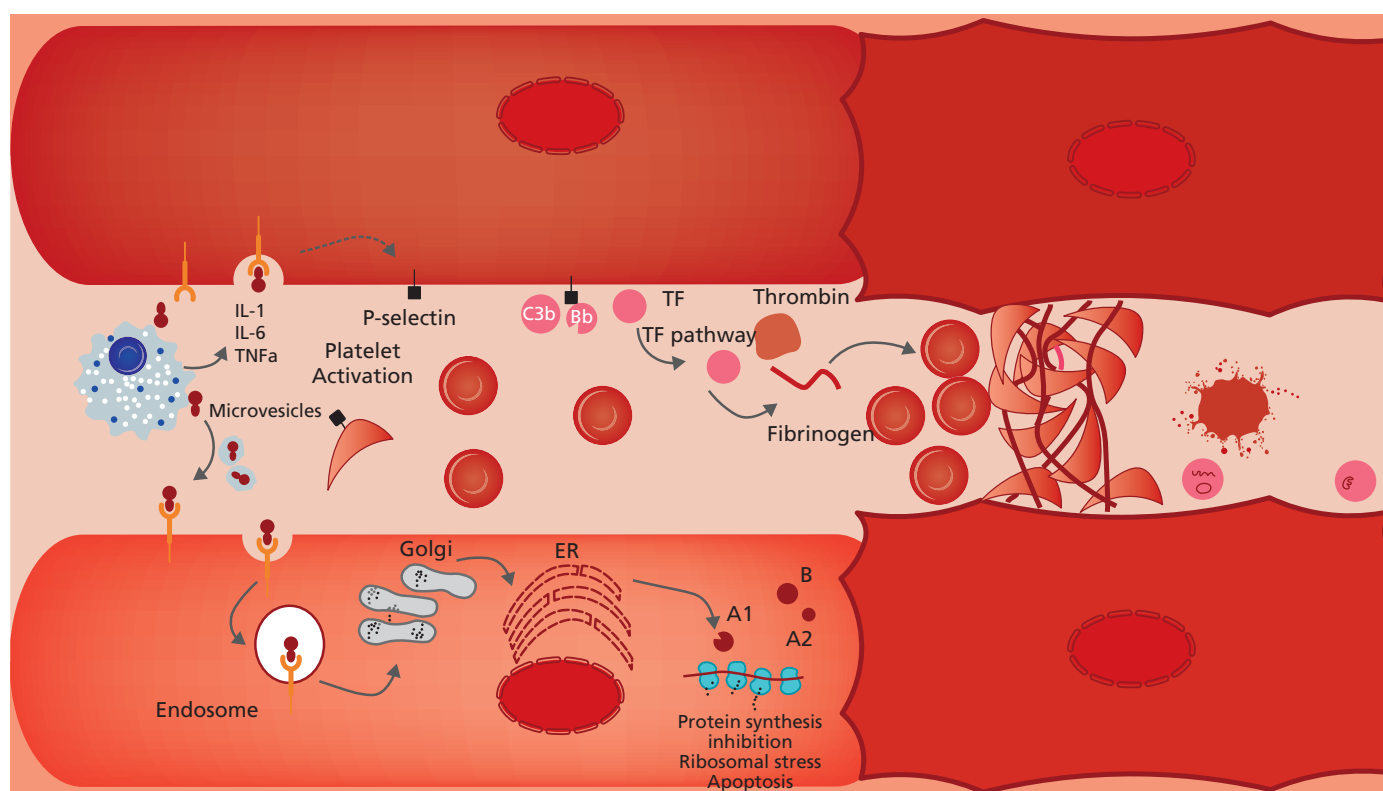
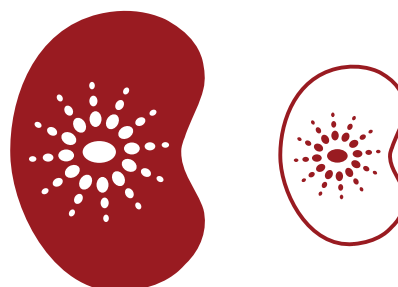
Causes of TMA

## 1.8.7 Microbiology Specialist Laboratories

### Enterohemorrhagic *E. coli* testing

Shiga Toxin induced HUS is one of the main causes of acute kidney injury in young children and occurs following infection with Shiga toxin-producing enterohemorrhagic *E. coli* (STEC) or Shigella. These bacteria produce Shiga toxin which is transported from the gut to the kidney via leucocytes, erythrocytes and platelets. The toxin is taken up by cells within the kidney where it inhibits protein synthesis, leading to endothelial cell death and exposure of the underlying basement membrane. Shiga toxin is also able to enhance the release of pro inflammatory cytokines, amplifying inflammatory events. Shiga toxin can also upregulate P- selectin and cause complement activation. The consequent thrombosis results in microangiopathic haemolytic anaemia and end organ damage.

As STEC-HUS is the commonest differential diagnosis of aHUS, rapid diagnosis is essential for timely appropriate treatment. The Public Health England reference laboratory in Colindale led by Dr Claire Jenkins provides these specialised services and we have established close links to expedite the results to facilitate decision making.



### Thrombus formation in STEC HUS

### Meningococcal vaccination response

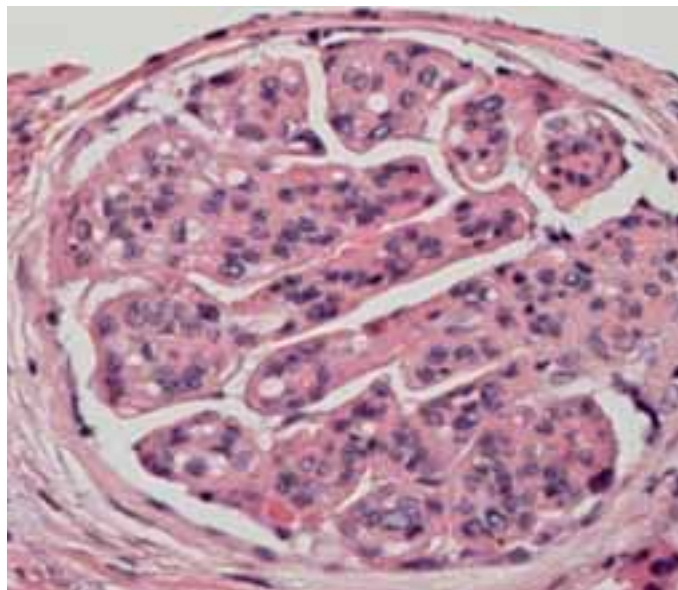
Susceptibility to infection with encapsulated organisms, particularly *Neisseria* infections, is the most serious side effect of Eculizumab treatment. Because of this meningococcal vaccination is mandatory for all patients receiving Eculizumab. The Public Health England meningococcal reference unit in Manchester led by Prof Ray Borrow is the national centre for England and we work closely with him to assess the response to vaccination to provide optimal protection against infection.



### Meningococcal serotypes and vaccination

### 1.8.8 Histopathology

The NRCTC work in close collaboration with the Imperial C3G team to provide expert review of renal biopsies as part of the implementation of the policy for Eculizumab treatment of recurrent C3G following renal transplantation. Eligibility for treatment with Eculizumab is dependent on confirmation of the C3G as the original cause of kidney failure and its recurrence in the transplant kidney. Eligibility also requires the presence of crescentic disease and of C9 staining in the transplant graft. A protocol has been in place since the start of the policy for Eculizumab for recurrent C3G following renal transplantation, ensuring appropriate samples are sent to the histopathology department at Imperial College NHS Foundation Trust. An expert pathology opinion is provided within 5 working days of receipt of samples.



## 1.9 Global Reach for Optimal Patient Care



### *NRCTC Global Consultations*

#### **European Reference Network on Rare Kidney Disease (ERKNet)**

ERKNet is the European Reference Network for rare kidney diseases. It is a consortium of 38 expert paediatric and adult nephrology centres across the European Union providing healthcare to more than 40,000 patients with rare disorders of the kidney. The NRCTC is proud to have been selected as a reference centre for TMA for ERKNet. ERKNet offers virtual consultation services to physicians throughout Europe who need advice for challenging cases with a rare kidney disease. The NRCTC has already demonstrated its global reach with consultations not only across Europe but also Asia, Africa and North and South America.



## 1.10 Education and Audit

### Improving Clinician Knowledge

The team at the NRCTC is committed to improving clinician knowledge to enhance patient care. As part of this programme, we have delivered presentations to thousands of delegates across local, national and international platforms.

The NRCTC have also hosted specialist staff from other units to share experiences of managing these rare diseases of the kidney. The highlight this year was meeting with Dr Bernd Schwahn, - consultant in paediatric metabolic medicine from Manchester, to discuss metabolic causes of HUS.

Members of the team also attended a national workshop to discuss how to improve diagnosis and management of STEC-HUS. Recommendations from the workshop have since been published (Jenkins et al, 2020)

### Ongoing Audit and Review of Practice

The NRCTC undertakes constant audit and research to optimise practice. We continue to review our data that allows us to continually refine our diagnostic and treatment pathways that we discuss with NHS England and the PNH National Service Leeds. Data from this process forms a key part of this report.

### Nurse Education

Our specialist nurses have continued to present at nursing study days in the UK to raise awareness of the National aHUS Service, the disease process and its treatment options. This year they also organised their second study day for nurses from all over the UK that focused on the management of patients with rare renal diseases, including aHUS and C3G – they take part in regular training updates for nursing teams delivering treatment to our patients in their home, as well as teams that deliver treatment in hospitals. This training includes important information about patient safety and harm free care in relation to aHUS and the risks of meningitis.

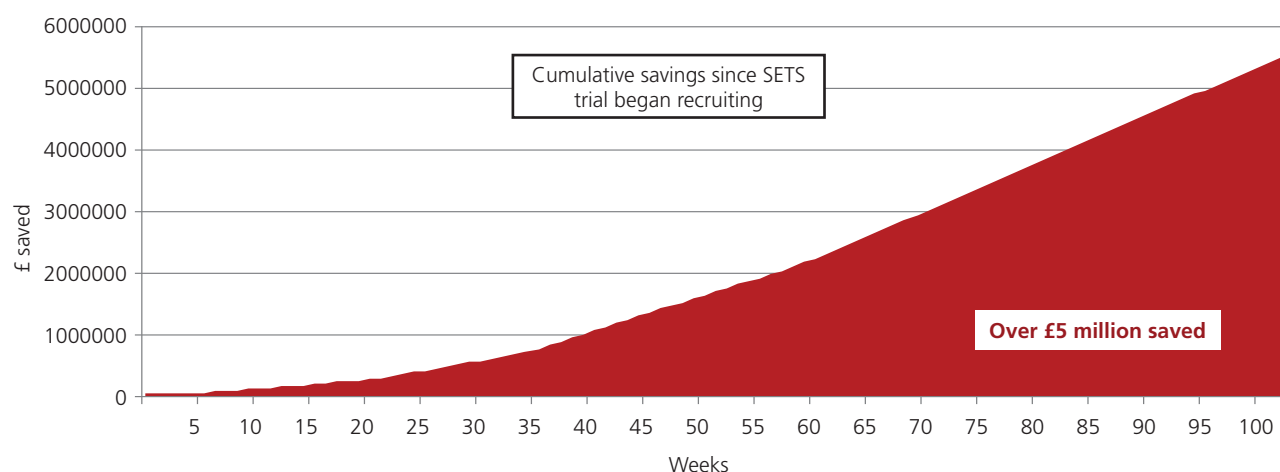
## 1.11 Research

*Professor Neil Sheerin is the Chief Investigator for:*

### **Stopping Eculizumab Treatment Safely in aHUS Study (SETS aHUS):**

The NICE appraisal recommended the use of Eculizumab on condition that a research programme with robust methods to evaluate when withdrawing treatment or reducing the dose might occur was developed. In addition, although the product licence is for life-long Eculizumab there is growing evidence that this may not be necessary and a proportion of patients may be able to withdraw safely from treatment. A National Institute for Health Research (NIHR) Health Technology Assessment award is funding a single arm, Bayesian study Eculizumab withdrawal in 30 patients currently on treatment. The primary endpoint is patient outcome over a two year period; and not relapse which we accept will occur but predict that relapse can be effectively treated with reintroduction of Eculizumab. The protocol will test the effectiveness of self-monitoring to detect relapse. There are also embedded health economic and qualitative arms of the study.

Recruitment into the trial was suspended during the Covid-19 pandemic but the trial is now re-opening and we have started to recruit patients again. To date 22 patients have withdrawn from eculizumab. Aside from minimising treatment burden to the patient, we estimate a saving to the NHS of over £5 million to date.



**Cost saving benefit to the NHS to date of the SETS trial of over £5 million**

*Professor David Kavanagh is the Chief Investigator for:*

### **CL011\_168 Trial:**

The CL011\_168 Trial is a, Double Blind Placebo controlled Phase 2 Study Randomised, Placebo Controlled Study Evaluating the safety and efficacy of Avacopan (CCX168) in patients with C3 Glomerulopathy (ACCOLADE). NCT03301467.

*Dr. Edwin Wong is the Chief Investigator for:*

### **Trial of LNP023 in C3G:**

This is an open-label phase 2 study studying the safety and efficacy of LNP023 in patients with C3 glomerulopathy (NCT03832114). The team recruited the first global patient for this trial. Patients who completed the initial 12 weeks of treatment were rolled over into an open-label extension trial (NCT03955445).

*Dr. Sally Johnson is the Chief Investigator for:*

### **ECULizumab in Shiga-Toxin producing Escherichia Coli Haemolytic Uraemic Syndrome (ECUSTEC):**

ECUSTEC is a randomised, double-blind, placebo-controlled trial which aims to determine whether eculizumab reduces the severity of STEC-HUS in children. The trial recruited 36 patients with STEC-HUS. Unfortunately, NIHR funding for the trial was stopped in 2020 following the COVID-19 pandemic. The trial team hope that data analysis will provide important information about the role of eculizumab in STEC-HUS.

### **ALXN1210-aHUS-311 - A phase 3, open-label, multicentre study of ALXN1210 in children and adolescents with atypical haemolytic uraemic syndrome.**

This trial studies whether ALXN1210, also known as ravulizumab, a long-acting version of eculizumab, is safe and effective in children and adolescents with aHUS.

## Translational Research at the Newcastle University Complement Therapeutics Research Group

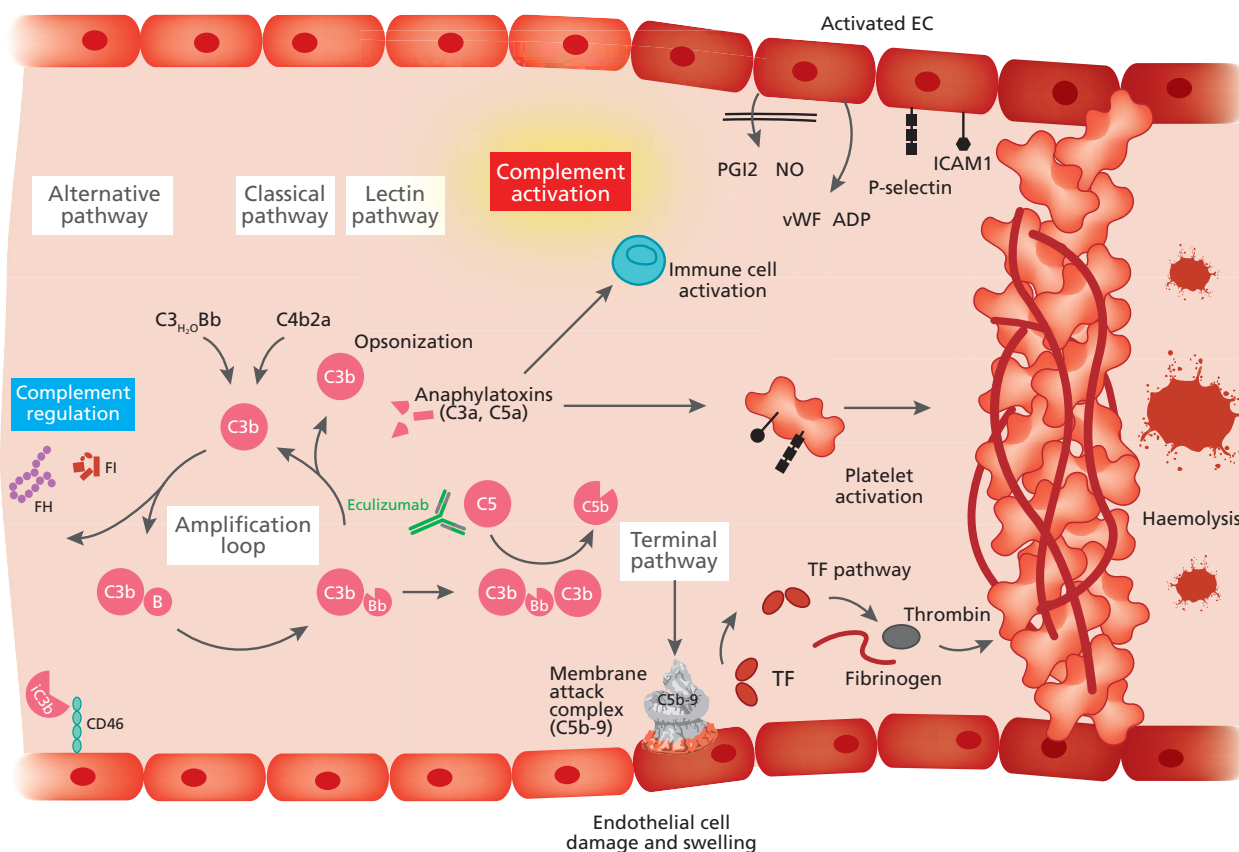
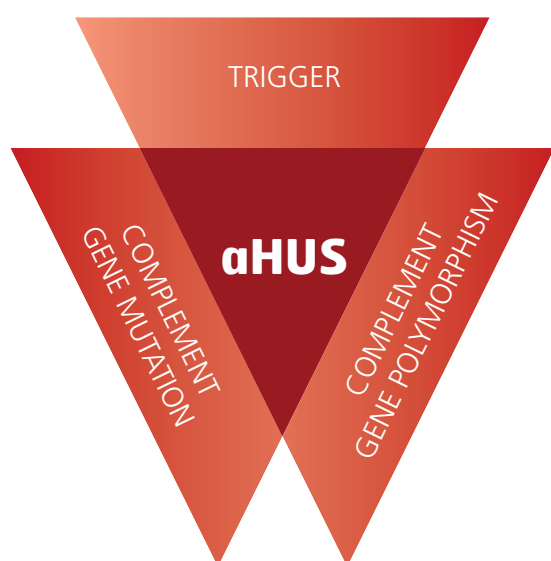
Professor Marchbank, Professor Harris and Professor Kavanagh also oversee an active bench to bedside research programme within the NRCTC. Research in the group encompasses basic, translational and clinical science, ranging from deciphering of disease mechanisms using intricate *in vitro* assays, through animal models of disease, to drug design for clinical use and testing of therapeutics.

Thriving collaboration between the scientific and clinical teams at Newcastle enables in-depth mechanistic insight into a number of renal diseases. This is provided by probing functional consequences of disease-associated gene and protein changes as they are identified in patient populations. Mechanistic data,

together with in-house multiplexed biomarker profiling, provides powerful knowledge into the causes of acute and chronic kidney disease. Insight into disease provided as a consequence of genetic, functional and biomarker analyses not only streamlines personalised management of patients, by enabling stratification for clinical trials, but also guides discovery of novel and targeted drugs.

Our drug discovery portfolio is supported by numerous interactions at a national and global level. We welcome collaboration with industry in order to support drug development, whether external or within Newcastle. Our preclinical work is supported by development of novel *in vivo* experimental models of renal disease, such as aHUS. These models provide unparalleled opportunities to improve patient care, both by defining triggers of disease and also by exploring the most effective therapeutic avenues.

The research team includes clinical fellows, research associates and assistants and supports training of a large number of students at all levels, including undergraduate, Masters and PhD students. While renal disease is our main research focus, we study other diseases, including ocular age related macular degeneration (AMD) and haematological paroxysmal nocturnal haemoglobinuria (PNH) disorders and enjoy numerous national and international collaborations including Cardiff University, the PNH National Service (Leeds), University of Manchester, University of Bristol, University of Edinburgh, Southampton University Washington School Of Medicine, St Louis, and Tufts University School of Medicine, Boston.



**Thrombus formation in patients with aHUS**

## 2. Service Activity

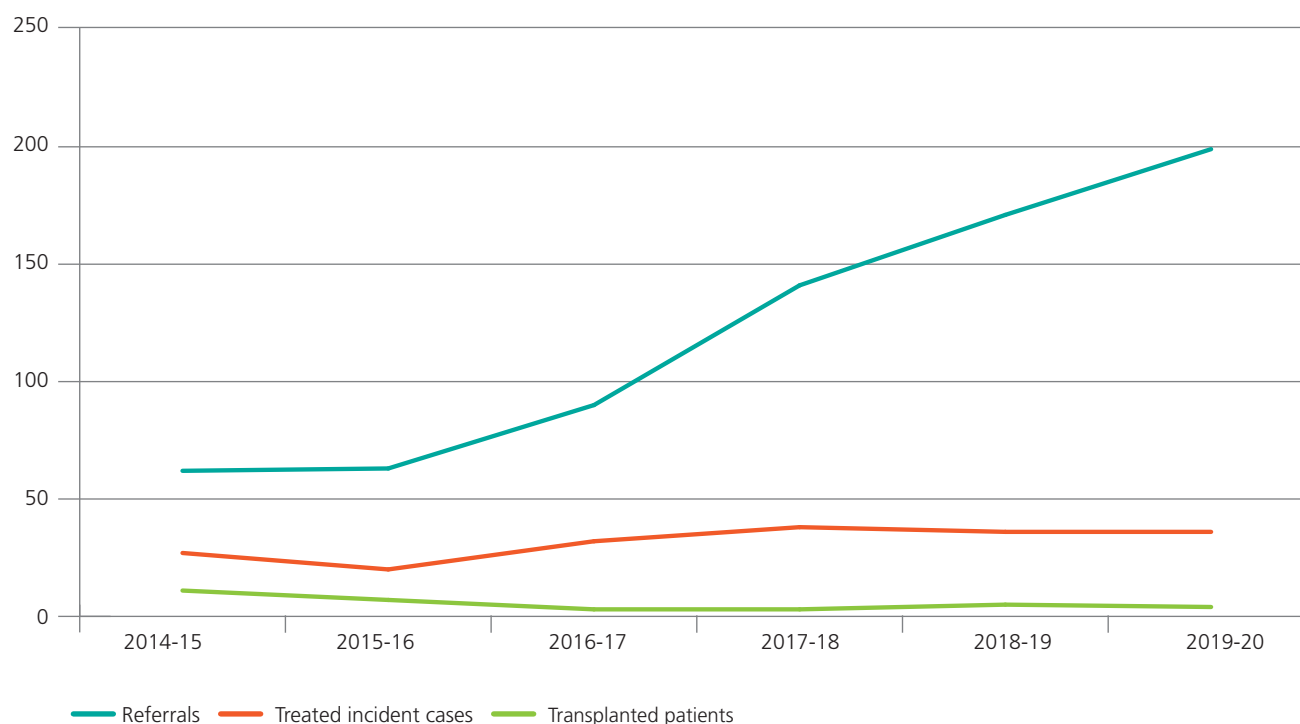
This report refers to the activity of the National aHUS Service and the National C3G service. The reporting period of this report is from April 1st 2019 until March 31st 2020.



## 2.1 aHUS service activity

### Increasing annual activity

Referrals to the National aHUS Service continue to increase. The annual referral numbers to the service in each of the last 6 complete financial years are summarised below. During the same reporting period, the number of incident patients treated with Eculizumab remains broadly unchanged. Use of Eculizumab in prevalent patients with aHUS as part of pre-emptive treatment at time of transplantation continues.



**National aHUS Service annual activity.** Line chart shows number of patients referred to the National aHUS Service, the number of patients recommended for treatment of incident cases of aHUS with Eculizumab and the number of prevalent aHUS patients receiving pre-emptive Eculizumab at time of transplantation in each of the last 6 complete financial years.

### Referrals during the 2019-2020 reporting period

In the 2019/20 reporting period, the National aHUS Service has received 199 referrals for Eculizumab in patients with a potential new diagnosis of aHUS. During the same reporting period, Eculizumab was initially recommended in a total of 36 patients.

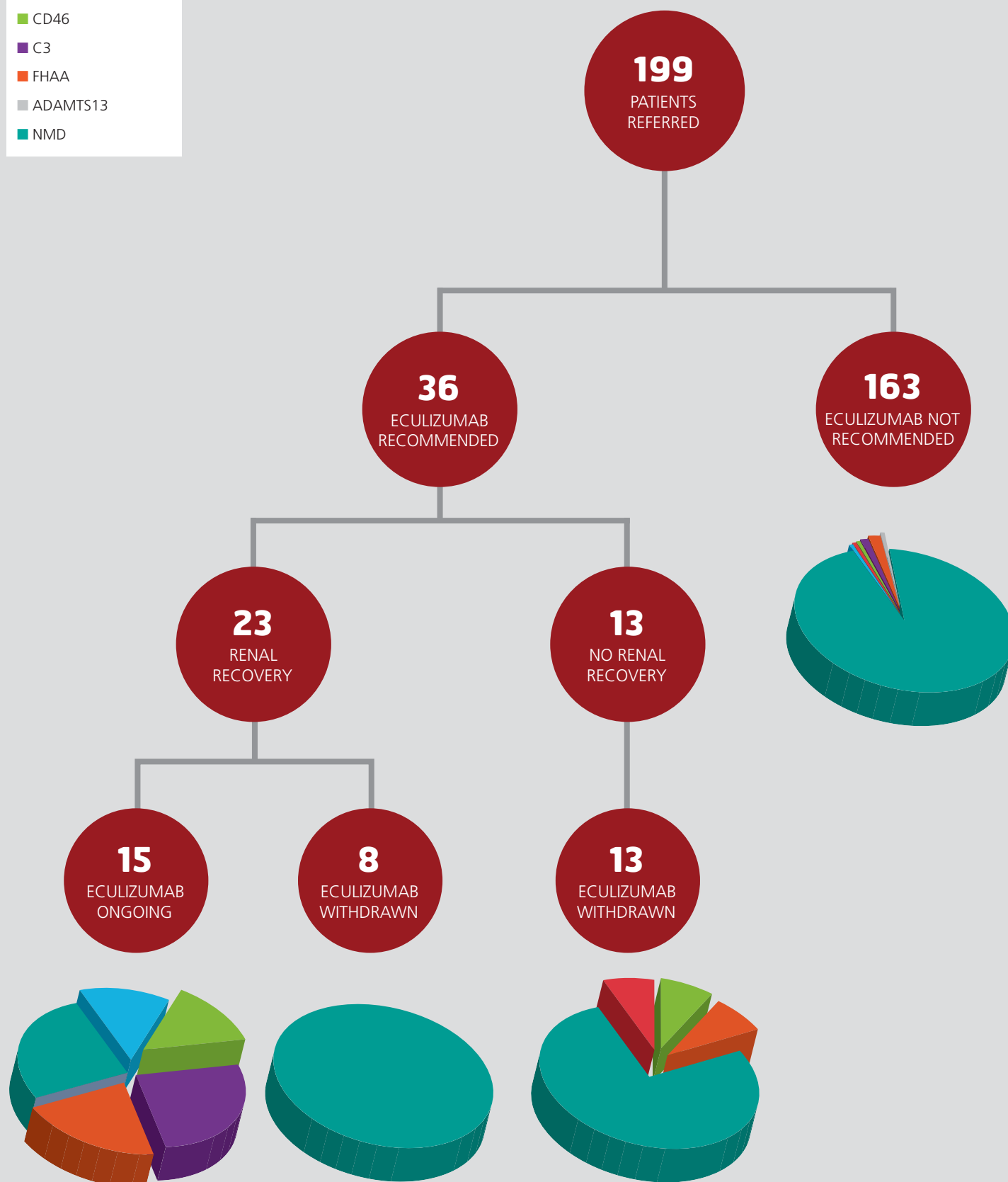
We have reported outcomes correct as of 30th June 2020. Of the patients treated with eculizumab during this period, 15 patients improved and remained on Eculizumab. Of these, 73% had a genetic or acquired complement abnormality. In a further 8 patients who also showed improvement, the diagnosis of aHUS was revised following the availability of additional clinical data and alternative diagnoses were made. Eculizumab treatment was therefore withdrawn.

Thirteen patients showed no significant improvement in renal function. In all of these patients, ongoing eculizumab was not recommended. A small number of patients were subsequently found to have a complement abnormality associating with aHUS. Failure to respond to treatment with eculizumab was related to other complicating factors.

A diagnosis of aHUS was considered in a further 163 patients that were referred to the National aHUS Service. Based on the available clinical information, eculizumab was not recommended by the National aHUS service on the basis that there would be likely to be little or no clinical benefit. Reasons for this include likely or confirmed alternative diagnosis and/or clinically improving, or likely futility of treatment based upon evidence of advanced / irreversible renal disease. We subsequently identified an acquired or genetic complement abnormality in eight cases patients (4.9%) out of this group. This process of screening for complement abnormalities in patients referred to us identified patients that could be given eculizumab pre-emptively in transplantation.

# KEY

- CFH
- CFI
- CD46
- C3
- FHAA
- ADAMTS13
- NMD



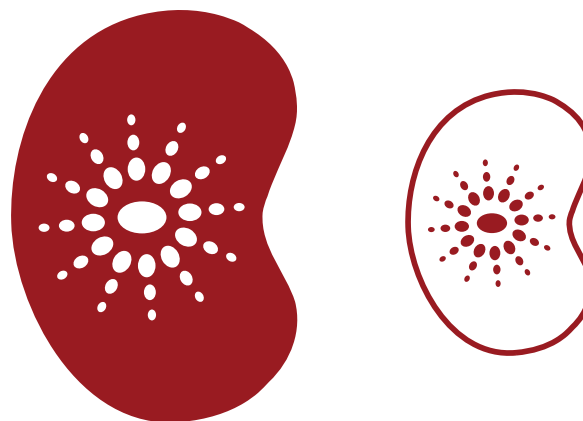
**National aHUS Service activity from April 2019 until March 2020.** Eculizumab was recommended in 36 patients. All patients receiving eculizumab were screened for complement genetic mutations and autoantibodies to factor H. The proportion of patients with either a genetic mutation (in each of the genes screened CFH, CFI, CD46, C3, CFB, DGKE, INF2, MMACHC and ADAMTS13 or nmd=no mutation detected) or autoantibody to complement factor H (FHAA) for each treatment arm is shown.

## 2.2 C3G service activity

A referral pathway has been in place for consideration of eculizumab in patients with recurrent C3G since February 2017. The initial point of contact is the NRCTC via email: [C3.glomerulopathy@nhs.net](mailto:C3.glomerulopathy@nhs.net). Treatment with eculizumab can only be recommended following review by an expert C3G panel comprising the NRCTC and Imperial C3G service.

Since the clinical commissioning policy for Eculizumab in recurrent C3G was introduced, a total of 27 patients with possible recurrent C3G were considered in the period until March 2020.

At this time, four patients had fulfilled eligibility criteria as set out in the commissioning policy and received treatment with eculizumab.

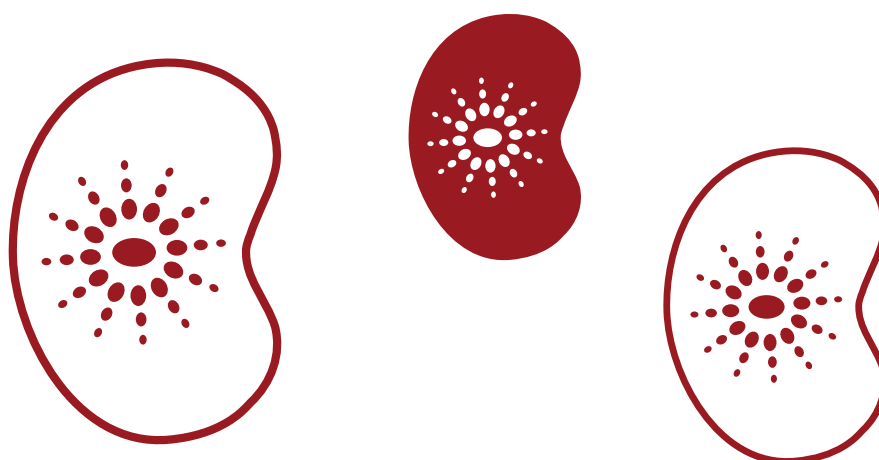


# 3. Performance Analysis

The service measures its performance across the NHS outcomes framework domains and quality indicators, detailed below.

Quality Requirement	Threshold	Method of Measurement	Consequence of Breach
<b>Domain 1: Preventing people dying prematurely</b>			
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero deaths	To be notified to the commissioners including HSS national team within 24 hours	To be addressed in annual service audit meeting
<b>Domain 2: Enhancing the quality of life of people with long-term conditions</b>			
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	Annual audit	To be addressed in annual service audit meeting
Publish an annual report from the aHUS registry	Report published to agreed timetable	Report received by NHS England	To be addressed in annual audit meeting
<b>Domain 3: Helping people to recover from episodes of ill-health or following injury</b>			
To provide advice to provider centres within 24 hours of request on treatment	90%	Annual audit report	To be addressed in annual service audit meeting
Written protocols agreed with units	100%	Annual audit report	To be addressed in annual audit meeting
<b>Domain 4: Ensuring that people have a positive experience of care</b>			
Achieve 90% data completeness of the of the aHUS register to which referring units are mandated to supply data	90%	Annual audit report	To be addressed in annual service audit meeting

## National aHUS Service - Quality Indicators



### 3.1 Domain 1: Preventing people dying prematurely

*Zero avoidable deaths in patients with a diagnosis of complement-mediated aHUS*



As of 31st March 2020 there were 125 patients receiving Eculizumab under the shared care agreement of the National aHUS Service.

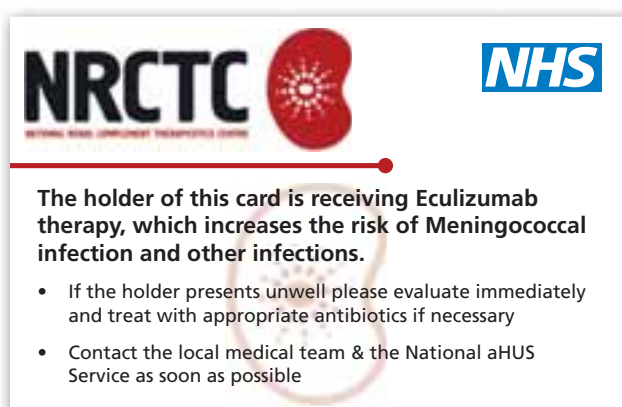
When the National aHUS Service is notified of the death of a patient a case review is performed to determine whether aHUS was active at the time and therefore contributed to the death.

*After assessment within our established morbidity and mortality review process, in conjunction with local teams, we concluded that patients who died had appropriate management of their illness and that their deaths could not be attributed to a diagnosis of complement-mediated aHUS or its treatment.*

#### Infection Prevention in patients receiving Eculizumab

We also recognise that there is a risk of morbidity and mortality due to the risk of infection in patients receiving Eculizumab. All clinicians are informed about the risk of meningococcal infection when their patients are approved for treatment and our recommendations are summarised on our website. Meningococcal vaccination is required prior to the initiation of Eculizumab treatment and long term antibiotic prophylaxis is recommended. One of the continuing challenges has been obtaining meningococcal antibody titres post vaccination to monitor the vaccination response (see domain 3). This now includes reaching re-vaccination against serotype B at 5 years regardless of titres.

Medical alert cards have been sent to patients receiving treatment to ensure they receive appropriate care when seeking medical treatment. The cards also contain the service website and contact details. The risk is also highlighted when we see patients in our clinics or at our aHUS roadshows.

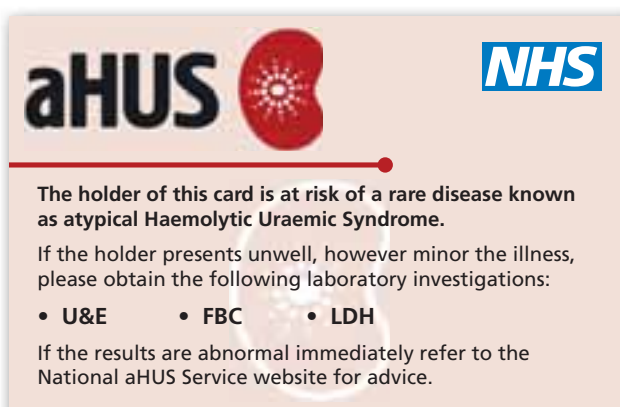


**Patient-held alert card - meningococcal risk**



## Familial risk of aHUS

We continue to offer genetic testing to all relatives of aHUS patients who carry a genetic mutation to identify those who are at risk of developing the disease in the future. Early recognition of the disease is important in preventing the morbidity and mortality associated with aHUS. At risk family members are provided with a medical alert card, stating that are at risk of developing aHUS and indicating where information can be found on our website.



**Patient-held alert card at- risk of developing aHUS**

### Summary of our previous implementation in this domain

- Regular morbidity and mortality meetings and case review to ensure high quality of care
- Emphasising the importance of meningococcal prevention
- Providing access to up-to-date monitoring guidance on our National aHUS Service website
- Highlighting risks of meningococcal infection through patient roadshows and newsletters
- Providing advice to relatives at-risk of aHUS and offering genetic screening

## 3.2 Domain 2: Enhancing the quality of life of people with long term conditions

**All patients with aHUS who are eligible for renal transplant will be listed for transplant**

**All patients referred to the NRCTC who are eligible for renal transplantation are listed for pre-emptive Eculizumab at the time of renal transplantation.**

All patients with aHUS who are being considered for renal transplantation should be referred to the National aHUS Service for consideration of pre-emptive Eculizumab. Guidance about this is documented within our transplantation protocol. Patients with aHUS who require a kidney transplant undergo extensive genetic and autoimmune testing to characterise their risk of recurrent aHUS. We are able to personalise treatment and recommend use of eculizumab at time of transplant in patients who are at significant risk of their disease recurring following transplantation.

Four patients received a renal transplant under Eculizumab cover between 1st April 2019 and 31st March 2020. Patients approved for pre-emptive Eculizumab are reviewed at regular meetings. As of 31st March 2020, there were 24 patients pre-approved for Eculizumab to enable listing for renal transplantation.

### Summary of our previous implementation in this domain

- Proactive discussions about patients referred to the NRCTC about risk of aHUS following renal transplantation
- Regular review of patients recommended for pre-emptive eculizumab

### 3.3 Domain 3: Helping people to recover from episodes of ill-health or following injury

*To provide advice to referring centres within 24 hours of request of treatment*

**All referrals to the National aHUS Service were answered within 24 hours**

We provide a 24 hours, 7 days a week consultant led on call service. The referral process has been shared nationwide in newsletters and at national meetings to the medical community. The service website was launched in 2017 and has an emergency referral page to ensure the referring team have all the essential information required for making a referral and how to contact the on call clinician.

We responded to all referring units within 24 hours of initial contact with the National aHUS Service.

**Written protocols agreed with units**

Shared-care Protocols were implemented in 2017 and are forwarded to clinicians at the outset of treatment as part of the referral pathway. We received shared-care protocols for 89% of treated patients.

**Summary of our previous implementation in this domain**

- Ensuring clear and up-to-date instructions for referral are outlined on the NRCTC website
- Collaborative effort with NHS England to ensure 100% concordance with shared care model
- Highlighting and sending shared-care protocols early on in the referral pathway



### 3.4 Domain 4: Ensuring that people have a positive experience of care

*Achieve 90% data completeness of the aHUS register to which referring units are mandated to supply data*

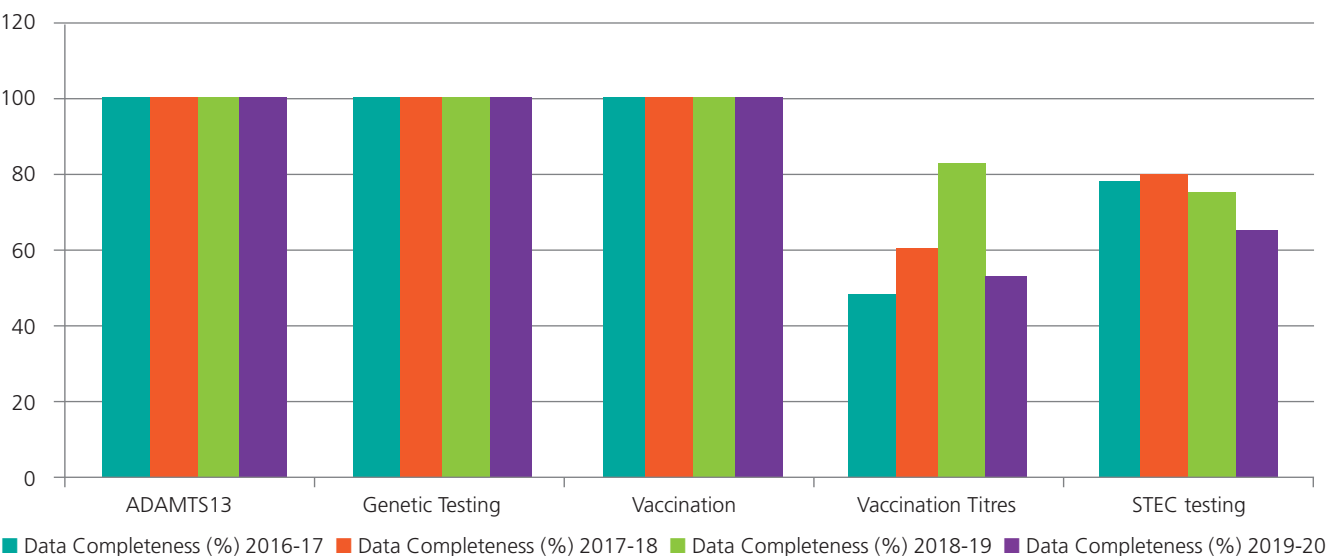
**90% data completeness in 5 audited domains**

Our key aims within this domain are to ensure that an accurate diagnosis of aHUS is made and to protect patients from treatment-related harm. A diagnostic checklist is forwarded to the referring clinician for completion to ensure data completeness. To ensure all relevant data is completed for patients commencing treatment, we have introduced a visual referral system which highlights what data is outstanding for the patient. Patients are regularly followed to review their outcome.

There are five categories of data we measure the standard of data completeness against for those patients approve for treatment:

- ADAMTS13 testing
- Genetic testing
- Vaccination against Meningococcal Infection
- Initial vaccination titres
- Shiga Toxin *E. Coli* (STEC) testing

The results of the data collected from patients requiring ADAMTS13 testing, genetic testing, vaccination, monitoring of vaccination response and STEC testing and are shown below. We had 100% data collection in 3 domains and <90% in two domains (STEC-testing and initial vaccination titres).



**Data completeness of the aHUS register.** Performance has been measured against 5 categories of data and compared with the previous reporting period on all patients treated. Data for genetic testing, vaccination and ADAMTS13 was above the 90% quality standard. Vaccination titres and STEC testing are routinely requested and compliance remains less than 90%.



### ADAMTS13 Testing

TTP was reliably excluded in all patients prior to commencing eculizumab.

### Genetic Testing

All patients receiving Eculizumab had testing to determine ensure they were not eculizumab non-responders. Additionally, all patients referred to the service were offered genetic testing to help make a genetic diagnosis.

### Meningococcal Prevention (Vaccination and Vaccination Titres)

All patients who commenced treatment received meningococcal vaccination (ACWY and BEXSERO).

Our specialist nurses follow up with individual clinicians and highlight the importance of vaccination titres in patients who remain on treatment with eculizumab when vaccination titres are due. We continue to use a bespoke laboratory form for measurement of meningococcal vaccination titres that is available from our website to allow easy accessibility to the Manchester lab.

However we continue to have issues obtaining titres at the level of the clinician and/or the patient that will need addressing.

### STEC Testing

Investigations to detect STEC can help ensure patients with STEC-HUS (self-resolving condition) are not subjected to potentially life-long eculizumab treatment.

The compliance with STEC testing remains sub-optimal. However, all patients that remain on eculizumab have a clear indication for ongoing treatment.

### Summary of our previous implementation in this domain

- Engagement with experts in the field (Professor Ray Borrow [National Meningococcal reference laboratory] and Dr. Claire Jenkins [National Gastrointestinal Bacterial Reference Unit] to ensure up-to-date recommendations are used in our referral pathway.
- During this reporting year, the NRCTC attended a workshop with colleagues from PHE and local Health Protection Teams to highlight the crucial importance of STEC testing, leading to a publication (Jenkins et al 2020) and support for the roll-out of regional Gastrointestinal PCR (GI-PCR) testing for STEC.
- NRCTC links directly with Public Health England laboratories and referring teams to ensure streamlined approach to requesting testing to monitor vaccination response and to detect STEC.
- Ongoing shared care between NRCTC and local team to confirm diagnosis and optimal treatment plan
- Work with NHS England to improve compliance with nationally agreed shared care protocols

## Outpatients Clinics

Outpatient Clinics were commenced in 2017; each patient is offered a minimum one hour appointment which may be increased to accommodate other family members. Over a hundred patients had either an out-patient appointment at the NRCTC, or a telephone consultation during the period 2019-20. During the consultation, patients are provided with a personalised description of their disease and the opportunity to ask specific questions they may have. Our patients are also informed about research, including clinical trials which may benefit them. We also discuss risk of disease in family members and ensure all have access to genetic predictive testing.



# 4. Achievement of Performance Targets

The results compiled in this report are for a complete financial year and encompass the activity of the National aHUS Service from the 1st April 2019 to 31st March 2020. The performance targets are summarised below.

Quality Requirement	Threshold	Percentage achieved
<b>Domain 1: Preventing people dying prematurely</b>		
Zero avoidable deaths in patients with a diagnosis of complement mediated aHUS (as per current diagnostic criteria)	Zero avoidable deaths	Zero avoidable deaths
<b>Domain 2: Enhancing the quality of life of people with long-term conditions</b>		
All patients with aHUS who are eligible for renal transplant will be listed for transplant	100% of patients on transplant waiting list	100%
<b>Domain 3: Helping people to recover from episodes of ill-health or following injury</b>		
To provide advice to provider centres within 24 hours of request on treatment	90%	100
Written protocols agreed with units	100%	89%
<b>Domain 4: Ensuring that people have a positive experience of care</b>		
Achieve 90% data completeness of the of the aHUS register to which referring units are mandated to supply data	90%	90%

**National aHUS Service – Performance during reporting period from 1st April 2019 until 31st March 2020.**  
Performance targets for all domains were met

# 5. Improving the Patient Experience

## 5.1 Impact of COVID-19

Towards the end of the reporting period of this report, a global pandemic was declared following the emergence of the SARS-COV2 virus and the disease COVID-19. During this difficult and uncertain time, patients and their carers were understandably concerned about the possible impact of this illness on the risk of aHUS and whether or not they were at greater risk due to eculizumab. This resulted in enquiries from patients and clinicians about the management of aHUS.

We were able to reassure patients and their carers with the latest advice, including our recommendation to continue with regular eculizumab as per the usual dosing schedules. Advice was summarised (and updated in accordance with national guidance) on social media via our twitter page and on our website as soon as it was available.



**Is it safe to go to school / work?**

**I am receiving eculizumab - am I at increased of COVID?**

**Could COVID symptoms mirror a relapse of an aHUS episode?**

**Are there any special precautions we should take over and above government guidance?**

## 5.2 Patient information

### Patient Roadshows

We have held roadshows in Durham, Manchester, Bristol, London and Birmingham since their inception in March 2018. Each has been met with growing popularity as well as a growing range of topics that have included pregnancy, meningococcal risk and the 'SETS' eculizumab withdrawal trial. Feedback from the roadshows has been positive, with patients and their families enjoyed talking to the team in an informal setting, listening to the team deliver presentations about their disease and meeting other patients.

At time of writing, we recognise the impact of COVID-19 and have a webinar planned in Autumn 2020 to take place instead of a roadshow.



## Newsletters

We continue to provide information about our service in our newsletters. We have also started a C3G newsletter. These are sent out to patients that have been referred to us and are shared on social media. They are also available to download on our website.

## Patient Pathway

As part of the pathway for patients with aHUS, our specialist nurses are usually the first members of the team to engage directly with patients referred to the NRCTC. They make the initial introductions to patients usually by letter or telephone call before sharing some of the NRCTC patient information that is part of our handheld records (separate record for children and adults), at-risk cards and alert wristbands.



**Regular newsletters are sent to patients known to the NRCTC and are available to download directly from our website**



**Screenshot from the website of the National Renal Complement Therapeutics Centre** depicting our videos that showcase aHUS and STEC-HUS disease mechanisms and treatment. The website also provides information for patients and their clinicians and also the referral pathway for Eculizumab [[www.atypicalhus.co.uk](http://www.atypicalhus.co.uk)].

## World Kidney Day 2020

This year World Kidney Day was on Thursday 12th March and this year's campaign slogan was 'The Big Topic Everyone's Ignoring #kidneysmatter'. Nicola and Lisa took part in an event locally designed to raise awareness of kidney disease and the multitude of services available.

## Online NRCTC

One of our key remits is to provide high quality advice to patients and clinicians about aHUS and C3G. Our website (<http://www.atypicalhus.co.uk/>) provides a professional hub of information and advice for patients and clinicians. For our patients, all of our previous news and events can be viewed, as well as videos to explain about aHUS and STEC-HUS. We also have a presence on social media on Twitter (@NationalaHUS and @NationalC3G) and hope to support patients via a Facebook group in the near future.

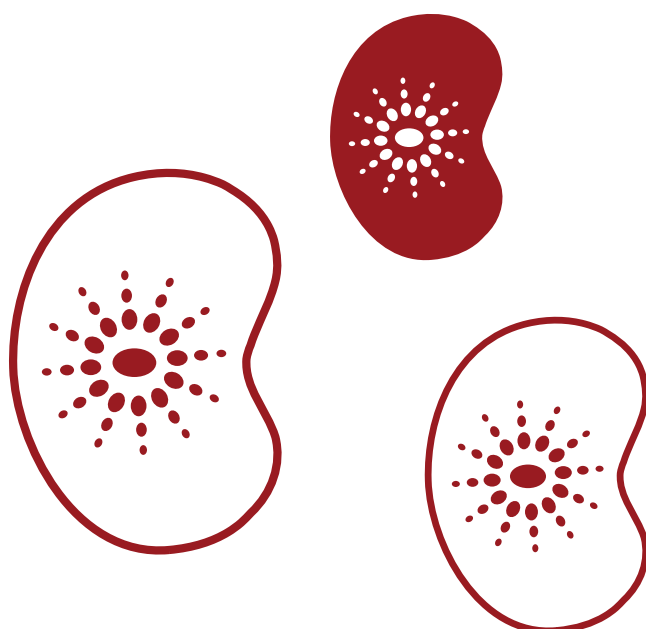
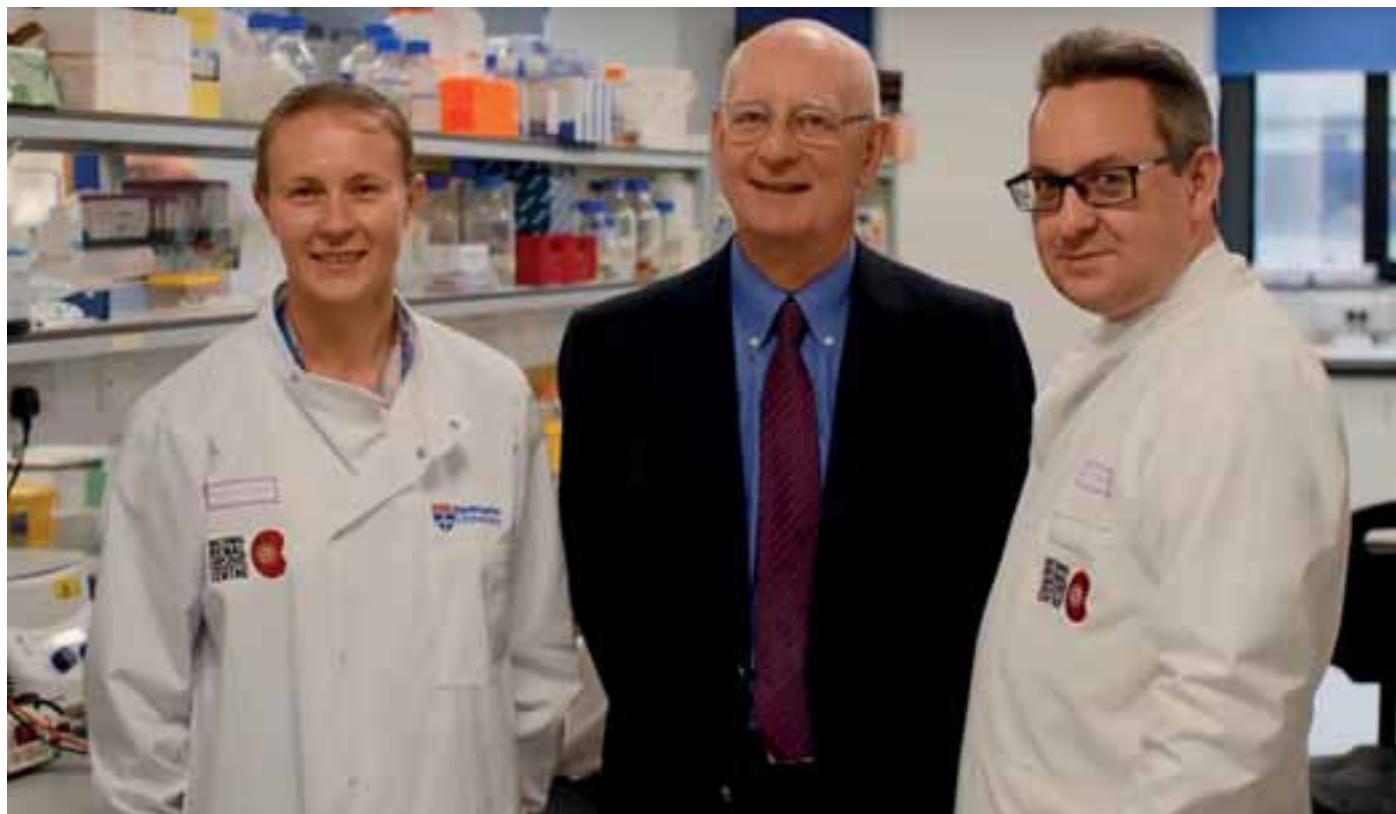
For clinicians the website continues to serve as a portal to access our full range of services as well as providing an up to date summary of complement mediated renal diseases and their treatments. An emergency referrals page (<http://www.atypicalhus.co.uk/emergency-referrals/>) highlights a 24 hour 7 day a week consultant led on call service. It provides a repository for clinicians to download diagnostic checklists, combined laboratory investigation forms including meningococcal and STEC request forms, as well as our shared care protocol.



### 5.3 Kidney Research UK

Kidney research UK has funded much of the ground-breaking research carried out at the NRCTC which ultimately led to a treatment for AHUS.

To celebrate the impact of the NRCTC's charity-funded research, Kidney Research UK commissioned a film demonstrating how genetic research changed the future for people with aHUS. The film, which featured three generations of charity-funded researchers at the NRCTC premiered in June 2019 at the annual conference of the Renal Association – UK Kidney Week, and won the People's Choice film of the year at the Charity Film awards .



# 6. NRCTC Key Recommendations

Subsequent to the review of our activity in 2019/20 and in light of the COVID-19 pandemic, the NRCTC have outlined key objectives for 2020/21 in the following domains:

## Clinical service

We will increase our use of remote technologies to deliver our clinical service, with a focus on specialist nurse-led patient consultations.

## Patient engagement

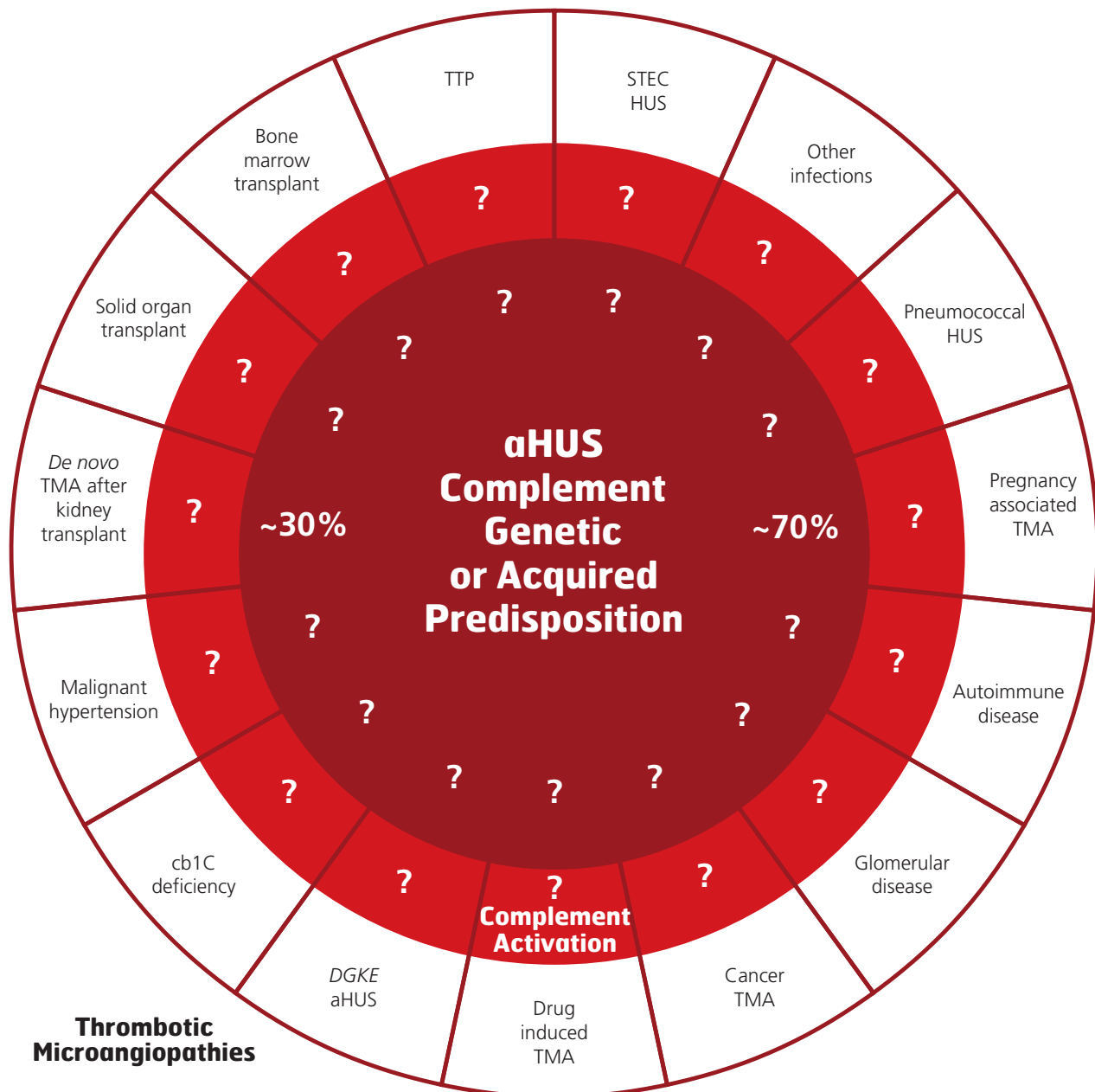
We will use remote technologies to reach a wider range of patients and ensure that their needs remain at the centre of our service.

## Clinical research

We will continue to improve optimal diagnostic and treatment pathways for patients referred to us through audit and research programmes that are embedded within the NRCTC.



# 7. Complement Research at the NRCTC



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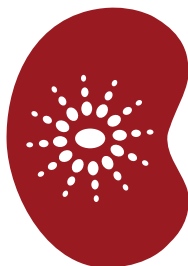
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