Haemochromatosis

Special Interest Group

13th June 2024

BRITISH SOCIETY OF GASTROENTEROLOGY

British Association for the Study of the Liver

1960–2020

British Society for Haematology

Listening • Learning • Leading

Haemochromatosis – SIG

Agenda

1. Introduction
2. Updates
   a. Blood sciences – ferritin assays – Sophie Paskauskas
3. Venesection
   a. BASL Venesection survey – Simran Singh
   b. The use of NHS B&T donor services – Lianwea Chia and colleagues
   c. Venesection best practice guidance
   d. Approach to the suspension of unnecessary venesection – a proposal
   e. Venesection trial plan - update
4. Sub-group updates
5. AOB
6. Date of next meeting – Thursday 5th September 2024

An Audit for the Provision of Biochemical Markers of Iron Overload and HFE Mutation Analysis.

Sophie Paskauskas

EASL recommendation for investigation of haemocromatosis

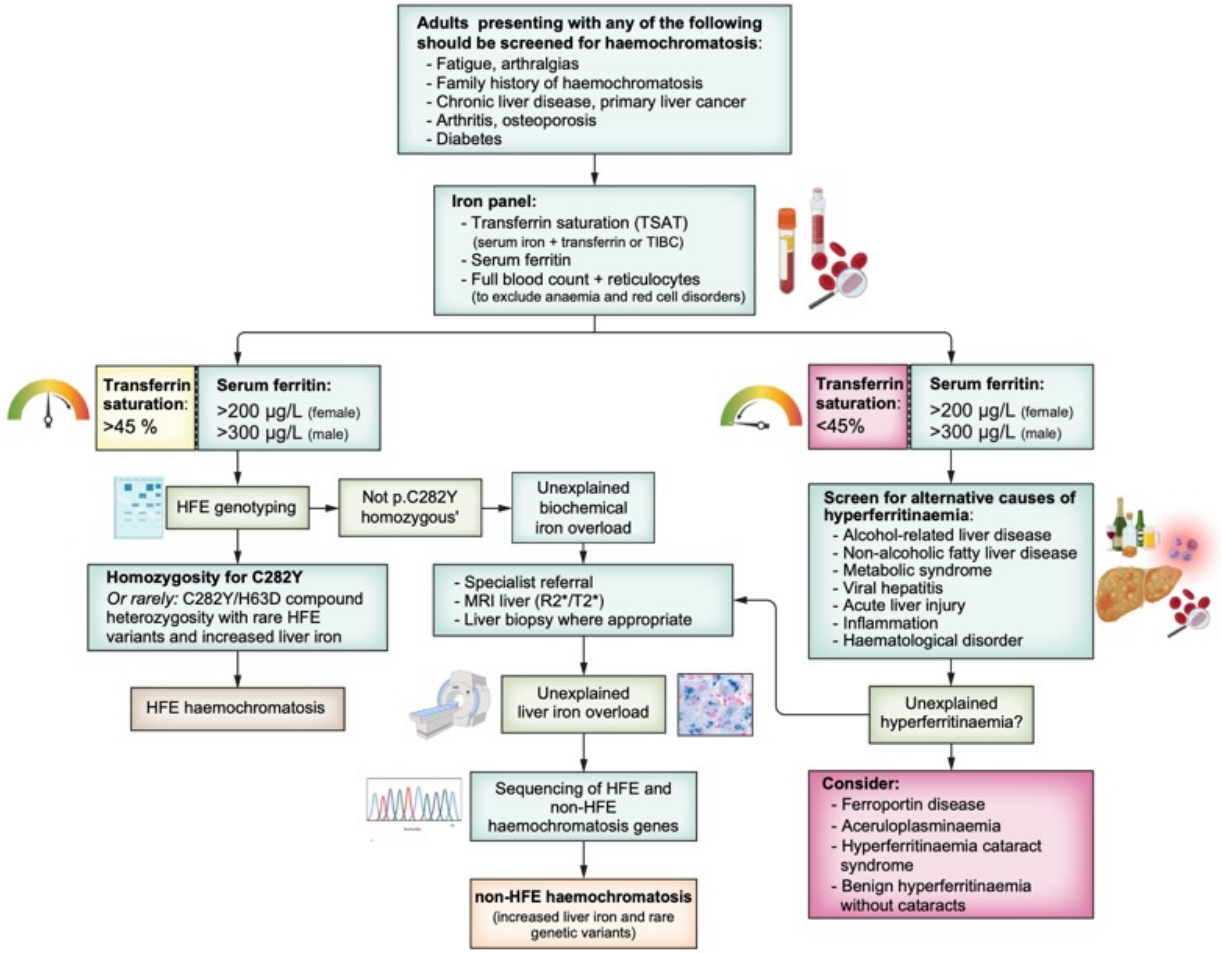


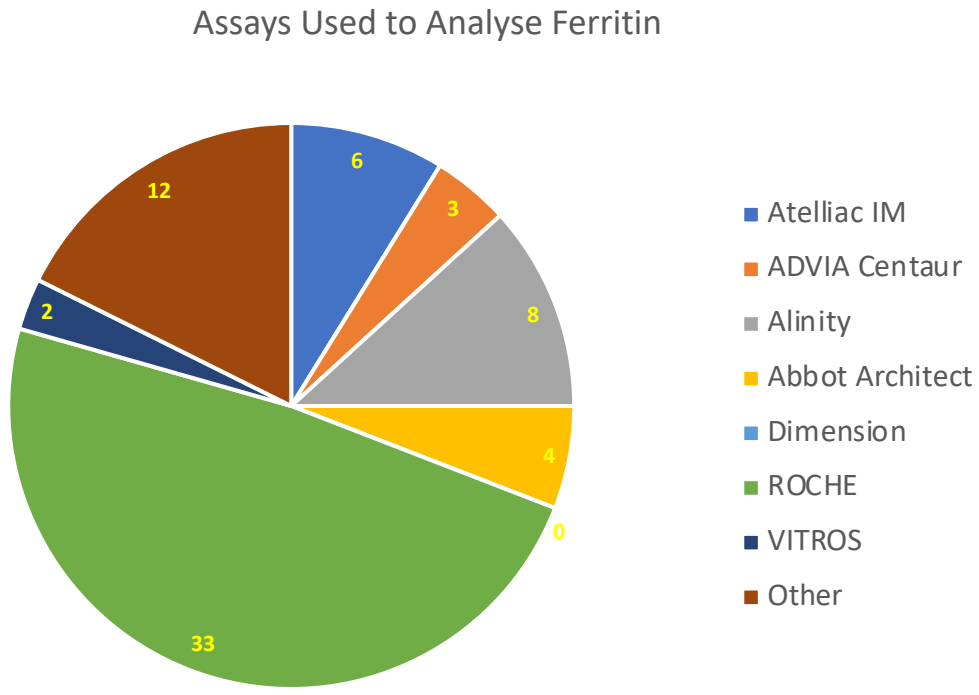
Fig. 3. Algorithm for the diagnostic approach to patients with hyperferritinemia and suspected haemochromatosis. In patients of non-European origin with clinical suspicion of haemochromatosis and elevated transferrin saturation and ferritin, the pre-test likelihood for detecting the p.Cys282Tyr variant in HFE is very low. Therefore, in individuals of non-European origin, direct sequencing of HFE and non-HFE genes may be considered without HFE genotyping. Non-HFE gene sequencing should encompass a panel of genes including *HFE, HJV, TFR2, CP* and *SLC40A1*. TIBC, total iron binding capacity.

Audit Summary

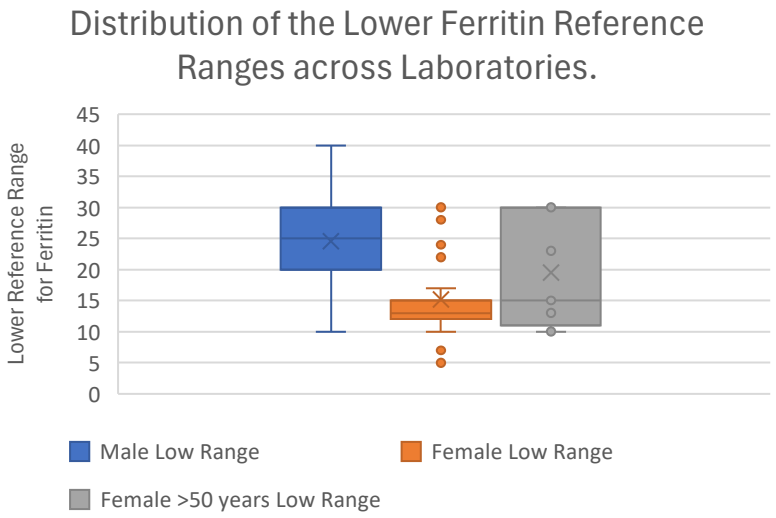
- General – assays, reference ranges.
- Ordering and Reporting of Tests – iron overload panels, transferrin saturation, HFE testing, and consent.
- Analytical Testing of Samples – Accreditation and EQA, HFE result comments, training, hyperferritinemia.
- Interpretation and Reporting of Results – interpretive guidance, monitoring HH patients.

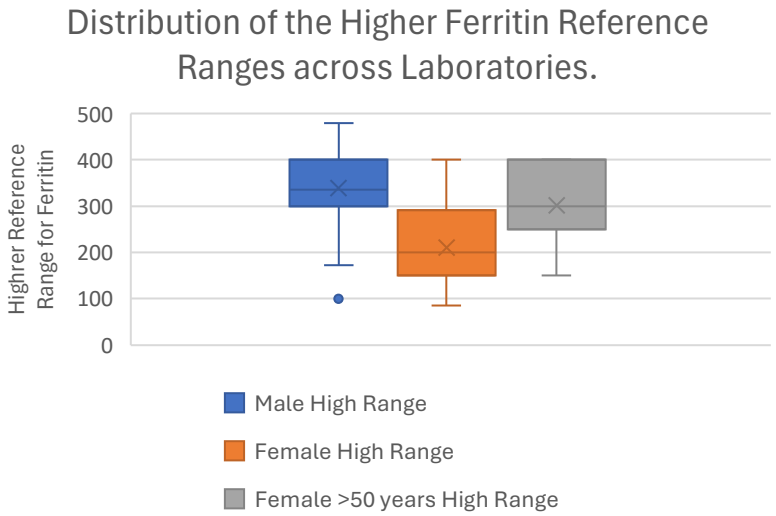
What assays/platforms are used for ferritin?

- Roche was the main assay used in Ferritin analysis across laboratories.
- Dimension was not used by any of the labs who responded.
- Various Beckman assays were listed in other.



Adult serum ferritin reference ranges.



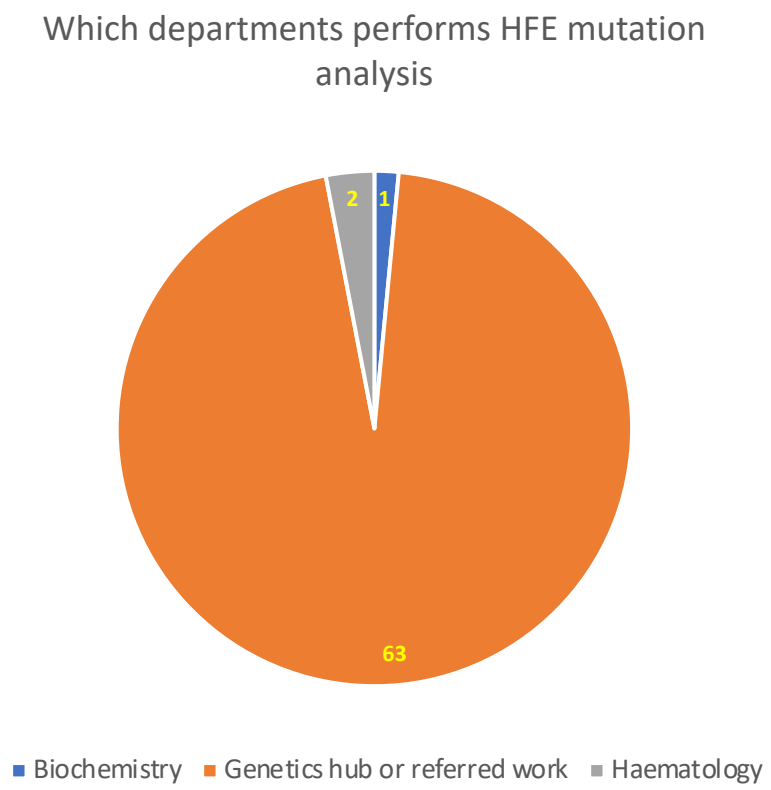


There appeared to be a little consistency across laboratories for ferritin reference ranges.

Ferritin Reference Ranges	Range for Lower Reference Value	Range for Higher Reference Value	Mean Lower Reference	Mean Higher Reference
Males	10-40	100-480	24.5	339.5
Females	5-30	50-400	15.1	210.1
Females >50 years	10-30	150-400	19.5	302.2

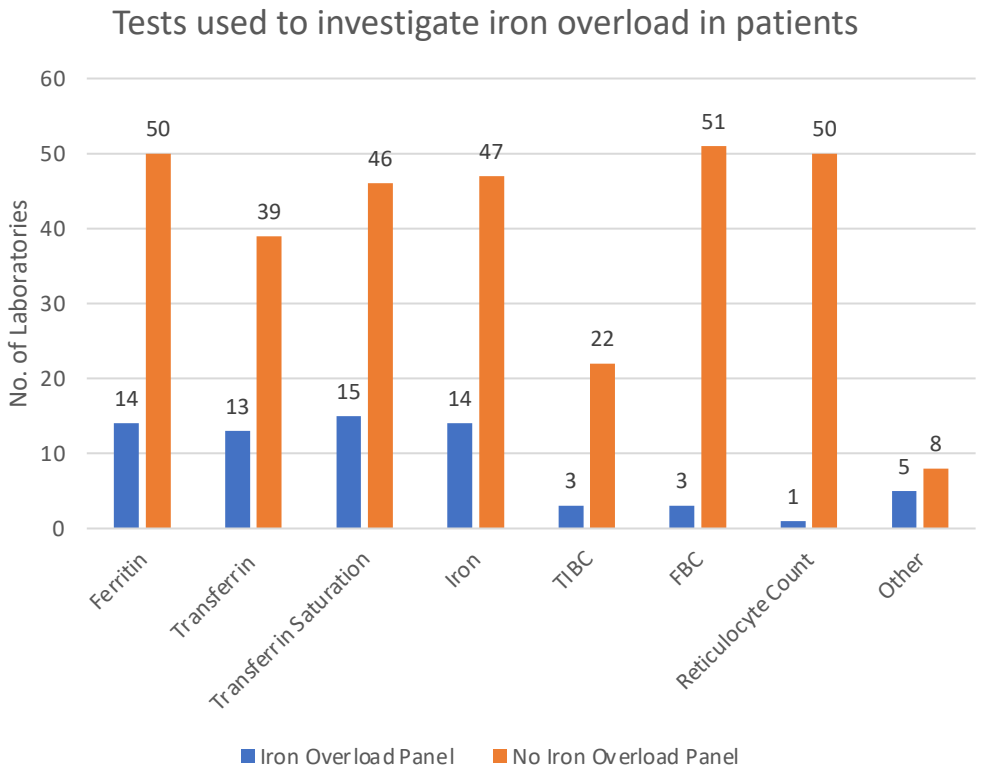
Who performs HFE mutation analysis?

- Most laboratories sent their HFE mutation samples away to a genetics hub or referral lab for testing.
- With only 3 labs performing HFE mutation analysis within Haematology or Biochemistry.



Iron Overload Test Panel

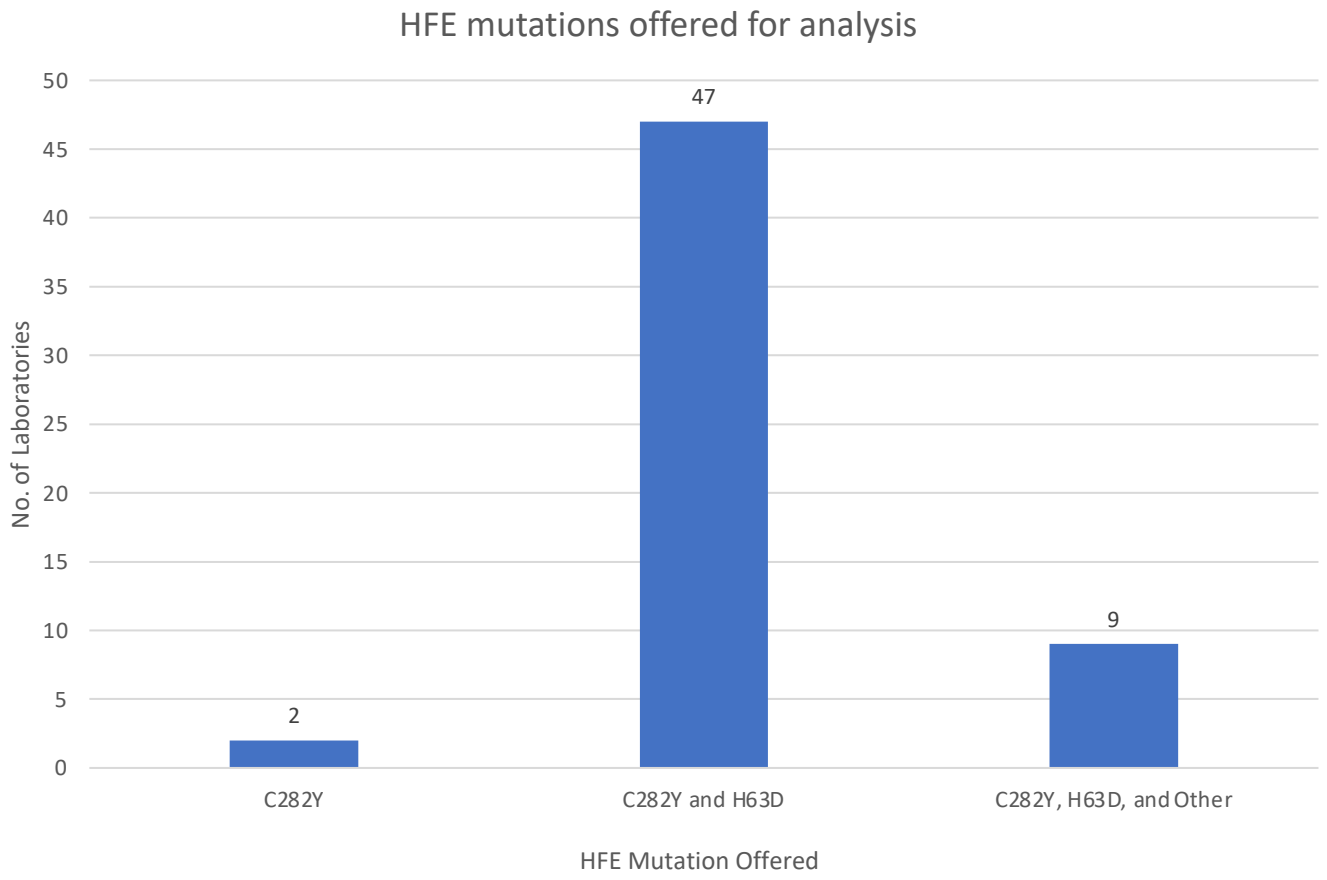
- Around 75% of labs did not offer an iron overload panel, however, individual tests were available for requesting.
- The majority used ferritin, transferrin, TS and Iron in the Iron Overload panel.
- Other: iron studies panel, Haemochromatosis panel, HFE gene, LFT, UE, and CRP.



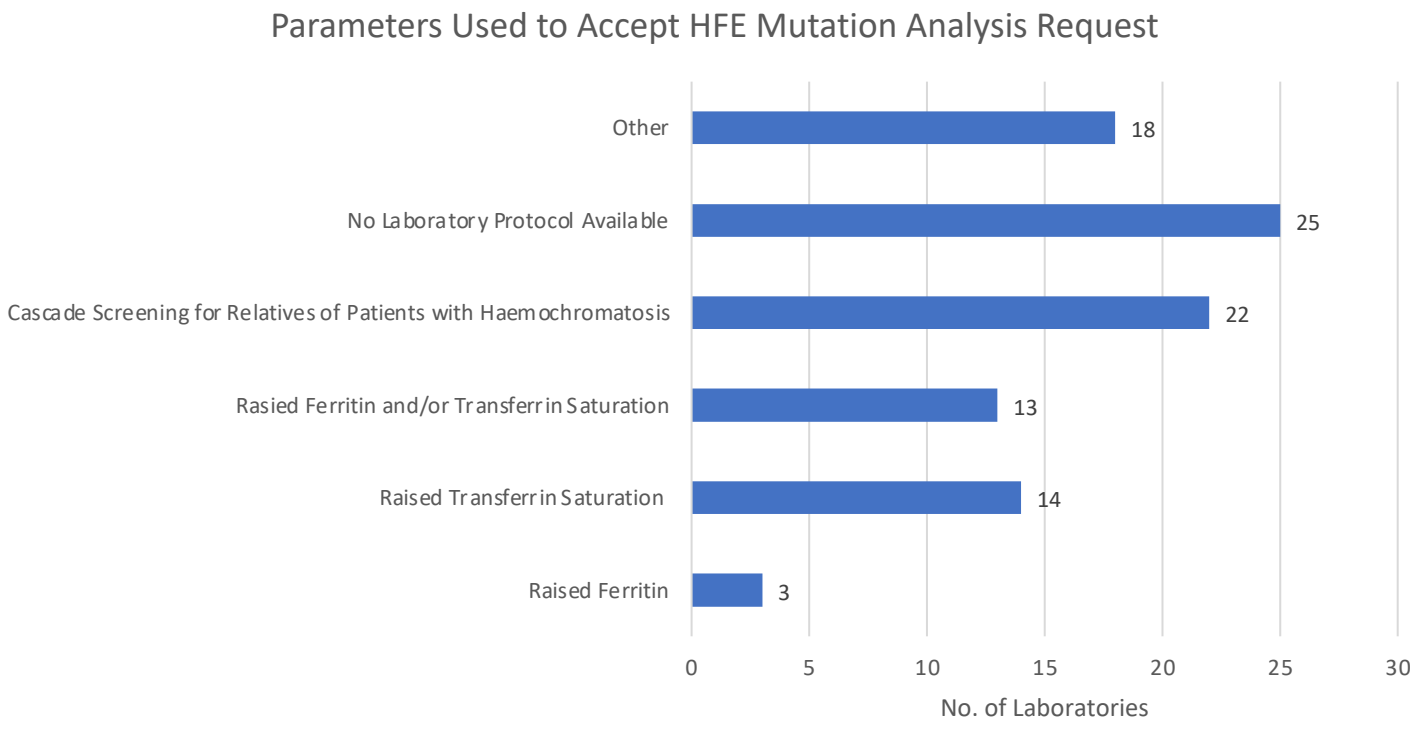
HFE Mutations Offered

Other mutation responses consisted of–

- R96 for Iron metabolism disorders - not common HFE Mutations,
- S65C,
- dependant on the referral laboratory.
- 81% of labs offered C282Y & H63D mutations for analysis.



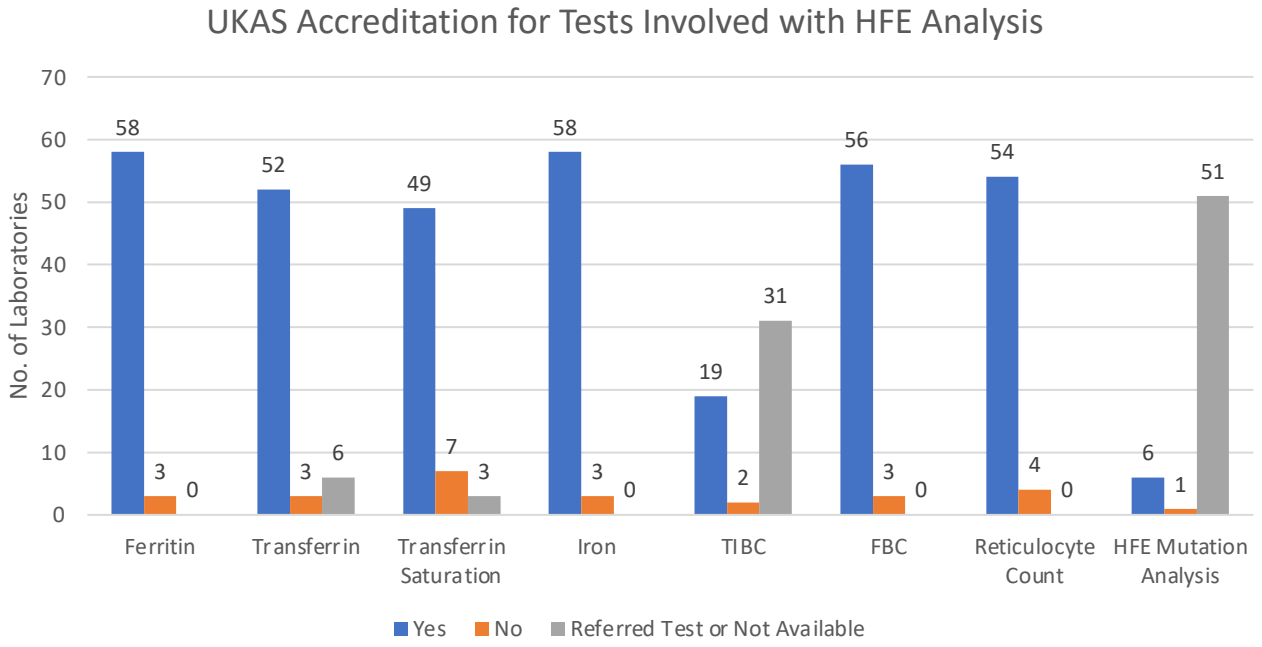
Parameters for Acceptance



- Other: did not vet, dependant on the requesting location, referred to local guidelines, reviewed by haematology medical staff or consultant haematologist and rejected if there was a previous HFE result.
- Less than 7% of labs having protocol for reflex testing.

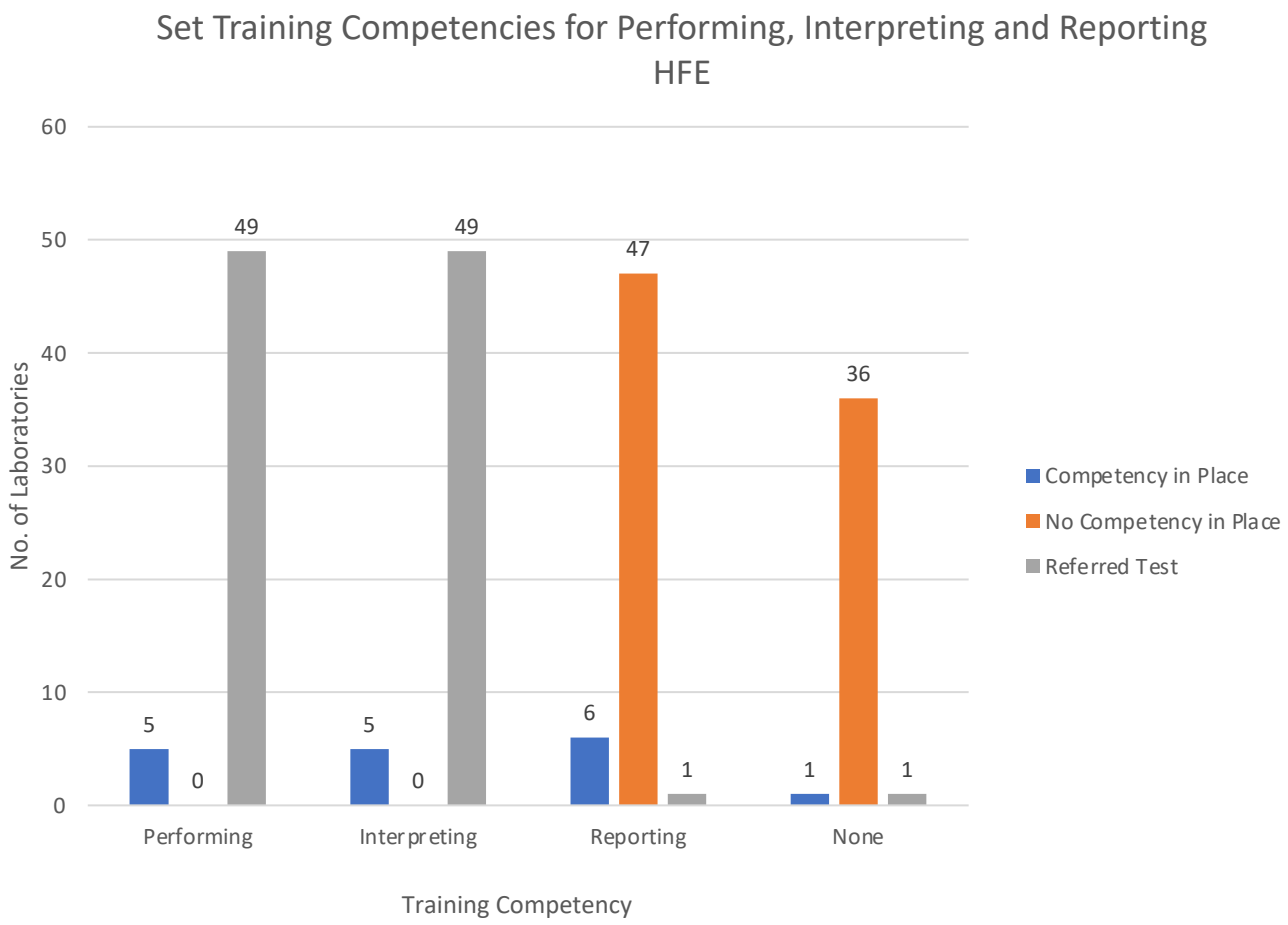
UKAS Accreditation

- Most labs had UKAS Accreditation for the tests provided.
- However, there were still some without accreditation.

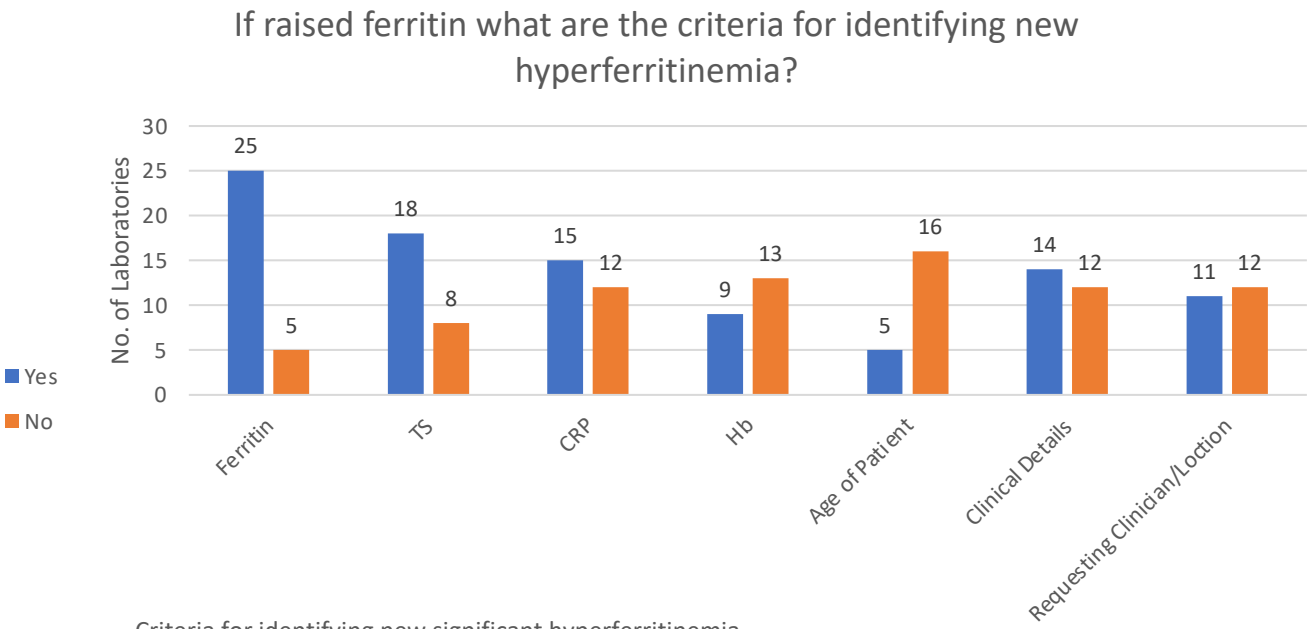


Training Competencies

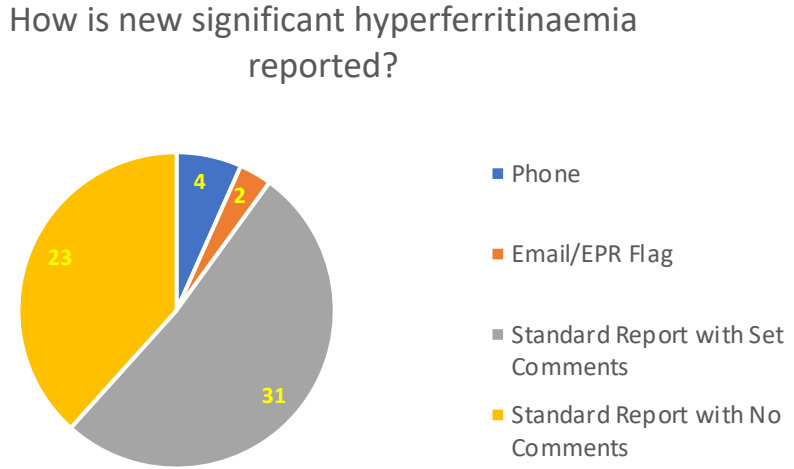
- As most labs refer there HFE work it for performing and interpreting HFE analysis.
- The majority of labs had no reporting competencies in place or none in place at all 3.



Identifying new hyperferritinemia



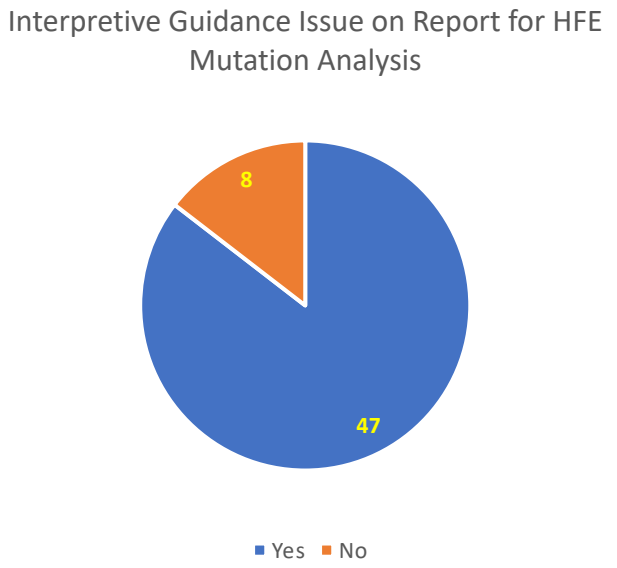
Criteria for identifying new significant hyperferritinemia.

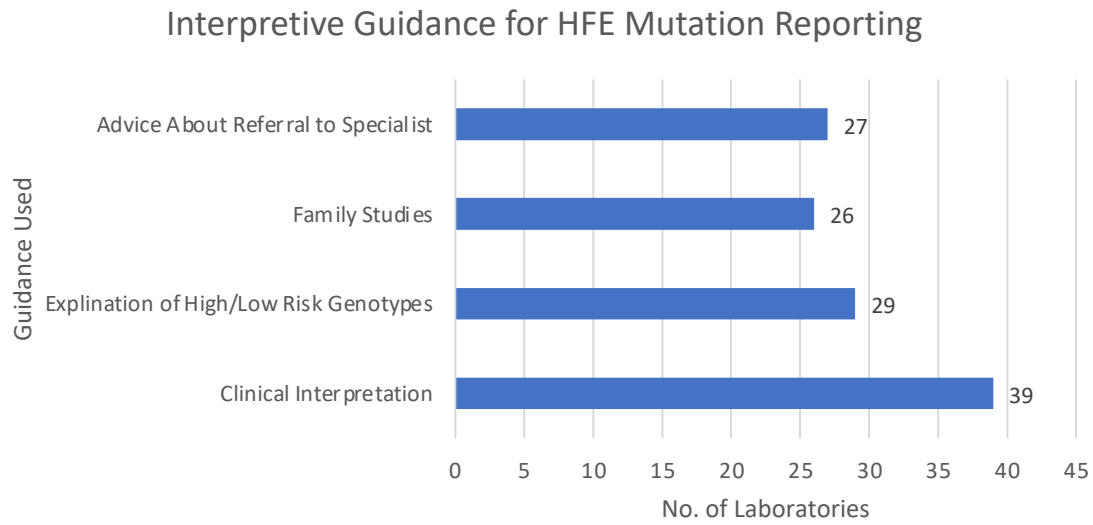


- The response was varying for the criteria used
- Ferritin and transferrin saturation identified as the main criteria for most labs

- New significant hyperferritinemia tends to be reported via a standard report with around 50% of labs including set comments.

Interpretive Guidance

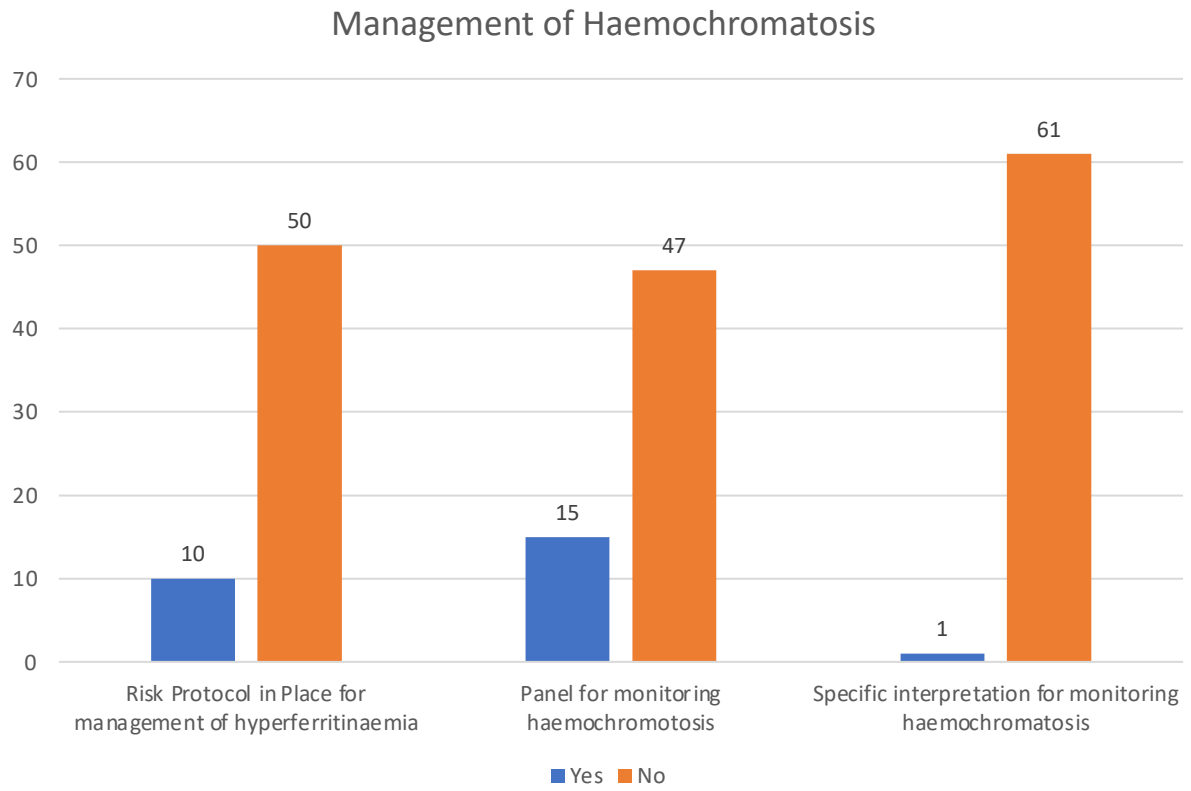




- 85% of labs offer interpretive guidance on their reports for HFE mutation analysis.
- Varied response to the type of guidance used.

Management of Haemochromatosis

- Most labs did not to have a management protocol in place for haemochromatosis patients or hyperferritinemia.



Conclusions

- Variation between labs shows a lack of standardisation throughout the process of HFE testing.
- Showed a lack in protocol for monitoring of HH patients.
- Improved training to be put in place.
- This audit has highlighted the areas need addressing across labs for future practice and the need for improved HFE guidance.

Venesection

The current provision of venesection treatment for haemochromatosis patients in the United Kingdom

Dr Prabhsimran Singh
Dr Gerri Mortimore
Dr Jeremy Shearman

Background

- NCEPOD topic proposal initially

Prevalence of HFE–related haemochromatosis and secondary causes of hyperferritinaemia and their association with iron overload in 1059 French patients treated by venesection

Gérald Le Gac [1] [2], Virginie Scotet [1], Isabelle Gourlaouen [1] [2], Carine L'Hostis [1], Marie-Christine Merour [1], Zoubida Karim [2], Yves Deugnier [3], Edouard Bardou-Jacquet [3], Thibaud Lefebvre [2], Suzanne Assari [4], Claude Ferec [1]

Results: Only 258 of the 488 patients referred for haemochromatosis had the p.[Cys282Tyr]; [Cys282Tyr] disease causative genotype (adjusted prevalence: 24.4%). Of the 801 remaining patients, 112 (14.0%) had the debated p.[Cys282Tyr];[His63Asp] compound heterozygote genotype, 643 (80.3%) had central obesity, 475 (59.3%) had metabolic syndrome (MetS) and 93 (11.6%) were heavy drinkers. The non-haemochromatosis patients started therapeutic venesection 9 years later than

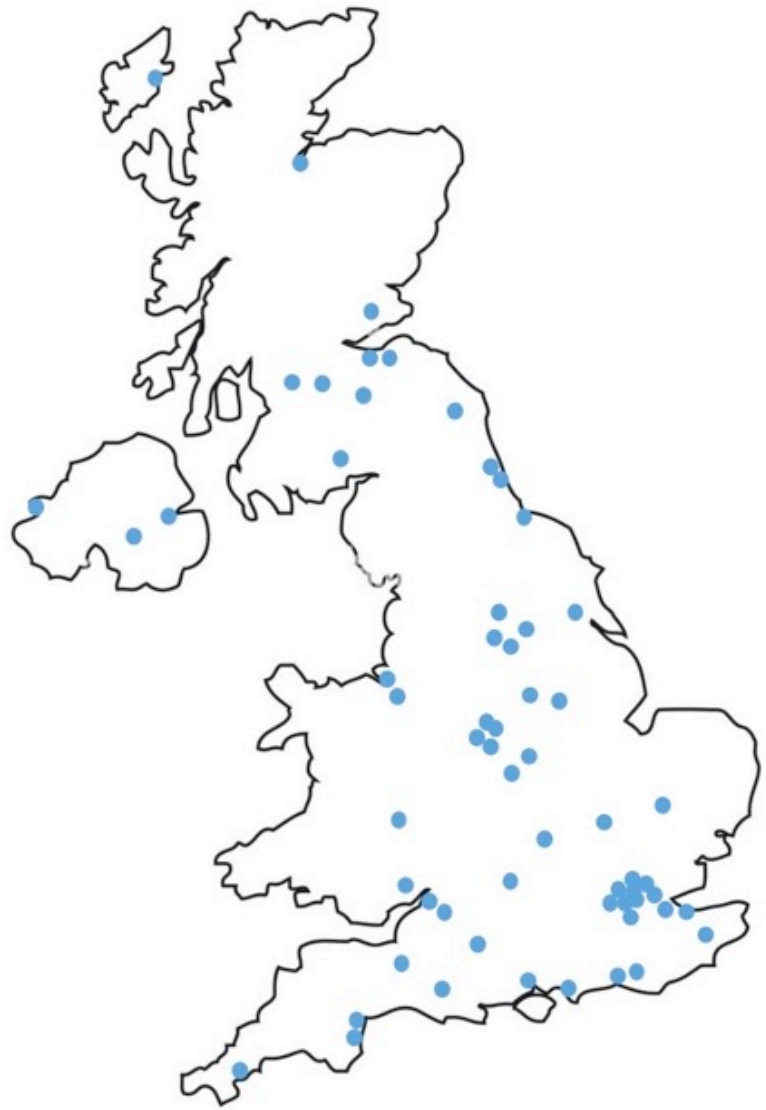
Methodology

- SurveyMonkey questionnaire
- Sent to all NHS Trusts/Health Boards in UK via NCEPOD & colleagues in NI/Scotland
- Survey open for a period of 4 weeks between May and June 2024

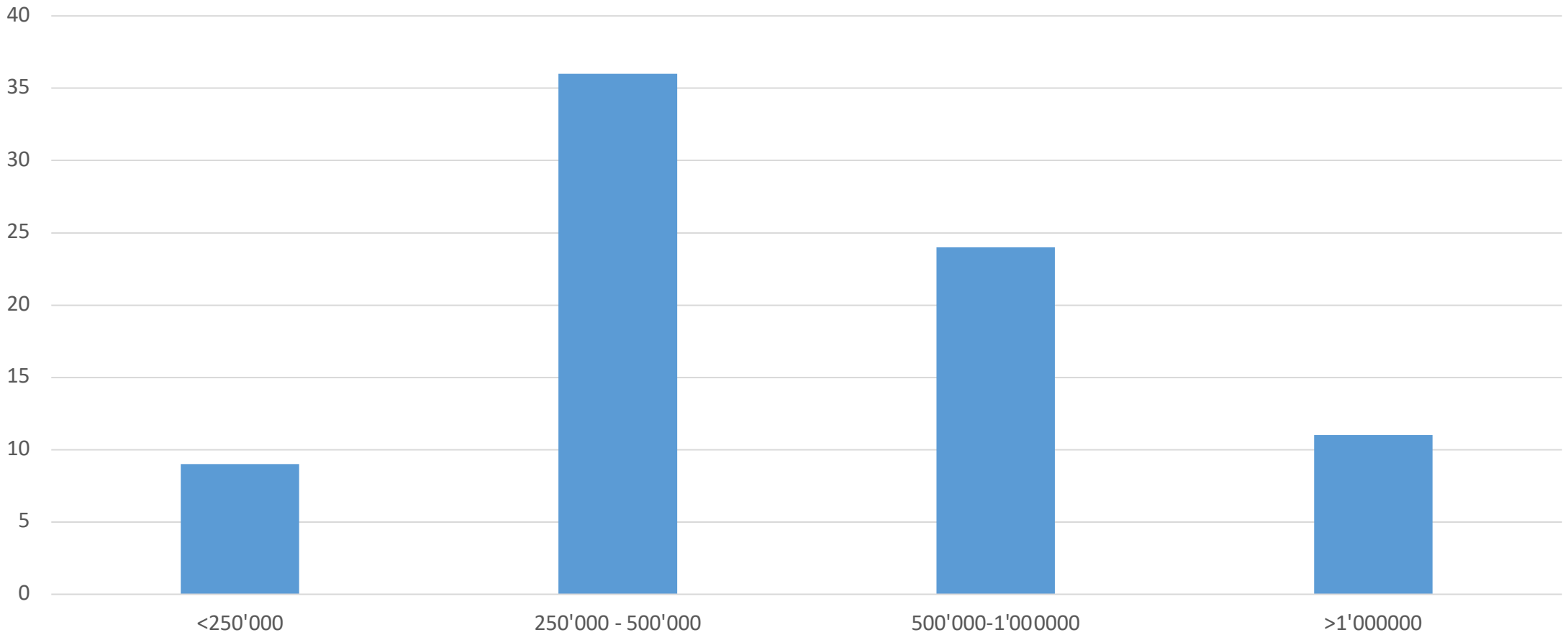
Responses

- Replies received from 59/142 NHS Trusts/Health Boards
  - Corresponding to 63 hospitals/organisations

- There are 142 Trusts in the UK that provide acute services excluding specialist hospitals (cancer centres, cardiac centres etc.)



Size of population served



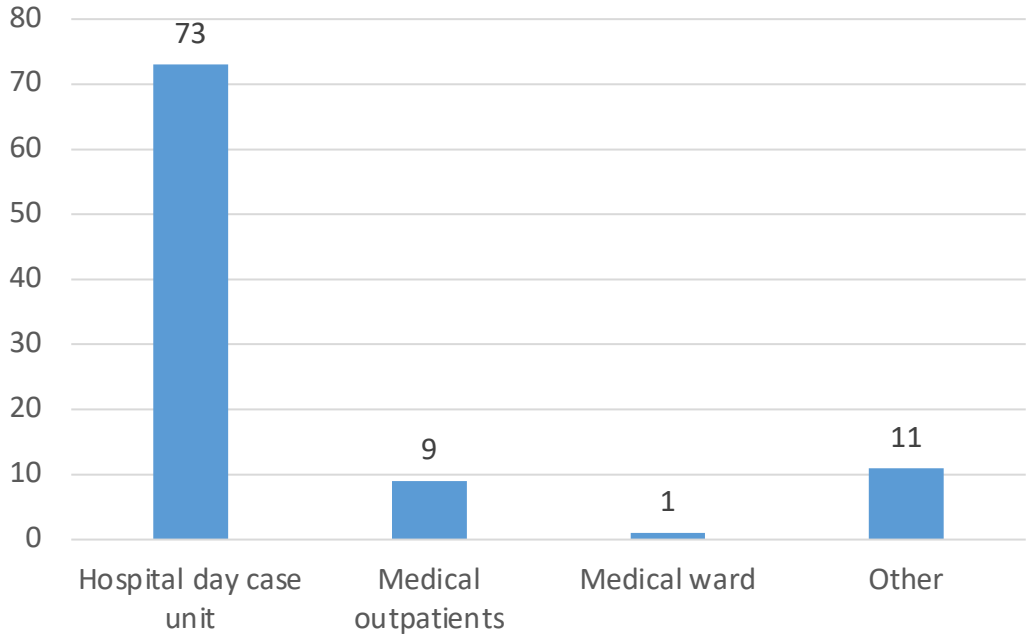
Service provided

- All acute Trusts that responded provide Venesection services

- Less than half (31/63) Trusts have a lead haemochromatosis consultant
  - In several Trusts clinical care led by CNS
  - Overlap between hepatology and haematology

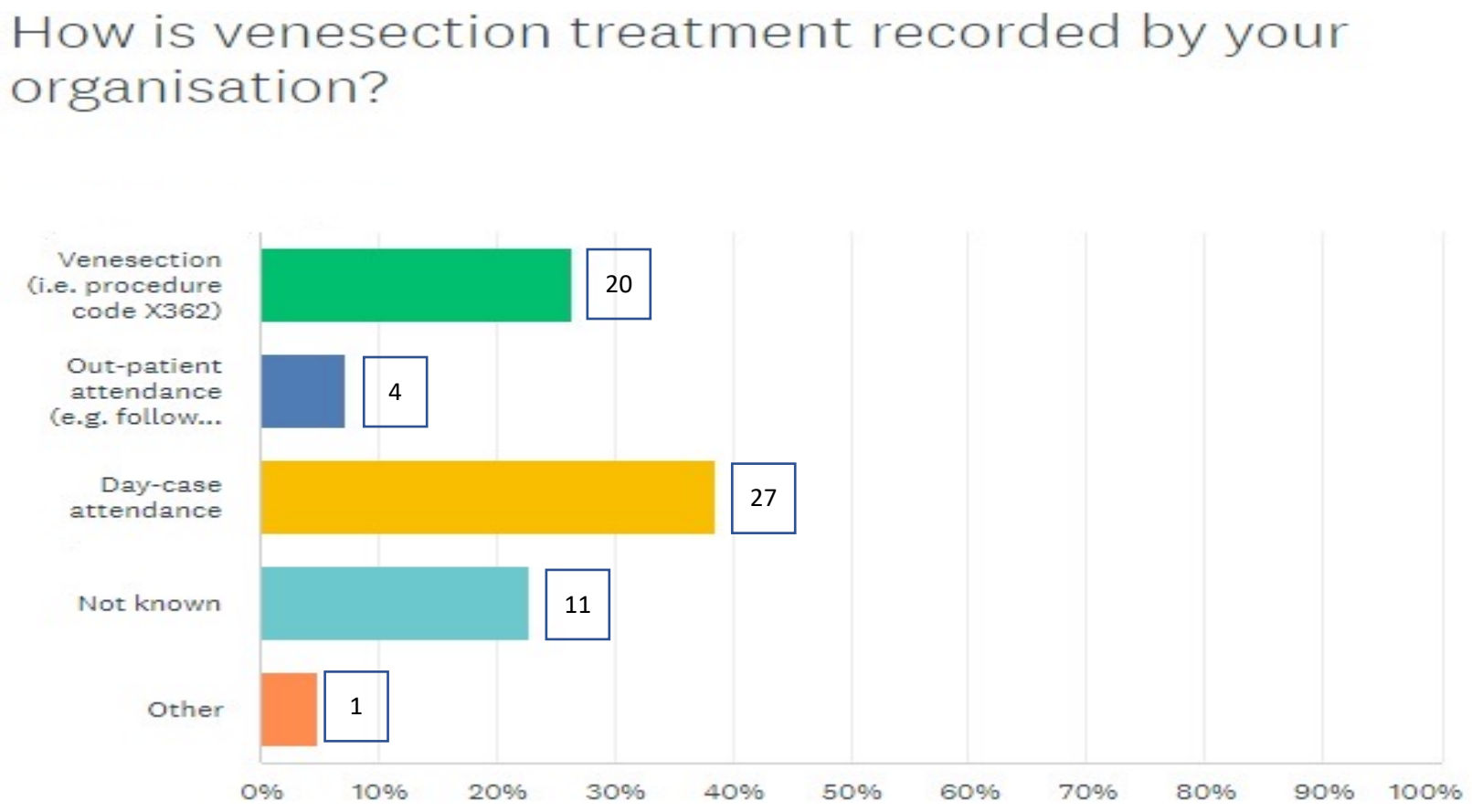
- Patients currently being treated in the UK ≈ 16000
  - 9 centres unable to provide data on exact/estimate number of patients undergoing Vs

Location of services



- Multiple sites have more than one place for Vs
- **Other includes:** GP surgeries in some rural areas and haem/oncology units

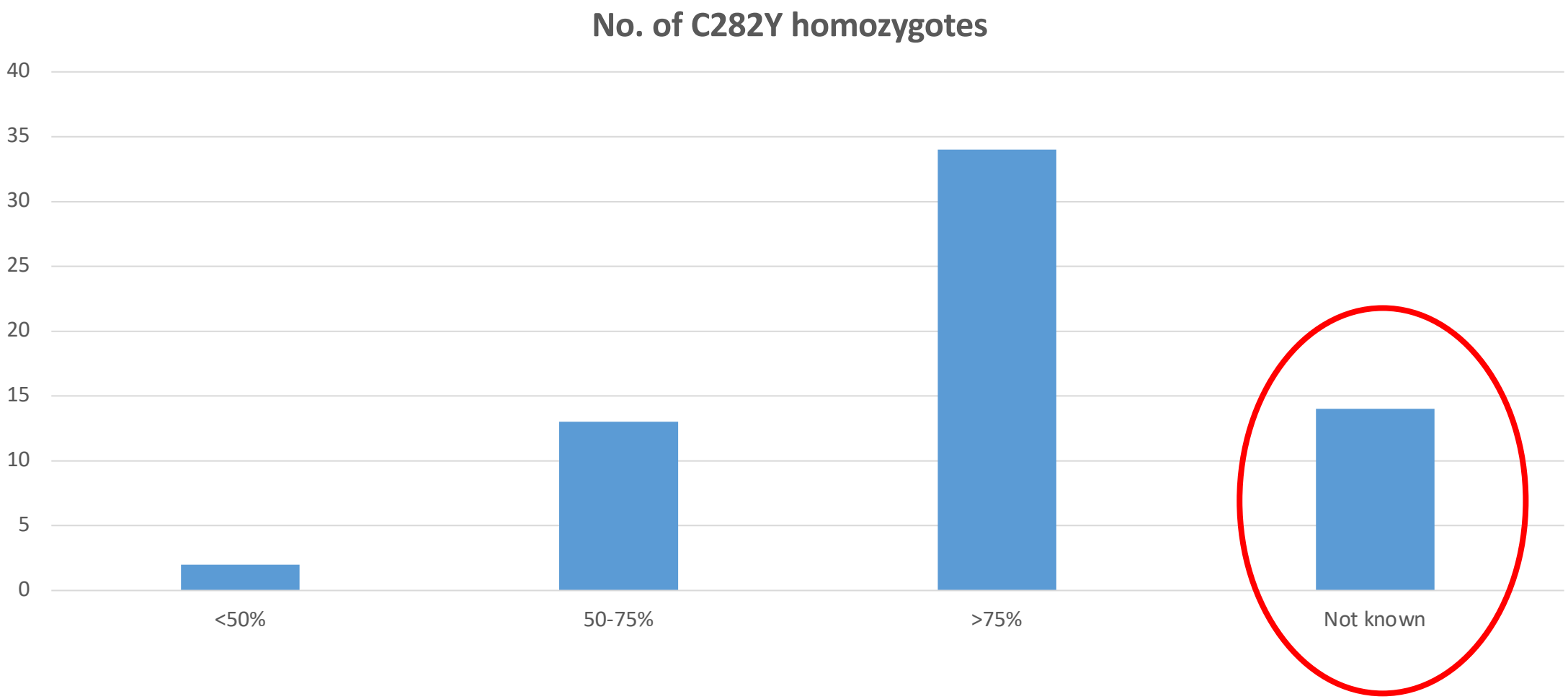
Recording of Vs treatment



Recording of Vs treatment

- Comments area provided useful info
  - Some units record day case attendance + coding (via discharge letter)
  - Many units have their own databases
  - Challenging to record in NI due to lack of payment by results

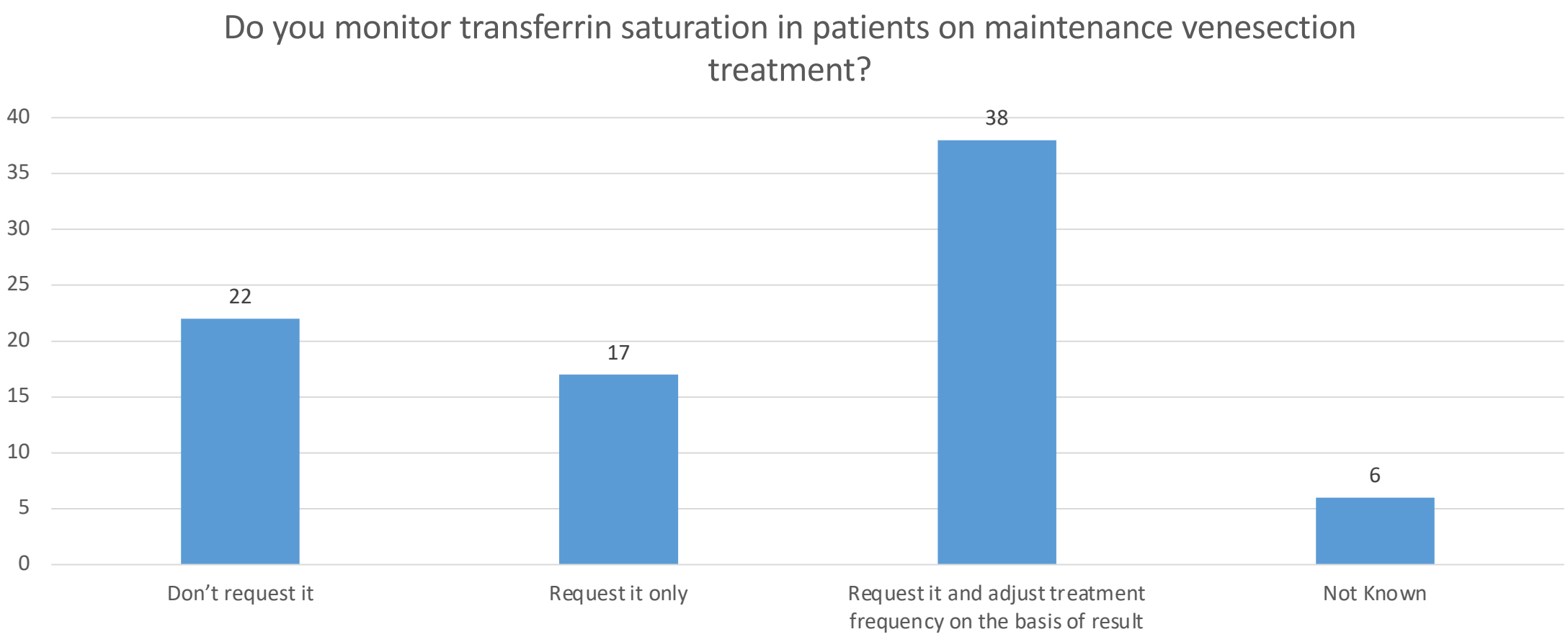
No. of C282Y patients



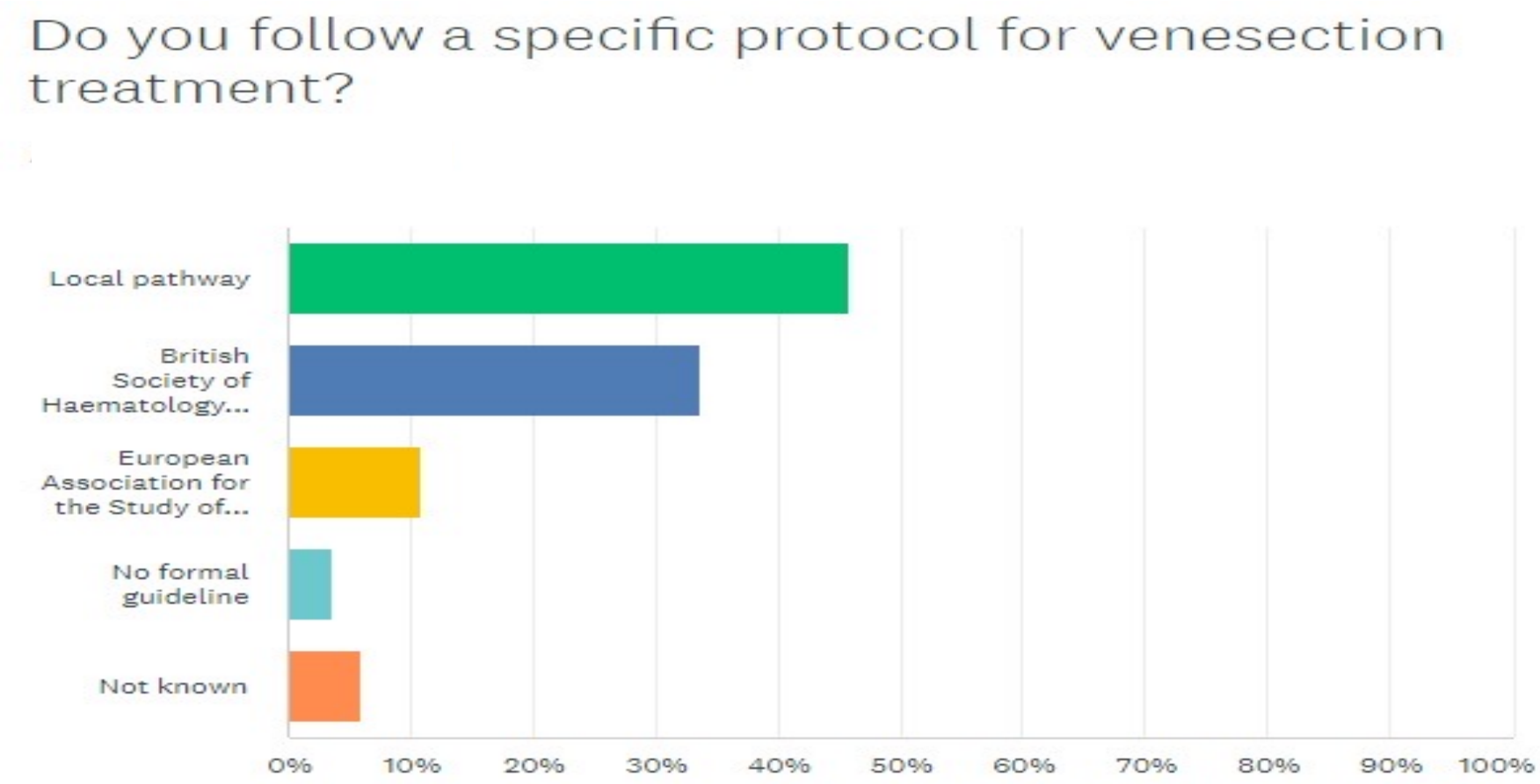
Serum ferritin targets

- **All respondents monitor serum ferritin with clear treatment targets**
  - Comments from several Trusts about using higher threshold in older/frailer patients
  - Some accept ‘normal’ SF in frail patients with x1 trust <300 if above 80
  - x1 Trust: ‘varies according to consultant’
  - Some Trusts aim <50 in patients who want/need better symptom control

Monitoring Tsats



Venesection guidelines



General themes from comments

- Struggle to access blood donation services for maintenance phase
- Challenges in service leading to monitoring and treatment frequencies not being adhered to i.e. changing targets
- Patients split between haematology and hepatology in some Trusts
- Follow up of patients following initial review increasingly nurse led in many Trusts

NHS Blood and Transplant

Genetic Haemochromatosis & Blood Donation

Dr Naim Akhtar, Dr Lianwea Chia, Prof Dave Roberts

NHSBT

Caring | Expert | Quality

Agenda

NHS Blood and Transplant

NHSBT approach to GH donors

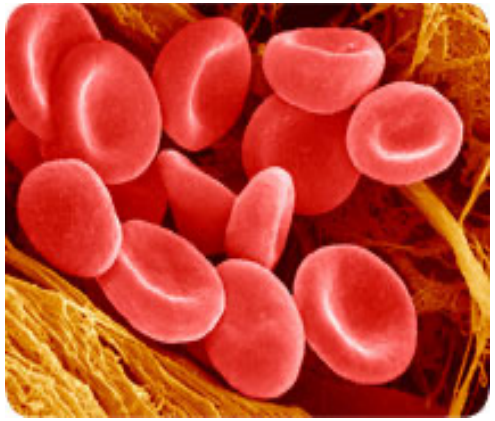
* Historically (prior to 2016)
* pandemic/post-pandemic changes
* open access

Future work

Induction of GH donors

NHS Blood and Transplant

- Referrals (self, specialist, GP), following de-ironing phase
- SP3 letter to donor, SP4 to specialist
- Information sheet (INF 935)
- Donor consent form (4058)
- Donation intervals (6 -12 w or > 12 w)
- Booking appointments
- Process issues
- Follow up



FRM 4058 (page 1)

FORM FRM4058/1 Effective: 01/10/12

Potential Blood Donor with Haemochromatosis

NHS Blood and Transplant (NHSBT)

Donor Agreement Form

	Please print
Name	
Address	
Date of birth	
Daytime contact telephone number	

How often do you want to donate? *Please tick*

Intervals **Less than 12 weeks** ☐ *(minimum of 6 weeks)* **12 weeks or more** ☐

I understand that NHS Blood and Transplant (NHSBT) collects blood for the benefit of patients.

I confirm that my haemochromatosis will continue to be the responsibility of my managing doctor.

I understand that in the event I am unable to donate blood regularly for whatever reason, then I will need to inform the doctor who manages my haemochromatosis.

I wish to become an NHSBT blood donor.

Signed .....

Date .....

PLEASE COMPLETE AND SEND OR GIVE FORM TO DOCTOR WHO MANAGES YOUR HAEMOCHROMATOSIS FOR COMPLETION OF FORM OVERLEAF

(Template Version 07/10/08)

Cross-Referenced in Primary Document: MPD740 Page 1 of 2

NHS Blood and Transplant

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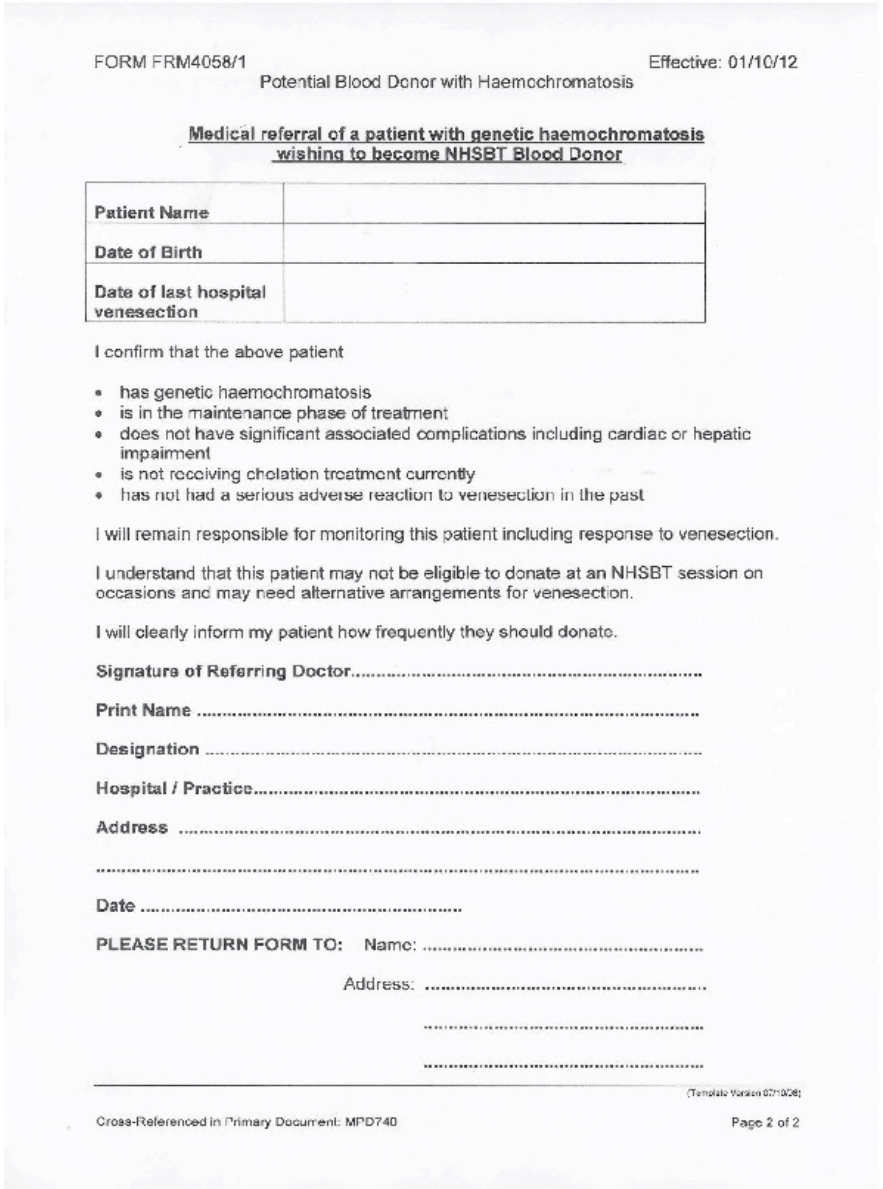
FRM 4058 (page 2)

NHS
Blood and Transplant



FORM FRM4058/1 Effective: 01/10/12

Potential Blood Donor with Haemochromatosis

Medical referral of a patient with genetic haemochromatosis wishing to become NHSBT Blood Donor

Patient Name	
Date of Birth	
Date of last hospital venesection	

I confirm that the above patient

- has genetic haemochromatosis
- is in the maintenance phase of treatment
- does not have significant associated complications including cardiac or hepatic impairment
- is not receiving chelation treatment currently
- has not had a serious adverse reaction to venesection in the past

I will remain responsible for monitoring this patient including response to venesection.

I understand that this patient may not be eligible to donate at an NHSBT session on occasions and may need alternative arrangements for venesection.

I will clearly inform my patient how frequently they should donate.

Signature of Referring Doctor.....

Print Name .....

Designation .....

Hospital / Practice.....

Address .....

.....

Date .....

PLEASE RETURN FORM TO: Name: .....

Address: .....

.....

.....

(Template Version 07/10/08)

Cross-Referenced in Primary Document: MPD740 Page 2 of 2

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Process issues

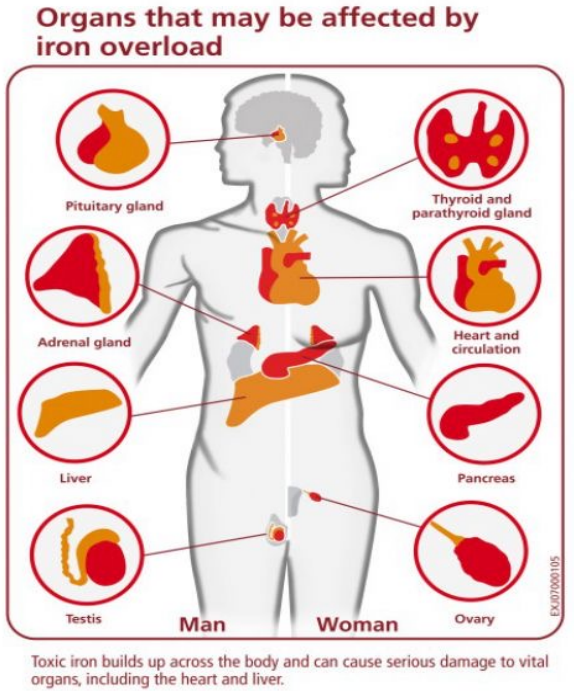
NHS Blood and Transplant

- Collect blood from donors for benefit of patients
- Happy to accept volunteers with GH as blood donors
- Frequent donors restricted to fixed sites
- Reduced access if blood group not in demand
- Do not provide iron/ferritin monitoring
- Do not provide bespoke/ad hoc phlebotomy
- Do not provide clinical advice on GH

Acceptance criteria

NHS Blood and Transplant

- Compliance with Donor health Check (DHC)
- GH managed by specialist, de-iron, maintenance phase
- No end-organ damage, no chelation
- Responsibility for iron/ferritin monitoring
- Additional phlebotomy
- Access to higher donation frequency on HAE code
- Majority on historical WB code



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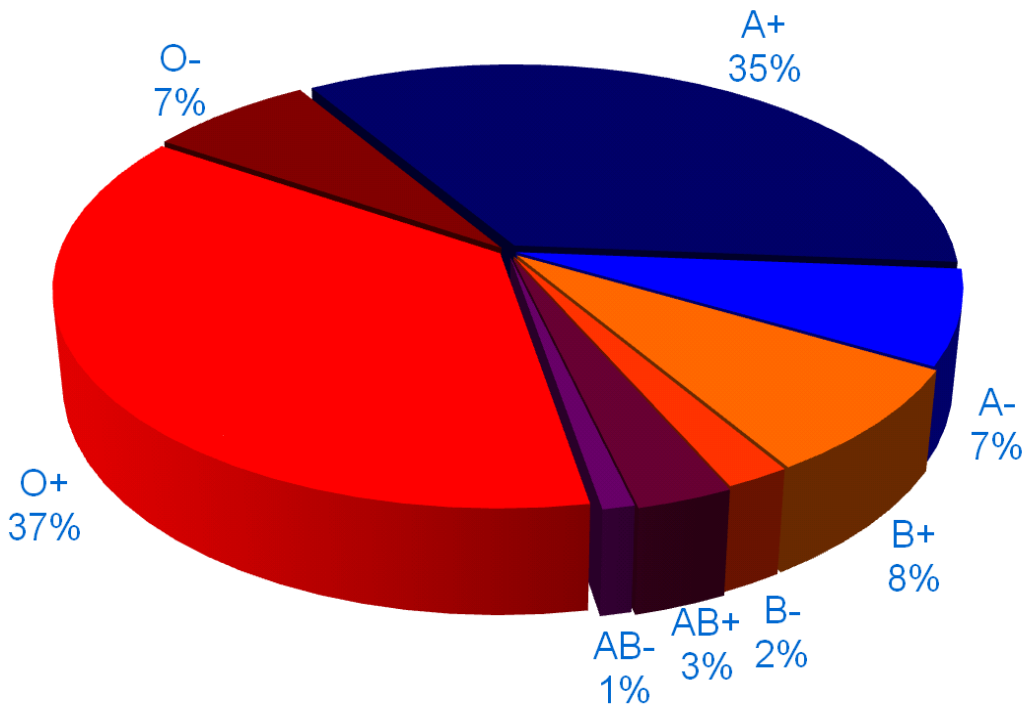
BLOOD TYPES

NHS Blood and Transplant

- **A, B, AB and O**

- **Antigens**
  A and B antigens
  Rh Antigen

- **33 major systems**



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Future opportunities

NHS Blood and Transplant

- Address access issues
- Stable donor pool
- Discussion (Dave Roberts and Genomics Programme)
  - Opportunities for research/studies – 8/1000 donors are C282Y homozygotes in NHSBT
  - Verify genotype – we can do in NHSBT H&I
  - Cascade screening of relatives – needs agreement and resources
  - Observe trajectory of ferritin and clinical outcomes and ensure continuity of venesection as far
  - Further work will need an extrenally funded project
  - Establishing clinical pathway and project proposal would need detailed discussion, advice and endorsement

NHS
Blood and Transplant

Thank you

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Venesection best practice guidance

- Agreed with BSG guideline committee
- Writing group in development
- Timescale – to submit by end of 2024

“Suspension” of unnecessary venesection

- What should we do when we identify patients with atypical genotypes already established in maintenance venesection???

- Proposal
  - Standardised information sheet – explaining benefit of stopping treatment
  - Suspension of venesection
  - Agreement on follow-up – e.g. ferritin measurement every 6/12 for 2 years
  - Measurement of QoL and psychological response

Trial of Venesection trial

- NIHR HTA application in progress
- To study pC282Y homozygotes undergoing venesection
- Randomised to differing venesection end-points (ferritin)
- Measuring cost (Healthcare and personal), quality of life/symptoms

Sub-groups and associations update

- Nurses group
- Primary care group
  - RCGP learning module
- BLT Patient Support group
- HUK/All Party Parliamentary Group
- Haemochromatosis International/EFAPH/HA

BRITISH LIVER TRUST

HI Haemochromatosis International

EFAPH Fe

Haemochromatosis Australia
Inherited Iron overload disorder

7. Any other business

- NICE clinical guideline
  - still awaiting notification of recommencement date

- NHS digital disease register
  - conversations currently paused
  - pC282Y homozygosity
  - Australian patient registry being launched in August

8. Date of next meeting

- Next SIG meeting - Thursday 5th September 2024

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