Haemochromatosis

Special Interest Group

7th March 2024

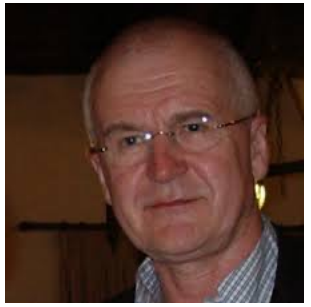
BRITISH SOCIETY OF GASTROENTEROLOGY

British Association for the Study of the Liver

British Society for Haematology
Listening • Learning • Leading

RIP - Dr Martin Johnson

Emeritus Professor of Nursing, University of Salford



Haemochromatosis – SIG

Agenda

1. Biobank update – Mitch Lucas, Exeter
2. Review of work to date
3. Blood sciences, including *HFE* mutation testing
4. Imaging (MRI)
5. Venesection
6. SIG sub-groups
7. Any other business

Haemochromatosis SIG

March 7th, 2024

Research title:

HFE genotypes, haemochromatosis diagnosis status and clinical penetrance to age 80 in the UK Biobank community cohort

Authors: Mitchell R Lucas[1]*, Janice L Atkins[1], Luke C Pilling[1], Jeremy Shearman[2], David Melzer[1]

*PhD student in the Epidemiology and Public Health team

University of Exeter Medical School

email: ml850@exeter.ac.uk

University of Exeter

Medical School

Acknowledgements

Janice Atkins

Prof David Melzer

Luke Pilling

Jeremy Shearman

Data source

biobank uk

Funders

NIHR | National Institute for Health and Care Research

Research question: To what extent do *HFE* genotypes predict the risk of hospital diagnosed complications, even in older ages?

UK Biobank community cohort:

Baseline (2006-2010):

- N= >500,000 community volunteers: England, Wales and Scotland
- 40 - 70 years old, some healthier volunteer effect
- C282Y+/+: 1,298 males, 1,604 females

Follow-up: now mean 13.3 years incident events, routine care

- Hospital inpatient records (including day patient/procedures)
- National cancer registry
- Death certificates

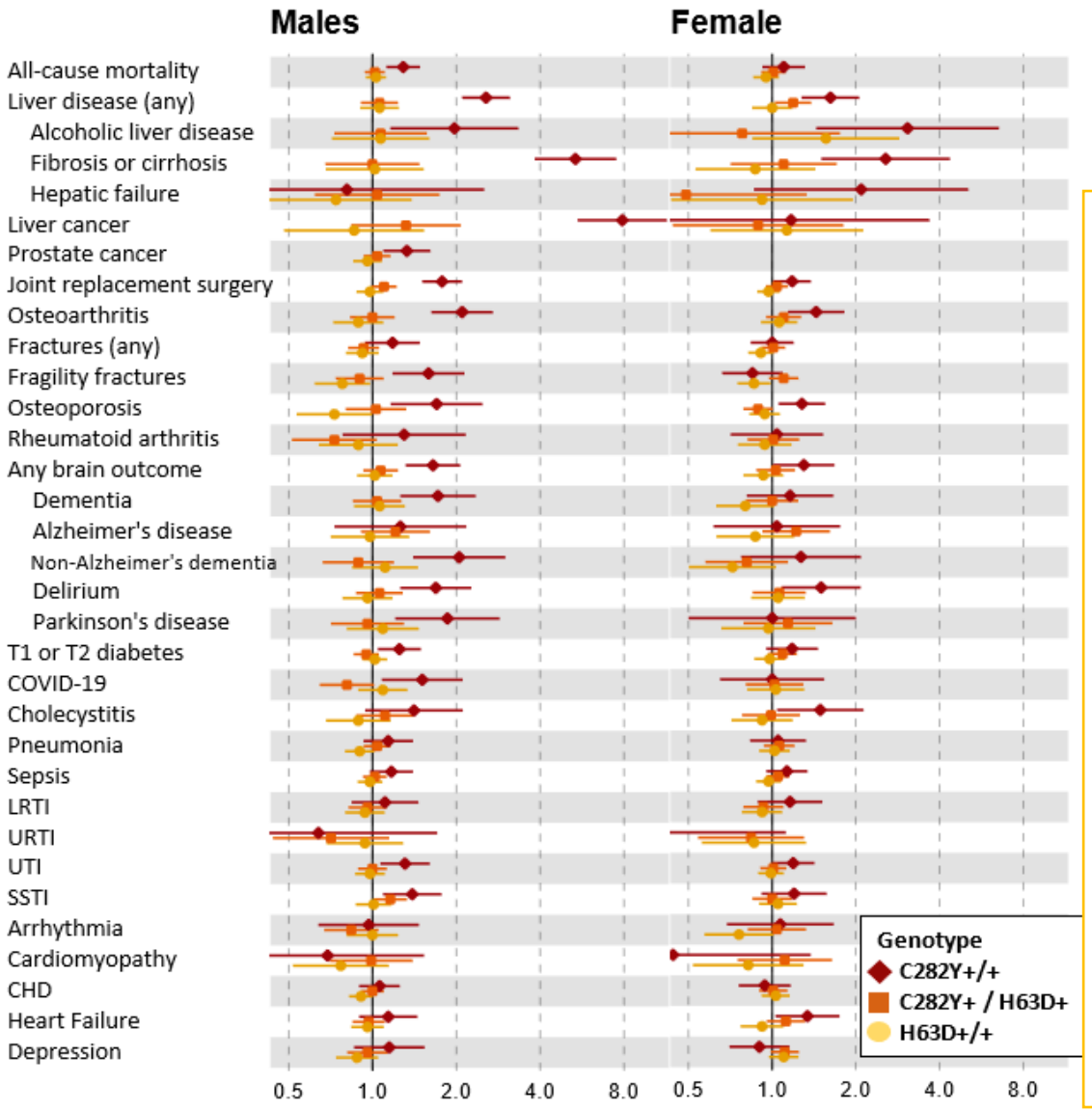
Studied 34 incident hospital-diagnosed outcomes:

- Haemochromatosis
- Brain related outcomes
- Liver related outcomes
- Musculoskeletal related outcomes
- Cancer related outcomes
- Diabetes
- Mortality

Hypothesis:

- ***HFE* gene mutations increase the risk of morbidity and mortality among males and females, even into older age**

‘Risk’ of being diagnosed by end of follow up:



Hazard ratios for incident outcomes (95%CI)

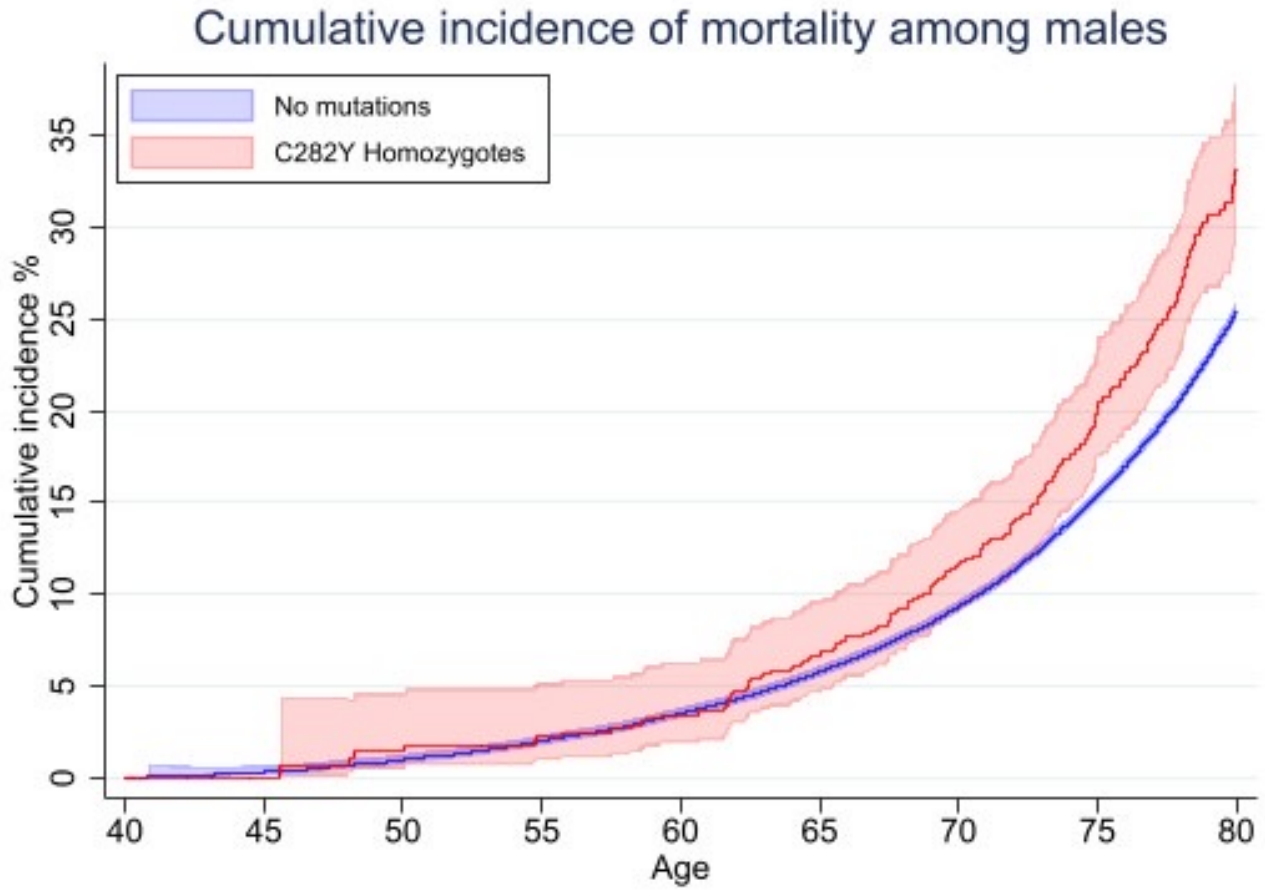
Important mentions:

- Increased risk of mortality in male p.C282Y+/+ but not in females
- Increased risk of brain related outcomes in male p.C282Y+/+ but only delirium in females
- Increased risk of joint replacement surgeries in male and female p.C282Y+/+
- Modest increased risk in diabetes in male p.C282Y+/+
- No increased risk in cardiac related outcomes in male or female p.C282Y+/+

From Lucas M et al (Melzer group) BMJ Open 2024

HFE C282Y+/+ (homozygous)

Excess mortality: n=1,298 males, UK Biobank



From Lucas M et al (Melzer group) BMJ Open 2024

Estimated by age 80:

- 33.1% of C282Y homozygotes die
- 25.4% without *HFE* variants
- HR=1.29 (95%CI: 1.12-1.48), $p=4.7*10^{-4}$

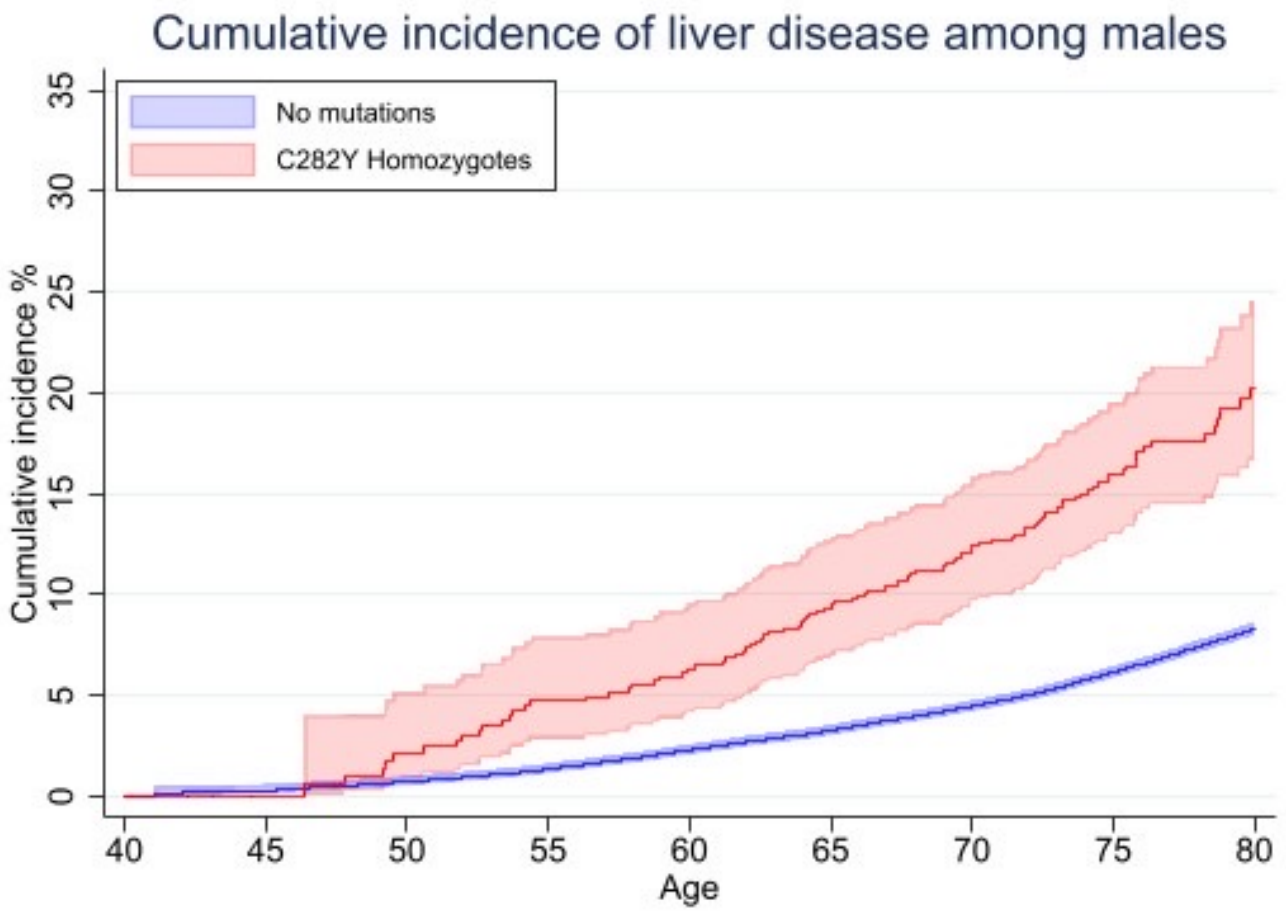
Excluding diagnosed hemochromatosis at baseline

- HR=1.22 (CI 1.05 to 1.43), p=0.01

Not statistically significant in female C282Y+/+

Liver disease: cumulative incidence clinically diagnosed

in 1,298 C282Y homozygous males, UK Biobank



Males - cumulative incidence liver disease by age 80:

- 20.3% (95% CI: 16.7% to 24.6%)
- 8.3% without *HFE* variants

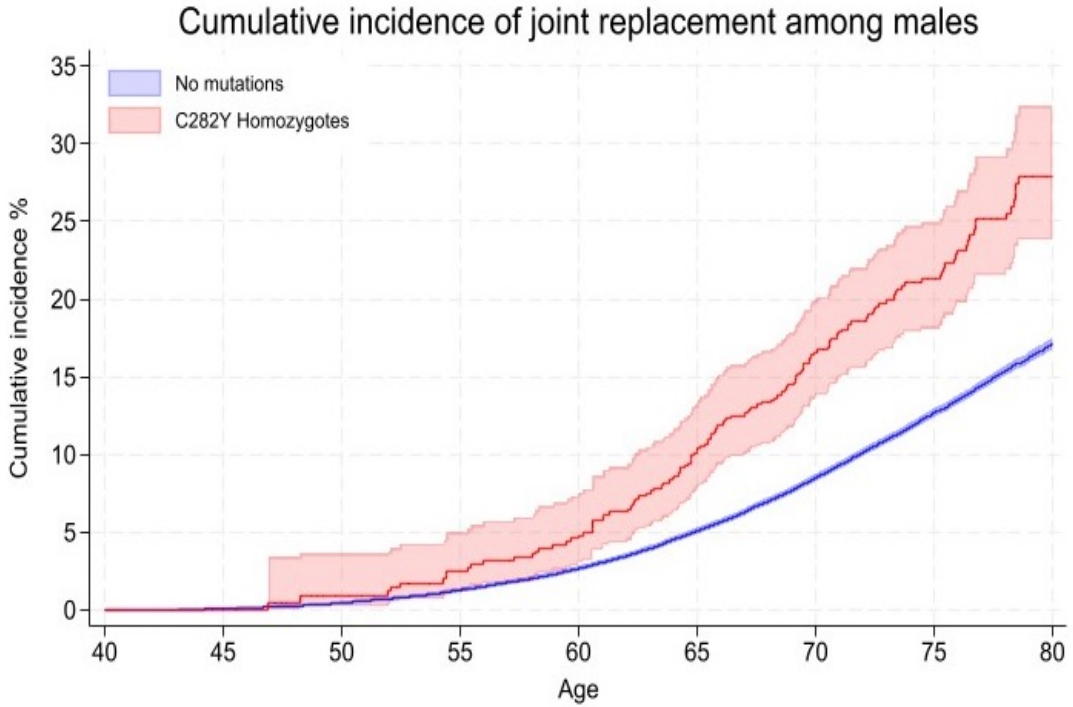
From Lucas M et al (Melzer group) BMJ Open 2024

Other outcomes

in 1,298 C282Y homozygous males, UK Biobank

Males - cumulative incidence joint replacement by age 80:

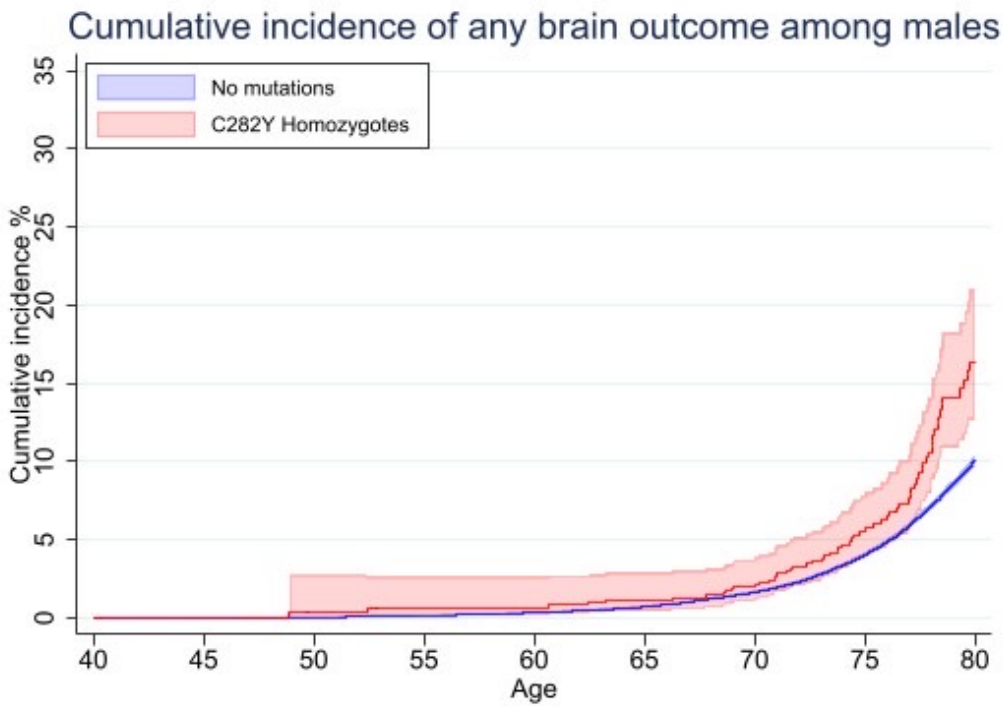
- 27.9% (95% CI: 23.9% to 32.4%)
- 17.1% without *HFE* variants



From Lucas M et al (Melzer group) BMJ Open 2024
Joint replacement surgery = hip/knee/ankle/shoulder

Males - cumulative incidence brain outcomes by age 80:

- 16.4% (95% CI: 12.1% to 21.1%)
- 10.0% without *HFE* variants

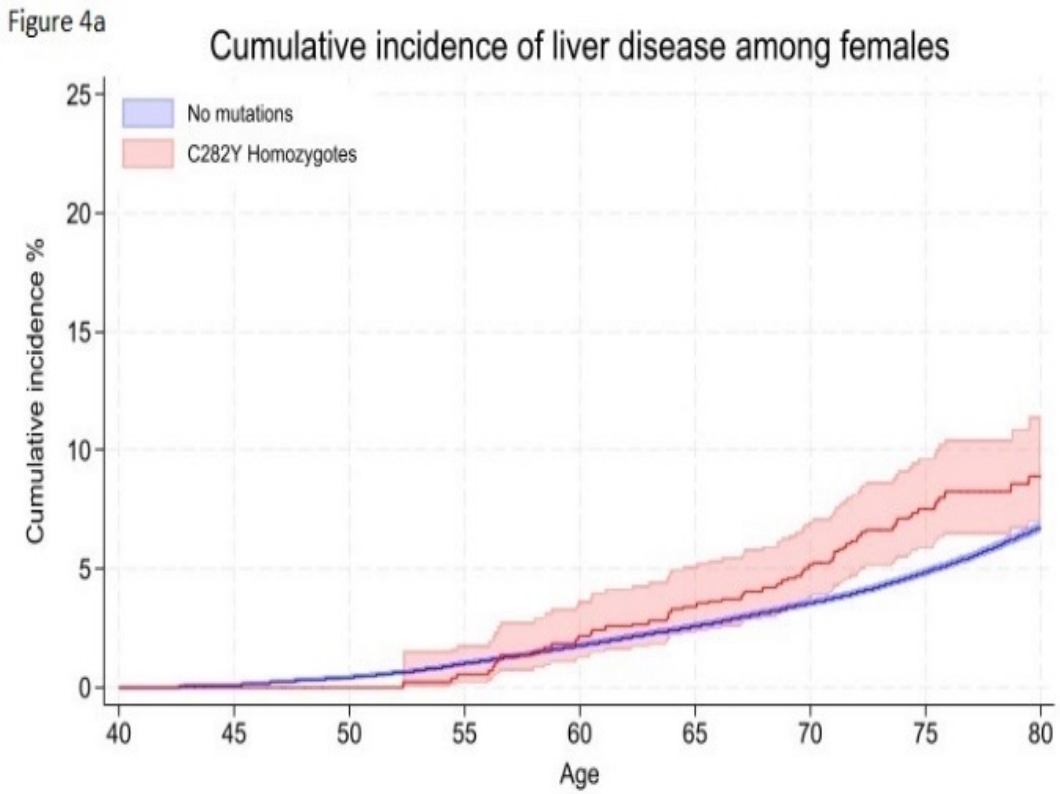


From Lucas M et al (Melzer group) BMJ Open 2024
Any brain outcome = delirium/dementia/Parkinson's disease

Female: cumulative incident clinical diagnosis

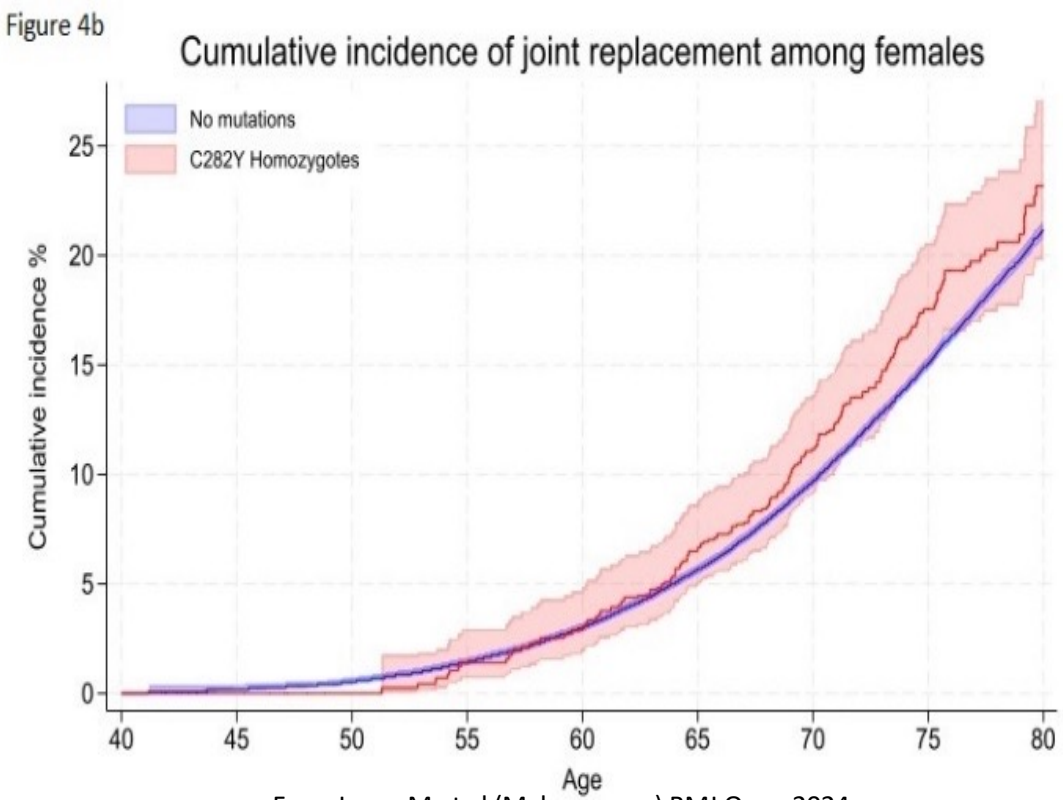
In 1,604 homozygous females, UK Biobank

Females - cumulative incidence liver disease by age 80:
8.9% (95% CI: 7.0% to 11.4%)
6.8% without *HFE* variants



From Lucas M et al (Melzer group) BMJ Open 2024

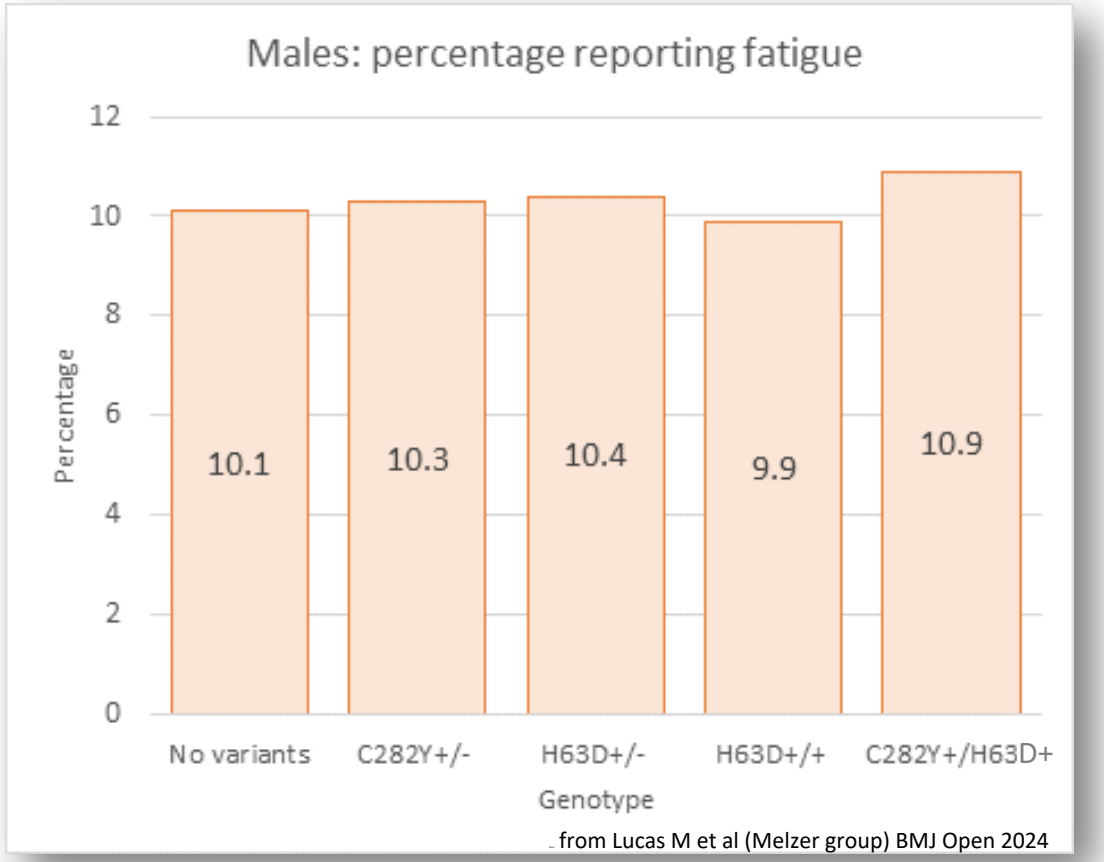
Females - cumulative incidence joint replacement by age 80:
23.2% (95% CI: 19.8% to 27.1%)
21.1% without *HFE* variants



From Lucas M et al (Melzer group) BMJ Open 2024

Less severe *HFE* variants

no statistically significant associations: baseline and 13-year follow-up



from Lucas M et al (Melzer group) BMJ Open 2024

"Over the past two weeks, how often have you felt tired or had little energy?":
fatigue = "more than half the days" & "nearly every day".

Very large groups studied:

- 268,535 people without HFE mutations
- 105,004 people with p.H63D+/-
- 10,253 people with p.H63D+/+
- 10,719 people with p.C282Y/p.H63D,
- 10,253 people with p.H63D+/+
- 53,857 people with p.C282Y+/-
- 2,902 people with p.C282Y+/+

Unfortunately, some people with these variants do develop fatigue, liver disease, arthritis, diabetes, etc
but at approximately the same rate as those without HFE variants
So other causes need to be identified and treated

Thank you

2. Review of work to date

Useful clinical terms …

- Haemochromatosis (i.e. HH/YY with iron overload)
- Hyperferritinaemia (e.g. NAFLD, HD/CY, DD/CC etc)
- Iron Overload (i.e. proven overload in non-HH/YY genotypes, Ferroportin disease etc)

Coding …

- ICD-10 - E83.1 Haemochromatosis

Bioiron classification

Novel classification	Molecular pattern	Note
HFE-related	*p.Cys282Tyr* homozygosity or compound heterozygosity of *p.Cys282Tyr* with other rare *HFE* pathogenic variants[106-109] or *HFE* deletion[110]	Low penetrance; consider presence of host-related or environmental cofactors for IO In subjects with other HFE genotypes (e.g. *p.Cys282Tyr/His63Asp* compound heterozygosity or *p.His63Asp* homozygosity) consider second-line genetic testing for rarer variants.
Non HFE-related	Rare pathogenic variants in "*non-HFE*" genes: - *HJV*-related - *HAMP*-related - *TFR2*-related - *SLC40A1* (GOF)-related	Potentially, mutations in any hepcidin-regulatory gene may be causative (the effects of novel mutations should be confirmed through functional and epidemiological studies). Molecular subtypes characterization only at specialized centers, but the diagnosis of non-*HFE* related HC is sufficient to start phlebotomies at non-specialized centers*.
Digenic**	Double heterozygosity and/or double homozygosity/heterozygosity for mutations in two different genes involved in iron metabolism (*HFE* and/or *non-HFE*)	More commonly, *p.Cys282Tyr* mutation in *HFE* gene might coexist with mutation in other genes; rarely, both mutations involve *non-HFE* genes
Molecularly undefined	Molecular characterization (still) not available after sequencing of known genes (provisional diagnosis)	Patients should be referred (or DNA should be sent) to specialized centers

- Requires consensus definition of iron overload
- Topic for exceptional SIG meeting – 28th March

3. Blood sciences

- Ferritin/Transferrin saturation
- HFE mutation analysis
- ACB survey
  - Results pending

Discussion

recommended phrases for HFE genotypes

C282Y homozygote

“Based on your genotype, you have a higher risk of haemochromatosis than the general population.

A diagnosis of haemochromatosis cannot be based on genetic information alone and you will require a clinical assessment and measurement of iron stores before considering the value/timing of any treatment.”

“Latent” haemochromatosis

Latent – definition (Wiktionary)

Adjective

Existing or present but concealed or inactive

Synonyms: hidden, invisible

Antonyms: apparent, patent, visible

(pathology, of a virus) Remaining in an inactive or hidden phase; dormant.

Synonyms: dormant; *see also inactive*

(biology) Lying dormant or hidden until circumstances are suitable for development or manifestation.

Alternative terms considered included **nascent**, **potential**, **dormant**, **quiescent**, **inactive**.

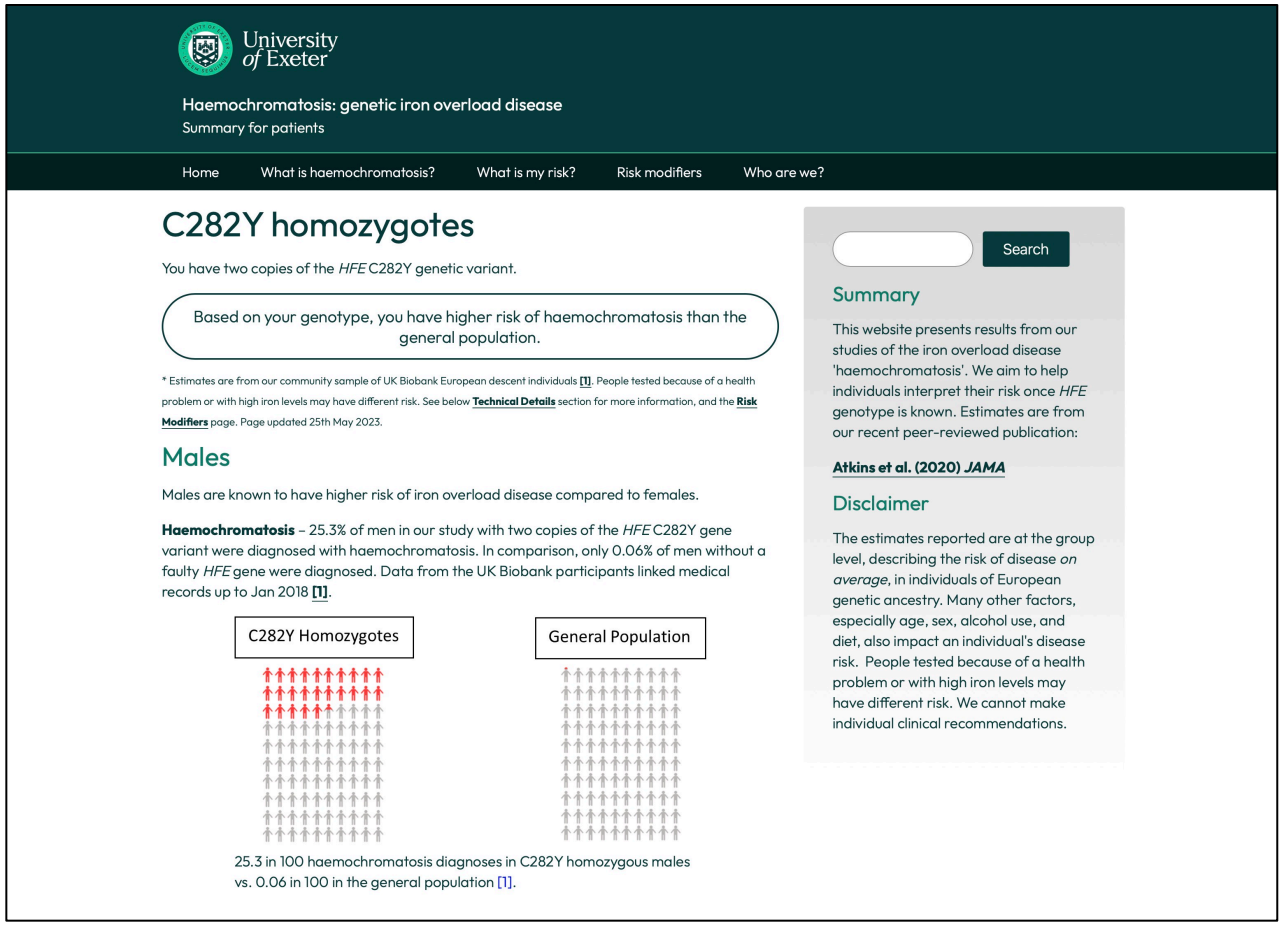
Are any better than **latent** when considering the need of individuals to be clinically assessed and monitored over time.

Compound heterozygote

“Based on your genotype, you have a small increase in risk of haemochromatosis, compared to the general population (for further details please see https://sites.exeter.ac.uk/ironoverload/patient-reports/c282y-h63d-compound-heterozygotes/)

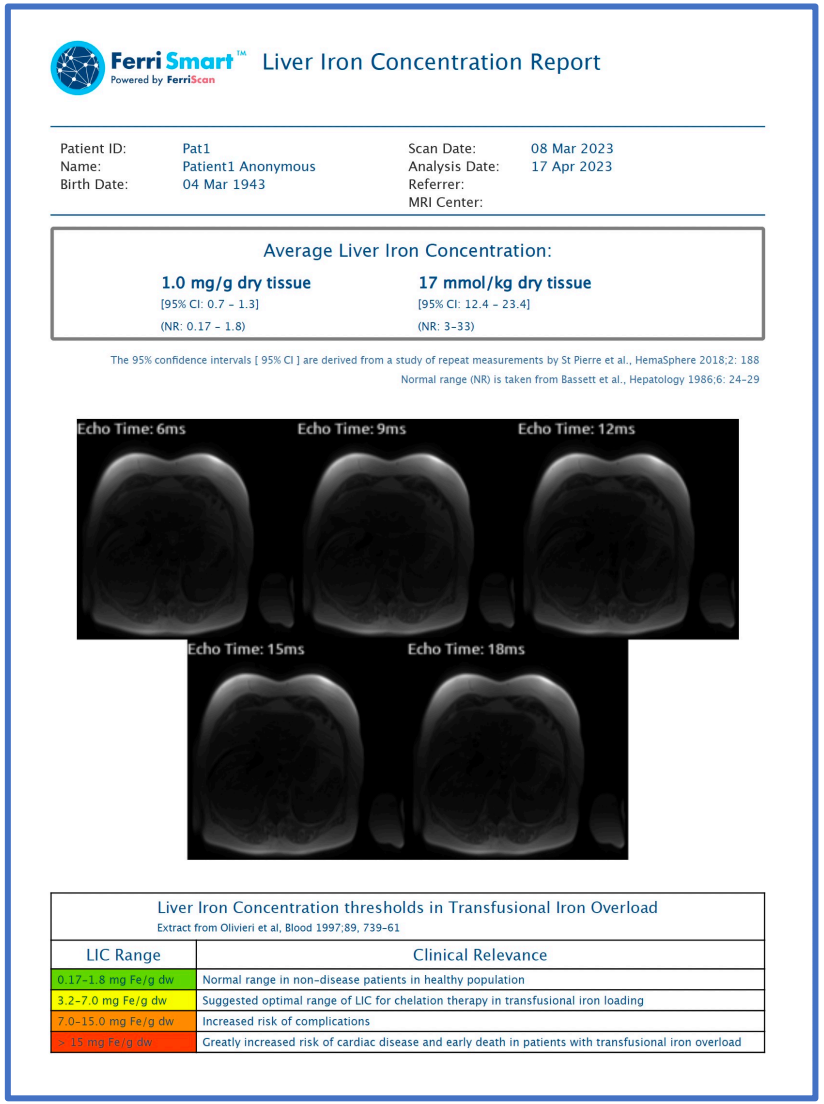
A diagnosis of haemochromatosis cannot be based on genetic information alone and you will require a clinical assessment and measures of iron stores. If you have symptoms these might be due to a number of causes other than haemochromatosis.”

HFE mutation analysis



https://sites.exeter.ac.uk/ironoverload/

3. MRI Imaging



FerriSmart™ Powered by FerriScan — Liver Iron Concentration Report

Patient ID:	Pat1	Scan Date:	08 Mar 2023
Name:	Patient1 Anonymous	Analysis Date:	17 Apr 2023
Birth Date:	04 Mar 1943	Referrer:	
		MRI Center:	

Average Liver Iron Concentration:

1.0 mg/g dry tissue	17 mmol/kg dry tissue
[95% CI: 0.7 – 1.3]	[95% CI: 12.4 – 23.4]
(NR: 0.17 – 1.8)	(NR: 3–33)

The 95% confidence intervals [95% CI] are derived from a study of repeat measurements by St Pierre et al., HemaSphere 2018;2: 188
Normal range (NR) is taken from Bassett et al., Hepatology 1986;6: 24–29

Liver Iron Concentration thresholds in Transfusional Iron Overload
Extract from Olivieri et al, Blood 1997;89, 739–61

LIC Range	Clinical Relevance
0.17–1.8 mg Fe/g dw	Normal range in non-disease patients in healthy population
3.2–7.0 mg Fe/g dw	Suggested optimal range of LIC for chelation therapy in transfusional iron loading
7.0–15.0 mg Fe/g dw	Increased risk of complications
> 15 mg Fe/g dw	Greatly increased risk of cardiac disease and early death in patients with transfusional iron overload

	HIC	
Insignificant	0 - <75 µmol/g	0 – 4 mg/g
Mild	75 - <100 µmol/g	4 – 6 mg/g
Moderate	100 - <150 µmol/g	6 - <8 mg/g
Severe	150 - <300 µmol/g	8 - <16 mg/g
Extreme	>300 µmol/g	>16 mg/g

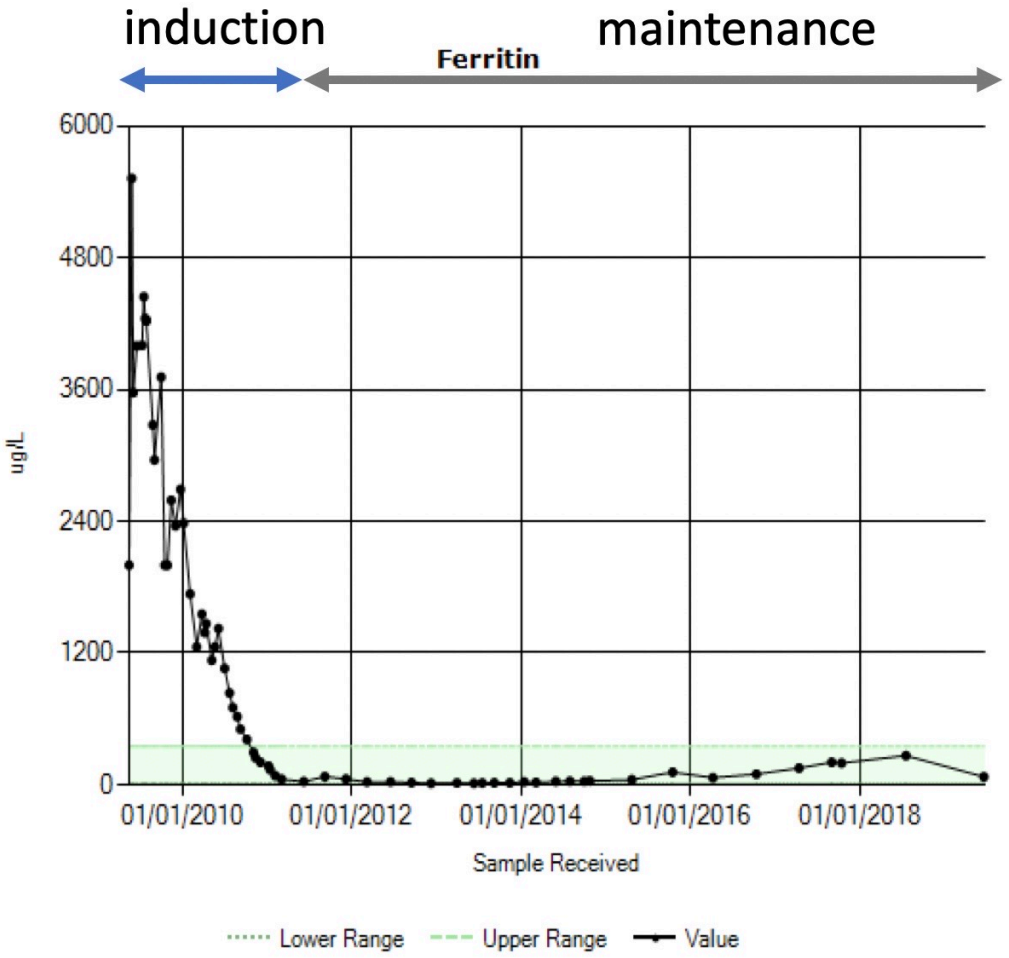
Ref Henninger et al, European Radiology (2020) 30:383-393

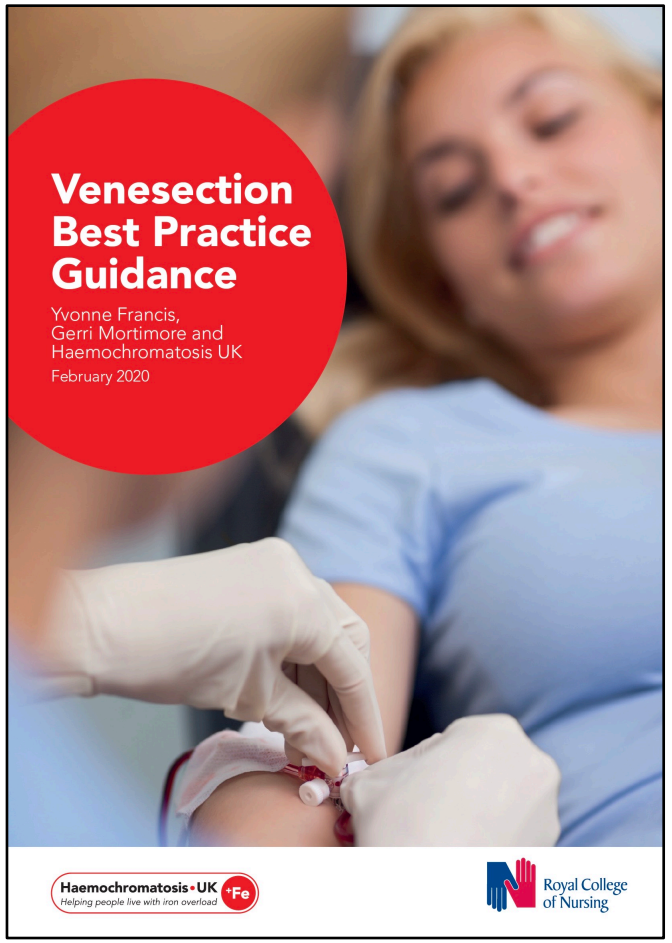
Discussion

service evaluation/study of MRLIC

- RfPB application in progress
- To test the hypothesis that MR LIC has clinical and cost effectiveness in the assessment of hyperferritinaemia
- Using Ferri-Smart (Resonance)
- Trial of venesection being standard of care

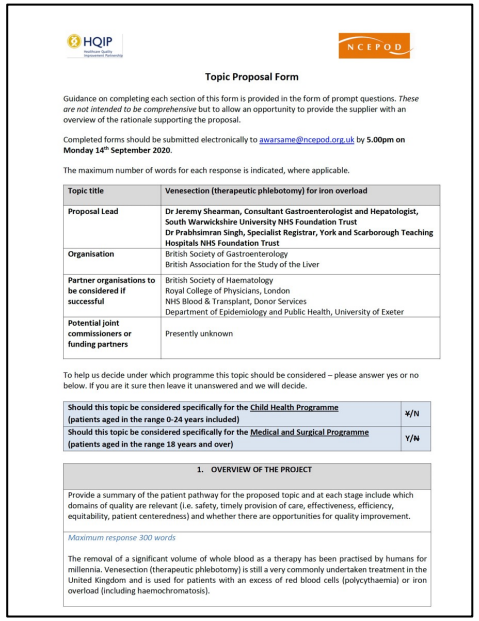
5. Venesection





National survey of venesection practice
(in association with NCEPOD)

- Questionnaire to be sent to all Trusts and health boards



HQIP

NCEPOD

Topic Proposal Form

Guidance on completing each section of this form is provided in the form of prompt questions. *These are not intended to be comprehensive* but to allow an opportunity to provide the supplier with an overview of the rationale supporting the proposal.

Completed forms should be submitted electronically to awarsame@ncepod.org.uk by **5.00pm on Monday 14th September 2020**.

The maximum number of words for each response is indicated, where applicable.

Topic title	**Venesection (therapeutic phlebotomy) for iron overload**
Proposal Lead	**Dr Jeremy Shearman, Consultant Gastroenterologist and Hepatologist, South Warwickshire University NHS Foundation Trust** **Dr Prabhsimran Singh, Specialist Registrar, York and Scarborough Teaching Hospitals NHS Foundation Trust**
Organisation	British Society of Gastroenterology British Association for the Study of the Liver
Partner organisations to be considered if successful	British Society of Haematology Royal College of Physicians, London NHS Blood & Transplant, Donor Services Department of Epidemiology and Public Health, University of Exeter
Potential joint commissioners or funding partners	Presently unknown

To help us decide under which programme this topic should be considered – please answer yes or no below. If you are it sure then leave it unanswered and we will decide.

Should this topic be considered specifically for the Child Health Programme (patients aged in the range 0-24 years included)	**Y/N**
Should this topic be considered specifically for the Medical and Surgical Programme (patients aged in the range 18 years and over)	**Y/N**

1. OVERVIEW OF THE PROJECT
Provide a summary of the patient pathway for the proposed topic and at each stage include which domains of quality are relevant (i.e. safety, timely provision of care, effectiveness, efficiency, equitability, patient centeredness) and whether there are opportunities for quality improvement.
Maximum response 300 words
The removal of a significant volume of whole blood as a therapy has been practised by humans for millennia. Venesection (therapeutic phlebotomy) is still a very commonly undertaken treatment in the United Kingdom and is used for patients with an excess of red blood cells (polycythaemia) or iron overload (including haemochromatosis).

Discussion

venesection best practice guidance

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

Discussion

controlled trial of venesection

- HTA application in progress
- To study C282Y homozygotes undergoing venesection
- Randomised to differing venesection end-points (ferritin)
- Measuring cost (Healthcare and personal), quality of life/symptoms

6. Sub-groups/associations

- Nurses group
  - Vicki Sugden, Becki Savage – Nottingham, Gerri Mortimore - Derby
- Primary care group
  - RCGP learning module
- BLT Patient Support group
  - PPIE for research
- All Party Parliamentary Group/HUK
- Haemochromatosis International/EFAPH

Haemochromatosis International

EFAPH Fe

Discussion

BLT patient information content

- Work in progress
- Patient group identified
- Funding being sought

7. Any other business

- NICE clinical guideline – decision expected April 2024
- NHS digital disease register – conversations currently paused
  - pC282Y homozygosity
- Our Future Health study – discussions ongoing
- NHS BT – topic for next meeting

Forthcoming iron meetings

www.eic2024.inviteo.fr

8. Date of next meeting

- Exceptional SIG meeting – Thursday 28th March 5-7pm
  - theme – Consensus definition of iron overload

- Next SIG meeting - Thursday 13th June 2024
  - Topic/theme – haemochromatosis and the NHS blood transfusion service

jeremy.shearman@doctors.org.uk
07778 659402