Haemochromatosis

8th June 2023

Jeremy Shearman

British Society for Haematology
Listening • Learning • Leading
1960–2020

BRITISH SOCIETY OF GASTROENTEROLOGY

British Association for the Study of the Liver

Haemochromatosis – sub-SIG
Agenda

1. Terminology/classification – recap
2. NICE/NCEPOD – update
3. Direct to consumer genetic tests – discussion
4. Research opportunities
5. Primary care – the challenge of hyperferritinaemia, HFE mutation analysis
6. Patient group – GH^{2+}
7. Recent publications of note
8. AOB
9. Date of next meeting – Thursday 7th September 2023

Terminology

What we have …

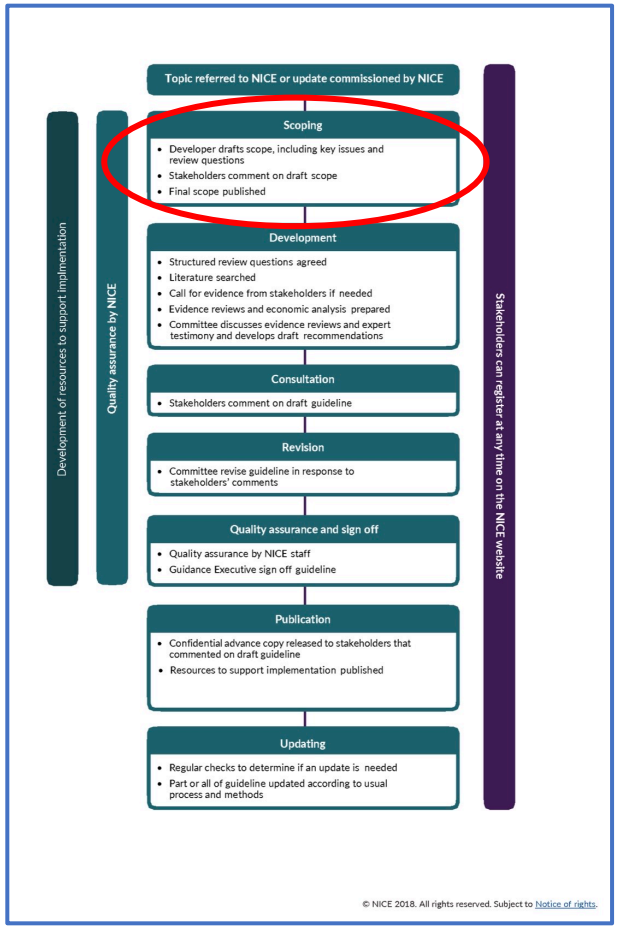
- ICD-10 - E83.1 Haemochromatosis

What we need …

- 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)

NICE

Clinical Guideline 10287



- Guideline scope finalized 8th March
- Further work now <u>suspended</u>
- New NICE interim director of the centre for guidelines

Professor Jonathan Benger, CBE MD FRCS FRCEM, chief medical officer and interim director of the centre for guidelines

Jonathan joined us in January 2023 as chief medical officer and from March 2023 will act as interim director of the centre for guidelines.

Prior to this he was the interim chief clinical information officer (CCIO) at NHS England (2022), the chief medical officer (CMO) of NHS Digital (2019 to 2022), and the national clinical director for urgent and emergency care at NHS England (2013 to 2019).

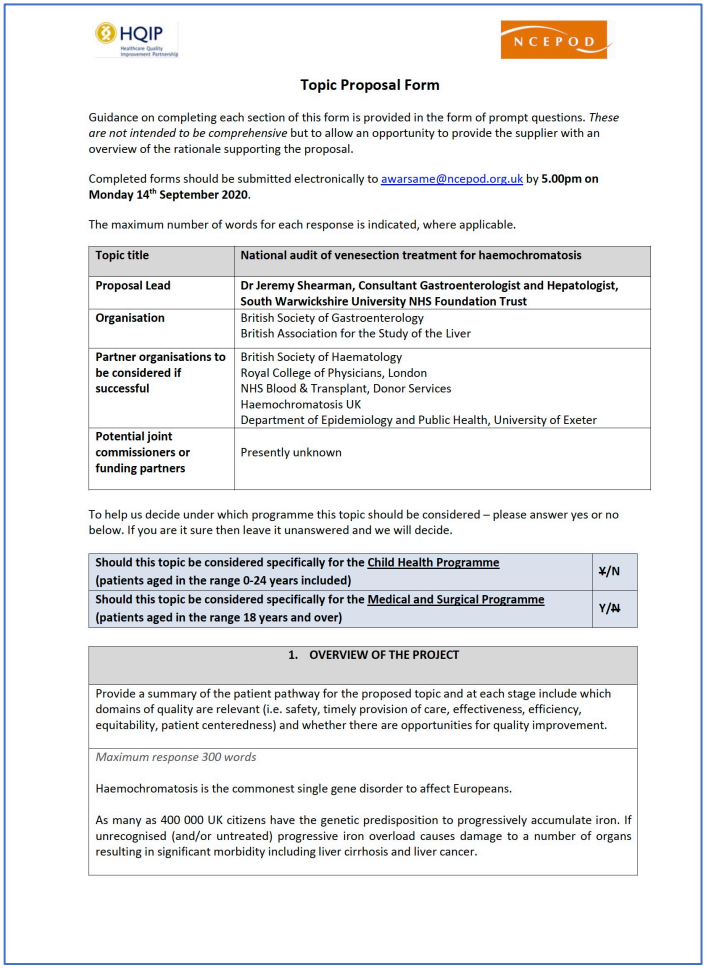
In his clinical work, Jonathan is a consultant in emergency medicine at the Bristol Royal Infirmary and also does regular shifts with the Great Western Air Ambulance, which he established as its first medical advisor between 2007 and 2011.

Jonathan is professor of emergency care in the school of health and social wellbeing at the University of the West of England, and a National Institute for Health Research (NIHR) senior investigator. His main research interests relate to cardiac arrest, emergency and pre-hospital care, service organization and delivery, and design research.

NCEPOD

- Topic proposal re-submitted
- Failed to progress once again
  - How to access the right patients?
  - “niche” topic

- Next step – possibly re-write focusing specifically on venesection as a treatment?



HQIP Healthcare Quality Improvement Partnership

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	**National audit of venesection treatment for haemochromatosis**
Proposal Lead	**Dr Jeremy Shearman, Consultant Gastroenterologist and Hepatologist, South Warwickshire University 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 Haemochromatosis UK 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 Haemochromatosis is the commonest single gene disorder to affect Europeans. As many as 400 000 UK citizens have the genetic predisposition to progressively accumulate iron. If unrecognised (and/or untreated) progressive iron overload causes damage to a number of organs resulting in significant morbidity including liver cirrhosis and liver cancer.

Direct to consumer genetic tests

PRACTICE POINTER

Direct-to-consumer genetic testing

Rachel Horton *clinical training fellow*[1 2], Gillian Crawford *principal genetic counsellor*[1 2], Lindsey Freeman *senior clinical scientist*[3], Angela Fenwick *associate professor of medical ethics and education*[1], Caroline F Wright *senior lecturer*[4], Anneke Lucassen *professor of clinical genetics*[1]

[1]Clinical Ethics and Law at Southampton (CELS), Faculty of Medicine, University of Southampton, UK,; [2]Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK; [3]Wessex Regional Genetics Laboratory, Salisbury, UK; [4]University of Exeter College of Medicine and Health, Exeter, UK

BMJ 2019;367:l5688 doi: 10.1136/bmj.l5688 (Published 16 October 2019)

Science and Technology Committee

22 June 2021

- **Pre-market assessment of direct-to-consumer tests** by an independent body. This assessment should cover the test's **clinical performance** (the extent to which it can provide information about treatment of a disease, and the likelihood of improved outcomes) in addition to the current requirement to achieve **analytical performance**, which describes how well the test can identify the presence of a particular gene.
- The development of **technical standards** for direct-to-consumer genomic testing, enabling the data generated to be used and **relied upon by Genomics England and the NHS**. Clearly defining such standards would facilitate research efforts and reduce the burden placed on the NHS to re-test patients following testing via commercially obtained tests. It would also **enable consumers to differentiate high quality, trustworthy products from those with lower standards**.
- Considering whether to revise regulation regarding the **advice and support** offered when supplying genomic testing directly to customers. This could, for example, include a requirement for provision of **genetic counselling** depending on the severity of the condition being tested, and stipulate the predictive power of the test alongside results.
- Reconsideration of the guidance on the **use of genomic testing on asymptomatic children**. After hearing evidence from the Nuffield Council of Bioethics and researchers in the field, the Committee note concerns about testing being used inappropriately on children who cannot give informed consent.
- The Government should **review the adequacy** of the UK's data protection framework for direct-to-consumer genomic testing, including the risks and opportunities presented by technological developments and growing numbers of consumers using direct-to-consumer genomic tests.

UK Parliament

Chair, Rt Hon Greg Clark MP

"For thousands of people, at-home genomic testing has opened the door to a wealth of new information about our ancestry, our health and even the likelihood of disease. Done properly, genomic testing offers great potential for individual knowledge and can provide data which can advance medical research.

"However, these technologies can give rise to questions of quality, which are difficult for consumers to assess, and can sometimes pose challenging ethical questions. The Government has committed to a 'gold standard' for ethical and regulatory standards for genomics in the UK. In our Committee's Report we set out perspectives we heard on the issues the Government should be considering as it devises a new regulatory framework."

UK Parliament

Example 1

Your patient recently undertook a genetic test for type 1 genetic haemochromatosis (HE mutation).

The test was conducted on their behalf by our UKAS-accredited pathology lab TDL.

The results of HFE mutation (type 1) genetic testing for your patient, tested on ……..

Patient :

Date of birth:

Address:

The results were

The patient is a **C282Y carrier for genetic haemochromatosis** and may be at risk of iron overload from novel or untested variants of the condition.

The genetic test undertaken looks only for the most common variants of genetic haemochromatosis, known as C282Y and H63D (type 1). In the UK, these variants account for over 90% of people with genetic haemochromatosis. However. there are other less common variants of the condition known as Type 2 (juvenile), Type 3 and Type 4 (also known as ferroportin disease). If serum ferritin (SF) and/or transferrin saturation (TSAT) levels are raised, you should consider referring for genetic testing of these less common types of genetic haemochromatosis.

If not already undertaken recently, your patient should have a serum ferritin (SF) and transferrin saturation (SAT) test as soon as practicable. If their iron levels are abnormal, a referral to secondary care is necessary. If levels are normal now, it is worth monitoring them every 2 years

If the patient is male, a serum ferritin (SF) over 300 ug/l and/or a transferrin saturation (TSAT) over 50% indicates iron overload. If the patient is female, a serum ferritin (SF) over 200 ug/l and/or a transferrin saturation TSAT) over 45% indicates iron overload.

Haemochromatosis • UK +Fe
Helping people live with iron overload

Cascade Screening of Genetic Haemochromatosis Patients

Dr Lina Boughetane[1], Dr Tiong Yeng Lim[1], Dr Frederick Chen[2], and Dr Sushma Saksena[1]

[1] *Department of Hepatology, Royal London Hospital, Barts Health NHS Trust,* [2] *Department of Haematology, Royal London Hospital, Barts Health NHS Trust.*

Barts Health NHS Trust

INTRODUCTION

Haemochromatosis is a common autosomal recessive disorder involving dysregulated iron metabolism, leading to excess iron deposition in body tissues. The principal gene involved is the *HFE* gene, and the most common genetic mutation implicated in this disease is the C282Y mutation.[1]

The British Society of Haematology (BSH) and European Association for the Study of Liver (EASL) both recommend cascade screening of first-degree relatives, which involves systematic genetic testing of first-degree relatives of those with a confirmed diagnosis of haemochromatosis.[2,3] This advice is also included in the draft NICE guideline for haemochromatosis which is due to be published in 2024.[4]

OBJECTIVES

1. To undertake an audit to assess the following:
   - **1A** The number of haemochromatosis patients under the care of Hepatology & Haematology departments at The Royal London Hospital who were provided with cascade screening advice at diagnosis.
   - **1B** The number of patients who acted on cascade screening advice provided.
   - **1C** If cascade screening led to new diagnoses of haemochromatosis.
2. To provide all patients with a standardised cascade screening letter as a quality improvement initiative.[5]

References:

1. Powell L, Seckington R, Deugnier Y. Haemchromatosis. Lancet. 2016; 388: 706-16.
2. Fitzsimons EJ, Cullis JO, Thomas DW, Tsochatzis E, Griffiths WJ. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). Br J Haematol. 2018;181:293- 303.
3. European Association for the Study of Liver. EASL Clinical Practice Guidelines on haemchromatosis. J Hepatol. 2022;77:479-502.
4. National Institute For Health and Care Excellence: *Guideline Scope, Haemochromatosis.* Available from: https://www.nice.org.uk/guidance/GID-NG10287/documents/draft-scope.
5. Shearman J (Haemochromatosis SIG lead, BASL). Cascade screening for haemochromatosis (Letter).

METHODS

An audit of patients with **C282Y homozygous haemochromatosis (HH YY)** identified from a prospective database was carried out to assess our objectives.

Screening guidance outlined in the **BSH[2] and EASL[3] guidelines** was used as a gold-standard reference.

Data collection involved sending patients a **postal questionnaire** enquiring about:

- *Was cascade screening advice given at diagnosis?*
- *Who provided cascade screening advice?*
- *Was cascade screening carried out?*
- *Positive diagnoses made as a result of screening advice given?*

Patients were also provided with a **screening letter*** for their first-degree relatives, outlining the recommended screening advice.

*Scan **QR code** for screening questionnaire & letter[5]*

SCAN ME

**We gratefully acknowledge Dr Jeremy Shearman for sharing this letter for cascade screening.*

RESULTS

68 patients with **C282Y homozygous haemochromatosis (HH YY)** were identified.

Patient Demographics	
Male / Female	72% (N = 49) / 28% (N = 19)
Mean Age	54 years (28-74 years)

72% of patients **(N = 49)** responded.

RESULTS

65% of patients **(N = 32)** confirmed receiving cascade screening advice on diagnosis.

Source of Screening Advice	
Haematology clinic	66% (N = 21)
GP	19% (N = 6)
Hepatology clinic	6% (N = 2)
Multiple	6% (N = 2)
Other	3% (N = 1)

81% of patients **(N = 26)** who received cascade screening advice acted on screening advice given.

38% of patients **(N = 10)** confirmed that following screening advice led to new diagnoses of haemochromatosis among family members.

CONCLUSION

We identified that approximately two-thirds of patients diagnosed with haemochromatosis had received cascade screening advice, which is suboptimal. Over three-quarters of patients who were provided with advice followed this advice, which led to at least one new diagnosis in over one-third of the cohort. These diagnoses may have otherwise been missed.

Cascade screening is effective at identifying new patients with haemochromatosis and it is important that it is offered to all patients at diagnosis. Providing a standardised cascade screening letter such as the one used in this project (*kindly provided by Dr J Shearman*[5]) may be an effective tool to help facilitate screening.

Example 2

The results of your recent genetic test for common variants of Genetic Haemochromatosis (type 1)

Following your recent genetic test, I can confirm that the results show that you are a carrier for one of the genes that causes genetic haemochromatosis

Genetic haemochromatosis is an inherited condition that can result in your body absorbing too much iron, leading to iron overload. The purpose of this letter is to explain the results of these tests.

Specifically, the test shows that you have this variant of the condition

Carrier H63D

What to do next

We have written to your GP with a copy of your results. Your GP is now aware that you have been genetically tested and what the results are. We have also sent them a cop of our "Quick Guide for General Practitioners" which explains what they should be doing next, depending on your circumstances.

If you would like to discuss your test results with our qualified Advanced Nurse Practitioner, please book an appointment online here: https://www.haemochromatosis.org.uk/genetic-appointment. We offer appointments for up to 45 minutes to discuss your results and to answer any questions you may have. Appointments are available weekly on a first-come first-served basis. Please book online.

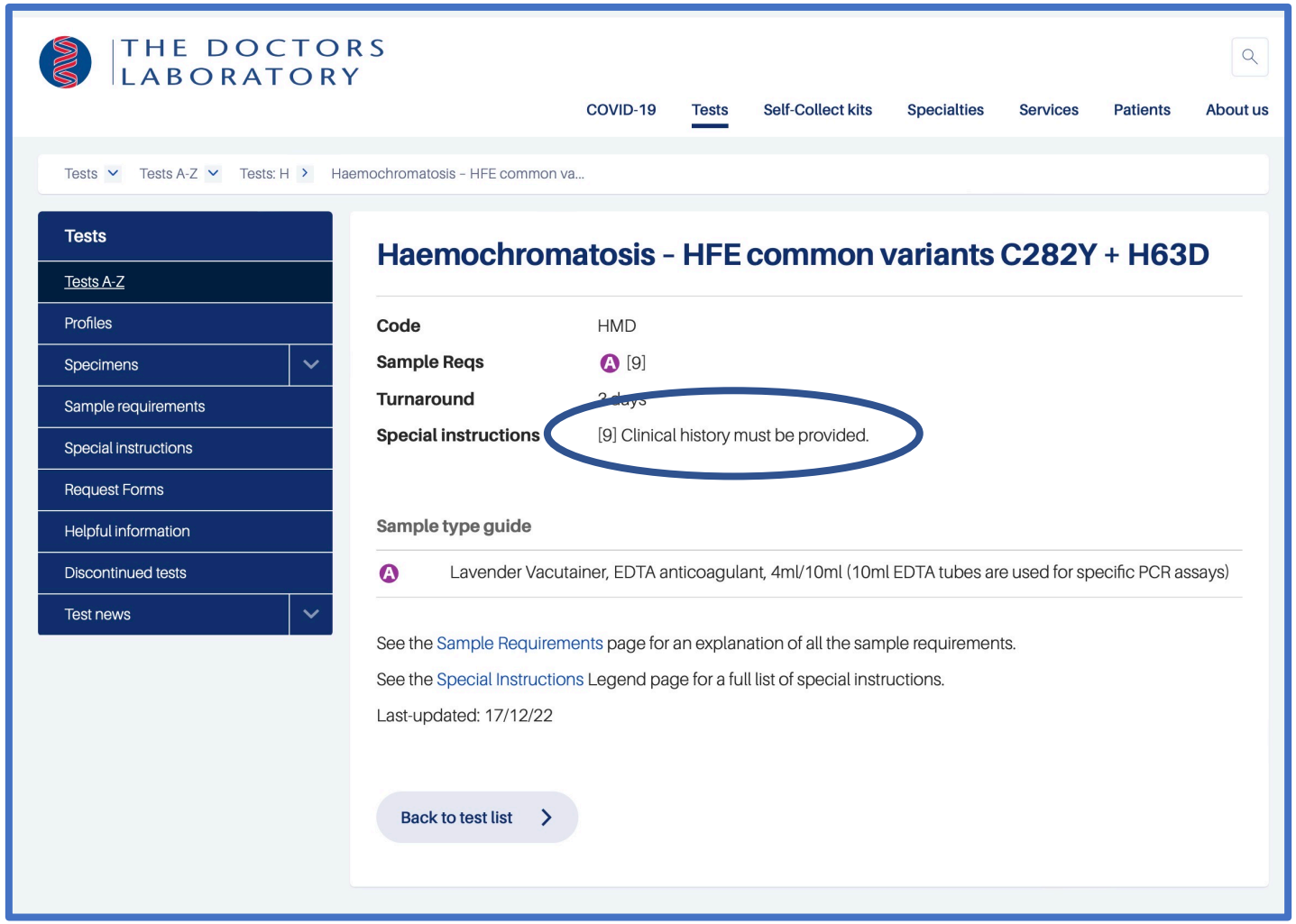
If you do have any concerns our charity has a helpline available on 03030 401 102* (Monday to Friday 12 Noon - 3pm) or email helpline@huk.org.uk. This service is free and is staffed by trained volunteers who have the condition. They can provide information and advice to you and your family.

If you are not already a member of our charity, you may be interested in joining. We provide a range of additional services for members, including.

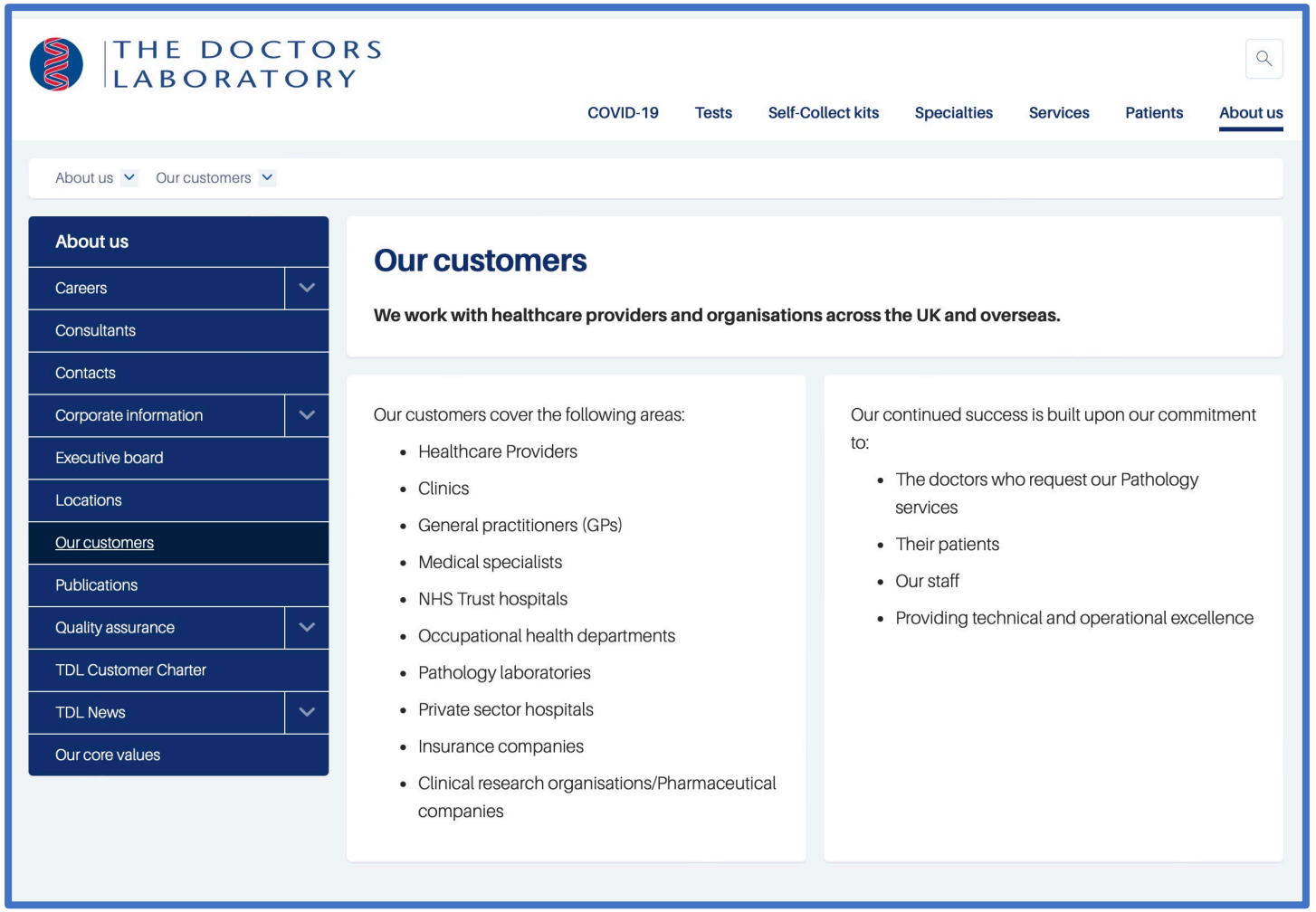
Over a dozen expert booklets, packed with useful information about living …..

Haemochromatosis • UK +Fe
Helping people live with iron overload

The Doctors Laboratory



The Doctors Laboratory



Example 3

23andMe

Hereditary Hemochromatosis (HFE-Related)

Hereditary hemochromatosis is a genetic condition characterized by absorption of too much dietary iron. This may lead to iron overload, which can cause damage to the joints and certain organs, such as the liver, skin, heart, and pancreas. This test includes the two most common variants linked to this condition.

, you have **two copies** of a genetic variant we tested.

Hereditary hemochromatosis is caused by certain combinations of genetic variants. People with this result are not likely at risk of developing iron overload related to hereditary hemochromatosis.

Variant detected

in the HFE gene

How To Use This Test

This test does not diagnose hereditary hemochromatosis or any other health conditions.

Please talk to a healthcare professional if this condition runs in your family, you think you might have this condition, or you have any concerns about your results.

Intended Uses

- Tests for the **C282Y** and the **H63D** variants in the HFE gene linked to hereditary hemochromatosis.

Limitations

- Does **not** test for all possible variants linked to HFE-related hereditary hemochromatosis.
- Does **not** test for variants in other genes linked to hereditary hemochromatosis.
- The interpretation of your genetic result depends on the sex you reported in your account settings.

Important Ethnicities

- The variants included in this test are best studied in people of **European** descent.

You are not likely at risk of developing iron overload related to hereditary hemochromatosis based on your genetic result.

However, if you have a personal or family history of iron overload, consider discussing this result with a healthcare professional.

23andMe

University of Exeter

Haemochromatosis: genetic iron overload disease

Summary for patients

Example 4

C282Y homozygotes

You have two copies of the *HFE* C282Y genetic variant.

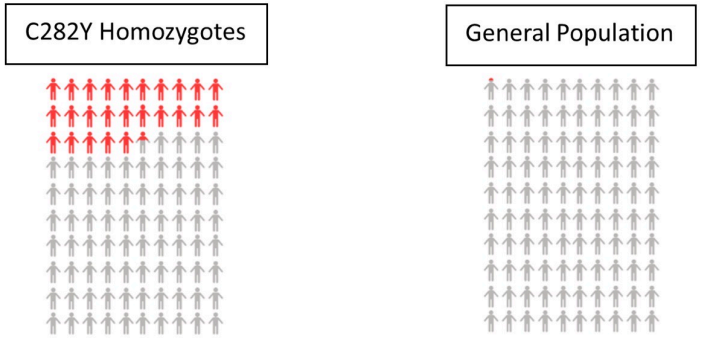
Based on your genotype, you have higher risk of haemochromatosis than the general population.

* Estimates are from our community sample of UK Biobank European descent individuals [1]. People tested because of a health problem or with high iron levels may have different risk. See below **Technical Details** section for more information, and the **Risk Modifiers** page. Page updated 25th May 2023.

Males

Males are known to have higher risk of iron overload disease compared to females.

Haemochromatosis – 25.3% of men in our study with two copies of the *HFE* C282Y gene variant were diagnosed with haemochromatosis. In comparison, only 0.06% of men without a faulty *HFE* gene were diagnosed. Data from the UK Biobank participants linked medical records up to Jan 2018 **[1]**.



25.3 in 100 haemochromatosis diagnoses in C282Y homozygous males vs. 0.06 in 100 in the general population [1].

Search

Summary

This website presents results from our studies of the iron overload disease 'haemochromatosis'. We aim to help individuals interpret their risk once *HFE* genotype is known. Estimates are from our recent peer-reviewed publication:

Atkins et al. (2020) *JAMA*

Disclaimer

The estimates reported are at the group level, describing the risk of disease *on average*, in individuals of European genetic ancestry. Many other factors, especially age, sex, alcohol use, and diet, also impact an individual's disease risk. People tested because of a health problem or with high iron levels may have different risk. We cannot make individual clinical recommendations.

Discussion

Definitions and Terminology

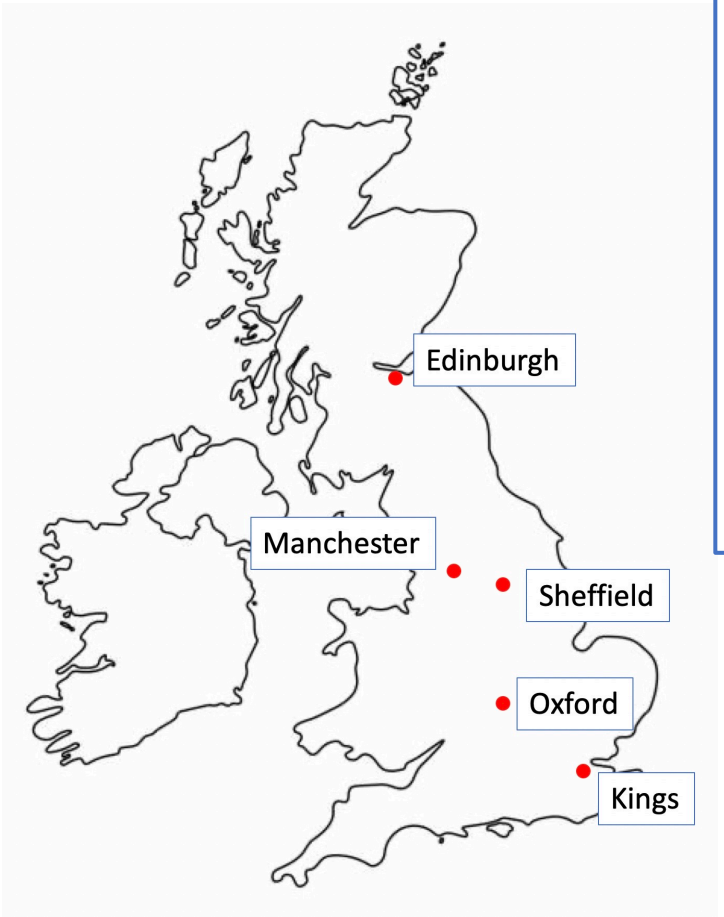
	HIC	
Insignificant	0 - <75 μmol/g	0 – 4 mg/g
Mild	75 - <100 μmol/g	4 – 6 mg/g
Moderate	100 - <150 μmol/g	6 - <8 mg/g
Severe	150 - <300 μmol/g	8 - <16 mg/g
Extreme	>300 μmol/g	>16 mg/g

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

Terms (consistency)

- Haemochromatosis – HH/YY with iron overload
- Hyperferritinaemia – including HD/CY, DD/CC etc
- (proven) Iron Overload – HH/CC, Ferroportin etc

Extended genetic testing



Oxford University Hospitals NHS
NHS Foundation Trust

Oxford Medical Genetics Laboratories

DISORDERS OF IRON REGULATION REQUEST FORM

PATIENT DETAILS (please fill in or attach addressograph)

Surname:		First Name:	
Sex:	D.O.B:	Post Code:	Hospital No:
NHS No:		Consultant/GP:	
Hospital/GP Practice:		*Ethnicity:	

*This must be filled in

REQUESTER DETAILS

Requesting Clinician:	Contact Telephone Numbers:
Address for report:	

INVESTIGATION REQUIRE

Please fill in the appropriate

Cost Centre*

TO AID INTERPRET

Please

Cardiomyopathy	Yes / N
hypogonadotrophic hypogonadism	Yes/No
Diabetes	Yes / N

UNIVERSITY OF OXFORD

Oxford Bi

NHS

National Genomic Test Directory

Testing Criteria for Rare and Inherited Disease

v3 April 2022 (Official)

R96 Iron metabolism disorders - NOT common HFE mutations

Testing Criteria

Iron overload (with raised transferrin saturation and/or serum ferritin) or features of other disorders of iron metabolism in which common HFE mutations have been excluded or are unlikely

Overlapping indications

- R95 Iron overload - hereditary haemochromatosis testing should be used where hereditary haemochromatosis due to common HFE mutations is likely

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics
- Haematology
- Hepatology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R96 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R96.1	Iron metabolism disorders Small panel	Singleton	Small variants	Panel of genes or loci	Iron metabolism disorders (515)	Small panel
R96.2	HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B	MLPA or equivalent

Research opportunities

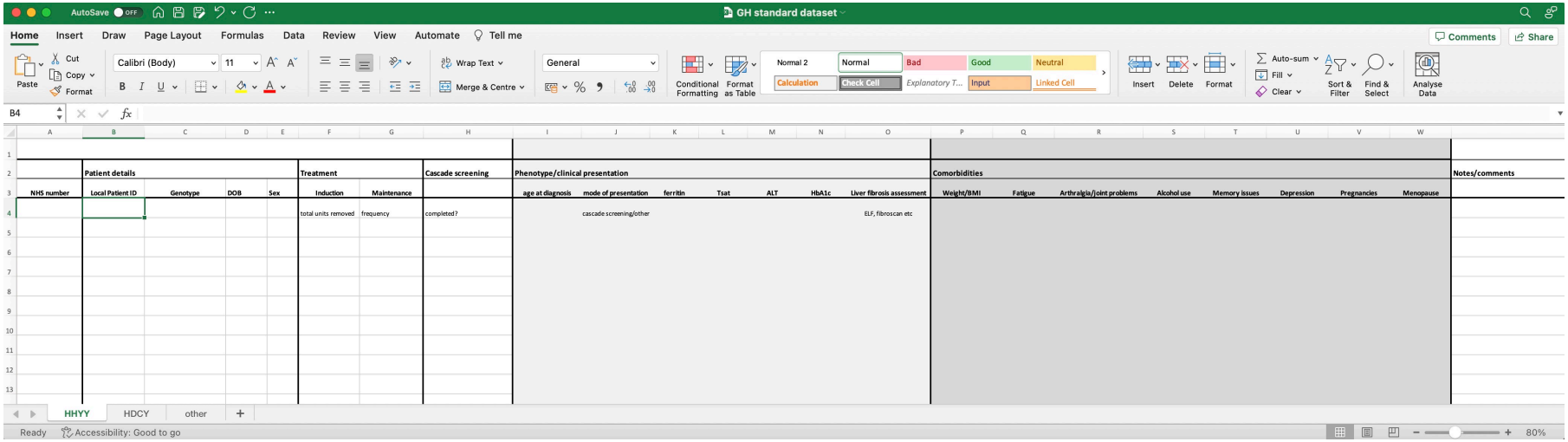
a. Existing patient populations
   - Curation of existing data – patient spreadsheet
   - Retrospective analysis of biomarkers (ELF, HbA1c etc)
b. New clinical presentations
   - Phenotypic characterization
   - Symptom scores/QoL measures - fatigue
c. Genotypically identified individuals
   - Our Future Health
d. Venesection trial

Common dataset

Tier 1 data

Tier 2

Tier 3

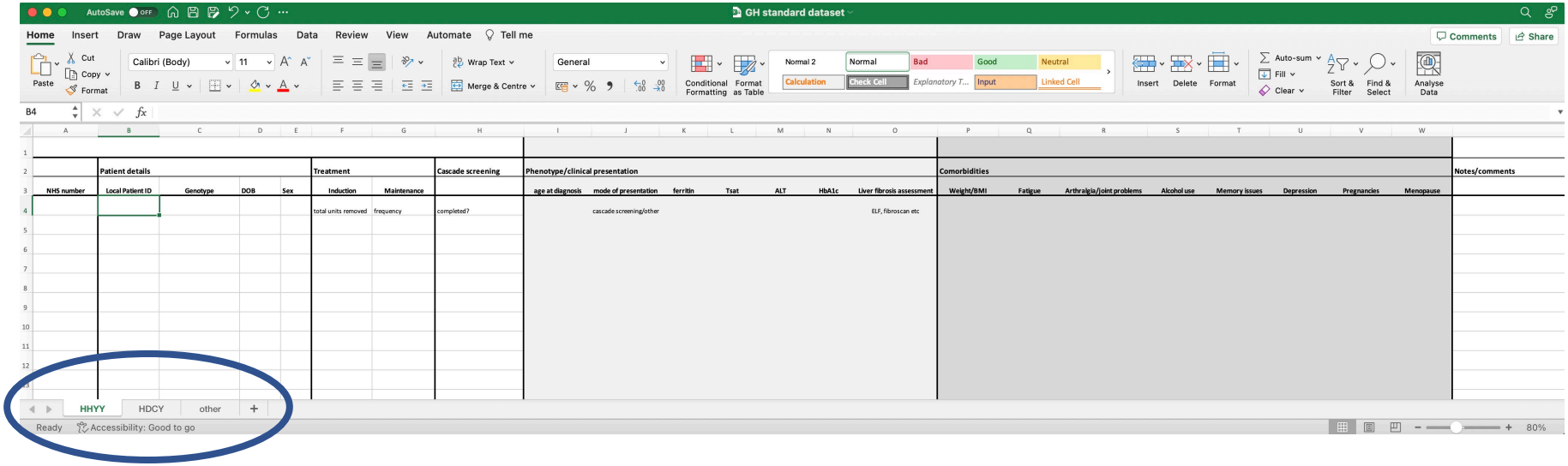


Common dataset

Tier 1 data

Tier 2

Tier 3



Patients sorted by genotype

Primary care group

- Hyperferritinaemia paper submitted to BMJ
  - Stewart *et al*
- Aligned to EASL guidelines
- Describes …
  - Other causes of hyperferritinaemia
  - Guidance on thresholds for HFE testing and referral
  - Use of cascade screening
- Possibility to create aligned GP educational materials

Patient group

- UK based
- A committee of expert patients to advise us on our work, patient-related activities and clinical research
- Seeking alignment with European and International groups/societies (e.g. EFAPH and HI)

Haemochromatosis International

Recent publications of note

Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-023-07873-w

ORIGINAL ARTICLE

Magnetic Resonance Liver Iron Concentration Can Guide Venesection Decision-Making in Hyperferritinemia

Meha Bhuva[1] · Ilse Patterson[2] · Edmund M. Godfrey[2] · David J. Bowden[2] · William J. H. Griffiths[1]

Received: 4 July 2022 / Accepted: 9 February 2023

doi.org/10.1007/s10620-023-07873-w

Digestive Diseases and Sciences
https://doi.org/10.1007/s10620-023-07880-x

INVITED COMMENTARY

Wrought Iron Thresholds: How Magnetic Resonance Liver Iron Concentration Can Guide Decision-Making in Hyperferritinemic Patients

Christopher Cussen[1,2] · Aftab Ala[1,2,3]

Accepted: 9 February 2023

doi.org/10.1007/s10620-023-07880-x

Haemochromatosis

Paul C Adams, Gary Jeffrey, John Ryan

Haemochromatosis is one of the most common genetic diseases affecting patients of northern European ancestry. It is overdiagnosed in patients without iron overload and is underdiagnosed in many patients. Early diagnosis by genetic testing and therapy by periodic phlebotomy can prevent the most serious complications, which include liver cirrhosis, liver cancer, and death. This Seminar includes an update on the origins of haemochromatosis; and an overview pathophysiology, genetics, natural history, signs and symptoms, differential diagnoses, treatment with phlebotomy, outcomes, and future directions.

doi.org/10.1016/S0140-6736(23)00287-8

MRLIC Survey – why now?

- EASL guidelines published June 2022 strongly support the use of MRLIC in the investigation of hyperferritinaemia:

"In patients with an unclear cause of hyperferritinemia, biochemical iron overload (increased transferrin saturation and ferritin) or positive liver iron staining, MRI should be used to quantify hepatic iron concentrations and to assess extrahepatic organ involvement **(LoE 4, strong recommendation, strong consensus)."**

- This is more definitive than BSH/ BSG 2018 or ACG 2019 guidance.

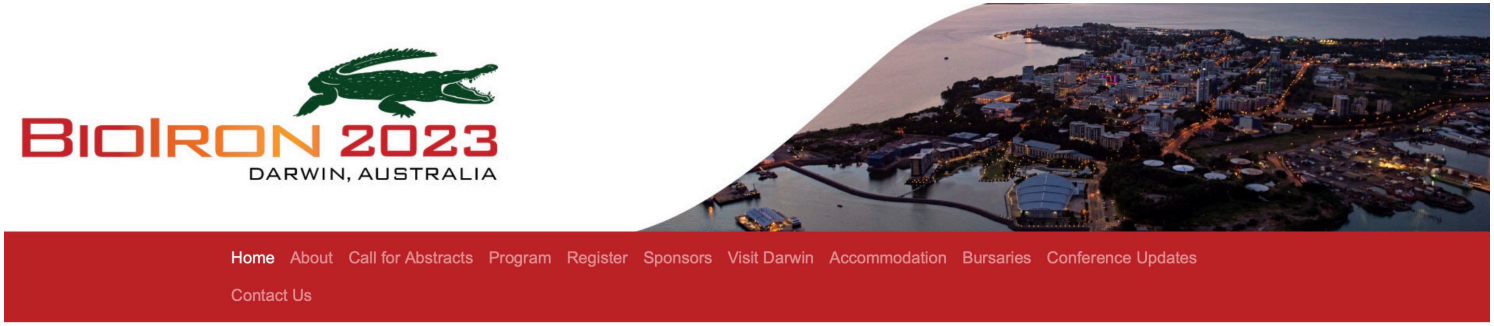
Chris Cusson

MRLIC Survey - aims

- We hope to gain insight into the use of MRLIC:
  - Is it universally available?
  - How is it being used?
  - Is there variation in its application? E.g. between specialties or care setting
  - Are there barriers to it's use?
  - Are liver biopsies still being used to assess LIC?
- Short electronic survey disseminated among radiologists, gastroenterologists/ hepatologists and haematologists

Chris Cusson

Forthcoming meetings



Any Other Business

a. Materials to share via BASL website
b. We would (still) welcome an endocrinologist
c. Date of next meeting
   - Thursday 7th September 2023
d. Apply to BSG, BASL and BSH to support combined iron disorders meeting/symposium??
e. Any further suggestions

jeremy.shearman@doctors.org.uk
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