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Scheme 5B - Interpretive: HFE Genotype and Hereditary Haemochromatosis

Clinical Scenario 5B 01/2024

GP Surgery: Dr Davenport, Davenport GP Practice, 219 Hill Road Leicester LE65, UK
Patient Name: Jane Fenton
Patient Address: 115 The Valley, Leicester LE64
DOB: 17/02/1974

Genotype: Homozygous for *p.Cys282Tyr* variant
Ferritin: 295 µg/L
TS%: 62% (non-fasting) & 52% (repeat fasting sample)
Other: Normal Liver profile & normal serum glucose.
Reason for request: Family screening for HFE; Brother (38yrs) tested homozygous for *p.Cys282Tyr* upon investigation of abnormally raised biochemical indices (ALT 60 IU/L, ferritin 500µg/l & repeat fasting TS of 80%) with arthralgia
Clinical information: Post-menopausal for 2 years
Other: One daughter **(**20yrs) & one son (28yrs**)**
Date of receipt of sample: 02/04/2024

You are required to write a genetic report to Jane's GP clearly stating diagnosis, risk & all follow up actions required. In the report you are required to state all HFE genetic results according to HGVS nomenclature. (Please refer to best practice guidelines. Porto, G., Brissot, P., Swinkels, D. *et al.* EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *Eur J Hum Genet* **24**, 479–495 (2016). https://doi.org/10.1038/ejhg.2015.128)

You are also required to comment on the clinical penetrance of HFE with regard to the patients age & biological sex as the has GP previously phoned the lab with a general query in relation age of onset of symptoms in HFE.

The report should contain sufficient information for the GP to determine what further action is required.

Clinical Scenario 5B 02/2024

GP Surgery: Dr Jones, Dinas Surgery, Scarlet Road, LL00 5SQ
Name: Arwel Thomas
Patient Address: 18 Violet Terrace, LL00 5SQ
DOB: 27/05/1990
NHS: 109 876 5431
Genotype: Homozygous for *p.His63Asp* variant
Ferritin: 150 µg/L
TS%: 44% (fasting sample)
Clinical details. Fatigue**.** Father had a haemochromatosis variant and died mid 60's with a hepatocarcinoma. Worried about his 18 year old son. Mother's genotype unknown.
Date of receipt of sample: 15th March 2024

You are required to write a report to Arwel's GP clearly stating diagnosis, risk & all follow up actions required for Arwel and his son. In the report you are required to state all HFE genetic results according to HGVS nomenclature. (Please refer to best practice guidelines. Porto, G., Brissot, P., Swinkels, D. *et al.* EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *Eur J Hum Genet* **24**, 479–495 (2016). https://doi.org/10.1038/ejhg.2015.128).

The report should contain sufficient information for the GP to determine what further action is required.

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General feedback/comments from the assessors:

For this distribution we felt the presentation of the reports was a key aspect to clarity and ease of interpretations. Some laboratories do this very well, in others the message can become slightly blurred.

The best examples use a table to present the results using the HGVS nomenclature (sometimes showcasing old style and current expected format for the variants) and give clear instructions to an unspecialised clinician in their follow up actions.

Where possible, it could be worth reviewing your report format and seeing how easy it is to process. However, We also understand not every laboratory produces a report as is required by this Scheme for presentation of their results clinically, but the key message of clarity remains.

Regarding current, expected format of the variants, HGVS nomenclature which includes cDNA and protein results [e.g. HFE c.845G>A p.(Cys282Tyr) and HFE c.187C>G p.(His63Asp)], should ideally be used at least once in the report, with correct punctuation marks etc. The use of shortened versions elsewhere throughout the report is acceptable. As a minimum requirement, HGVS nomenclature in reports for assessment purposes should be p.(Cys282Tyr) & p.(His63Asp).