Scheme 5B – Interpretative HFE Genotyping and Hereditary Haemochromatosis

General Comments Scenarios 3 and 4 /2017 **Distributed August 2017**

Scenario 3

In this scenario the patient was the sister of someone known to be homozygous for the C282Y mutation. The patient was found not to have C282Y or H63D and therefore the risk of developing HH due to the known family history is virtually excluded, no further investigations are warranted unless there is clinical or biochemical evidence of iron overload. It is disappointing that only 4 reports specifically referred to the family history when interpreting the risk to the patient. Few labs interpreted the risk to the family: namely that the risk of C282Y homozygosity in the parents has been excluded, there is no risk to her children but the risk to any of the patient's untested siblings remains. Several labs did not provide any comments on the result for H63D testing even though this information had been supplied in the scenario.

Scenario 4

In this scenario the patient was the son of a C282Y/H63D compound heterozygote. The patient was found to be homozygous for the H63D mutation. Again it is disappointing that few reports specifically referred to the family history when interpreting the risk to the patient.

Returns for scenario 4 contained a wide range of suggested actions for the management of the patient with H63D homozygosity (without current documented evidence of iron overload) reflecting differences between the 2006 King and Barton and the 2016 Porto et al best practice guidelines in this respect. The Porto guidelines suggest that additional comments may refer to the uncertainty and controversy regarding the role of p.H63D as a risk factor for mild to moderate iron overload. However, Labs should be aware that testing and monitoring of iron indices is not suggested in the Porto guidelines and investigation of H63D homozygous individuals without known iron overload is not supported by substantial evidence and frequent monitoring is not indicated. The assessors have not penalised labs which suggested moderate monitoring, however a careful balance needs to be made between the lifetime expense of monitoring, particularly if a short interval is suggested, offset against the very low risk of developing HH with this genotype.

Some labs failed to mention that the C282Y mutation had not been detected and only mentioned the H63D result.

Reports scores

Overall the standard of reports was good with a few clerical or typographical errors noted. Some reports still include only minimal or no statements about the genotyping method used, without supplying specific information (e.g. a reference, or other information about primer or probe sequences, or specificity and sensitivity of the method. Just under half of the labs submitting reports included full HGVS nomenclature, and some included "CCDD" as a genotype annotation which the

assessors considered not to be good practice. The latest best practice guidelines (Porto et al, 2016) state it is considered essential that reports follow HGVS guidelines for reporting variants, however, this should not be at the expense of a clear and succinct description of the genotype. The guidelines do not exclude the inclusion of the legacy nomenclature which most clinicians will be familiar with. HGVS nomenclature should include an up to date reference sequence (ideally LRG_748t1 or NM_000410.3) with mutations named at both nucleotide and protein level:

Legacy name	HGVS nucleotide name	HGVS protein name
C282Y	c.845G>A	p.(Cys282Tyr)
H63D	c.187C>G	p.(His63Asp)