Scheme 5B – Interpretative HFE Genotyping and Hereditary Haemochromatosis

General Comments Scenarios 1 and 2 /2017 **Distributed February 2017**

Scenario 1

In this scenario the patient is a compound heterozygote for the C282Y and H63D mutations. The current transferrin saturation level of 43.1% is not suggestive of iron overload. The ferritin level is raised and warrants immediate further investigations to identify its cause, reports should have stated this. One or two of the submitted reports incorrectly interpreted the iron indices as consistent with iron overload or suggested phlebotomy before further investigation of the raised ferritin. Heterozygosity for the C282Y and H63D mutations excludes the most common cause of HFE related HH, but nonetheless confers a moderate risk of developing HH and therefore some recommendation for monitoring ferritin and transferrin saturation should be given. The assessors recognise that in the absence of clear recommendations in the latest guidelines (Porto et al, 2016) it is difficult to decide what is a suitable transferrin saturation and ferritin monitoring interval to recommend for C282Y/H63D compound heterozygotes. It is however the job of specialists providing interpretive reports to GPs to suggest an interval if monitoring is suggested. Although the evidence is poor, it is logical for labs offering H63D testing to suggest some monitoring and that the interval for follow up could be longer than that suggested for C282Y homozygotes. Annual monitoring places a burden of cost and effort on patients and health care providers and without supporting evidence is probably too frequent, although pragmatically it may be easier to ensure monitoring actually occurs if it is done annually. Monitoring every 3-10 years is supported by some published recommendations and could be modified by patient status e.g. elderly, pre-menopausal etc.

Heterozygosity for the C282Y and H63D mutations has implications for other adult first degree relatives and the majority of laboratories made an appropriate comment to this effect in their reports. A small number of labs were penalised for not specifying first degree relatives, having implied that testing to the wider family could be offered; which is not considered appropriate. No labs received penalties for using the term offspring without qualifying with aged over 16, a noticeable improvement compared to previous years.

Scenario 2

In this scenario the patient was undergoing a predictive test and was heterozygote for the H63D mutation. The risk and follow up actions were handled well by the majority of labs. A few labs made assumptions about iron overload in the patient which were not implied in the referral information, and consequently their reports suggested further investigations or monitoring that was not required. Cascade testing for the H63D mutation to offspring or the wider family is not warranted. However, many labs failed to recognise that either parent of this patient could be a C282Y homozygote and one must be a C282Y/H63D compound heterozygote; any sib could have either of these genotypes. As both genotypes are associated with some risk of developing HH the assessors felt that some comment recommending testing of the patient's parents and other siblings was warranted and a penalty was awarded where this was not addressed.

Reports scores

The overall standard of reports was good with very 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) and therefore the statement may be of little use. Just over half of the labs submitting reports included full HGVS nomenclature. The latest best practise 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)

The assessors apologise for the unintentional typographical error in the date of birth of the patient in scenario 1 (31/06/1968). Only one lab highlighted this error, other labs corrected to 30/06/1968 assuming the error was in the day rather than the month.