Scheme 5B – Interpretative HFE Genotyping and Hereditary Haemochromatosis

General Comments Scenarios 1 & 2 /2015 **Distributed January 2015**

The overall standard of reports was reasonable with very few clerical or typographical errors noted. Most reports have a statement about the genotyping method used, but many do not give specific information (e.g. a reference, or other information about primer or probe sequences), and therefore the statement may be of little use. The recommendation that the method should be indicated is so that a reader of the report (including another lab testing family members using a different method) can know the specificity and sensitivity of the method (e.g. in RFLP methods, the specificity depends on whether a restriction site has been created or abolished). Once again less than half of the labs submitting reports included full HGVS nomenclature and have received a comment on this as in previous years. The use of HGVS nomenclature is widely accepted and recommended as the standard for the documentation of mutations and provides an unambiguous and consistent naming convention. HGVS nomenclature may not yet be familiar to some clinicians, but this is not a reason to shy away from including it.

Scenario 1

This scenario is perhaps not atypical of some of the referrals received for HFE testing, a 68 year old male with raised ferritin and no further details supplied. The absence of both the C282Y and H63D mutations makes a diagnosis of HFE related (type 1) haemochromatosis extremely unlikely, however, other types of haemochromatosis (primary and secondary) have not been excluded. A report with sufficient information for the GP to determine what further action is required should consider the causes of elevated ferritin and offer clear advice on further testing. Hardly any reports commented on ferritin as an acute phase protein which can be raised due to infection, inflammatory disorders or malignancy for example. Similarly some reports did not consider the possibility of secondary overload as the cause of raised ferritin in this patient. Therefore, further actions for the GP to investigate the raised ferritin were either absent or unclear and penalties were deducted accordingly. Repeating the serum ferritin test should be recommended followed by fasting Tfsat if iron overload is still suspected, test that the GP could request in the first instance without onward specialist referral. Testing for rare genetic causes can be considered if iron overload is confirmed and secondary causes have been excluded.

Scenario 2

This scenario concerned predictive testing for the 81 year old father of a son with a diagnosis of haemochromatosis. As carrier of only the C282Y mutation Geoffrey Ford is at reduced risk of developing HFE related (type 1) haemochromatosis. However, in the absence of information that his son has confirmed HFE related haemochromatosis, Geoffrey may be still at risk as other rare genetic causes have not been excluded. Many reports failed to recognise or comment on this or offer any further advice. If the son is not a C282Y homozygote or compound heterozygote for C282Y/H63D measurement of serum ferritin and fasting Tfsat would be advisable for Geoffrey with further investigations if there is evidence of iron overload.

As a carrier of C282Y many reports correctly recommended genetic testing for Geoffrey's first degree relatives, however some did not clearly specify adult first degree relatives. Children under 16 are not at risk of developing haemochromatosis and testing should be deferred until adulthood when able to independently seek a consultation and consent to testing. Laboratories should clearly state adult first degree relatives. Penalty marks have been deducted when this hasn't been clear, this has been highlighted previously on several occasions in the 5B scheme general comments.