## Scheme 5B – Interpretative HFE Genotyping and Hereditary Haemochromatosis

**General Comments Scenarios 3 and 4 /2016** **Distributed June 2016**

### Scenario 1

In this scenario the patient has two highly elevated ferritin levels and one raised transferrin saturation level, which taken with homozygosity for the C282Y (c.845G>A, p.(Cys282Tyr)) mutation is suggestive of type I haemochromatosis. However, a formal diagnosis of HH can only be made with proven evidence of hepatic iron overload.

Several reports stated that that the genotype was consistent with a diagnosis of HH without any further qualification. Without further comment and recommendations for further investigations (i.e. confirmation of iron overload) there is the potential for mis-interpretation of the results.

Many reports neglected to mention that this genotype requires lifelong monitoring of iron indices, and if iron overload confirmed treatment by quantitative phlebotomy to normalize iron stores would be required. Whilst onward referral is acceptable, the assessors felt that mention of ongoing monitoring should be included in the report in case the advice of specialist referral is ignored.

Information on testing for other family members should include first degree relatives (particularly siblings) to be advised of the benefits of screening. Reports could include the information that Roy's offspring will be obligate carriers of C282Y, however, screening of children <16 years of age should in most cases be deferred until they reach 16.

### Scenario 2

In this scenario the patient is identified as a compound heterozygote for C282Y (c.845G>A, p.(Cys282Tyr)) and H63D (c.187C>G p.(His63Asp)) which gives her an increased risk of developing HH (higher than general population but lower than C282Y homozygosity). The submitted reports dealt with this risk in variety of ways, but simply stating that the risk is low without any further qualification could be misleading and could be interpreted that no further action is required.

One report which the assessors felt succinctly conveyed very well an appropriate level of risk said "this genotype confers susceptibility to HH but the majority of patients will remain asymptomatic". A comprehensive report should suggest immediate tfsat and ferritin test and suggest further investigations if ferritin is raised. If ferritin levels are normal regular monitoring is advisable, although there is no consensus in the literature on frequency of monitoring for compound heterozygotes.

Risks to other family members should have addressed the risks to Alison's offspring given that the referral information stated that her husband is a carrier of C282Y. Therefore, offspring will have a 1 in 4 chance of being C282Y homozygotes and therefore at risk of type 1 HH. Their children also have a 1 in 4 chance of being C282Y/H63D compound heterozygotes with a smaller but significant risk of type 1 HH. Genotyping of offspring can be offered to offspring (deferred until they reach 16 years of age) and other adult first degree relatives.

**Report Comment**

There were a number of errors where incorrect information regarding patients' family histories was either incorrectly transcribed or incorrectly inferred from the referral information supplied. This is of particular importance when a risk figure is then provided for other family members and lead to incorrect risk figures or inappropriate advice for monitoring of other family members in several reports.

Many reports have minimal description of the methodology used without references to source of methodology, statements on analytical or clinical sensitivity or limitations of the assay used.

There are still a number of laboratories that are not using HGVS nomenclature for the description of mutations. HGVS nomenclature is an internationally accepted standard in reporting the results of molecular testing for mutations. It requires description of variants at both nucleotide and protein level and use of a correct reference sequence. See http://varnomen.hgvs.org/ for full details and explanations and best practise guidance referenced below.

Participating laboratories will find useful information in the follow best practice guidelines from the professional bodies of the Association for Clinical Genetic Science (ACGS) and European Society of human Genetics (ESHG) which cover general recommendation for the reporting of molecular test results.

http://www.acgs.uk.com/media/949852/acgs_general_genetic_laboratory_reporting_recommendations_2015.pdf

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3895644/