Appendix 3. Evaluation of phenotypes in heterozygotes (PS4)

Note: When evaluating cases be aware of potential complex genotype interactions.

	Evidence	Parameter	Impact threshold	Alternative terms	Points per case	Max	Comment
alpha thalassemia [AR]	Reduced MCV Reduced MCH	MCV (fL) MCH (pg)	<79 <27	Microcytosis Hypochromia	0.15	1.5	Primarily for thalassaemias and thalassaemic Hb variants. Do not use if the RBC count is decreased or iron deficiency is present
	Reduced MCV Reduced MCH Normal HbA2	MCV (fL) MCH (pg) HbA2 (%)	<79 <27 <3 (normal)	Microcytosis Hypochromia	0.15	1.5	Caution needed for other possible causes, e.g. iron deficiency, beta+delta thalassaemia or large beta-locus deletions. Do not use if the RBC count is decreased or iron deficiency is present.
	Reduced MCV Reduced MCH Normal or increased RBC count	MCV (fL) MCH (pg) RBC (10^12/L)	<79 <27 4.7–6.1 for men (normal); 4.2–5.4 for women (normal)	Microcytosis Hypochromia	0.2	1.6	Primarily for thalassaemias and thalassaemic Hb variants. Do not use if there is an indication of recent correction of iron deficiency.

	Reduced MCV Reduced MCH excluding iron deficiency (i.e. normal serum ferritin, transferrin saturation, TIBC)	MCV (fL) MCH (pg)	<79 <27	Microcytosis Hypochromia	0.3	3	Primarily for thalassaemias and thalassaemic Hb variants

*only consider independent (unrelated) cases. Multiple cases in a family are counted as one

** do NOT use multiple point levels for the same case

Point sum and evidence strength

Supporting	Moderate	Strong	Very Strong
0.5-1.49	**1.5-3.49**	**3.5-15.99**	**≥16**