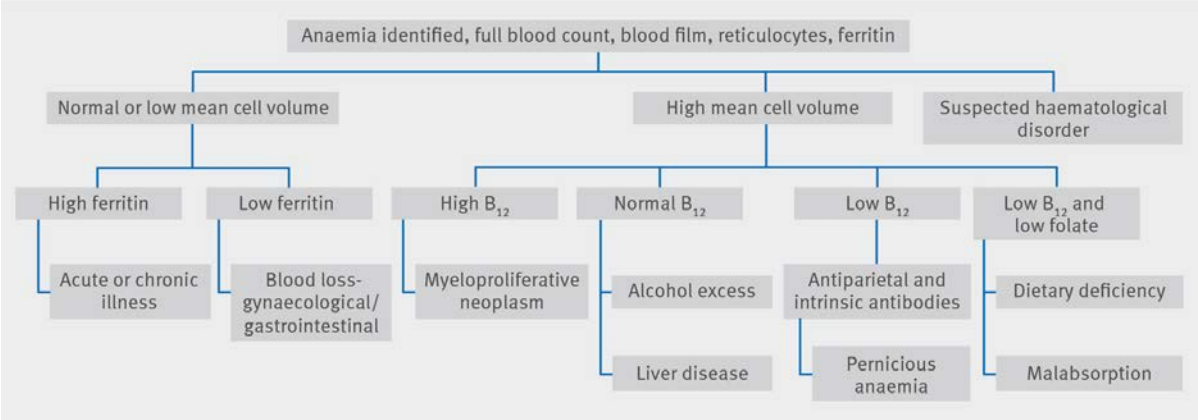
Appendix 1.

Diagnostic Algorithm for the diagnosis of microcytic and macrocytic anaemias.



[Expert reviewer's comment: There are other details that could be added to this algorithm:

- high B12 levels are not specific for myeloproliferative disorders. B12 supplements are a common cause (obviously) but other causes exist, and in fact myeloproliferative disease will be a rare cause
- B12 should not be tested in pregnancy (unless compelling clinical features suggest you do so). It is likely to be falsely low, and cause anxiety and further unnecessary testing.

Low B12 and folate - on the right of the above diagram - does not simply imply poor diet – true low B12 levels will lead to low folate levels.]

Appendix 2: Patient Information Leaflet: Inheritance of Haemochromatosis

Haemochromatosis is a disorder of the ways that iron is absorbed from the bowel, resulting in iron accumulating in many organs throughout the body, especially the liver. Inherited disorders are caused by defective genes in the cells which make up the body. Genes, which are sections of DNA, contain the information the body needs to develop from the egg and to maintain itself in good working order. There are about 30,000 genes, and every cell in the body (except sperm and egg cells) contains two copies of each. One of these copies is inherited from the mother and one from the father.

In 1996 the “HFE gene” was identified as the major gene affected in haemochromatosis. A small change (mutation) is present in both copies of the HFE gene in over 90% of those diagnosed with genetic haemochromatosis (GH). We now know that there is more than one gene mutation known to cause GH. GH is a 'recessive' disorder. This means that the risk of absorbing excess iron will only occur if ***both*** copies of the gene are abnormal. If only one copy is defective, an individual will be perfectly healthy but will be a 'carrier'. This means he or she will be able to pass on the abnormal gene to a son or daughter.

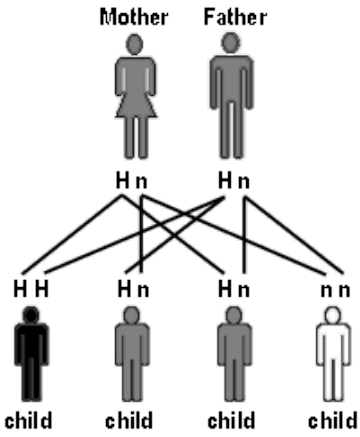
Sperm and egg cells have only one copy of each gene, and on average half the eggs or half the sperm of a carrier will contain the defective version. By contrast, ALL the eggs or sperm of an individual in whom both gene copies are defective and who, as a result, suffers from GH, will carry the abnormal gene.

To develop GH you have to inherit a defective gene from both your parents. This can happen in three ways:

1. If both parents are carriers (most common method - about 12.5% of the population are carriers, so 1.6% of marriages will be between carriers). On average a quarter of the children will develop GH, half will be carriers, and a quarter will be completely normal – see diagram below.
2. If one parent has GH and the other is a carrier (about 1 in 2000 marriages), on average half the children will develop GH, the other half will be carriers.
3. If both parents suffer from GH, (a very rare event, occurring in about 1 in 100,000 marriages) all the children will inherit two defective genes, and will have GH.

It should be emphasised that the proportions given in examples 1 and 2 above are averages for the whole population. For example in any family where both parents are carriers (example 1, and diagram below) it would be possible for all children to be affected, all to be carriers, or for all to be normal. It’s a matter of chance, every time a child is conceived.

The diagram below shows how recessive inheritance works, on average, when both parents are carriers: n= normal gene, H= gene for GH, Hn = carrier, nn = completely normal, HH = at risk of developing haemochromatosis.



Relatives who are at risk should be tested for the HFE gene. This is **absolutely essential** in the case of brothers and sisters (siblings) who stand at least a 1 in 4 chance of being affected. Parents, partners and children from the age of 18, should also be tested. If you have symptoms suggestive of GH, you should raise the possibility with your doctor.

Not everyone in the family may wish to be tested. This is a very personal decision – some people believe that they “would not wish to know what will happen” when they get older. It can cause anxiety if not properly discussed at the time of testing. However in the case of GH there is good evidence that knowing about the risk to your iron stores in advance - and being able to have treatment and advice about your lifestyle before symptoms develop – can prevent you becoming ill at all. Treatment simply involves having your blood taken regularly to keep the iron stores down to a normal level. Thus having the test can make sure that people in your family at risk of GH can live entirely normal lives.