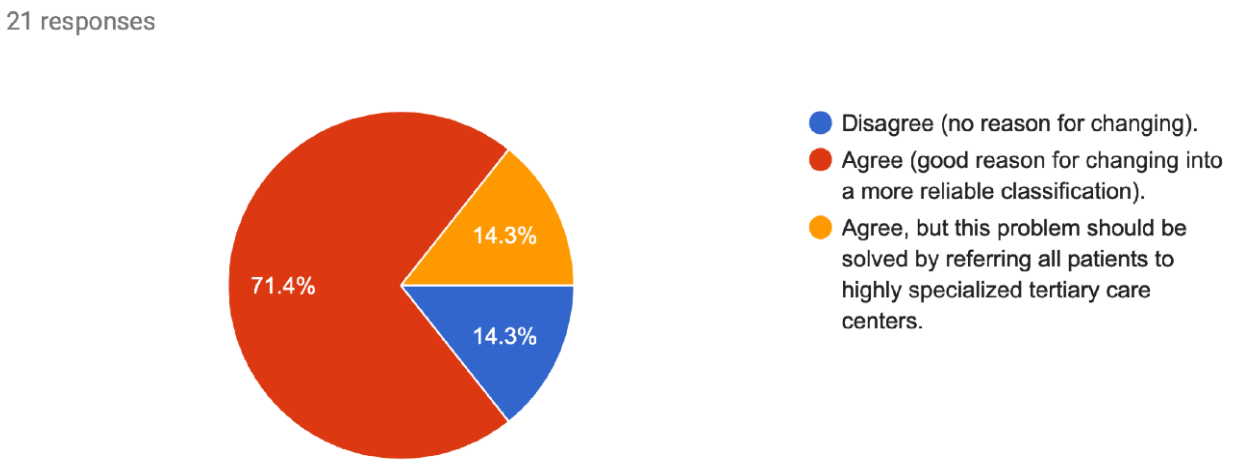
Supplementary Material (S1): Initial survey sent to panelists.

This survey was conceived by the writing committee (DG, FB, PB, IC, GP, and MM), created by Google Surveys (by GM) and sent to all the panelists several weeks before the Meeting of the BIOIRON Society held in Heidelberg on May 5-10, 2019. Results were presented during the Meeting and served as a basis for an extensive critical discussion during a specific session held on the last day of the Meeting. Responses ("R") are presented as pie charts. Separate charts are presented for clinicians and non-clinicians when initial differences were evident between the two subgroups. Final consensus on the major points was reached during the Meeting discussion.

R1: The most widely reported classification of genetic hemochromatosis (in textbooks as well as in authoritative reviews) distinguishes 4 types (and 2 subtypes like 2a/2b and 4a/4b) of hemochromatosis, according to the different genes involved. It appears very accurate from molecular and pathophysiological viewpoints, but often poorly applicable in daily clinical practice because of multiple barriers. Your opinion regarding the last sentence is:



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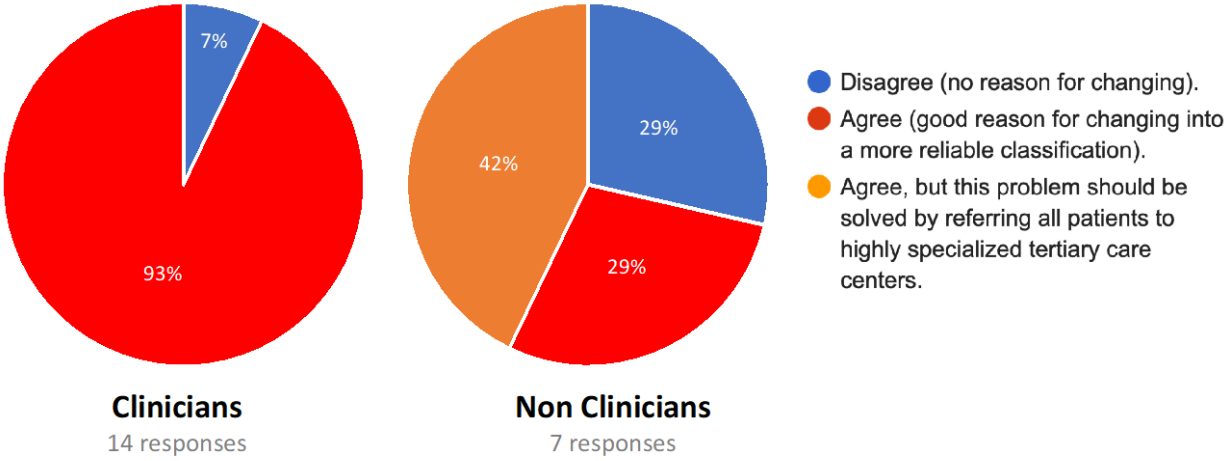
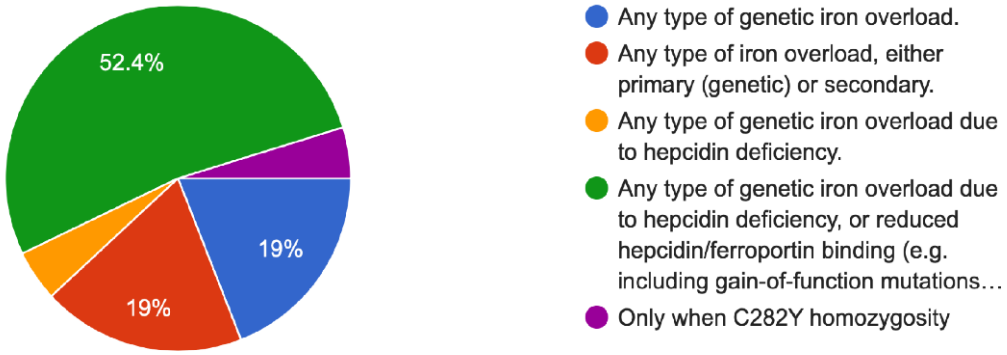


R2: In your opinion, the term “hemochromatosis” most appropriately applies to:

21 responses



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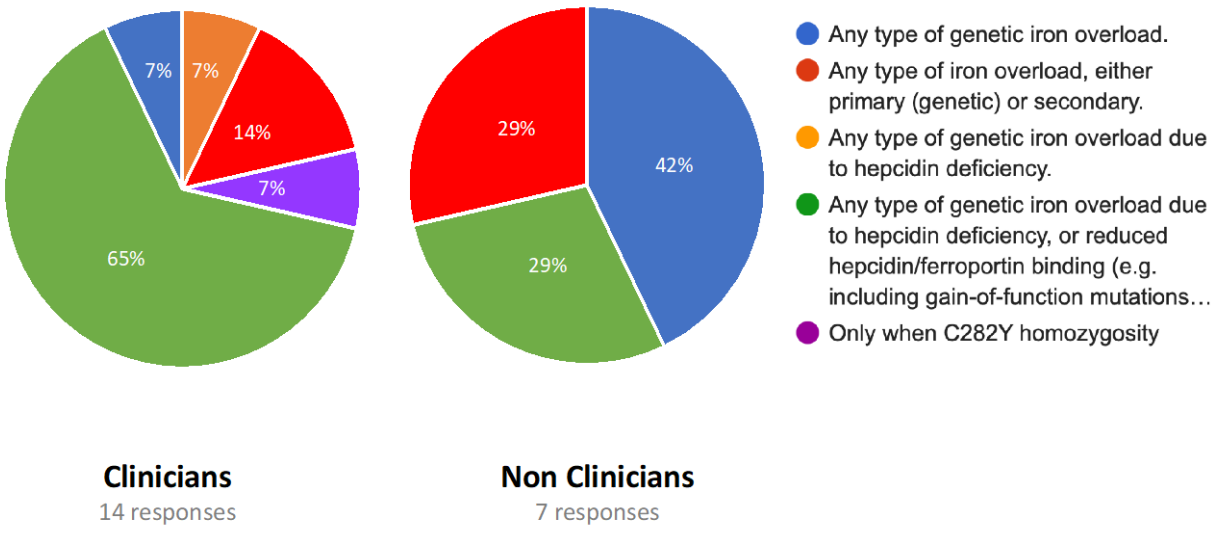
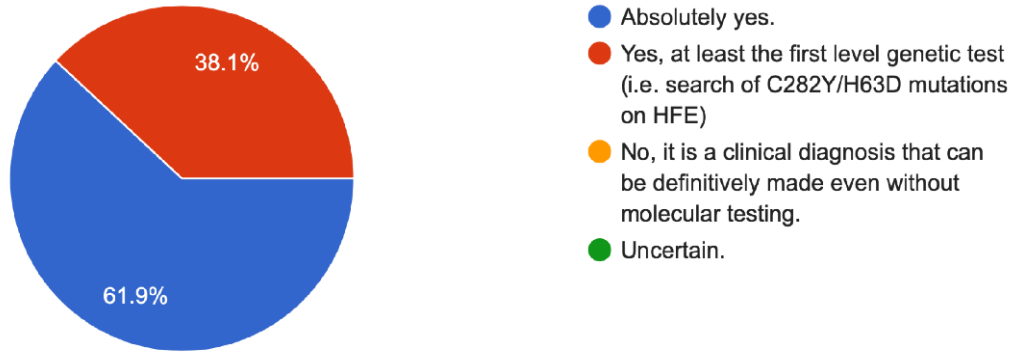


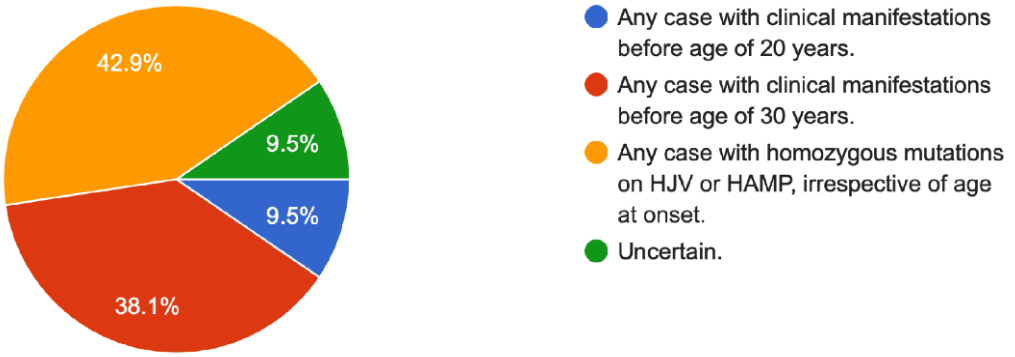
R3: Generally speaking, do you think that molecular testing should be always required for diagnosing genetic hemochromatosis?

21 responses



R4: In your opinion, the term “juvenile” hemochromatosis should be used for:

21 responses



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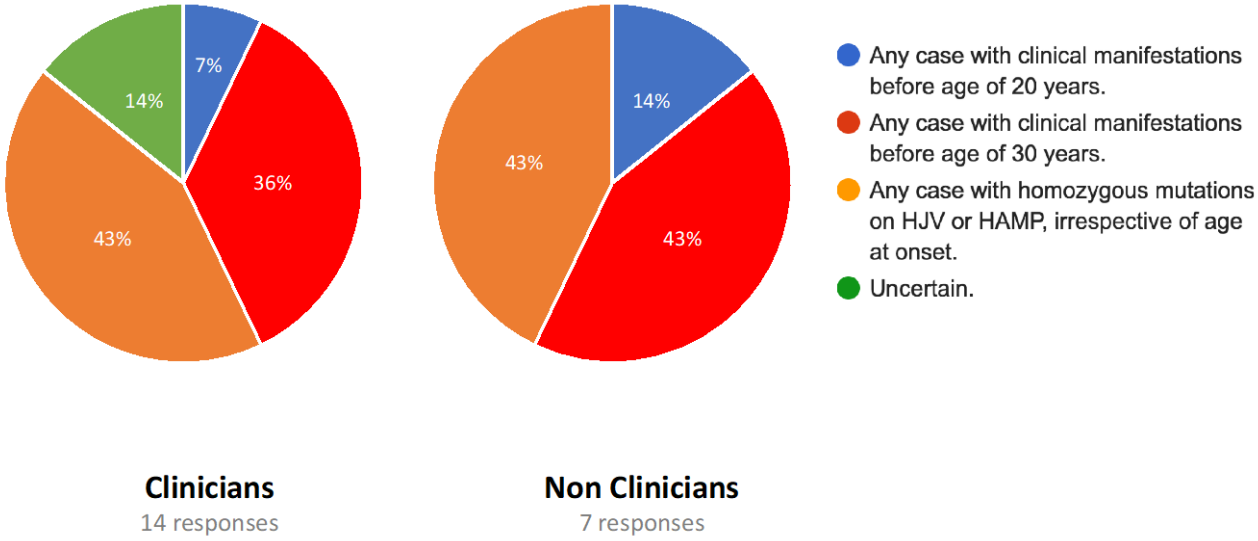
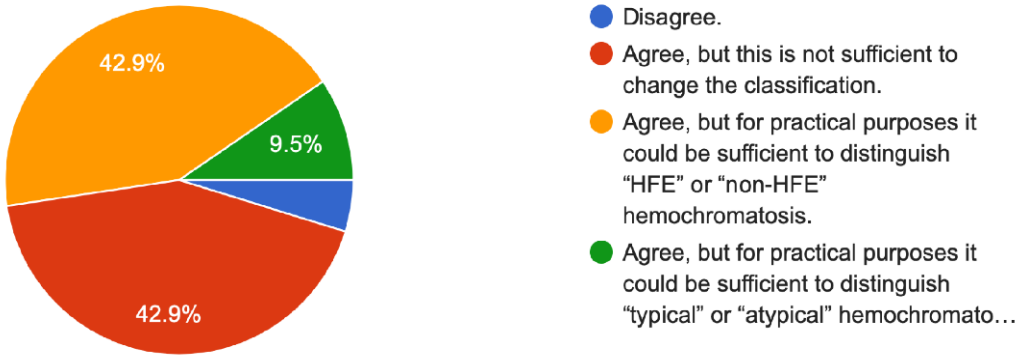


R5: In daily clinical practice, a limitation of the current classification of genetic hemochromatosis into 4 types is that second level genetic tests based on sequencing are available only at few referral centers, so that many cases not due to C282Y homozygosity often remain “undefined”. Your opinion on this point:

21 responses



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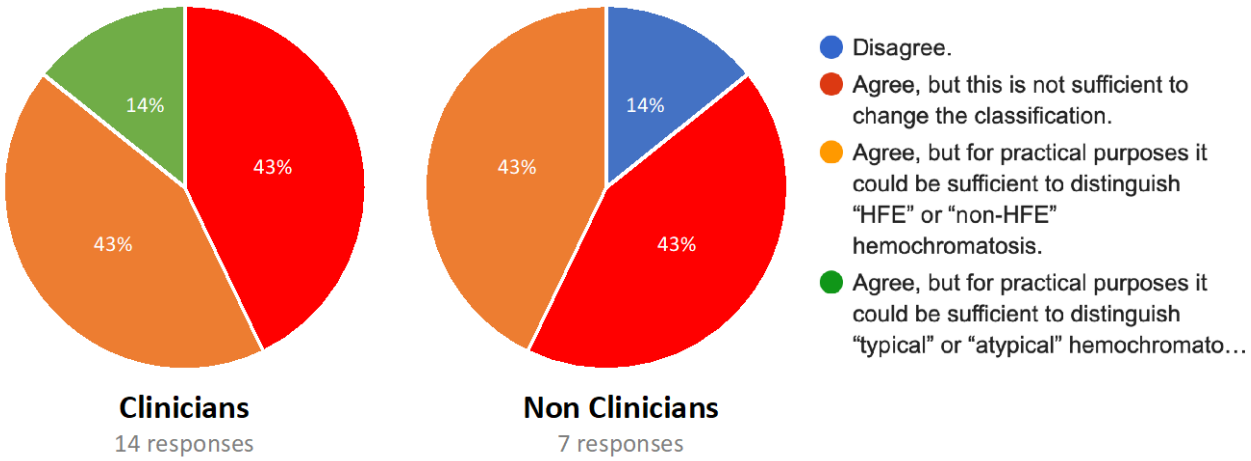
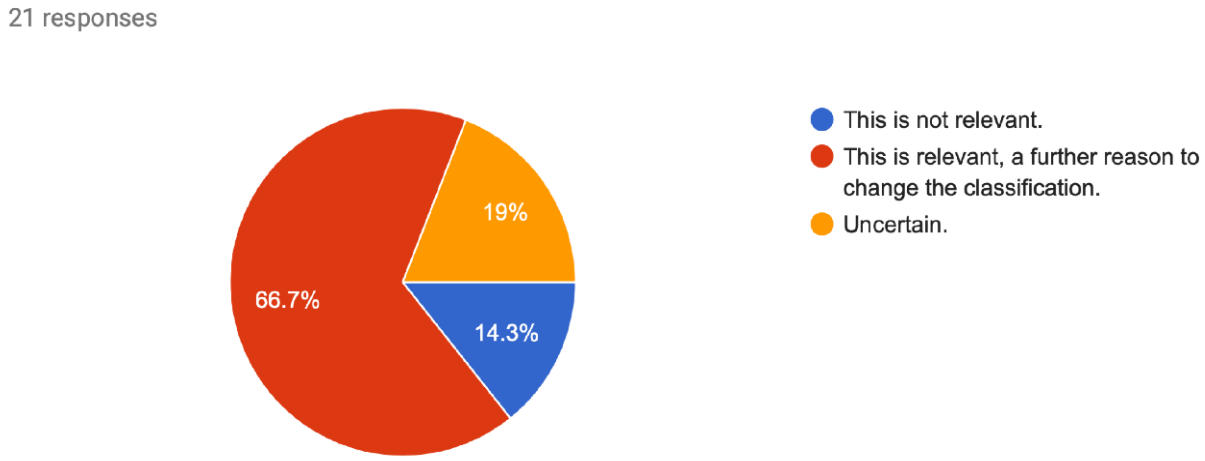
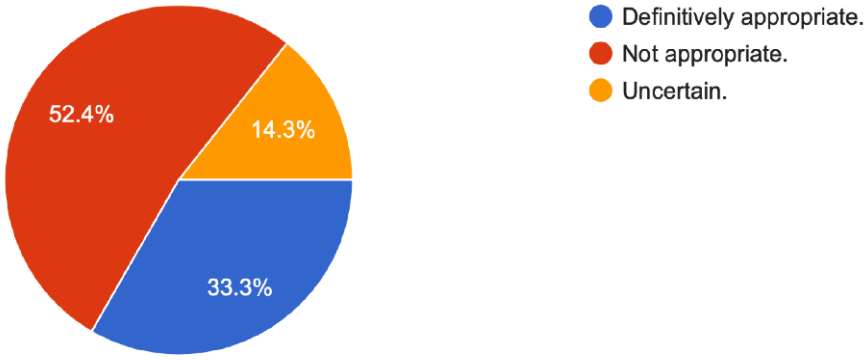


R6: Another possible limitation of the current classification of genetic hemochromatosis into 4 types is that cases due to digenic inheritance (e.g. double heterozygosity for mutations in HFE and HAMP) are not included. Your opinion on this point:



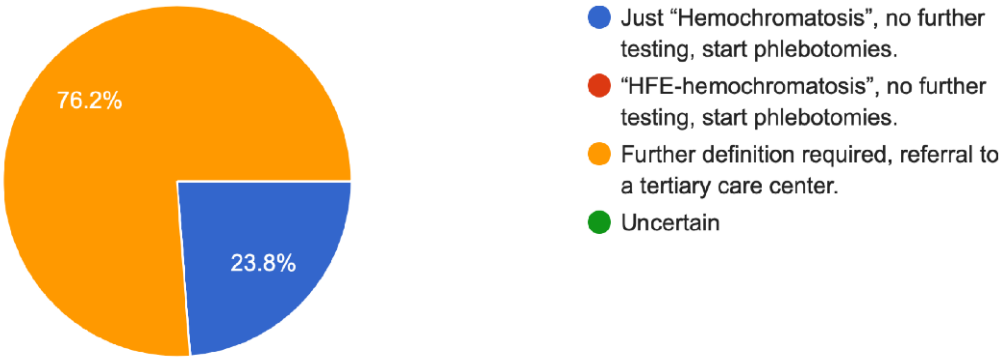
R7: Hemochromatosis due to C282Y homozygosity on HFE is frequently termed as “classical”. Your opinion on this term:

21 responses



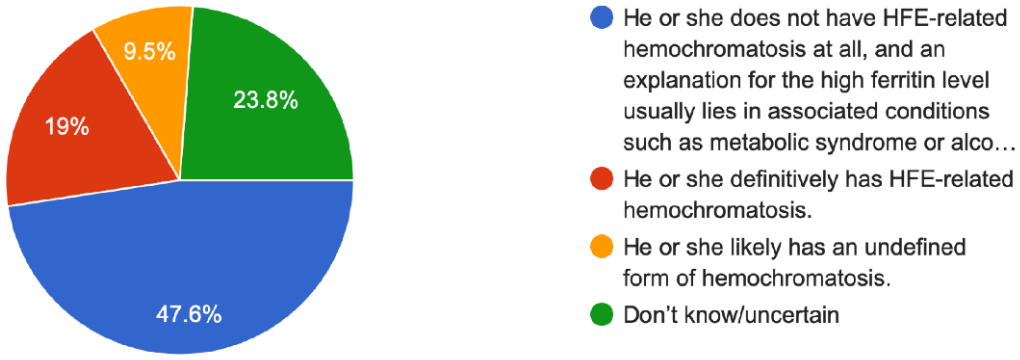
R8: “Classical”, “type 1”, or “HFE-related” hemochromatosis are generally interchangeable terms used for C282Y homozygous patients. Suppose you have a patient with ferritin 1200 ng/ml (no alternative explanation), TSAT 85%, parenchymal iron overload with fibrosis at liver biopsy, and “simple” C282Y heterozygosity (H63D wt) on first level genetic test. Most likely the patient would carry another mutation on HFE gene that would require sequencing (not available at your site). How do you diagnose/classify/manage this patient?

21 responses



R9: How would you diagnose/classify a patient referring because of ferritin 850 ng/ml, TSAT 51%, first level genetic test showing compound heterozygosity C282Y/H63D on HFE, minimal or moderate increase of LIC at MRI:

21 responses



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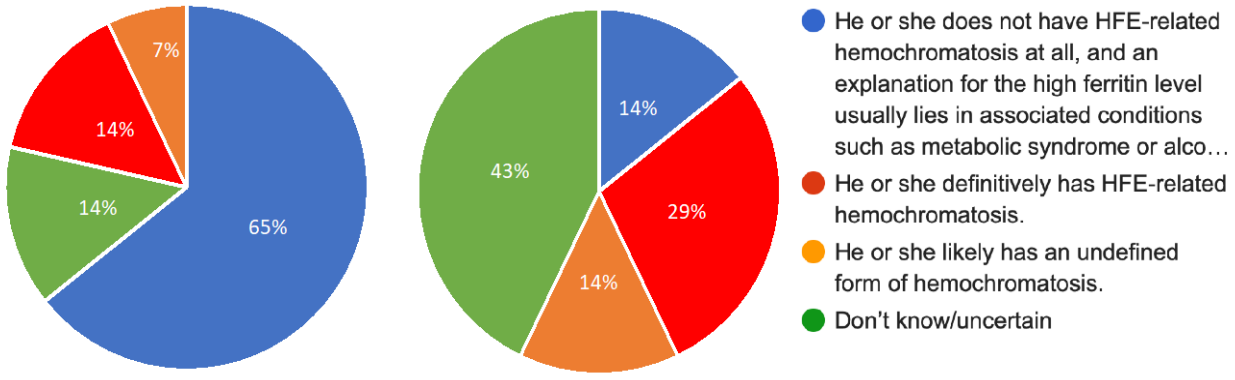
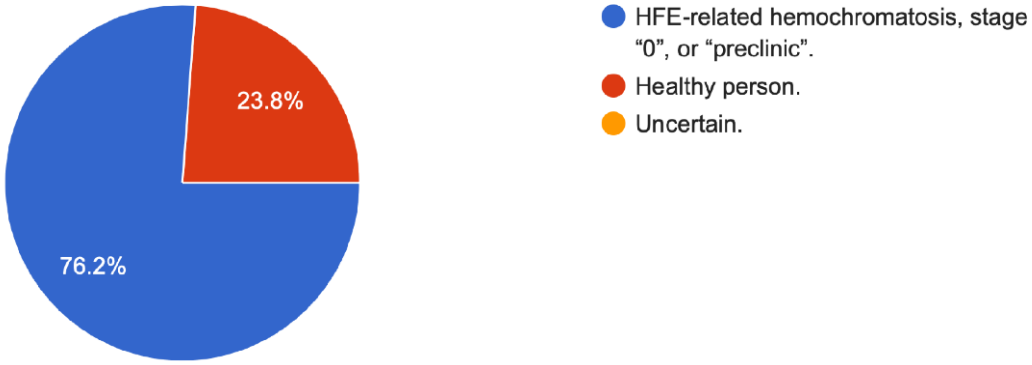


Clinicians
14 responses

Non Clinicians
7 responses

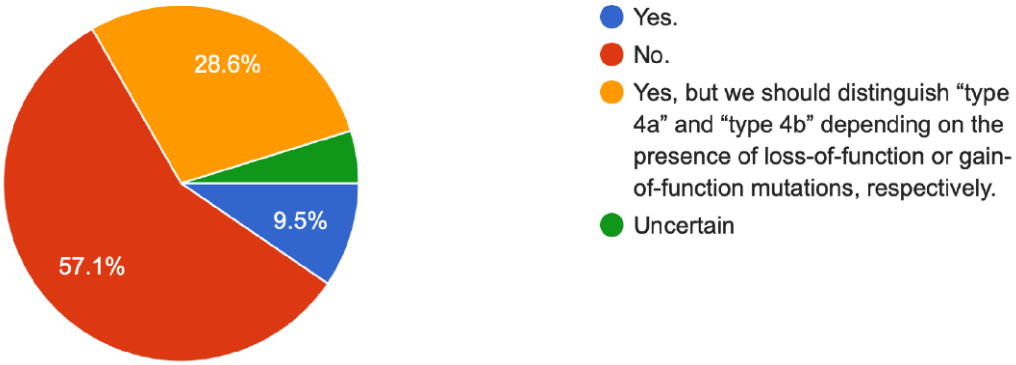
R10: How would you diagnose/classify an asymptomatic subject screened because of the recent diagnosis of hemochromatosis in a first-degree relative, presenting with the following results: ferritin 75 ng/ml, TSAT 40%, C282Y homozygosity:

21 responses



R11: Do you think that genetic iron overload due to any mutation on SLC40A1 gene should be classified as "type 4 hemochromatosis"?

21 responses



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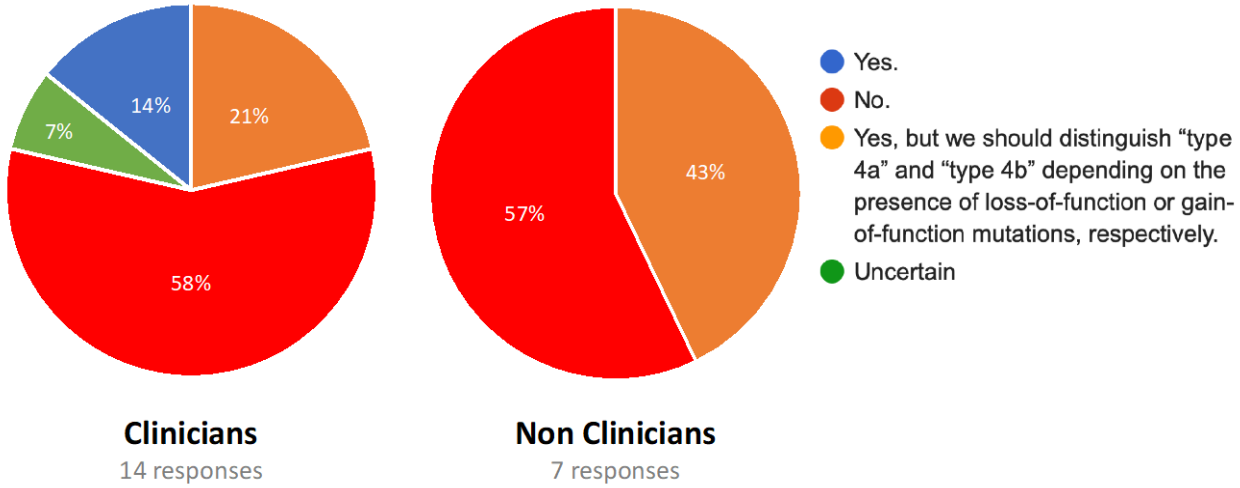
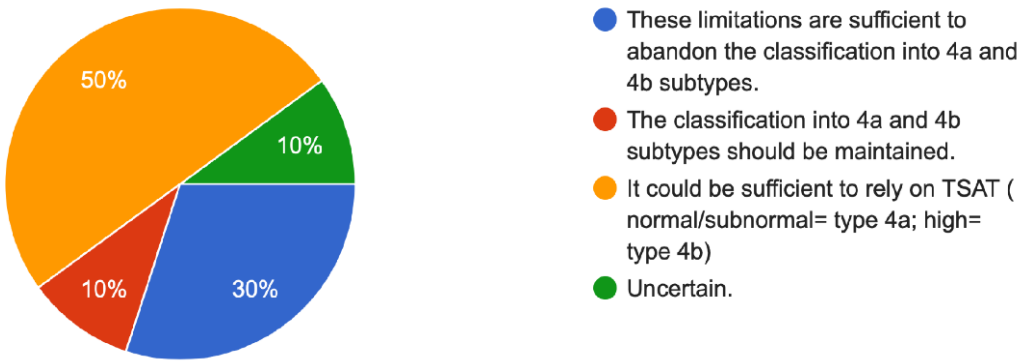


R12: Regarding the previous query, functional studies on a given SLC40A1 mutation can be cumbersome, available only at highly specialized centers, with difficult standardization of methods and results. Moreover, sometimes a clear- cut distinction is hardly possible. Do you think that:

20 responses



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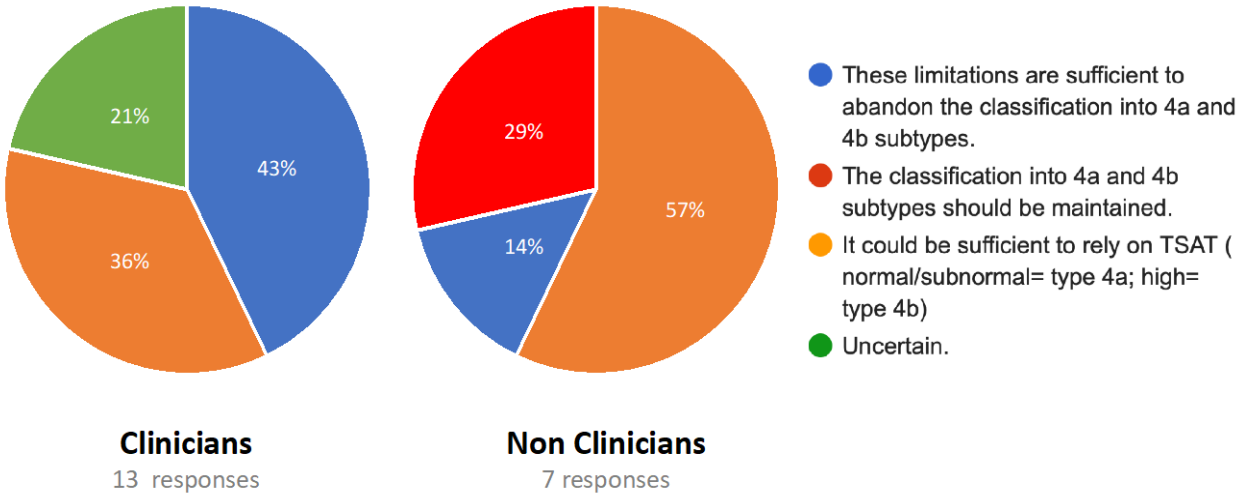
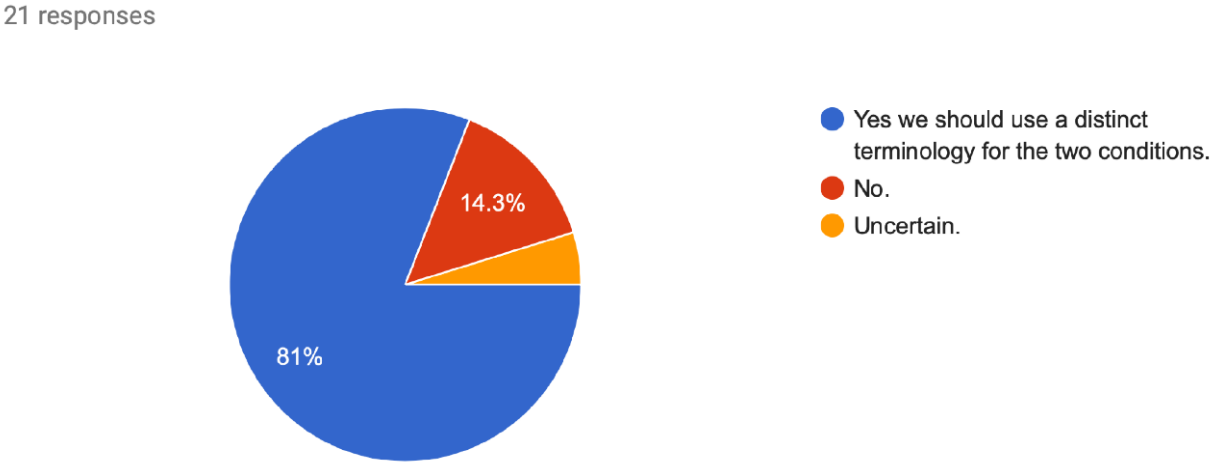


R13: Do you think that genetic iron overload due to mutations on SLC40A1 gene should be defined as “Ferroportin Disease” when there is clear evidence of a loss-function mutation (and/or normal/subnormal TSAT), and as “Hemochromatosis” when there is clear evidence of a gain-of-function mutation (and/or high TSAT)?



R14: In low-resource and/or non-specialized settings, the availability of molecular diagnosis could be limited to first level genetic testing for C282Y (H63D), if any. In many other genetic disorders, either monogenic or genetically heterogeneous, the classification into subtypes is mainly based on clinical phenotypes (e.g. Gaucher Disease, according to

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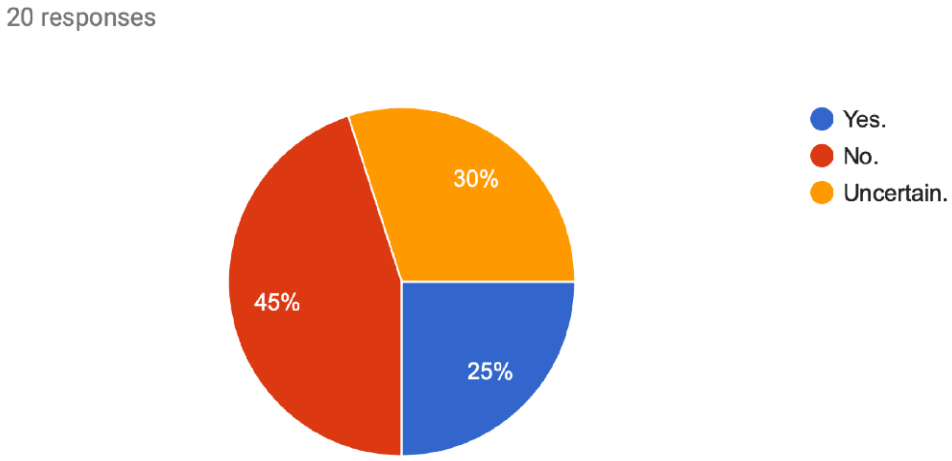

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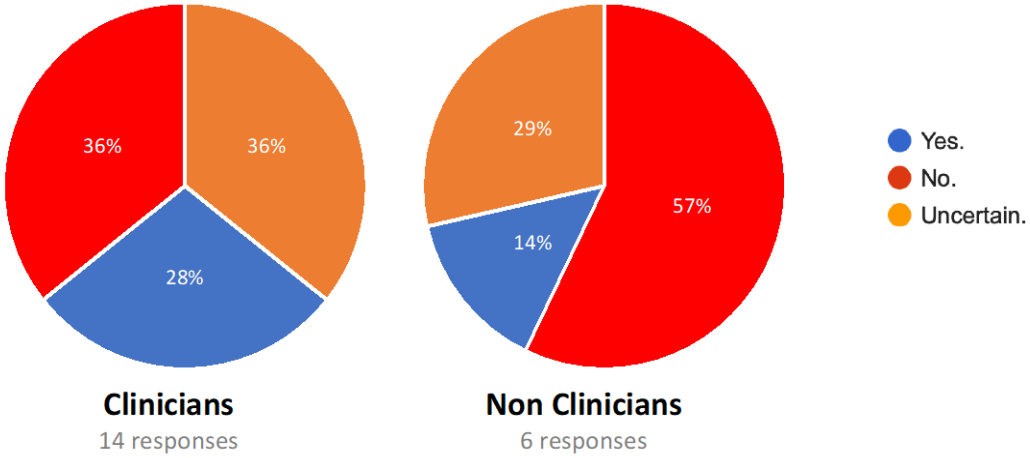
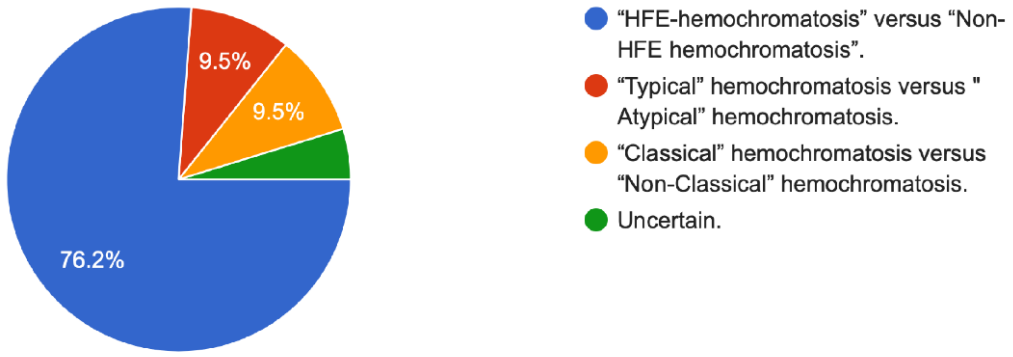


R15: What do you think maybe the best terminology for differentiating hemochromatosis associated with C282Y homozygosity from all other forms after first level genetic testing?

21 responses



*(HFE vs NON-HFE for 100% of non clinicians)

R17: Are you directly involved in care of patients with hemochromatosis?

21 responses