To the editor:

Screening for hemochromatosis

In their recent article, Waalen et al[1] address an important question connected to screening programs for hemochromatosis: How to find the individuals that would benefit from treatment. Based on their own results and those of others,[1,2] including ours,[3,4] they recommend serum ferritin as a better screening test than transferrin saturation (TS) for detecting clinically significant hemochromatosis (defined as C282Y homozygotes at risk for liver cirrhosis, that is, serum ferritin above 1000 μg/L). According to Waalen et al[1] our phenotypic screening of 65 238 unselected individuals in a geographically stable Norwegian population, using TS as the primary test,[3] "would only have detected approximately one-half of the C282Y homozygotes." This statement may be true for women, but is definitely not correct for men. By genotyping subjects with confirmed high TS, we estimated a C282Y homozygous prevalence of 0.68% in the male population,[3] a figure virtually identical to a prevalence estimate of 0.67% (allele frequency 0.081) based on genotyping 3050 randomly selected subjects from the same general population.[5] Thus, our screening with TS picked up very close to 100% of homozygous men.

In the Norwegian study, 70% (32 of 46 individuals) of those with ferritin above 1000 μg/L were C282Y homozygotes (Table 1), compared with the 34% (20 of 59 individuals) in the material of Waalen et al.[1] Thus, if the primary goal of the screening is to detect C282Y homozygotes with serum ferritin above 1000 μg/L, a prescreening with TS or the equivalent test unsaturated iron binding capacity (UIBC) obviously increases the positive predictive value compared with serum ferritin alone. Reserving serum ferritin testing for men and women with TS above 45% would detect all C282Y homozygous subjects with high serum ferritin in the Waalen et al material.[1] This procedure would also be less expensive, as TS and UIBC tests are cheaper than serum ferritin.[6] However, the serum ferritin limit of 1000 μg/L may not be optimal. Among 12 C282Y homozygous subjects with liver fibrosis and/or cirrhosis we detected 4 subjects (including 1 with possible cirrhosis) with serum ferritin well below 1000 μg/L (range 311-629 μg/L).[3]

On the other hand, if the primary goal is to find all subjects with serum ferritin levels above 1000 μg/L and treatable diseases, then measuring serum ferritin would be the right thing to do. However, the utility of screening for all causes of serum ferritin above 1000 μg/L is unknown. And then again, it would not be screening for hemochromatosis.

Lastly, Waalen et al argue that using serum ferritin as the screening test may reduce the anxiety of screening.[1] The opposite may also be true: Knowing that you screened negative but your serum ferritin level was 900 μg/L might not be very reassuring.

In our opinion, the present knowledge does not support the statement of Waalen et al[1] that "the use of serum ferritin as a screening tool for hemochromatosis seems well worth implementing."

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References

1. Waalen J, Felitti VJ, Gelbart T, Beutler E. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. Blood. 2008;111:3373-3376.
2. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G–> A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet. 2002;359:211-218.
3. Åsberg A, Hveem K, Thorstensen K, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. Scand J Gastroenterol. 2001;36:1108-1115.
4. Åsberg A, Hveem K, Krüger O, Bjerve KS. Persons with screening-detected haemochromatosis: as healthy as the general population? Scand J Gastroenterol. 2002;37:719-724.
5. Aamodt AH, Stovner LJ, Thorstensen K, Lydersen S, White LR, Aasly JO. Prevalence of haemochromatosis gene mutations in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78:315-317.
6. Adams PC, Reboussin DM, Leiendecker-Foster C, et al. Comparison of the unsaturated iron-binding capacity with transferrin saturation as a screening test to detect C282Y homozygotes for hemochromatosis in 101,168 participants in the hemochromatosis and iron overload screening (HEIRS) study. Clin Chem. 2005;51:1048-1052.

Table 1. Findings in 46 subjects with serum ferritin above 1000 μg/L

HFE genotype	n	Age, y*	Serum ferritin, μg/L†	Clinical diagnosis‡
C282Y/C282Y				
Men	28	48.6 (10.9)	1612 (1383-1879)	Hemochromatosis: 28
Women	4	54.8 (17.3)	1164 (912-1484)	Hemochromatosis: 4
Other *HFE* mutations				
Men	1	55.0	1473	Alcohol overuse: 1
Women	4	76.8 (8.3)	1989 (1084-3651)	Hemochromatosis: 1; chronic iron overdose: 2; uncertain: 1
No *HFE* mutation or *HFE* genotype unknown				
Men	5	51.0 (14.6)	1766 (1072-2908)	Hemochromatosis: 2; lymphoma: 1§;leukemia: 1§; chronic iron overdose: 1
Women	4	75.5 (12.4)	1489 (1077-2059)	Chronic iron overdose: 4¶

Subjects were detected among 609 individuals with confirmed high transferrin saturation and hemochromatosis not previously known, from a population of 65 238 screened individuals.[3] Only the *HFE* mutations C282Y and H63D were studied.

*Mean (SD).

†Geometric mean (95% CI).

‡Given without knowledge of *HFE* genotype.

§Unknown *HFE* genotype.

¶Including 2 with unknown *HFE* genotype.