Appendix Table 7. **Longitudinal Studies of Disease Development in C282Y Homozygotes***

Study, Year (Reference)	Population	Criteria/Sequence and Results for Screening†	Criteria and Results for Iron Overload†	Definition and Results for Morbidity	Quality
Olynyk et al., 2004 (46)	Retrospective examination of 3011 randomly selected participants (age 20–79 y) from Busselton, Australia, cohort genotyped in 1998 Available data from 1981, 1994, and 1998	*HFE* genotype 16 of 3011 C282YY homozygotes, 4 previously diagnosed and undergoing TP (those 4 were excluded) Serum available for 10 of 12 patients Elevated iron measures 1981: 3 of 9 Median age: 30 y 1994: 9 of 10 Median age: 43 y 1998: 10 of 10 Median age: 47 y SF level > 300 μg/L 1981: 5 of 10 1994: 5 of 10 (4 of 5 were same as 1981) 1998: 6 of 10	> 90 μmol/g 5 of 6 had biopsy in 1998 Possible iron overload Men: 4 of 4 (calculated) with TS > 0.50 and SF level > 300 μg/L Women: 2 of 6 (calculated) with TS > 0.45 and SF level > 200 μg/L	Fibrosis (6 had biopsy): 2 of 6 Cirrhosis: 1 of 6 (cirrhotic patient drank > 6 alcoholic drinks/day) Diabetes: 1 patient at age 19 y; thought to be unrelated to HC Arthralgia: 4 of 10	Good—potential for selective mortality bias, but effect appears to have been minimal because of reasonably complete follow-up of cohort (85%). Very small sample; not all patients were of the age at which disease expression would be expected (i.e., women ≥ 50 y).
Andersen et al., 2004 (47)	Retrospective cohort from Copenhagen Heart Study, 1976–2001; *n* = 9174 White persons > 99% 47% (9174 of 19 698) of original Copenhagen study sample	*HFE* genotype C282Y:C282Y 23 of 9174 20 still alive TS > 0.50 in 2001 Men: 5 of 7, women: 13 of 16 SF level > 250 μg/L in 2001 Men: 6 of 7 SF level > 200 μg/L in 2001 Women: 10 of 16 Iron measure progression (1976–2001) Mean TS Women Mean age, 25 y: 0.50 Mean age, 85 y: 0.70 Men Mean age, 35 y: 0.70 Mean age, 80 y: 0.80 Mean SF level Women Mean age, 25 y: 120 μg/L Mean age, 85 y: 500 μg/L Men Mean age, 35 y: 800 μg/L Mean age, 80 y: 400 μg/L	Possible iron overload Men: TS > 0.50, SF level > 300 μg/L, and CE: 5 of 7 (calculated) Women: TS > −0.45, SF level > 200 μg/L, and CE: 9 of 16 (calculated) Liver biopsies not done	Diabetes: 1 of 23 (4%) Liver disease: 0 of 23 (0%) (Defined by AST level > 50 U/L; alkaline phosphatase level > 275 U/L; coagulation tests < 70%; bilirubin level > 17) Clinical work-ups in 2001 for liver disease, hypogonadism, cardiomyopathy: 0 of 23 Work-up for arthralgias: 2 of 23 Subclinical HC: 1 of 23	Fair—results may be compromised by selective mortality bias due to large attrition of the cohort. No liver biopsies to confirm disease expression or iron overload.

* AST = aspartate aminotransferase; C282YY = C282Y/C282Y; HC = hemochromatosis; SF = serum ferritin; TP = therapeutic phlebotomy; TS = transferrin saturation.
† Criteria defined in Table 2.