

Population Screening for Hemochromatosis CDC Webinar

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Origins of Hemochromatosis



Rathlin Island, McCuaig's Pub

Anthropologist : Dan Bradley

Photographer : Brian Sloan

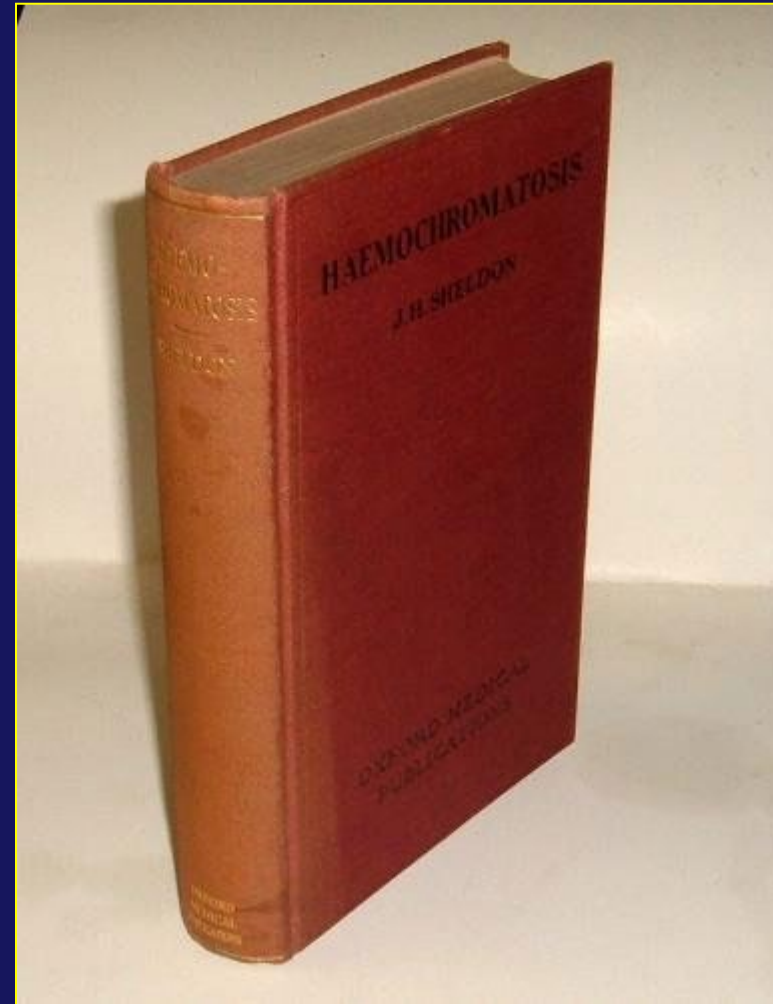
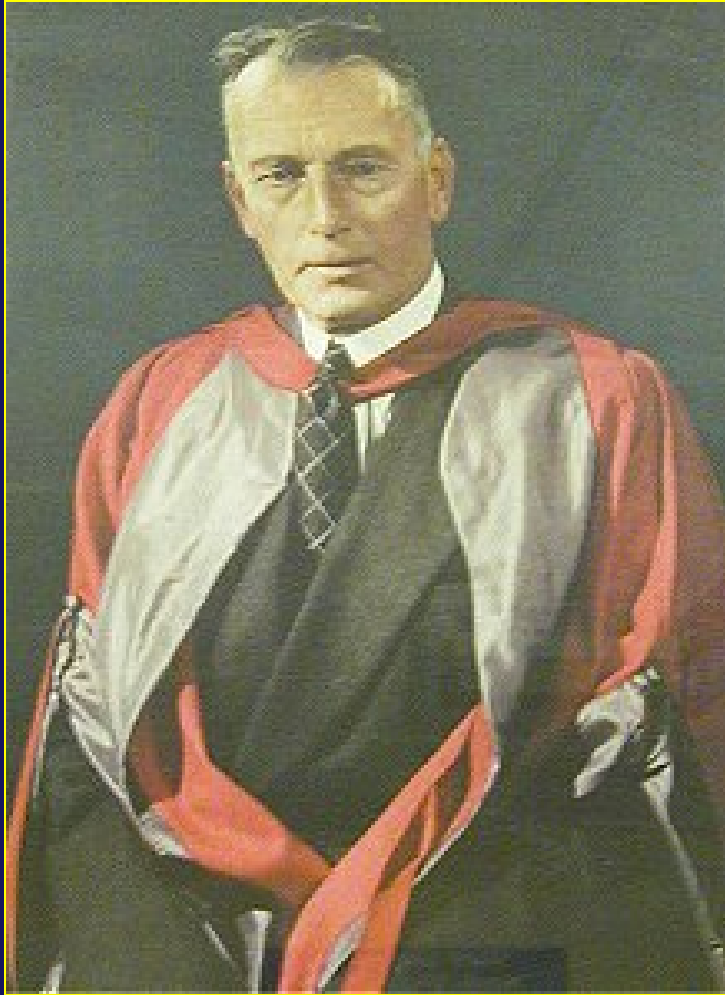
Curator: John Ryan

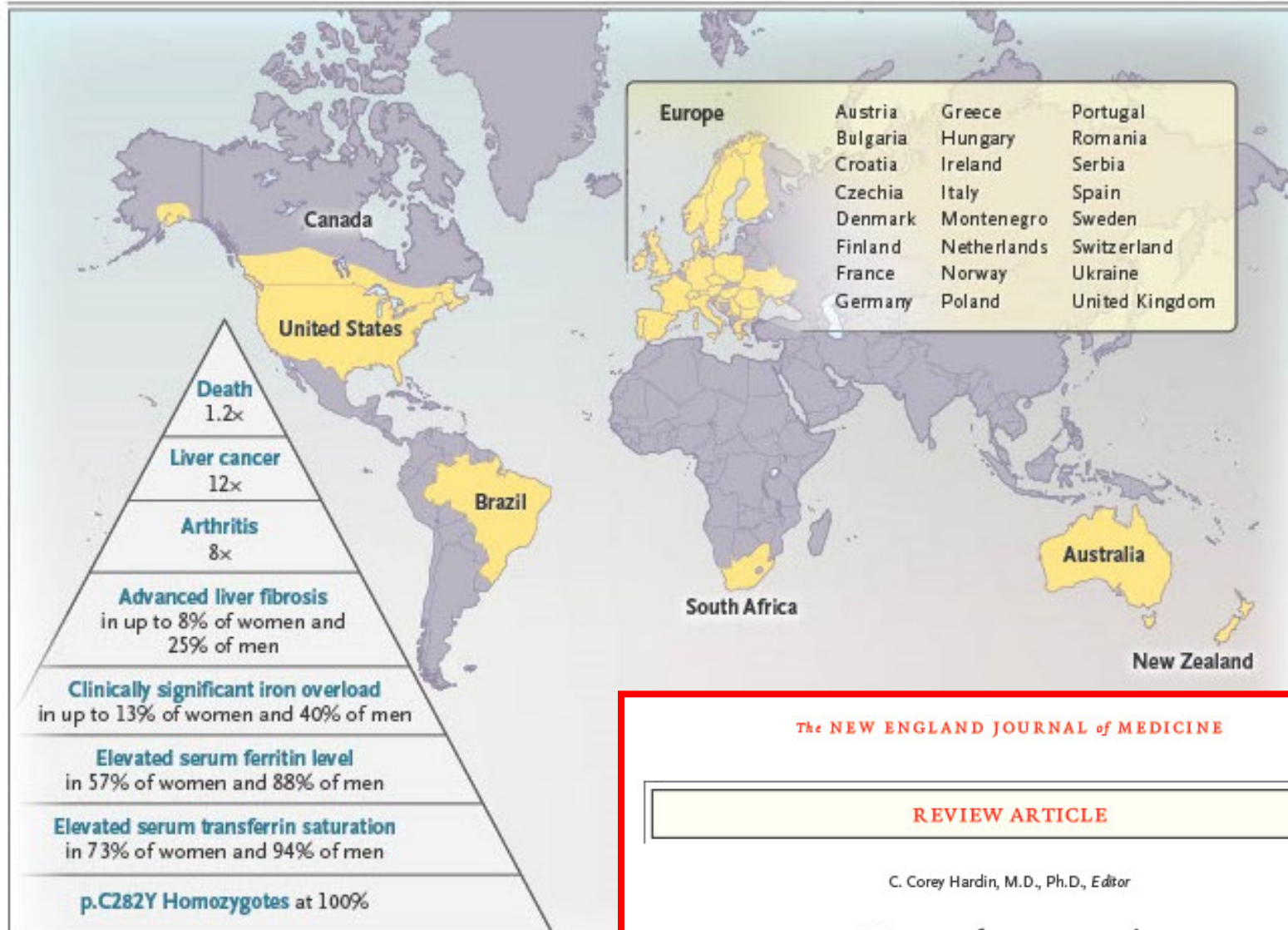
Adams PC, Jeffrey GP, Ryan JD

Lancet, May 27, 2023



Haemochromatosis – J.H. Sheldon 1934





REVIEW ARTICLE

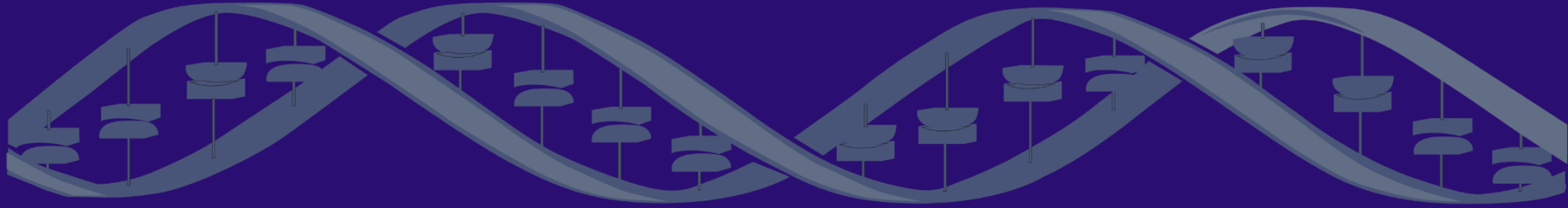
C. Corey Hardin, M.D., Ph.D., Editor

Hemochromatosis

John K. Olynyk, M.D., and Grant A. Ramm, Ph.D.

GENE FOR HEMOCHROMATOSIS DISCOVERED

Now What ?



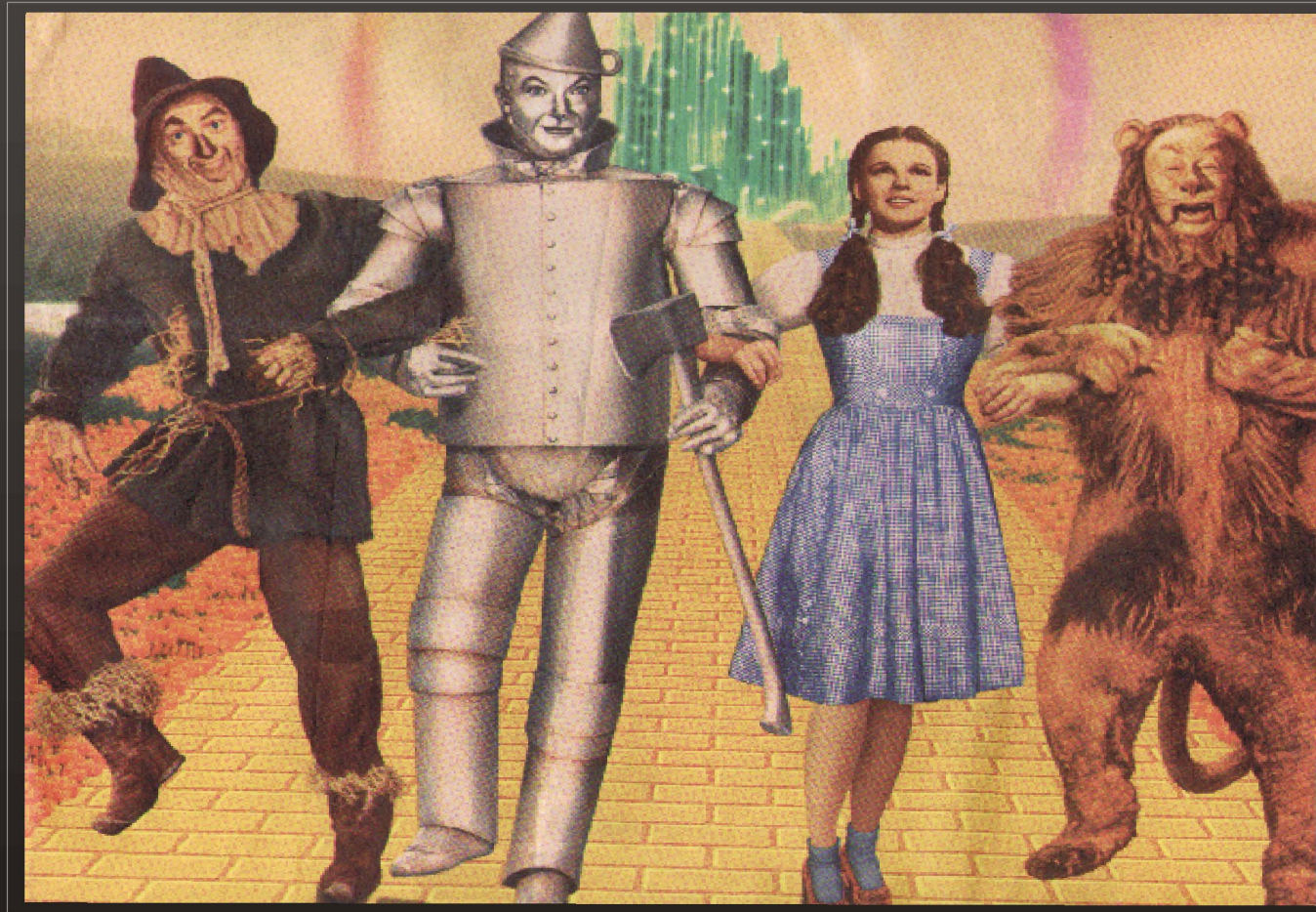
Identification of gene product leading to pathogenesis of disease

Development of new therapeutic strategies

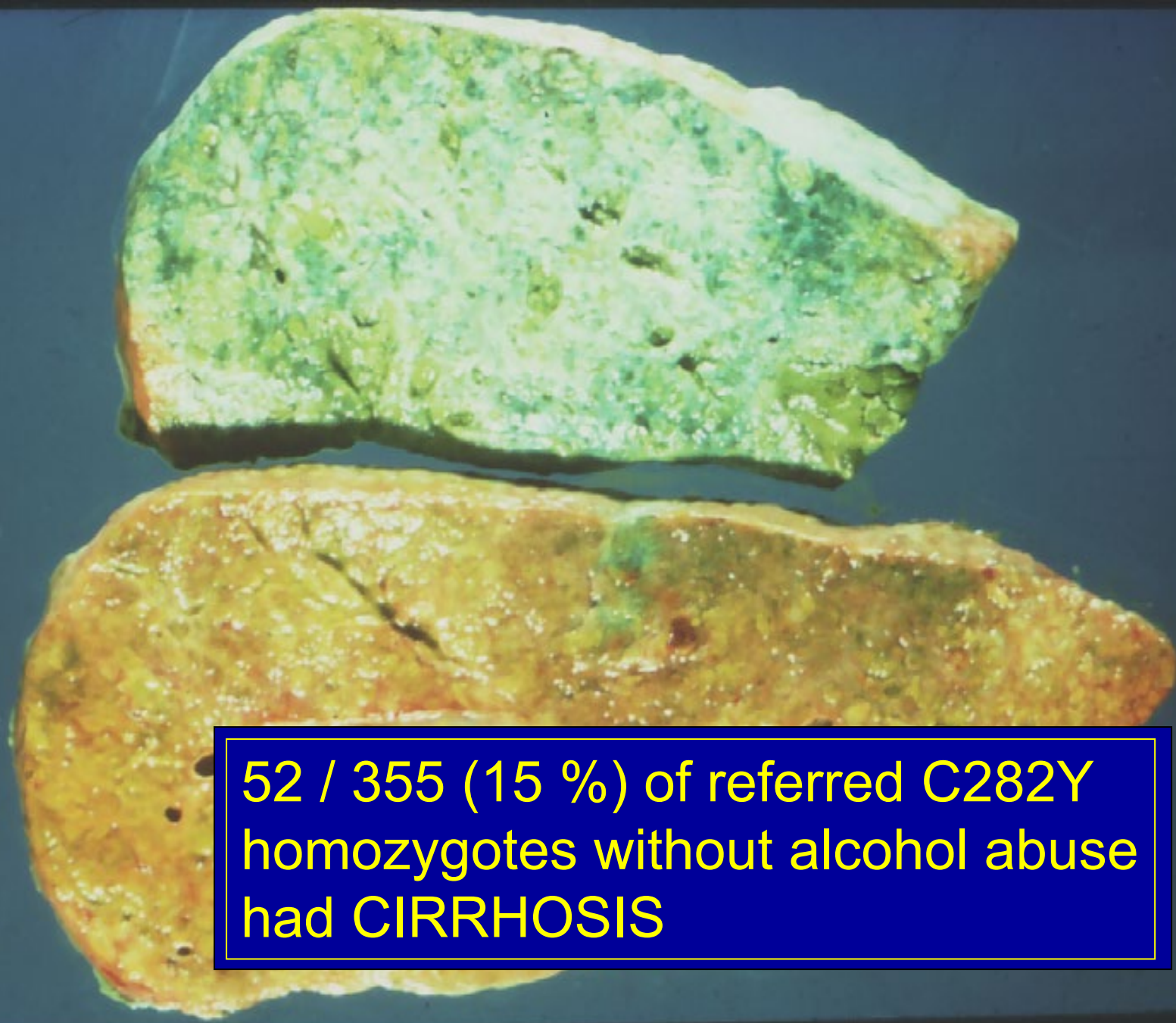
Screening of hemochromatosis families

Population screening

Genetics of Hemochromatosis



C282Y + / - + / + + / - - / -

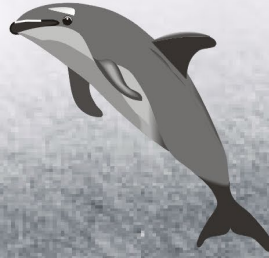


52 / 355 (15 %) of referred C282Y
homozygotes without alcohol abuse
had CIRRHOSIS



This 55 year old urologist gave up his surgical practice because of disabling arthritis in his MCP joints secondary to hemochromatosis

**1: 227 C282Y homozygotes
in Caucasians (HEIRS 2005)**

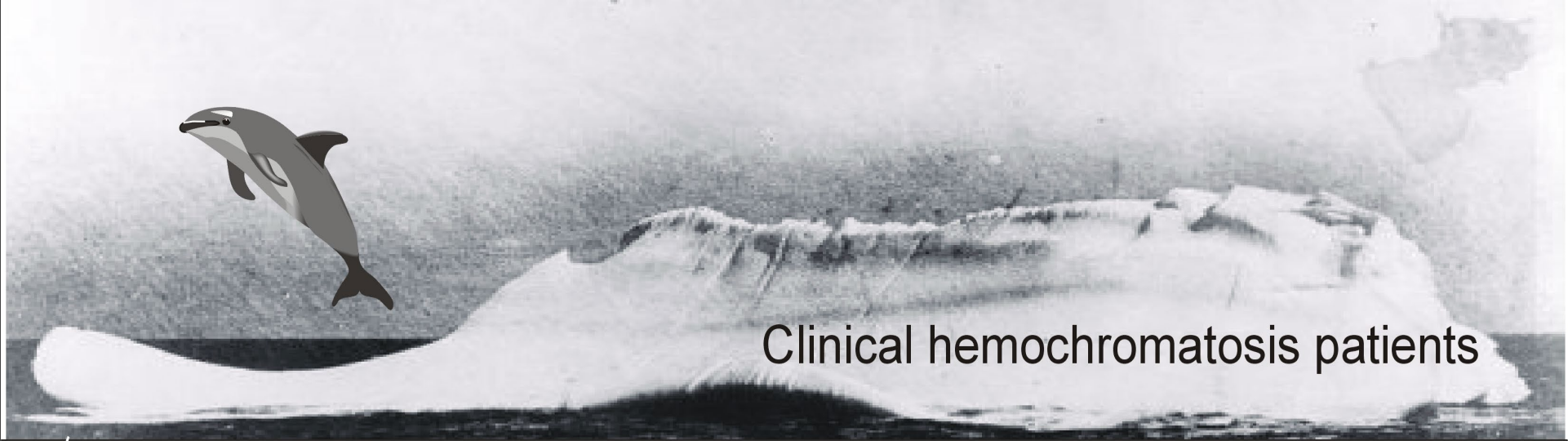


Clinical hemochromatosis patients

Non-expressing hemochromatosis patients

Undiagnosed hemochromatosis patients

PC Adams



Clinical hemochromatosis patients

Non-expressing hemochromatosis patients

Latent hemochromatosis

Non-penetrant, at risk

Undiagnosed hemochromatosis patients

PC Adams



Genetic Testing (C282Y mutation of the *HFE* gene)

Transferrin Saturation

Serum Ferritin

Serum ferritin + transferrin saturation

Unsaturated iron binding capacity (UIBC)

Detection of iron overload



The Long and Winding Road of Population Screening for Hemochromatosis



Screening for Hemochromatosis - 2001



Widespread genetic testing, EASL international consensus conference, NIH consensus conference, CDC conference, HEIRS study

Screening for Hemochromatosis - 2002



Beutler study, plenty of genes but not much illness

ORIGINAL ARTICLE

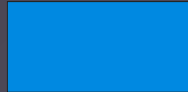
Hemochromatosis and Iron-Overload Screening in a Racially Diverse Population

Paul C. Adams, M.D., David M. Reboussin, Ph.D., James C. Barton, M.D.,
Christine E. McLaren, Ph.D., John H. Eckfeldt, M.D., Ph.D.,
Gordon D. McLaren, M.D., Fitzroy W. Dawkins, M.D., Ronald T. Acton, Ph.D.,
Emily L. Harris, Ph.D., M.P.H., Victor R. Gordeuk, M.D.,
Catherine Leiendecker-Foster, M.S., Mark Speechley, Ph.D.,
Beverly M. Snively, Ph.D., Joan L. Holup, M.A., Elizabeth Thomson, M.S., R.N.,
and Phyliss Sholinsky, M.S.P.H., for the Hemochromatosis and Iron Overload
Screening (HEIRS) Study Research Investigators*

Race/Ethnic Group	n	C282Y /C282Y
White	44,082	281
Native American	648	1
Hispanic	12,459	7
Black	27,124	4
Pacific Islander	698	0
Asian	12,772	0

101,168 Transferrin saturation (TS %, > 50M, 45F)
Ferritin (> 300M, > 200F), C282Y, H63D

12,993



Elevated ferritin


5,997



Elevated TS

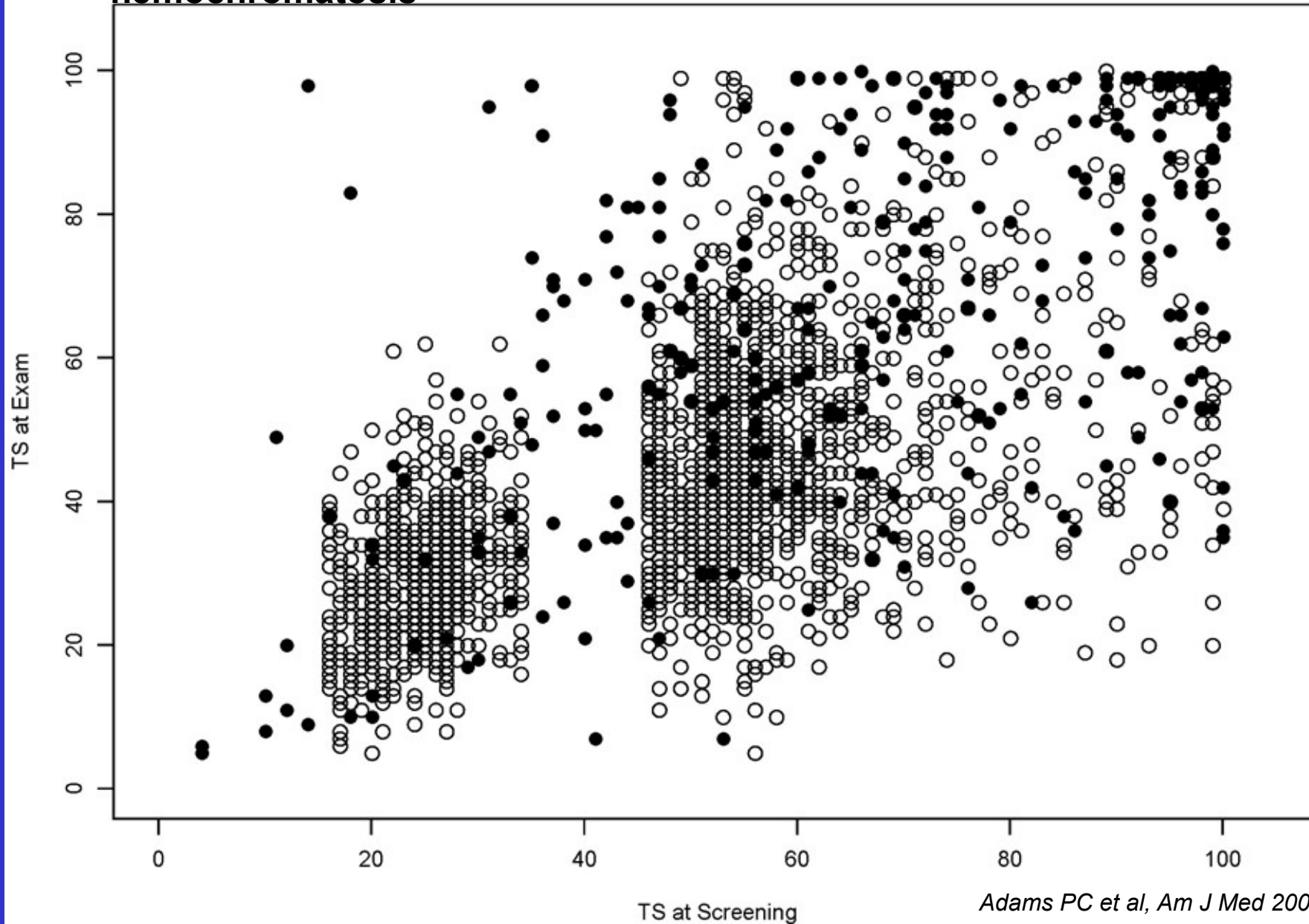
**C282Y Homozygotes – 299
(70 % elevated ferritin)**

HERS Study 2004

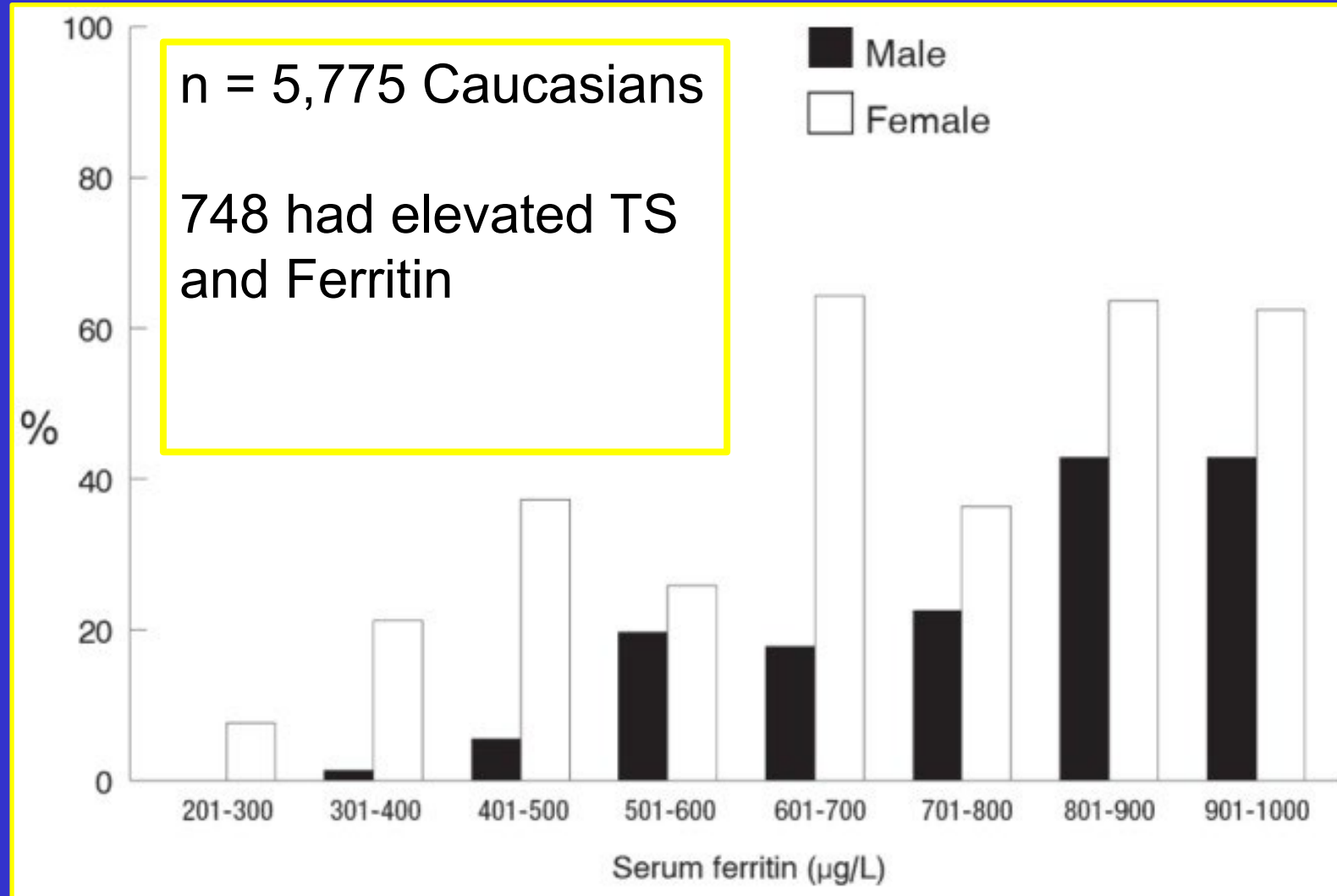
A photograph of a person's midsection, showing a large, protruding belly. The person is wearing a blue and white checkered button-down shirt and dark pants. The background is a solid blue color.

Metabolic Syndrome
Dysmetabolic Syndrome
Fatty Liver
NASH / MASH
Alcohol related liver disease
Alcohol induced ferritin synthesis

Transferrin Saturation is not a good screening test for hemochromatosis



C282Y Homozygotes with an elevated transferrin saturation and ferritin



Genetic screening for iron overload: No evidence of discrimination at 1 year.

Hall MA, Barton JC, Adams PC, McLaren CE, Reiss JA, Castro O, Ruggiero A, Acton RT, Power TE, Bent TC.

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Abstract

PURPOSE: This study measured the extent of insurance and employment problems associated with population screening for hereditary hemochromatosis and iron overload.

METHODS: 101,168 primary care patients from the US and Canada were screened for iron phenotypes and HFE genotypes associated with hemochromatosis. Those identified to be at risk (2253) were offered a clinical examination, which 1677 (74%) accepted, and the 1154 of these who responded to an initial questionnaire about psychosocial issues were surveyed 1 year later about whether they had experienced problems with insurance or employment that they attributed to hereditary hemochromatosis and iron overload.

RESULTS: 832 (72.1%) of the 1154 participants surveyed after 1 year responded to the second survey. Three (0.4%) had verified problems with insurance or employment that they believed were related to hereditary hemochromatosis and iron overload. Two had problems with life insurance, and one with long-term care insurance. All 3 had elevated iron levels but not a relevant HFE genotype. One of the life insurance problems was resolved; the second one was not serious. The participant who was denied long-term care insurance had other health conditions unrelated to hereditary hemochromatosis and iron overload that could have contributed to the denial. No problems were verified for health insurance or employment, or from any of the comparison group participants (controls and those with inconclusive screening results).

CONCLUSIONS: The risk of insurance or employment problems 1 year after phenotype and genotype screening for hereditary hemochromatosis and iron overload is very low.

High Ferritin ≠ Iron Overload

**Most patients with an elevated serum ferritin
do not have iron overload**

**Most patients having phlebotomy with a high ferritin
do not have iron overload (Le Gac et al, APT 2022)**

**Most patients having advanced genetic testing
(ferroportin, TS2, hemojuvelin, hepcidin)
do not have iron overload (Viveiros A, et al, Hepatology
2021)**

**To exclude iron overload, patients can have liver MRI
instead of liver biopsy**

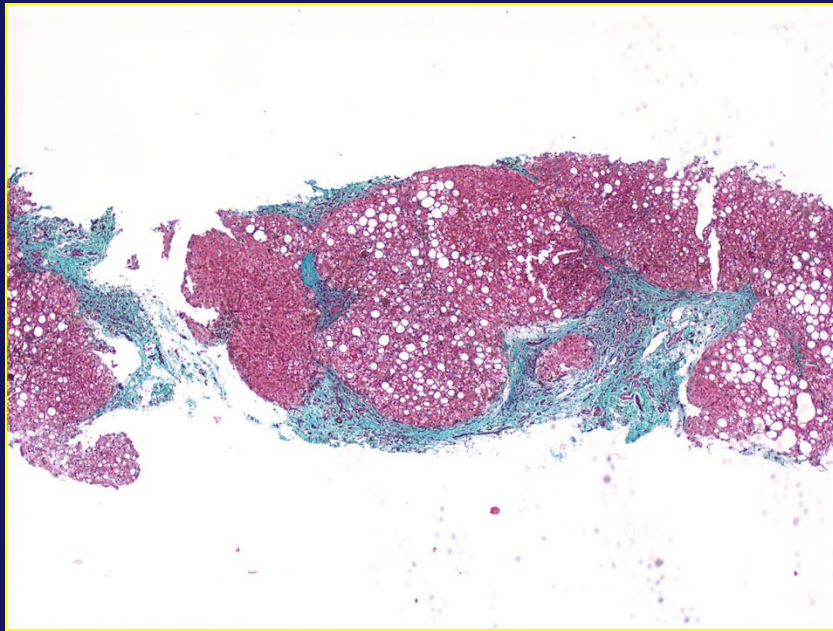
A trial of phlebotomy is a waste of resources



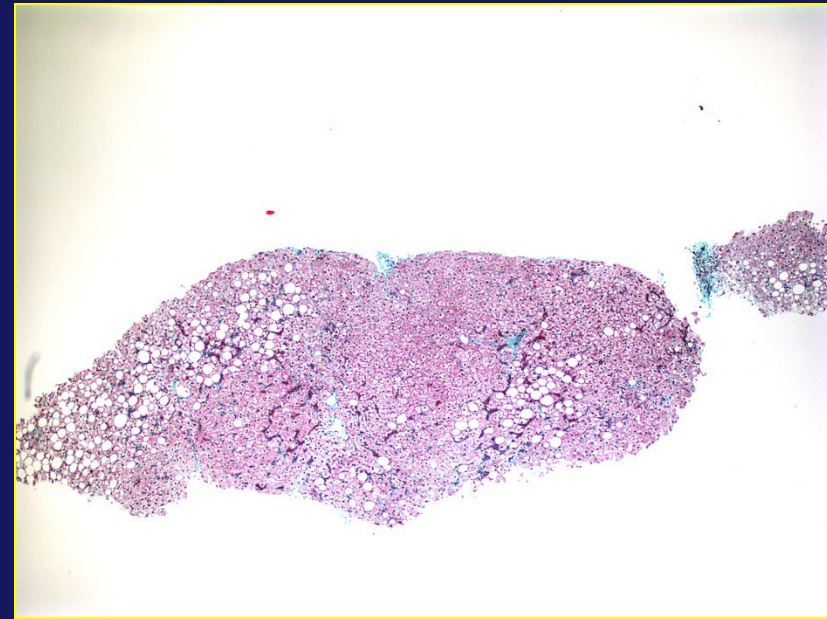
Phlebotomy
Erythrocytaphoresis
No Treatment

Effect of iron depletion on liver fibrosis

C282Y homozygote – 46 year old man



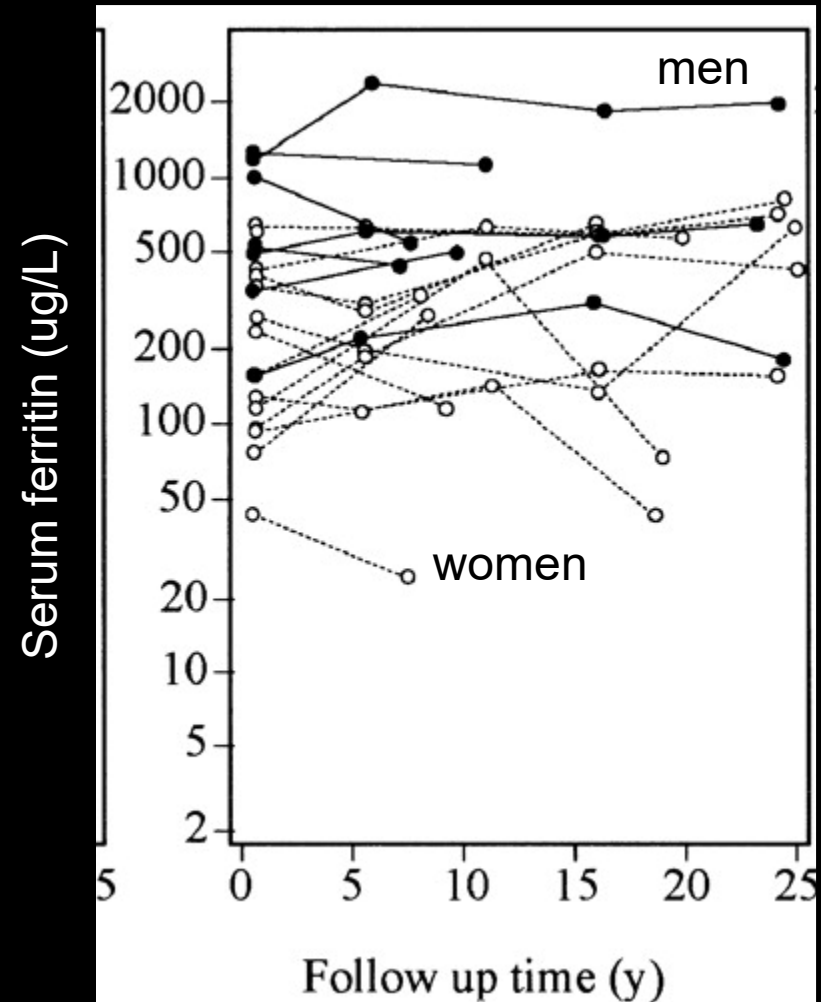
Serum ferritin = 3,833



Serum ferritin = 157, 3 years later

Natural history of untreated C282Y hemochromatosis

Copenhagen Heart Study



Family Screening in Hemochromatosis



Siblings 1:4

Transferrin saturation, ferritin, genotype



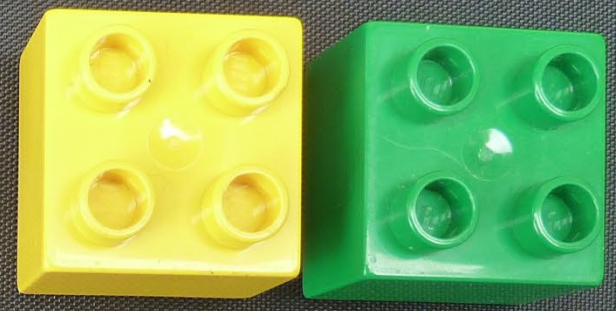
Children > 1:20

Transferrin saturation, ferritin, genotype

- C282Y



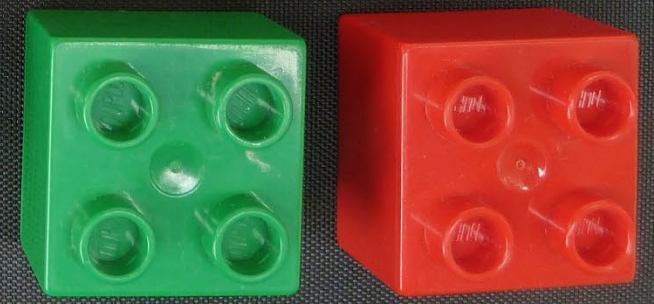
- H63D



- -



H63D C282Y



Population Screening for Hemochromatosis

Population Screening for Hemochromatosis

Half empty or half full ?



The feasibility of screening has been demonstrated in large studies

Screening has identified iron overloaded cases and persons at risk

Cirrhosis and liver cancer have been identified in screening studies and could have been preventable

The absence of adverse effects of screening have been investigated