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# TOO MUCH OF A GOOD THING: DIAGNOSIS & MANAGEMENT OF HEREDITARY HEMOCHROMATOSIS

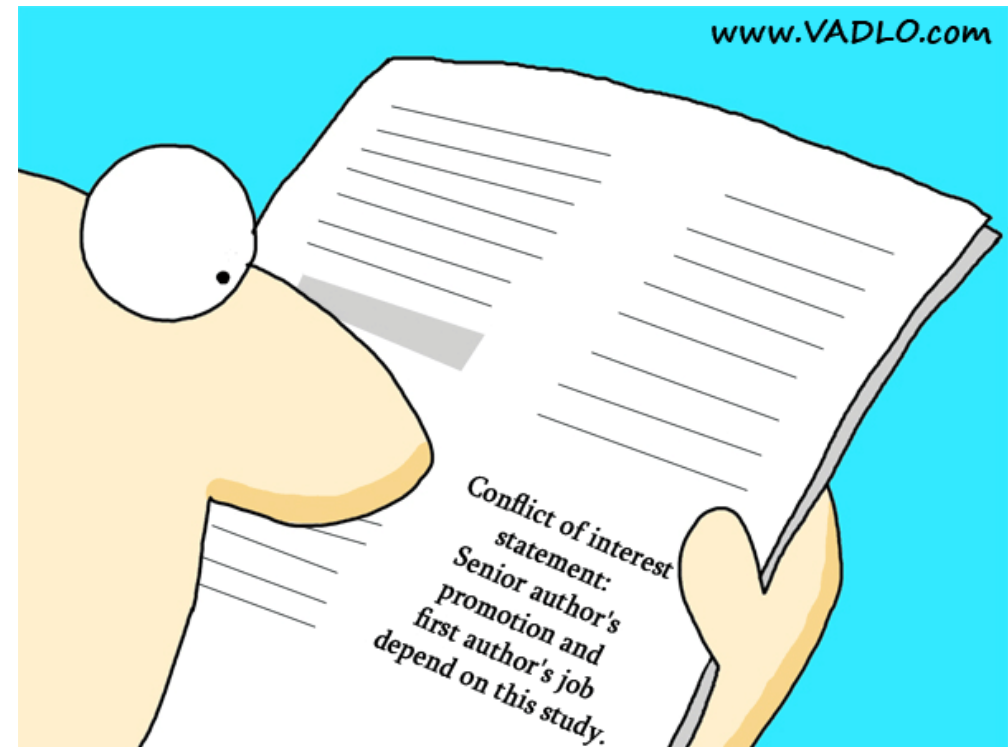
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# DISCLOSURE STATEMENT

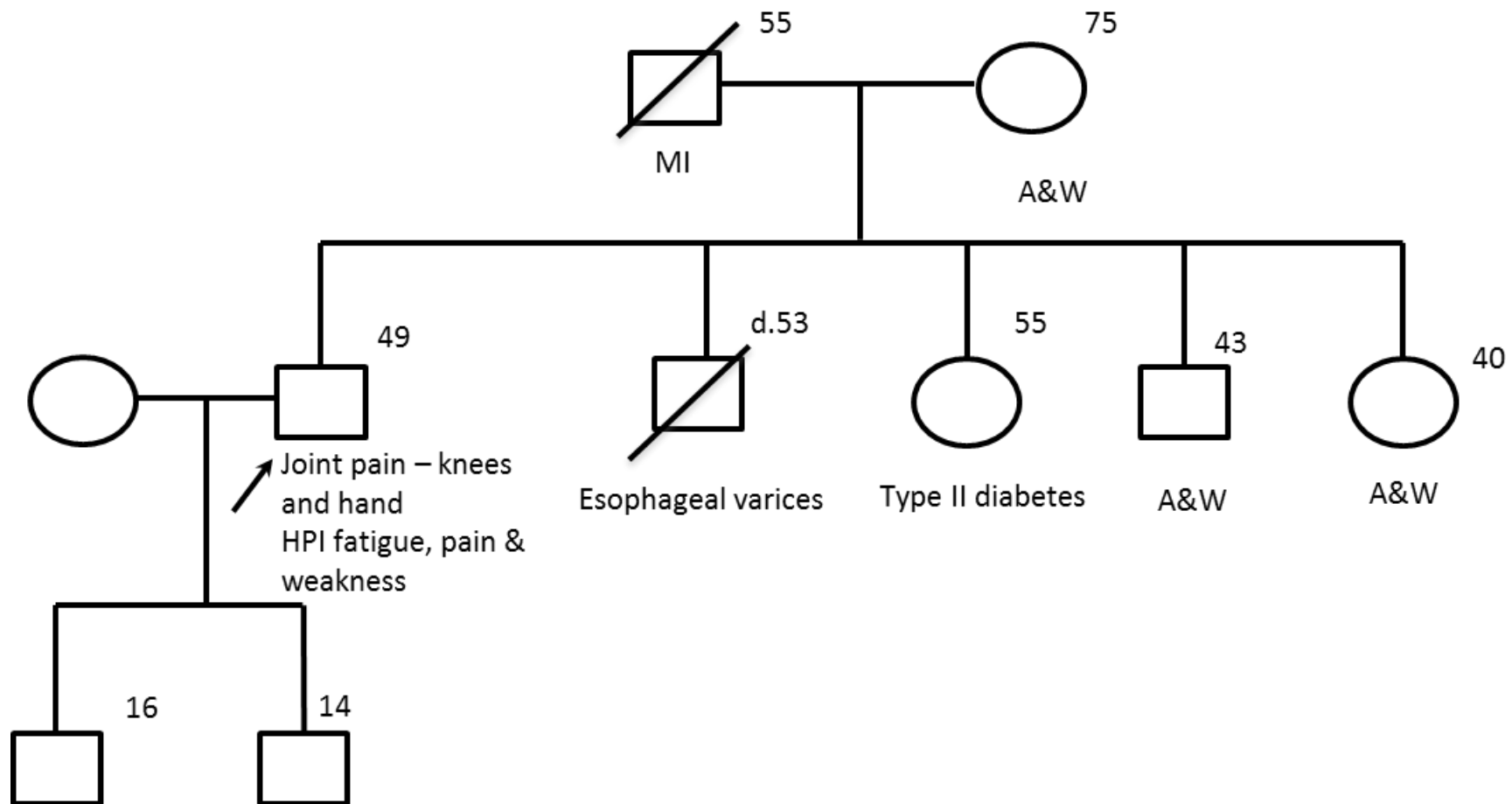
- I have no conflicts of interest to disclose



## CASE STUDY

- Michael is a 49-year old male of European descent with a complaint of joint pain in his hands and knees
- Past medical history includes numerous office visits over past several years with fatigue, weakness, and pain
- Family history:
  - Michael is married, with 2 healthy teenage sons (ages 14 & 16)
  - Father died at 55 from MI
  - Mom is 76, alive and well
  - Sister, 55, has Type II diabetes; brother died at 53 from chronic liver disease
  - Brother, 43, and sister, 40, alive and well

# FAMILY HISTORY



## CASE STUDY

- Social history
  - Drinks “a couple of beers a week”, no tobacco or recreational drug use
  - No multivitamin use
- Physical Exam
  - Mild hepatomegaly
  - Modest enlargement of 2<sup>nd</sup> and 3<sup>rd</sup> MCP joints

# HEREDITARY HEMOCHROMATOSIS (HH)—BASIC FACTS

- HH is a common disease of iron metabolism that causes iron overload in the body
- Two gene mutations of the HFE (**H**igh iron **Fe**) gene, C282Y and H63D, located on chromosome 6, account for majority of cases
  - Known as “classic” or Type I HH
  - Other subtypes of HH, caused by other mutations, exist but are rare
- HH affects up to 1% of individuals of northern European descent
- Untreated HH may cause irreversible damage to the liver & pancreas, which may lead to cancer and diabetes
  - Joint involvement may also be present
- Signs and symptoms may be vague and non-specific, causing delay in diagnosis
- Therapy consists of blood removal via therapeutic phlebotomy or blood donation
- Prompt detection, monitoring and treatment can prevent complications

# PRESENTATIONS OF HH

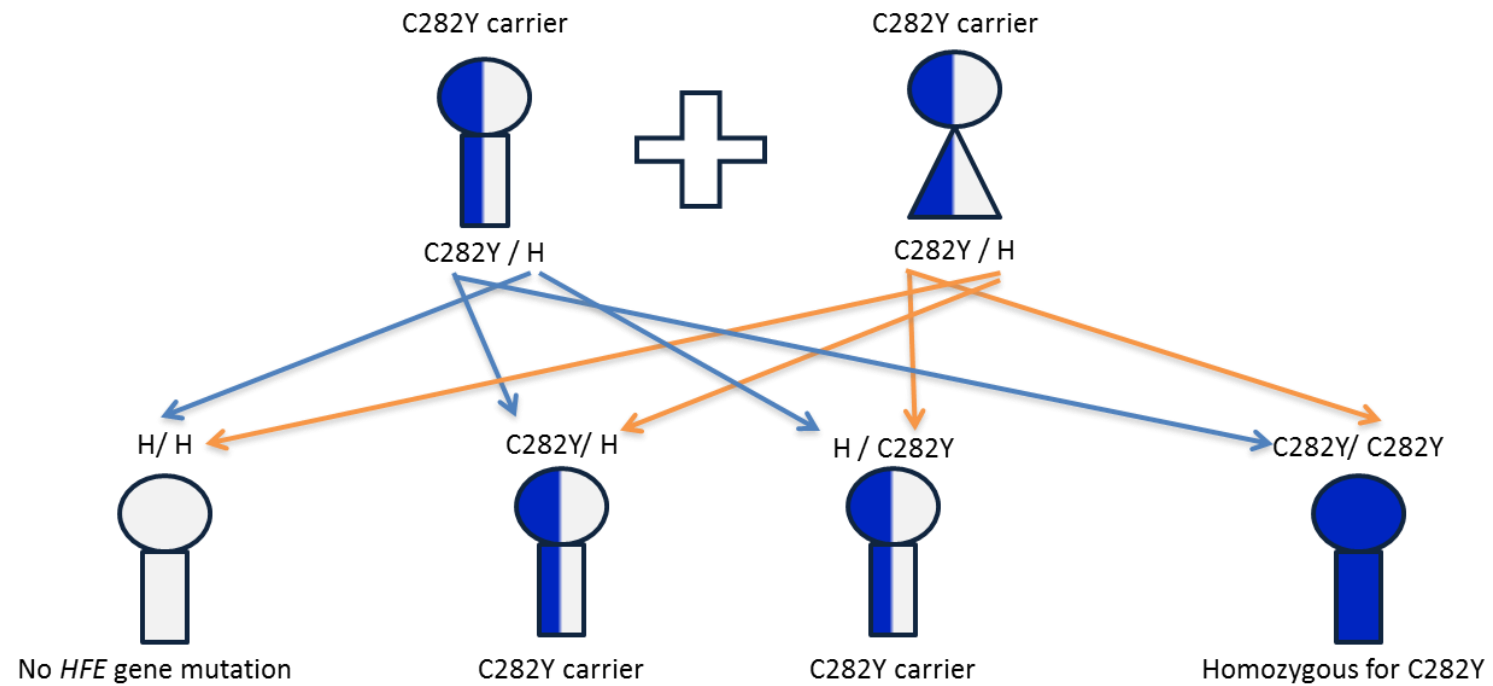
- Symptoms of HH may include:
  - weakness, lethargy
  - skin discoloration (bronze or grey)
  - abdominal pain with or without hepatomegaly
  - joint pain and/or stiffness, arthritis
  - diabetes
  - cardiomyopathy
  - cirrhosis and/or hepatocellular carcinoma
  - testicular atrophy, erectile dysfunction
  - menstrual irregularity
- Symptoms may be non-specific, but having 2 or more increases suspicion that HH may be present in an at-risk individual
- HH may present between 40-60, but also earlier or much later

# HH GENETICS

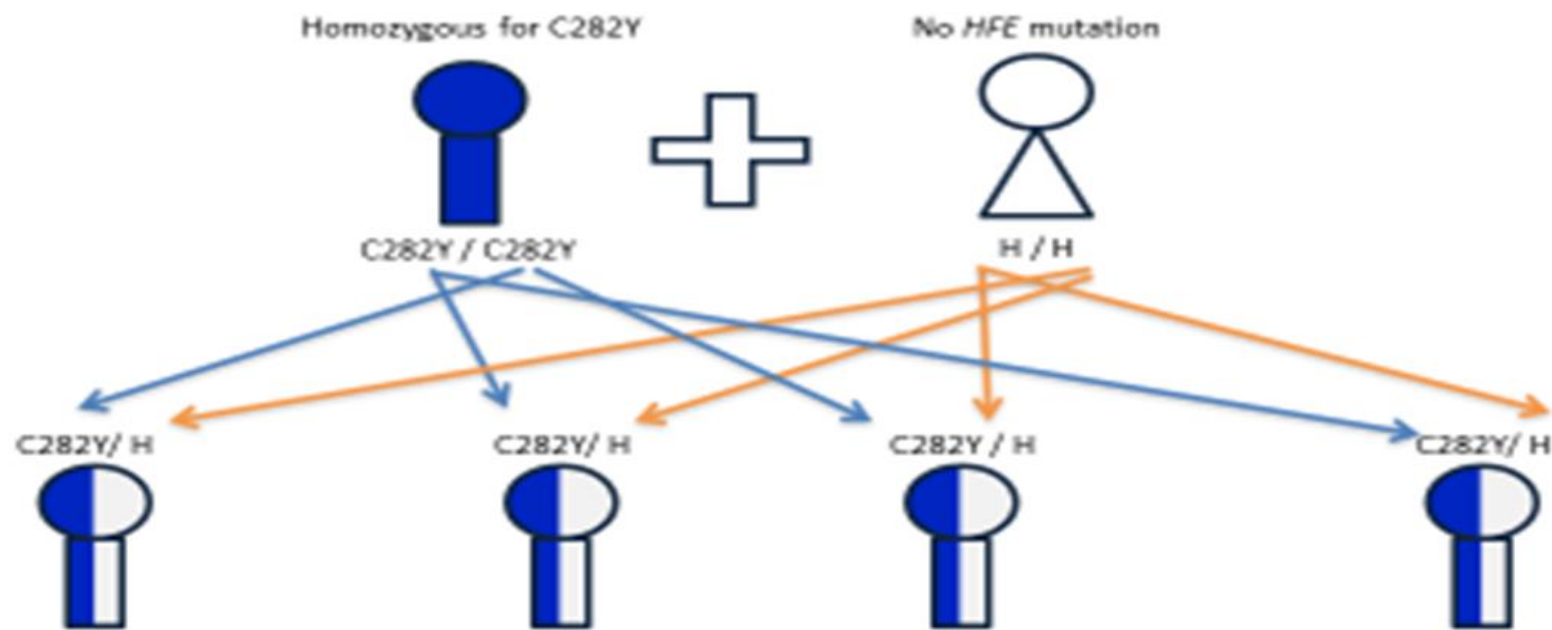
- Standard testing by North American molecular genetics laboratories is targeted mutation analysis
  - Looks specifically for the two most common *HFE* mutations, C282Y and H63D
  - These account for over 90% of hereditary hemochromatosis
- About 1 in 3 individuals of Northern European ancestry are carriers (heterozygotes) of the C282Y or H63D *HFE* gene mutations
- About 1 in 260 individuals have two copies of (are homozygous for) the C282Y *HFE* gene mutation (genotype C282Y/C282Y)
- Genes are autosomal recessive—meaning 2 copies are necessary to produce HH
  - Reduced penetrance of these genes leads to variable presentation of HH
  - Variable clinical presentations are also due to individual and/or environmental factors affecting iron intake & absorption



# AUTOSOMAL RECESSIVE INHERITANCE REFRESHER



# Autosomal Recessive Inheritance Refresher



100% will be heterozygous for C282Y HFE mutation  
\*can reveal non-paternity

# WHO SHOULD BE OFFERED BIOCHEMICAL TESTING FOR IRON OVERLOAD?

- If the patient has suggestive symptoms, physical findings or a family history of HH, **transferrin saturation and serum ferritin (“iron studies”)** are ideally ordered together to determine presence of iron overload
- **Transferrin saturation (TS)**
  - TS is a reliable screen for iron overload
  - **Fasting TS of >45%** is considered a sensitive but not specific threshold for identifying iron overload
- **Serum Ferritin (SF)**
  - In combination with persistent elevation in fasting TS, elevated ferritin is suspicious for iron overload
  - SF is an acute phase reactant, that may be elevated by other inflammatory processes; an elevated SF does not necessarily imply iron overload & is not a reliable first or only screen

## WHO SHOULD BE OFFERED GENETIC TESTING FOR HH?

- Any adult with biochemical evidence of iron overload
  - $>45\%$  TS &  $>300 \mu\text{g/L}$  SF in men and post-menopausal women or  $>200 \mu\text{g/L}$  in pre-menopausal women
- Unexplained chronic liver disease and increased TS
- Adults with first-degree relative (sibling, parent or child) with one of the following genetic test results:
  - C282Y/C282Y homozygote
  - C282Y/H63D compound heterozygote
  - C282Y heterozygote
- Family history of iron overload, liver disease, type II diabetes, arthritis, heart disease
- With normal TS & elevated ferritin, high clinical suspicion of HH, or if patient has a positive family history of HH, testing is also recommended

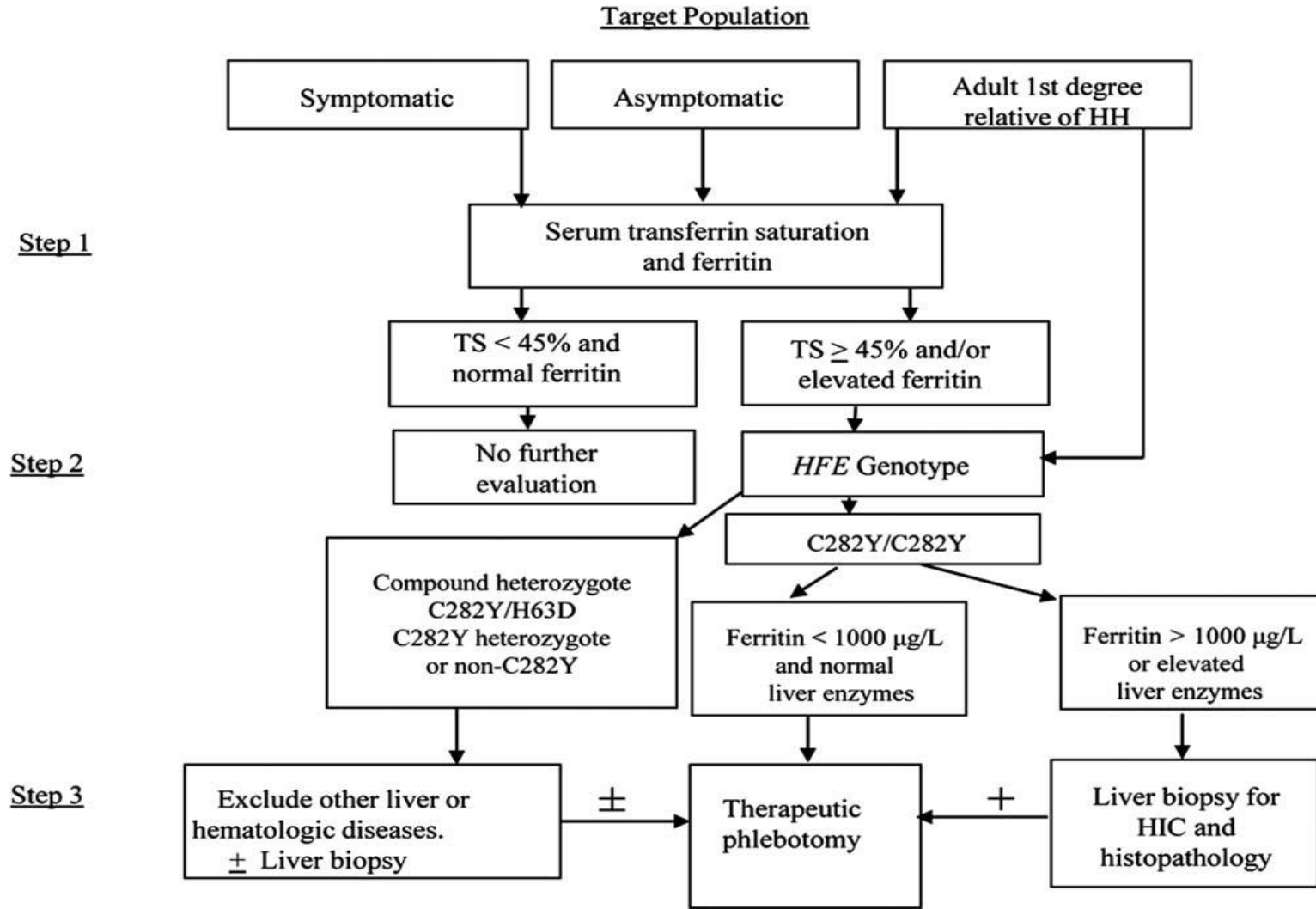
# MEANING OF GENETIC TEST RESULTS

- Actual risk of developing iron overload is dependent on which & how many mutations are inherited
- Other genetic and non-genetic factors also play a role
  - Gender
  - Alcohol intake
  - Use of iron and vitamin C supplements-both increase total body iron!
  - Menstrual/pregnancy related iron losses
- Two mutations in an individual with biochemical evidence of iron overload confirm HH diagnosis
- Two mutations in an asymptomatic individual suggest a risk of developing iron overload
  - Yearly assessment of iron indices is justified

## MEANING OF GENETIC TEST RESULTS

HFE mutations present	Risk of iron overload
C282Y/C282Y	Highest risk of developing iron overload (40-50%) Many patients don't accumulate enough iron to cause disease; only about 10-33% will develop symptoms
C282Y/H63D	About a 2% lifetime risk of developing iron overload
C282/565C	Similar risk to C282Y/H63D individuals
H63D/H63D	About a 1% lifetime risk of developing iron overload

# ALGORITHM FOR ASSESSMENT OF POSSIBLE HH



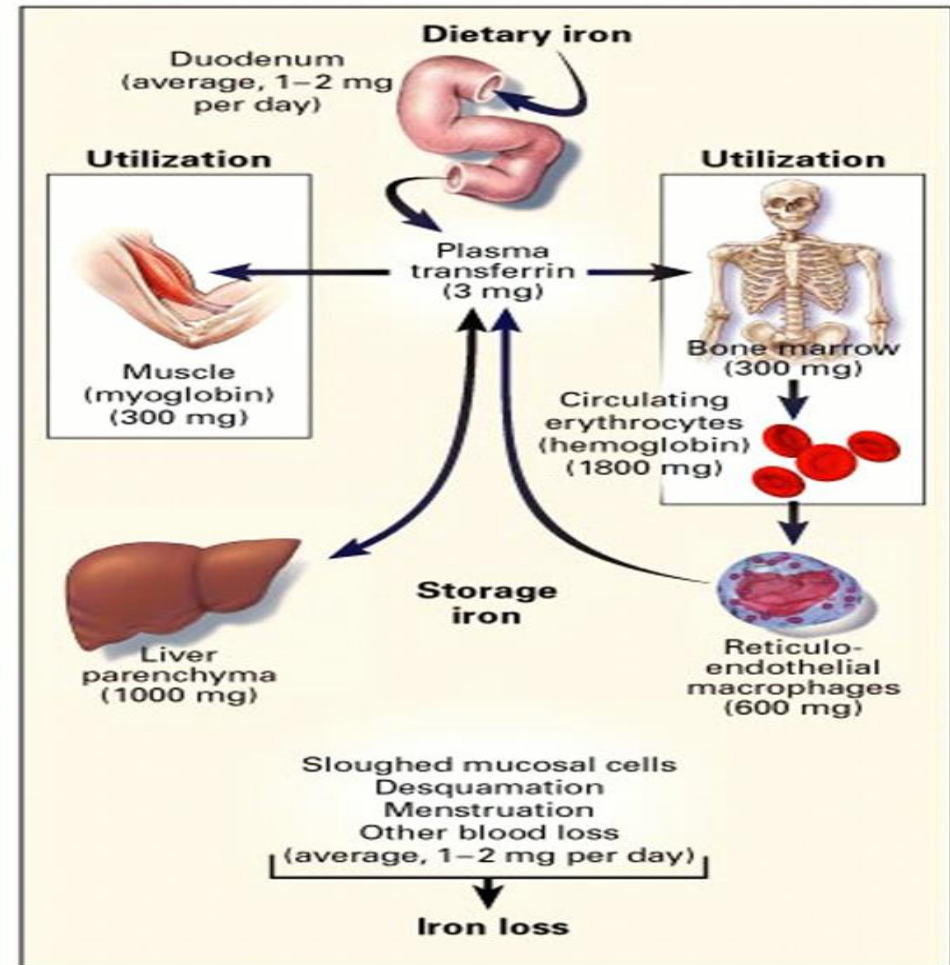
## CASE STUDY

- Michael's laboratory testing demonstrates biochemical evidence of iron overload
  - Serum ferritin is 1200  $\mu\text{g/L}$ , & TS 72%
- Family history—MI, liver disease with cirrhosis, type II diabetes in first degree relatives—is suggestive of HH
- Genetic testing is offered and Michael accepts this
- Test results indicate that Michael is genotype C282Y/C282Y homozygote, and this confirms HH diagnosis
- As a result, therapeutic phlebotomy is prescribed
- A liver biopsy is recommended due to high SF level and right upper quadrant pain
  - Liver function testing was also mildly elevated



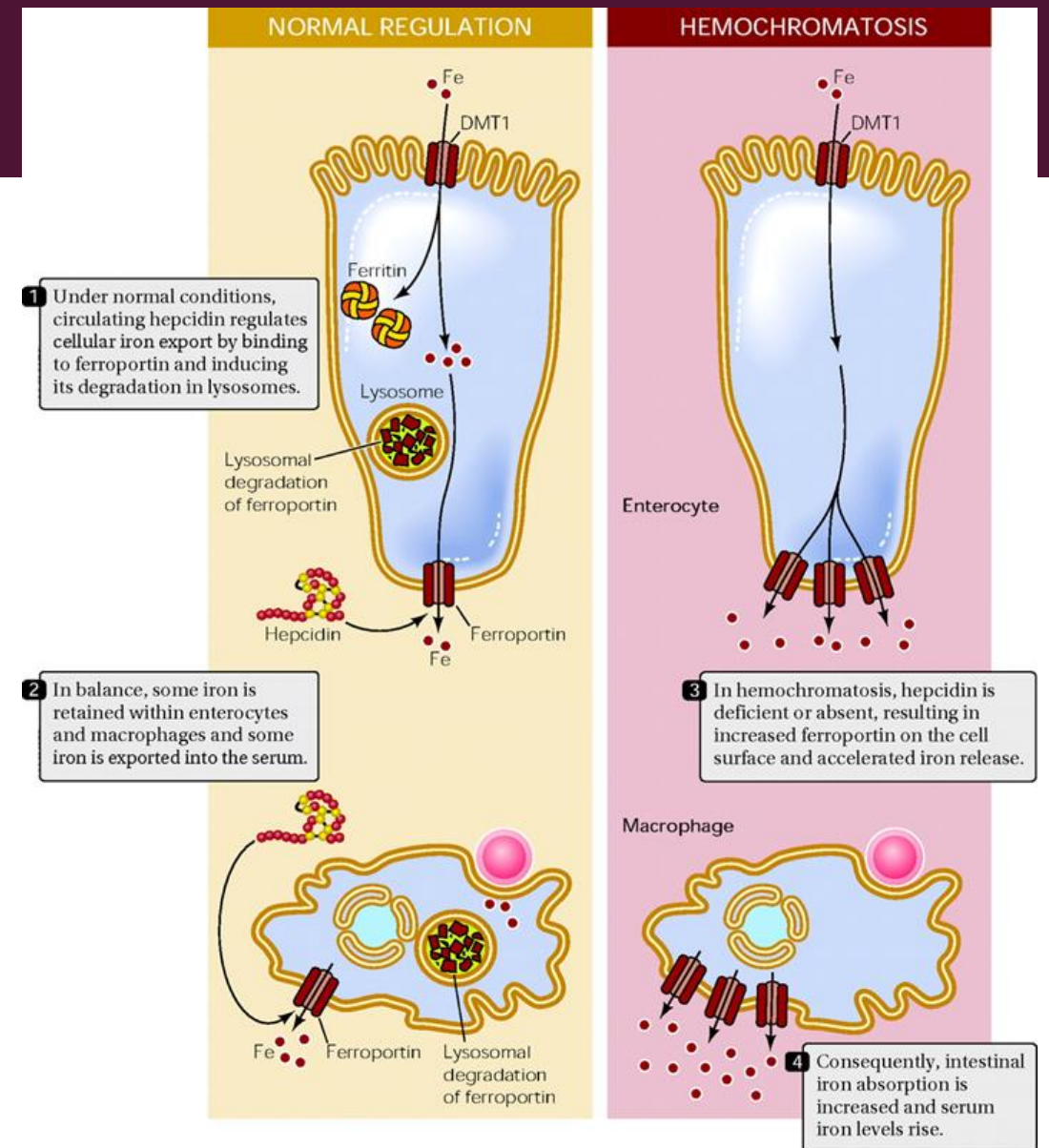
# SUMMARY OF THE BODY'S IRON CYCLE

- Dietary iron is absorbed primarily via the duodenum
  - Absorption of heme iron is more efficient than plant-based iron or inorganic (supplemental) iron
- From duodenal cells, some of this iron is utilized by the blood forming cells of the bone marrow, and some by muscle to produce myoglobin
- Iron is stored in liver cells and in macrophages of the reticuloendothelial system
- Iron loss occurs via sloughing of mucosal cells and skin cells, menstruation, and other blood loss
  - Whole blood donation results in 220-250 mg iron loss



# IRON REGULATION: NORMAL VS. HH

- In HH, hepcidin, which normally regulates iron export from duodenal cells, is deficient or absent
- As a result, ferroportin, an iron transport channel on cellular surfaces, is increased, and more iron is absorbed
- More iron is also exported from both duodenal cells and macrophages, resulting in increased serum iron levels



# THERAPEUTIC PHLEBOTOMY IN HH



- Although no randomized, controlled trials exist supporting phlebotomy, overwhelming clinical evidence suggests that starting phlebotomy prior to a patient developing cirrhosis or diabetes significantly reduces the risk of morbidity and mortality
  - This reduction is largely due to the prevention of cirrhosis, responsible for 20% of deaths from HH, and hepatocellular carcinoma (HCC), responsible for 30% of deaths
- Asymptomatic individuals with homozygous HH and markers of iron overload, as well as those with evidence of increased hepatic iron, should be treated with phlebotomy
- If a patient has cirrhosis, phlebotomy should also be done to decrease iron stores and risk of HCC
- All patients' TS and SF levels should be monitored to guide phlebotomy frequency and duration
  - Patients with cirrhosis also require periodic screening, via liver biopsy, for HCC

# THERAPEUTIC PHLEBOTOMY IN HH



- Initiation of phlebotomy
  - Phlebotomy is like a blood donation, but a doctor's prescription is required, designating the amount of blood to be removed per visit—a common practice is to order 500 cc removed per phlebotomy
    - If the patient otherwise qualifies as a blood donor, and blood is being removed at a blood donor center, the order may be to remove “one unit” of blood per visit, to account for extra blood drawn for donor infectious disease testing
    - Blood donor centers need to have a special FDA variance to their whole blood collection procedure to collect HH units from qualifying donors to use for transfusion—not all centers have this variance
    - Whether the HH patient's blood is transfused or discarded, blood center must provide this service free of charge
  - During the initial stage of phlebotomy, 1-2 units of blood should be removed per week, as tolerated
  - Each unit removed contains around 250 mg of iron
    - Serum ferritin drops about 30 µg/L with each phlebotomy
  - If total body iron stores are very high (25-30 gm), it may take 2-3 years of frequent phlebotomy to reduce iron stores adequately
    - Patients with very high SF levels should be advised that this is NOT a rapid process!

# THERAPEUTIC PHLEBOTOMY IN HH



- Serum ferritin (SF) should be assessed every 10-12 phlebotomies, or about every 3 months, during the initial stage of treatment
- Excess iron stores have generally been mobilized when SF level drops to between 50-100  $\mu\text{g/L}$ 
  - Some clinicians prefer to maintain SF at slightly higher levels, around 200-300  $\mu\text{g/L}$ , if the patient has lower initial SF, no symptoms or iron-associated disease processes
  - As SF nears this level, testing may be done more frequently, to avoid inducing iron deficiency
  - At this point, patient should be assessed for need of maintenance phlebotomy
- Some patients require maintenance phlebotomy monthly or bimonthly, while others may need phlebotomy only 1-2 times per year
- During treatment, vitamin C supplements should be avoided, as these accelerate iron mobilization to a level that may saturate transferrin and result in toxicity
- In C282Y homozygotes with SF < 1000  $\mu\text{g/L}$ , normal liver function tests, and no symptoms, phlebotomy may be debated
  - Generally, these patients will undergo phlebotomy, as it is safe, relatively inexpensive, and may result in benefit via blood donation where this is allowed
  - Current clinical recommendations favor prophylactic phlebotomy in these patients

# THERAPEUTIC PHLEBOTOMY VIA ERYTHROCYTAPHERESIS

- A few studies have investigated whether RBC, and thereby iron, removal may be accelerated during the initial phlebotomy phase in HH patients via automated erythrocytapheresis
- Removal of the equivalent of 2 units of RBCs by automated erythrocytapheresis has been found to increase the efficiency of RBC removal in HH, polycythemia vera, and secondary erythrocytosis patients in these studies
- In one study (Evers, et al), removal of the equivalent of 2 units of RBCs by apheresis was found to be about 1.5 times more efficient with automated procedures than single unit phlebotomy, particularly in patients with blood volumes greater than 4500 cc and higher hematocrits
  - Median initiation phase length in this group was about 38 weeks or 10.5 procedures
  - Maintenance treatment procedure intervals were medially 13 weeks

# THERAPEUTIC PHLEBOTOMY VIA ERYTHROCYTAPHERESIS

- Medical considerations for use of erythrocytapheresis in HH
  - Patient's blood volume, hematocrit, and total body iron
  - Patient tolerance for double RBC removal procedure every 2-3 weeks
- Blood center considerations for use of erythrocytapheresis in HH
  - Expense of procedure over single unit phlebotomy-automated instrument, nursing time, bag & tubing sets, etc.
  - Does the center have an FDA variance to utilize blood from qualified HH patients for transfusion?
    - Cost recovery is greatly improved by ability to distribute blood to hospital customers vs. discarding it!
  - Does the center have a sufficient number of HH patients in its region to support such a program?
    - Outreach to physicians in the area, as well as to the public, may be necessary to raise awareness of HH in the community
  - Is blood center nursing staff familiar and comfortable with the automated technology?
    - FDA mandates that these collections in blood centers must be done by licensed staff



# HOW DO PATIENTS WITH HH RESPOND TO PHLEBOTOMY?

- Reduction of tissue iron stores to normal
- Improved survival if diagnosis and treatment before development of cirrhosis and diabetes
- Improved sense of well-being, energy level
- Improved cardiac function
- Improved control of diabetes
- Reduction in abdominal pain
- Reduction in skin pigmentation
- Normalization of elevated liver enzymes
- Reversal of hepatic fibrosis (in approximately 30% of cases)
- No reversal of established cirrhosis
- Elimination of risk of HH-related HCC if iron removal is achieved before development of cirrhosis
- Reduction in portal hypertension in patients with cirrhosis
- No (or minimal) improvement in arthropathy
- No reversal of testicular atrophy



## CASE STUDY

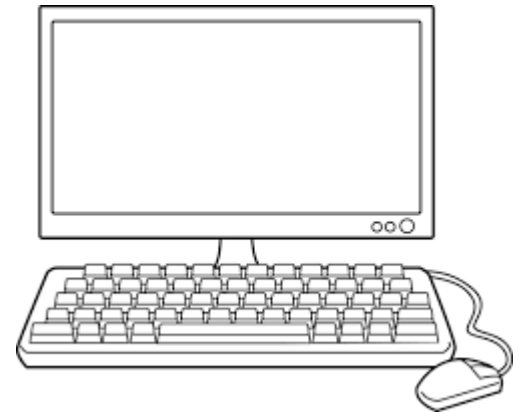
- Michael began manual phlebotomy of single whole blood units twice per week, which he tolerated well
- Liver biopsy revealed very mild fibrosis, but no evidence of cirrhosis; total hepatic iron was increased
- Future genetic testing of Michael's sons was recommended to determine their risk of HH
  - If mom is not a carrier, both sons are obligate carriers (heterozygotes) for C282Y, with no risk of developing iron overload
  - This information will be important for sons when they start families

## REFERENCES

- Alanson J, Morrison S, Carroll C. Hereditary Hemochromatosis. Genetics Education Canada Knowledge Organization. [http://www.geneticseducation.ca/ppt/hereditary\\_hemochromatosis\\_gecko2014.ppt](http://www.geneticseducation.ca/ppt/hereditary_hemochromatosis_gecko2014.ppt) [Accessed October 2016]
- Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; 54: 328-43
- Centre for disease Control and Prevention. National Center on Birth Defects and Developmental Disabilities. Hemochromatosis. <http://www.cdc.gov/ncbddd/hemochromatosis/index.html> [Accessed October 2016]
- European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol* 2010; 53:3–22.
- Evers D, Kerkhoffs JL, Van Egmond L, et al. The efficiency of therapeutic erythrocytapheresis compared to phlebotomy: A mathematical tool for predicting response in hereditary hemochromatosis, polycythemia vera, and secondary erythrocytosis. *J Clin Apheresis* 2013;29(3): 133-38
- Kowdley KV, Bennett RL, Motulsky AG. HFE-Associated Hereditary Hemochromatosis. 2000 Apr 3 [Updated 2012 Apr 19]. In: Pagon RA, Adam MP, Bird TD, et al., editors. *GeneReviews™* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1440/>
- Wallace DF, Walker AP, Pietrangelo A, Clare M, Bomford AB, Dixon JL, Powell LW, Subramaniam VN, Dooley JS. Frequency of the S65C mutation of HFE and iron overload in 309 subjects heterozygous for C282Y. *J Hepatol* 2002; 36(4):474-9

# RESOURCES FOR PATIENTS

- [www.hemochromatosis.org](http://www.hemochromatosis.org) Provided by the Iron Disorders Institute
  - Excellent site with basic and more advanced information for patients, as well as information for clinicians
  - Includes dietary and lifestyle recommendations for HH patients, as well as downloadable forms and charts for patients to maintain records of their treatments and laboratory results
- [www.irondisorders.org](http://www.irondisorders.org) Iron Disorders Institute
  - Detailed information on various iron disorders and anemias; patient videos of their experience with these disorders
  - Step-by-step guide for patients
- [www.americanhs.org](http://www.americanhs.org) American Hemochromatosis Society
- [www.americanliverfoundation.org/abouttheliver/info/hemochromatosis](http://www.americanliverfoundation.org/abouttheliver/info/hemochromatosis)
  - Brief general overview of HH with emphasis on liver issues
- [www.mayoclinic/diseases-conditions/hemochromatosis/home/ovc-20167289](http://www.mayoclinic/diseases-conditions/hemochromatosis/home/ovc-20167289)
  - Excellent review of HH in lay language, with illustrations of genetics and disease process



QUESTIONS?

