My talk today will be about hemochromatosis. Unfortunately we’ve not made a huge amount of progress to update you very much on hemochromatosis so this will be more of a review than talking about new developments. But we’ll talk about the genetics of hereditary hemochromatosis, the prevalence and penetrance of disease, typical clinical features, diagnosis management and then briefly touch on secondary iron overload states and management, which is a more complicated group of patients that we more frequently see I think.

So I’ll start with a case. I put together a couple of cases, they are meant to be illustrative rather than comprehensive so try not to get caught up in the details but think about them in general terms. This first case is a 51 year old asymptomatic Caucasian male who sends his DNA for analysis from one of those internet companies that will test your genome. I’ve actually seen this, I’m sure many of you have as well. But he came in and said he has two copies of the G-to-A missense mutation leading to substitution of tyrosine for cysteine at amino acid position 282 of the HFE protein product. So he has homozygote for C282Y and is told to go to his primary care physician to figure out whether he has hemochromatosis or not. He doesn’t smoke or use any alcohol, he has a family history of diabetes but no family history of liver disease.

When you examine him he is healthy, a BMI of 24, no hepatomegaly, splenomegaly, no cutaneous stigmata of chronic liver disease. His liver enzymes are normal, ALT 28, AST 16, t billi and alkaline phosphatase normal as well. CBC and chemistries are within normal limits. His iron saturation is 30% and ferritin is 80. Does he have hereditary hemochromatosis?
So in order to answer that we’ll talk briefly about the genetics of hereditary hemochromatosis which is an autosomal recessive genetic disease, therefore you need two copies of an abnormal gene to develop the disease. The most common mutations are in the HFE gene, they are the C282Y mutation, the H63D and the S65C mutations. But iron overload really only occurs in 3 – well I take that back, iron overload can occur in people that are homozygous for C282Y, or they are compound heterozygous, that is they have one copy of C282Y and a second copy of either H63D or S65C. Now you’ll commonly see homozygous for H63D, they are not thought to be at risk for iron overload with organ damage.

So 85 to 90% of people with inherited forms of iron overload are homozygous for C282Y. Somewhere around 3 to 5% are compound heterozygous and then the remaining 10% probably have a mutation in other genes and proteins related to iron metabolism such as hepcidin, hemojuvelin, transferrin receptor 2 or ferroportin.

In order to understand the pathophysiology of disease you start with an understanding of the normal iron metabolism in the body, the duodenum absorbs the iron that is taken in through the GI tract. There is a protein transporter called ferroportin that takes iron from inside the enterocyte and puts it into the blood. Normally hepcidin that’s produced by the liver will bind to ferroportin. Well when it binds it internalizes the receptor complex and then iron cannot get into the blood.

So if you have hereditary hemochromatosis then you have less hepcidin, you are unable to bring your ferroportin into the cell, and your ferroportin continually absorbs the iron and brings it into the blood,
leading to toxic accumulation of iron in your liver or your heart, your pancreas and some other organs. Other mutations in hemouvelin are ferroportin can lead to changes in the pathway as well but by and large the mechanism is that ferroportin is not internalized into the cell and you have continual influx of iron.

So hereditary hemochromatosis is the most common identified genetic disorder in Caucasians with a prevalence of C282Y homozygosity somewhere around 1 in 200 to 300 individuals. And that would be the most common genetic disease if it weren’t for the fact that most people won’t actually develop clinically significant disease that have the homozygous C282Y genotype. Phenotypic expression with elevated iron parameters occurs in about 70% of people, but severe iron overload with organ damage and clinical manifestations are in less than 10%. So this provides the basis by which we are not currently doing general population screening for hereditary hemochromatosis.

It’s really uncertain at the present time what it is that will take somebody from the genetic predisposition to the clinical manifestations of disease. There is definitely a relationship between alcohol and hemochromatosis so people that drink heavily are more likely to develop more significant disease and fibrosis. Concurrent viral hepatitis can worsen the disease as well. And there is probably some other genetic modifiers that are acting together to result in the phenotypic expression of hereditary hemochromatosis in people that are predisposed with the genetic disorder.

So there is three stages of hereditary hemochromatosis which may reframe your thinking about that original patient who I think originally I would have said does not have hereditary hemochromatosis
but based on this staging you would say that he has Stage 1 which is that he has the genetic disorder with no increase in iron stores, but is susceptible to developing the disease. Stage 2 is having the genetic disorder with phenotypic evidence of iron overload, perhaps no iron saturation or ferritin, but no evidence of any organ damage with that. And Stage 3 is the genetic disorder with iron overload and iron deposition in organs to the degree where you begin to have tissue damage.

Looking at the diagnostic algorithm this is present in the ASLD clinical guidelines and I think it’s a good algorithm to follow. You’ll start with a target population, so whether that be somebody that has elevated liver enzymes, someone that’s a first degree relative of someone with hereditary hemochromatosis. The first thing you want to do is check their iron stores with the iron saturation and ferritin level. If the iron saturation is less than 45% and their ferritin is normal you can stop, no further evaluation. I would add for this particular patient though because he has started with knowing that he has the predisposition to disease that you would want to follow him yearly with iron studies to make sure he doesn’t develop manifestations of the disease. In somebody that you are assessing elevated liver enzymes you can stop with just the normal iron saturation and ferritin. If you have an elevated iron saturation or ferritin you will go on to test the HIV genotype and this will be illustrated in a case later in the talk.

Moving on to case number 2, this is a 51 year old Caucasian male who has diabetes diagnosed a couple of years ago coming to you not feeling very well. He’s been having more fatigue, his skin is darker, he has intermittent right upper quadrant pain. On further history you find out that he drinks 2 glasses of wine per night, he’s not a smoker, he has no other risk factors for chronic viral hepatitis or
any intravenous drug use. There is a family history of elevated liver tests but can’t give you any more information than that.

On physical exam he’s a well appearing male but you do note he has some bronzing of the skin, he has normal heart and lung sounds but you do feel some hepatomegaly with the liver edge a couple of centimeters below the costal margin. The spleen tip is palpable and he has some stigmata of chronic liver disease with spider angiomata of his chest and pulmonary erythema.

When you check his labs you see he has a mild thrombocytopenia with a platelet count of 130, his elevated – or his ALT and AST are mildly elevated at 60 and 70. You check for other sources of chronic liver disease. His serologies for A, B and C are negative, other evaluation for live test is normal but his serum ferritin is elevated at 1100 and his iron titration is 75. You then go on to check his HFE gene mutation and find that he is C282Y homozygous.

So this is a patient that more classically has Stage 3 hereditary hemochromatosis, he’s got the genetic predisposition, the elevated iron parameters and now he’s got the manifestations of organ injury. In fact he has physical exam and lab evidence that he’s now gone on to develop cirrhosis.

Hemochromatosis is the most common inherited cause of cirrhosis in adults, a much smaller percentage of children can blame hemochromatosis on cirrhosis. That’s probably because this disease takes many decades to cause a problem, it’s a slow, slowly progressive disease. Other inherited
causes of cirrhosis like Wilson’s disease, cystic fibrosis and alpha 1 antitrypsin deficiency comprise a smaller percentage of the causes of hereditary or inherited causes of cirrhosis.

Clinical manifestations of hereditary hemochromatosis range from an asymptomatic state with you either find elevated iron studies on routine testing or you find – or you are working up elevated liver enzymes or someone has a family history and you are further investigating that. People can have nonspecific systemic symptoms, fatigue, weakness, apathy, weight loss. More organ specific related symptoms are related to organ involvement like abdominal pain with hepatomegaly. You can get an arthritis and have some arthralgias, diabetes due to the pancreatic involvement of the iron, amenorrhea, loss of libido and when the heart is involved also you can get congestive heart failure and arrhythmias. So the physical findings are going to mimic those as well. They may be asymptomatic with no physical findings, there may be simple hepatomegaly or they may have cutaneous stigmata of more chronic liver disease, cirrhosis, liver failure. They may have joint swelling or chondrocalcinosis, they may have a dilated cardiomyopathy, increased skin mutations, sorry pigmentation, porphyria cutanea tarda, testicular atrophy, hypergonadism, hyperthyroidism; all things to consider in these patients.

Moving on to the diagnostic algorithm for this particular patient, we start with a symptomatic patient who has elevated transferrin saturation and ferritin, any C2Y2 homozygote, so therefore he moves down this pathway here where you see that he does have pretty markedly elevated ferritin, over 1000 and he has elevated liver enzymes and that would buy him a liver biopsy based on this algorithm. And he also should be treated with phlebotomy.
Serum ferritin is interesting, it’s a pretty accurate predictor of presence of absence of cirrhosis. If it’s less than 1000 it’s pretty accurate at saying that a patient does not have cirrhosis, fewer than 2% of patients will have cirrhosis in the absence of other liver diseases. If the serum ferritin is greater than 1000 they are at increased risk of cirrhosis with a prevalence of 20 to 45%. Now if you have elevated ALT, AST and a platelet count less than 200 you are – in addition to a serum ferritin over 1000 your chance of cirrhosis is about 80%, or 80% of people with that picture will have cirrhosis.

Liver biopsy is recommended in that particular line of patients if the ALT/AST is elevated or the ferritin is greater than 1000. And I explained the rationale for the ferritin but the ALT/AST because the hemochromatosis is not necessarily an inflammatory disease often will not become elevated until a patient has cirrhosis. So that’s a reason for a biopsy in someone with elevated liver enzymes. Additionally in people that have non-hemochromatosis related iron overload a liver biopsy can provide some information about the amount of iron that’s in the liver and can prognosticate things that can tell you the amount of scar tissue that’s formed. Iron is scored in the liver from a scale of 1 to 4, 1 is good, 4 is bad. We used to look more at the hepatic iron concentration when we were diagnosis hemochromatosis, but now that we have the gene testing we don’t use that number as often and it’s actually as you can tell not even in the diagnostic algorithm at this point.

So management continues to be phlebotomy. We recommend one phlebotomy with removal of 500 milliliters of blood weekly or every 2 weeks, and we recommend that you check a hemoglobin hematocrit prior to each phlebotomy. You don’t want your hemoglobin hematocrit to fall by more
than 20% of the prior level. You want to check the serum ferritin, it says every 10 to 12 phlebotomies, you are going to want to check more frequently as they start to approach your goal of ferritin levels between 50 and 100. And you will try and continue your phlebotomy at intervals to keep the ferritin between 50 and 100 whether that be every couple of months or every year. People may need ongoing maintenance phlebotomies once a year for example.

And you want to counsel your patients to avoid vitamin C supplements, particularly when they are undergoing phlebotomy. The influx of iron or the changes in the iron levels can cause some conduction problems in the heart and that can be worse with the combination of phlebotomy and vitamin C supplement, so that is one thing you want to tell people. You don’t need to necessarily make any dietary recommendation since there is not very much that you can do from a dietary perspective to decrease the iron load. And if you do a biopsy and you see that someone has cirrhosis or they have frank evidence of cirrhosis on visible exam you want to make sure you are monitoring for hepatocellular carcinoma by the ASLD guidelines of either an ultrasound every 6 months or a yearly dedicated CT or MRI. People with hemochromatosis are at much higher risk for hepatocellular carcinoma, somewhere around an incidence of 3 to 4% once they develop cirrhosis and it’s about twice as frequent as the development of hepatocellular carcinoma from other chronic liver diseases. There doesn’t seem to be an increased risk with just prior to developing cirrhosis as we see with viral hepatitis and some other diseases. So that screening can start once cirrhosis is actually present.
The benefits of phlebotomy, there are some things that can improve by phlebotomy, things like malaise and fatigue, the skin pigmentation, insulin requirements and abdominal pain. You may be able to reverse some of the fibrosis, people that have advanced cirrhosis probably cannot reverse the damage completely or at all, and other features that don’t improve with phlebotomy are things like arthropathy and hypogonadism.

Family screening should be offered to anyone, any family members of somebody with diagnosed hereditary hemochromatosis. To screen somebody in the family it’s recommended that you do both iron saturation ferritin and HFEG mutation testing at the same time. If you’ve got a family member that is homozygous for the C282Y mutation and elevated ferritin levels you start phlebotomy. If they are homozygous for C282Y and normal ferritin follow them yearly with iron studies to monitor for the development of disease. If they are C282Y heterozygote you can reassure them that C282Y wild type I meant to say you can reassure them they are not at risk for developing iron overload and if they have two copies of H63D you can counsel them they are probably not going to develop iron overload, they might have mild abnormalities in their ferritin or iron saturation but they are very unlikely to develop the severe clinical disease of progressive fibrosis, cirrhosis and heart and other organ manifestations.

The third case is something that we see very, very frequently in the liver clinic. This is a 51 year old male who comes in with a diagnosis of alcoholic cirrhosis, was recently diagnosed a year ago. He comes in with encephalopathy. When you do a basic lab evaluation or a thorough lab evaluation you see his ferritin is 1500 and iron saturation is 90% and you based on the diagnostic algorithm go on to
check the HFE gene mutation. He is none of the known mutations that cause hereditary hemochromatosis. We see this all the time in chronic liver disease, about 50% of people that have chronic viral hepatitis, NAFLD or alcoholic liver disease will have elevated iron stores. There is also a pretty high prevalence of secondary iron overload in people with iron overloading anemias and I’ve also pretty frequently seen patients with hemolytic anemia like sickle cell disease that get lots of transfusions and have lots of hemolysis have a lot of iron accumulation in the liver and often these people will go on to have liver biopsies and I’ll talk about the management in a minute.

With respect to treating people with chronic liver disease with phlebotomy in the absence of the HFE gene mutations there is mixed data out there. It appears that an alcoholic liver disease it does not help to phlebotomize people to get the iron levels down to improve liver histology. It might be helpful in some patients that have hepatitis C or NAFLD, there has been some studies that have shown increased iron make you less likely to respond to hepatitis C therapy or develop more progressive NAFLD. Some studies show a benefit, others don’t and so I think the jury is still out. We are not routinely doing this in the absence of HFE gene mutations in our patients with chronic liver disease and iron overload.

When people have elevated iron from iron loading anemias or transfusion overload you can use iron chelating agents Deferoxamine at 20 to 40 mg/kg of body weight or Exjade orally. It’s harder to follow the iron stores in these patients, the ferritin is not as good of a marker of direct iron stores so you often have to repeat a liver biopsy in these people in order to determine whether you are making any progress. These medications are also expensive and associated with other side effects and so
best prescribed in conjunction with probably hematology and perhaps hepatology to make that decision.

I’ve included the ASLD guidelines just for your reference here, I think that they are a pretty good reference as far as management. They are very clear and direct. I think I covered most of them in the talk. So I won’t read through them but they are in your packet to refer to and I also recommend looking over the guidelines in order to better manage your patients. And I’m happy to take any questions. Please email me, I’m here in the Liver Disease Center so you might see my name on your referrals and I’m happy to see any patients with any liver disease at all. Thank you.