What do they really mean when you see abnormal liver blood tests? So a brief introduction, the term LFTs which you and I use very commonly is a misnomer. Most of these tests really reflect the health of the liver and are not truly direct measures of its function and it’s important to realize that these liver tests may be abnormal even in patients with a healthy liver. And what I would like to add to this is just because quote your liver blood tests are normal does not mean the individual does not have liver disease and sometimes even advanced liver disease can have quote normal LFTs.

So traditionally what do we include on the LFTs? These are the lab tests mentioned here the serum ALT, AST, the alkaline phosphatase. I added GGT because this is a liver function test, it’s not in the usual panel that you order but I can’t tell you how useful this is when you have certain differential diagnoses, bilirubin is always there. And then the true, the true liver function tests are really measurement of the synthetic function of the liver which is the serum albumin and prothrombin time. So all these put together come under the so called package of LFT’s.

Now we see patients and you pick out patients in different ways, I mean they come to me, I mean this is picked up as part of an annual physical exam because patients are usually asymptomatic at this time. These are screening tests, a comprehensive metabolic panel. I can’t tell you but between 30-50% of patients are picked up when they go for these lab tests as part of you know insurance applications or disability applications and hence the clinical significance is very, very available. There’s a wide spectrum of liver problems that can be and the question is really how much should I chase this and this question I’m asked a lot of times and we’ll see as we go through this talk later.
Clearly it’s fair to say that serious disease, serious underlying liver disease is uncommon when liver tests are picked up in this fashion. Now when you come across different studies and you are looking at the epidemiology I think you’ll see a smattering of data there, and it’s kind of very difficult to really you know how do you use these studies to translate them into practice. So clearly there’s a variation in the prevalence of liver disease and I think it’s more important what kind of population is being studied and I’ll show you what I mean by that as I go through different situations.

And it’s also fair, you know how much you chase this I mean the degree to which you chase an underlying cause is more likely to reflect the cause of the problem. So this is a very elegant piece of data, it’s the NHANES data. The NHANES is a large database in the NIH and these are door to door surveys conducted every decade and if you look at between 1999 and 2002 the overall prevalence of “abnormal liver tests” was roughly about 10% of the overall population. That’s a huge number. Now if you exclude hepatitis C or alcohol, it still comes down to about 8% and this 8% basically reflects what today’s going to be the new epidemic of liver disease or non alcoholic fatty liver disease. Clearly the predictors of a high ALT or abnormal liver tests; obesity, alcohol use, there is a male preponderance, there’s an ethnic preponderance, clearly decreasing age and the presence of HCV antibody.

So if you look at the, this is what, these are non-biased population, a door to door survey that reflects the incidence of this problem. Clearly if you look at different types of abnormal, I’ll show you about 2 or 3 studies out there, there’s about 20,000 air force trainees, okay, clearly a subset of the population and this is not equal to the general population. Again, abnormal ALT .5% and if you
really look at the cause of the elevation there were barely 12 people who you could find a cause and these are the causes listed there, hepatitis B, C, autoimmune liver disease etc.

If you go to a blood bank and look at again 100 consecutive blood donors clearly this is more reflective of the everyday population because as you know blood banks have a very stringent screening mechanism before you donate blood, 50% is going to be alcohol. And you can use this data to translate this into your practice. Fatty liver disease which, non-alcoholic fatty liver disease, hepatitis C is becoming a big problem and I want to talk a little bit more about it later, and then again despite you know all the tests about between 10% will have no known cause.

And then lastly if you look at you know people who actually go one step further, so you have an abnormal LFT and you do a liver biopsy even then again fatty liver which is again as I said the new epidemic of liver problems, more than half the patients will have nonalcoholic fatty liver disease, non-A, non-B which means we still don’t know the cause of the liver damage, alcohol, hepatitis B, etc. So I think it’s fair to say that the diagnoses can be established noninvasively in most patients and what kind of testing you actually do should be determined by your pretest probability. And I think this is a difficult statement and I’ll try and highlight how you could go about a different way in the order when you order all these tests because these tests are expensive and then sometimes values come back and you don’t know what to do with them.

I think it’s clear that most will turn out to have fatty liver, clearly the most common cause of fatty liver is alcohol. I can’t tell you how difficult it is to diagnose alcoholic liver disease, despite all
these years in practice I still think it’s probably the most difficult history to take and I think sometimes despite 1 or 2 or 3 meetings in the office or the hospital it just ultimately turns out to be alcohol, and clearly nonalcoholic fatty liver disease which I highlighted earlier.

So I’m trying – going to take you through a few steps which I think all of you do in practice. First is confirm the abnormal value. I can’t tell you, you know, these unexpected AST and ALT values sometimes could just be a lab issue. You know if that tube sits in the container for a certain amount of time you are going to get hemolysis and these AST, ALT values will suddenly look abnormal. So always confirm the test with another lab value. If it’s still abnormal now you look at the degree of elevation. And I think it’s important to look at the upper limit of normal because over the years the upper limit of ALT has changed, you know in the good old days it used to be 40, today different labs have different upper levels of normal. I mean some have gone up to as high as 60 and 70, so see what is the upper level of normal because it’s fair to say that minor elevations, which means less than 2 times normal, may not be clinically really important, and they may not even be abnormal. And you know how did we come up with normal LFTs? Clearly if you look at how a lab test is designed or evaluated you take a few thousand patients, you come up with two standard deviations on either side and you say this is normal. But 5% of patients will actually fall on both sides of this, so clearly and I think we are not there yet but I think the better way to define a normal ALT we may need to have normal ALTs based on age, body mass index and sex. As I said we are not ready to share this in a general fashion as to what is normal and abnormal based on these, but clearly 5% of patients will fall outside that normal range. And then of course you are aware of the physiologic elevations, a simple example is pregnancy and an elevated alkaline phosphatase.
So I think I just put up, I mean this is a busy slide which I think the clinical clue is always there so clearly alcohol use, alcoholic liver disease, obesity, risk factors for nonalcoholic fatty liver disease takes you to what’s NASH, previous IV drug use, etc., so I’m not going to spend too much time on this slide because all of you are very familiar with these clinical clues that may guide your further testing. I think it’s fair to say that you know that I tell Fellows on rounds of residents when we have them in our clinic that if you said it’s a medication causing the abnormal liver function tests you are never going to be wrong because somewhere in the algorithm the use of medications is always going to be implicated as the cause of the abnormal liver tests. Now I think the challenge here is it a prescription medication, is it an over the counter medication, herbals and I think the latter two are the important over here because many of our patients are taking these over the counter preparations or herbals which is you know a big thing right now and these are probably the cause of the abnormal liver value.

Clearly you are going to find out how long this has been present. And in the liver world, I mean the way we differentiate acute versus chronic means anything that’s more than 6 months would be classified as a chronic liver disease, so clearly if the LFTs have been abnormal for more than 6 months we classify that as chronic liver disease. And then of course you go through symptoms which are kind of obvious out there, but as I shared with you, you know liver disease, early liver disease has no specific symptoms so by the time you get jaundice you know systemic symptoms it’s probably a little late and the diagnosis would be kind of obvious.
You take – you look for parenteral exposures, a blood transfusion history is very important, a transfusion IV and intranasal drug use, a history of tattoos, sexual activity, needle stick injury, travel important for acute liver disease not so much for chronic, and then I put there you know a host of other environmental factors which I think alcohol consumption is the most important there.

You obviously do a good physical exam, you are going to look for features for chronic liver disease, so muscle wasting, temporal, you look for stigmata of chronic liver disease and then complete your physical exam. Clearly these are all features of advanced liver disease, i.e. established cirrhosis of the liver or portal hypertension.

When things do not add up, and this is a rare case, this was during rounds at Montefiore. I had this 35 year old state trooper, a real healthy guy who was actually flown in from another hospital because he had this combination, you know he had abnormal liver tests, he had acute hepatitis, he had features of pancreatitis and he had a way low platelet count. And all of us were like wondering what the hell is going on? So you know I’m on rounds, I have two Fellows, 3 or 4 Residents in a large team at the bedside and the state trooper tells me, doc, can you tell your colleagues to just step out, I need to talk to you in private. I said okay. So this is what happened. He said doc, I’m very embarrassed to tell you this but my friends took me out you know for my birthday celebration and I consumed 18 Jaeger Bombs over a period of 3 hours and I just passed out. And I said you know I mean I didn’t know what a Jaeger Bomb was. So I go to the – I said what is a Jaeger Bomb? He said – he kind of laughed at me, anyway I went out of the room, I Googled you know Jaeger Bomb and this is what it is – so apparently it’s a combination of a German liquor the Jaegermeister which
still I think I’ve not been able to find out what the true contents of Jaegermeister are in combination with this drink and the Red Bull and this together is the Jaeger Bomb. I just show this because clearly I think our patients are consuming or ingesting all kinds of you know agents and when things don’t add up you know always try and get a better history.

So going to the next level, you know I think this is still a very useful exercise because I was taught this in med school and I still use this at the bedside, I can’t tell you how useful this is, this exercise. So whenever you see a panel that comes back try and classify them you know what type of liver function is truly abnormal, and I think the traditional teaching is, is it hepatocellular, is it cholestatic or mixed? And this is a nice textbook definition because in life there is usually a combination of both. But this fit for definitions a predominant hepatocellular injury is when the ALT or AST are more than 5 times the upper limit of normal. So normal ALT 40, anything more than 200. Clearly that patient can have an elevated alkaline phosphatase but we will accept you know 2 or 3 times the upper limit of normal. On the other hand, a cholestatic pattern is defined as when the alkaline phosphatase is predominantly elevated up to 3 or 5 times the upper limit of normal. Again that same patient will have elevations in ALT, AST which would be minor. I think for the rest of the talk I’m going to restrict my discussion to the hepatocellular pattern because the cholestatic pattern is much easier to sort out and we’ll go through some of these scenarios and look for the detail.

The next exercise which I think you all do is how much is the degree of elevation, minor, moderate, severe? I think the last category is usually an ER patient or hospitalized patient so you know anything more than 1000 is going to either an acute drug injury, you know Tylenol, acute viral
hepatitis, shock, ischemic liver. I think the difficult one is the middle group, this is what you see commonly in practice, the moderate or the minor elevations and we go through this in more detail.

I’m going to quickly skip alkaline phosphatase because I think this is a much easier algorithm to sort out because you know alkaline phosphatase I mean you quickly want to sort out medical or surgical, you want to rule out biliary obstruction so you know large duct bile duct obstruction whether it’s a stone, etc. I mean you start with imaging and ultrasound is probably enough and then you quickly if that’s normal you go into the medical causes. So I’m not going to spend more time on the cholestatic pattern of injury.

So let’s talk about the elevated hepatocellular pattern, and I’m going to focus on the chronic which means more than 6 months, mild less than 250 units. And this is the so-called stepwise evaluation which I think is useful in practice. Clearly when we see the patients at the Center for Liver Disease and I think we get criticized a little bit, you know we do these 15, 20 tests all at the same time but I think this is more focused because it’s probably more convenient for us to do this on you know at one occasion, patients have taken the time to come and see us, or you know have traveled long distances. But clearly the order of the testing you do may change based on your initial evaluation and then this is what I said earlier, the pretest probability of a diagnosis.

So I think going through these steps is useful. Medications and supplements, you really dig deep. I mean I had a patient 2 weeks ago where I had to call two pharmacies to find out exactly which antibiotic she was prescribed, she had a Zithromax related cholestatic hepatitis. So I think spend
some time because it’s worth it, and I think sometimes the answer will be right there. Assess for alcohol use, this is not easy and I’ll share with you some you know clinical scenarios, but as I shared with you this is still a very difficult diagnosis. Testing for viral hepatitis and then hemochromatosis is a very rare disease and testing for fatty liver. I think this is the so-called step 1 approach.

If all this comes out to be negative step back, this may not be a liver problem, okay. And I’ll tell you over the years I think these are the things from the book that I picked, muscle disorders and you can order a CK or an aldolase, not common. Thyroid disease, I can’t tell you how many times I’ve picked up subclinical hypothyroidism, not hyper, but hypo, and the presenting or the reason I was seeing the patient in the liver clinic was a high ATL or AST. Clearly celiac disease and you might see this in different scenarios, I mean celiac diseases is a very underdiagnosed disease. I think the median interval to diagnosis for celiac in the U.S. today is like 7 years or 9 years because these patients go from you know doctor to doctor because the manifestations are not classic so I think step back, these are simple lab tests to order and you may have your answer.

Now if that is also negative then you go into the rarer. I mean this is again for completion, these are very rare diseases in clinical practice, autoimmune hepatitis, rare, Wilson’s disease, the incidence 1 in 10,000, alpha-1-antitrypsin deficiency affecting the liver, 1 in about 12,000. So these are tests that we order but clearly I think you need to realize this is not a common cause in practice. And then lastly this is where we come in or the specialist will come in, I think clearly a liver biopsy is where we would go to if we are not – if we haven’t you know or you’ve had these tests done by yourselves and this is the last kind of step by us.
So a little bit further into some of the important areas that I think I would like to highlight. Medications, and as I said almost any medication can cause elevation in liver enzymes. I think over the years I personally have reported to the FDA up to 5 drugs that maybe I was the first person to pickup this problem, but the problem is these are not picked up in Phase II studies, these drugs get FDA approved and then when they are used on a much larger scale that we really pickup the problems. I’ve listed some of the commonly used drugs but clearly any medication, every medication can cause this.

One question that comes up a lot in primary care practice and I basically see referrals for this, statins and the liver, so I’m going to give you a little timeline because I think and some of you may be familiar with this. In 2006 the American College of Cardiology put together a Lipid Consensus Panel and they had different types of doctors, hepatologists were a part of this and this is what the Consensus Panel said in 2006 and I’ll show you what the FDA said in 2012, so there was a 6 year kind of gap before the FDA decided to approve this. Clearly I think all of you before you start a statin you check liver tests and that’s the right thing to do. If these tests are abnormal you may do additional tests to see if there is any chronic liver disease. And this is what the panel said in 2006, that despite elevations in serum transaminases or once you start therapy you should recheck the liver blood tests in 3 months or whenever you are going to make any changes in dosing. However this is what the panel said at that time, routine monitoring of liver tests was not supported by the available evidence and they actually put forward the recommendations to the FDA. Clearly as a clinician I mean if you have obvious symptoms and signs of liver problems, jaundice, malaise, etc. you are
going to obviously know that this is toxicity and you can evaluate the patient further. I think a good test to use because ALT and AST are not always reflecting liver disease, clearly when the bilirubin starts going up that’s a true sign of hepatotoxicity and I think they tried to highlight that the bilirubin was more important as compared to the other lab tests.

And if an isolated elevation in transaminases, meaning you could ignore elevations up to 3 times the upper limit of normal there was no need to discontinue the statin. Clearly I think was in 2006 the FDA actually adopted this in 2012 and you are all aware that in July of ’12 the need for routine monitoring of liver tests was removed by the FDA. Clearly you should still do the liver tests before you start the statin and then as clinically indicated thereafter. I think it’s important to share with your patients and reassure you know yourselves that serious liver injury with statins is very rare, it’s unpredictable, it’s idiosyncratic and you know routine monitoring is unlikely to be you know effective in detecting this problem.

I think from a clinical standpoint this is what I would tell you, whenever you are making those changes, whenever your dose escalate that’s when I see the problem. So this is not an FDA, this is just a clinical pearl that I would share, I think where I’ve seen problems is when you start dose escalating that’s when you may run into a problem but you know I can’t give you an overall guideline that this is what you should be doing. So this finishes medications, I think I’m going to skip this in the interests of time.
We’ll talk a little bit about alcohol because I think as I shared with you this is a very difficult history to elicit in practice. All of you have the art of patient interviews and all of you probably do a very good job. I still think this is a challenge, you can come up with many different types of tools. Blood tests are a clue, I mean the AST to ALT ratio is very useful. Clearly the ALT can be normal, so AST to ALT they are the higher, I mean you can see that if it’s 3 to 1 most of them had alcoholic liver disease. I think what’s difficult is you know I mean you take a history what is accord a standard drink? And I put this out there because I think all of us including our patients have different – have different understanding of what a drink is and this is just to give you an idea you know, 12 ounces of beer is equal to you know 8 ounces of malt liquor, a glass of table wine, etc. This is very useful for you to keep in mind because when you take a history many people do not really know what counts as a standard drink and I think clearly in mixed drinks it’s even more difficult to quantify. And I’ll tell you why because over the years we’ve lowered the bar as to what the amount of alcohol is I wouldn’t say safe, because when I was – when I was training and I read the first textbook of liver disease by Dame Sheila Sherlock this is what was written, for men up to 8 drinks a day was okay, for women up to 6 drinks a day was okay. Clearly women are more susceptible to alcohol as compared to men. This is the latest definition by the NHANES, and we use this in practice now, so for women more than 1 drink a day and for men more than 2 drinks a day has been implied as you know excess alcohol consumption, and we use this definition because you know one of the things to sort out in practice is the liver enzyme you know alcohol related or non-alcohol related, and clearly quantifying the amount of alcohol is very useful.
I put this up and this is my last slide on alcohol because I share this with patients because I think it’s fair to highlight that this disease is reversible provided you intervene at the right time. So up to steatohepatitis, these are just the histologic stages how alcohol liver disease progresses. So if an individual is able to quit alcohol or lose weight until the stage of steatohepatitis the disease is still reversible, because you remember liver disease is very unforgiving and you know I use this to talk to my patients all the time. Any disease leads to scarring in the liver, i.e. fibrosis. Once you have cirrhosis it’s irreversible. And liver disease carries a very you know sinister meaning and cirrhosis as you know is clearly a very dangerous medical condition to have. So I think you can use this to talk to your patients and counsel them with respect to alcohol use.

I think the last disease I want to highlight here because I think you are going to see more in practice and there are some new guidelines put out by different societies which the primary care practitioners will embrace. It’s a very common problem in the U.S. right now, you know 3.9 million people infected chronically with hepatitis C, clearly there are certain risk factors that you are aware of. This is the natural history of hepatitis C and I think it’s important to know this because when you see a patient in practice this is what you should use to counsel your patients. It takes a long time to develop cirrhosis, probably 20 to 30 years, sometimes even 40 years. Clearly spontaneous resolution of the infection will occur in a very minor about 10 or 15% so 75 to 85% of patients will develop chronic disease. Those who develop chronic disease most will develop chronic liver disease. And roughly about you know out of every 100 patients that you see 20% will develop cirrhosis over the timeframe that I put out there. So I think this is very useful to kind of start talking to your patients you know before they are sent to the specialist.
Clearly three are certain risk factors which you are all aware of, and I’ll tell you where this has changed. The initial blood test is a HCV antibody, it’s a very simple test, it’s a very inexpensive test, it’s an ELISA based assay with a very high sensitivity and specificity. We at UPMC are working with Steve Shapiro and Valtrau to come up with you know pathways and these should be available in Epic Care very soon. Clearly once you get a hepatitis C antibody that’s positive you want to confirm it and you can do an RNA level by PCR and I think you can start there before you send your patient to a specialist, in. a group of people who will treat hepatitis C, I say who will because I think it will be beyond liver doctors, it will be infectious disease specialists who will be treating hepatitis C and I foresee this actually going into the primary care level just like HIV has done over the last few decades.

This is what’s new. Recently, and this is as of June of this year, the USPTF has now embraced this guideline. It was clearly endorsed by a lot of other societies, you know the Liver Society, the ID Society, etc., etc. But this is what they said, screening for hepatitis C patients at high risk you were already aware of this, but this is the second recommendation is brand new, a onetime screening for baby boomers. So anyone born between 1945 and 1965 should be offered HCV screening irrespective of the risk factor, because this is what the data shows. I think the USPTF as you know is a very tough society to get you know to endorse your guideline and they clearly have changed what they said in 2006. So and it’s reason being that it’s very elegant data to show this patient population accounts for about 2/3 of chronic illness in the U.S. This is just to highlight you know the problem and I call this my job security slide because there is a lot of hepatitis C to come. You know clearly
these infections took place between those years, it takes 30 to 40 years so the peak of cirrhosis, the peak is going to be somewhere between 2010 and 2020, and cirrhosis also leads to liver cancer so I think we still haven’t seen the peak of this illness, the chronic illness which accounts for cirrhosis and liver cancer.

So I think – I’m just reinforcing some risk factors, so past or current injection drug use, a transfusion before the cutoff date which is 1992, because after that every blood bank in the U.S. was mandated to screen for hepatitis C. I put some other risk factors there which are not as – you know as closely associated but are what screening? I think long term hemodialysis is about the incidence of HCV is about 10%, HCV infected mother about 5%, incarceration is a risk factor, intranasal drug use is a risk factor. I think the soft risk factors are the ones that I’ve listed here. I think getting a tattoo, other percutaneous exposures and you know this is applicable to healthcare workers or having surgery before 1992 is a soft risk factor, and then what I would call as inefficient transmission is you know high risk sexual behavior, this clearly has not been shown to be as efficient as a risk factor for screening.

And I think this is why you need to – we need to be aggressive in screening because I think there is clear evidence that antiviral therapy will improve clinical outcomes. This is the end point that we use, sustained biologic response which means you treat with antiviral drugs, you stop the antiviral drug and get cured. And I use the word cure because hepatitis C can be cured, and I’ll show you in a couple of slides what the new data is. And there is a clear link, if you cure hepatitis C you have a better clinical outcome. There is a decrease in the risk of all cause mortality, I mean these are very
elegant studies over several decades now which is reinforced with – actually led to that new guideline. Clearly the liver related mortality will go down, so less transplants, less risk for liver cancer.

One clinical situation which I have started seeing over the last 2 or 3 years is hepatitis C and pregnancy. Not all of you are mandated to screen for hepatitis C in pregnancy, it’s not a requirement unlike hepatitis B, but the problem is we at the current drugs cannot be used during pregnancy so you know – and the other thing that we provide to the high risk OB practices is there is no specific labor management, so C sections have not been shown to change the risk of transmission. And the last thing that comes up is breast feeding is safe.

So I’m going to end on a couple of slides, the evolution of hepatitis C therapy because we are truly at a real new era that we can see. In 2001 we had these two drugs out there, the Interferon and Ribavirin. A decade later, we had actually nothing for a decade, came these Protease Inhibitors so now we use triple therapy, we use Interferon Alpha, we use Ribavirin and we use a Protease Inhibitor. But this is where we are going to go and this is all like the HIV field you know. Today the cure rate for hepatitis C is somewhere in – look at the blue box to the right, the upper blue box, it’s about 75% with current available drugs. So I mean when I first started treating hepatitis C it was 5%, we’ve now – we are 75% as of 2013 and this is where we are headed in the next maybe year. There are new agents out there, these are Protease Inhibitors, Polymerase Inhibitors, etc, etc. and the cure rates are close to 100%. I mean this is amazing. I mean we are going to treat this disease completely and I think at least some of these agents will start getting approved maybe in another
month or two and I think a year from now or 2 years from now I think this will be a very different disease.

So I hope I’ve been able to convince you that this is the right thing for our patients and I think on that note I’m going to stop here. I’ll be happy to take any questions, and again thank you very much for your attention.