I’m going to spending the next few minutes on this next half an hour session showing some information about the possible interaction between celiac disease and IBD. In the interest of time we’ll spend the first few minutes defining the disease and review the data on who has celiac disease and whether there’s any increased incidence in people with IBD and vice versa as well.

I have a brief word about the history of the disease and then we’ll move on to genetic vs environment which has been the theme of a lot of the diseases you’re going to be hearing about this morning as well.

I think I’ll spend a couple of slides also describing the physiology of this for the physicians in the audience and then highlight most of the session discussing the possible link between celiac disease and IBD. And then for clinical purposes for all of us in here, what are some of the tests that we can do if people walk into the office and ask us about – do I have celiac disease? Do I have to worry about it because my aunt or my dad has the disease and then what’s new? Now in spite of all these interesting things over the past several years the hallmark of management of celiac disease still remains the avoidance of the inciting factors.

So what is celiac disease? I guess the simplest definition of this remains that its an immune mediated enteropathy which is stimulated after an exposure to dietary wheat or the substances that contain the antigen in people who are genetically predisposed to develop celiac disease. All of us have learned about HLA associated genes and I’ll be highlighting that as we go along. But more
recently there are other non-HLA related genetic predisposition factors for people to develop celiac disease.

If you’re a history buff, what back in the second century, some historical physicians have described diseases that were thought to be celiac in those days. And then in the 18th century, other people reported certain other GI diseases which were thought to be celiac. But much more importantly during the Second World War there was an astute physician, Dr. Bickel who I mentioned up there, who noticed that the kids who was seeing with diarrhea in his office which could not be explained seemed to do very well when there was a shortage of food. So anytime there was a shortage of wheat containing foods, these kids stopped seeing him in the office. And based on the work that he did during the Second World War, others followed on all of these and now we have what we know as the initial scientific basis of celiac as we know it now.

The individuals with the highest prevalence of celiac remain those of Irish and Northern European ancestry. It is said to be rare in black people and people from the Far East, Japanese as well. But it’s important to remember that this has been reported in virtually every part of the world. And the most recent reports have described this in the Sahara desert region of the Mediterranean Africa. There are also recent reports talking about this in South America. So it’s important not to rule out people showing up in our office simply because they may not have the traditionally described genetic predisposition of appearance belonging to a group of people who have celiac.
I think the most widely cited paper out there as far as the prevalence of the disease and the USA, it goes way back to a paper that was published about 7 years ago from the University of Maryland. What they did was they asked for ___ blood samples from all over the US and then did serological markers on these samples. And they described that if you take everyone who shows up, your risk of having positive serology is about 1 in 133. Some people cite this to be about 1 in 100. If you take people who have symptomatic GI symptoms, most likely related to the upper GI, this number reduces to 1 in 56.

Then if you have a diagnosis of someone who has celiac disease and then you ask for 1\textsuperscript{st} and 2\textsuperscript{nd} degree relatives the number is significantly higher. Now this becomes relevant because when you make a new diagnosis of celiac, do we ask them to bring in all family members or do family members need to worry about this and it gives us a guide as to who we can ask to come in to do serological markers on.

So I think remains the theme of most diseases as we know them now. If you look at HLA identical siblings, 3 out of 10 of them would have positive serological markers. If you stretch this to people who are identical twins, the number goes up to 7 out of 10. It is also important to remember that up to 95 percent or even 99 percent in some series describe the presence of HLA DR2 and DQ8 in people with celiac disease.
If you compare this to the general population, so you take a random sample of people out there, only 4 out of 10 have the same genetic predisposition as well. And this is the reason why as a last resort if there’s a discordance between histology and serology, these are some of the things that we screen for.

There are clearly well defined haplotypes as I just mentioned and for those of you who – I did it scientifically and methodologically predisposed, these are the specific areas which have been looked at. So you don’t need to have both of these HLA genetic predispositions but obviously when you have both of them, then your risk of celiac is much, much higher. And as I mentioned in the previous slide as well there are new celiac disease predisposed antigens which have been identified from chromosome 6. At the last count there are about 7 of these out there.

So what happens in people who have celiac disease? If you eat any of the wheat containing foods that has a specific antigen which has been well defined, you suddenly develop abdominal discomfort, cramps and then sometimes diarrhea and this doesn’t develop over several days. It actually shows up in just a few hours of being exposed to this. For people who know they have celiac and avoid it something as little as sharing a plate, a spoon or a bowl with someone who’s eaten these foods can predispose you to these symptoms as well. And Mark will elaborate a lot more on this when he speaks to us.

It is also important to remember that all of us have antigens present themselves. But in people with celiac disease these are modified in those who have the HLA DQ2 and DQ8 and they present these
antigens in a very specific way so the inflammatory cascade develops. And I’ll show you an image which helps us to understand this a little more. In the future the relevance of this is that perhaps there might be immunological mechanisms where we can modify the gut-associated lymphoid tissue so we can determine that certain people with celiac may be able to be exposed to some bread containing foods or oats or wheats as well.

The new response is driven, as is shown in here, and then it leads to inflammation, you begin to leak products, your absorption becomes poor and then the villi which leads to the absorption becomes flat, and in the interest of time I don’t have any slides talking about the criteria, so it depends on how bad the exposure is and how bad your response is. You can have partial villous atrophy all the way to complete atrophy of your villi, and if we remember the physiology that we are all familiar with, clearly this begins to affect your absorption of vitamins and iron because this disease is predominantly seen in the proximal part of the small bowel.

There is also an intestinal expression of tissue transglutaminase, which all of us will read about celiac disease or see about all the time in our books, and this is what leads to a lot of the serological markers that we see and also the intestinal damage that has been described in celiac.

If you look on top of this simple diagram in that you eat something that contains wheat or substances that we are not supposed to be exposed to, then it gets germinated in the gut, so this looks like the normal intestine, a cross-sectional of the normal intestinal view. The antigen presents
themselves that we spoke about bind to these agents and then present them, and within a few hours you begin to express those antigens, IGA related antigens, to tissue transglutaminase. There are two types of immune responses that predispose the damages that we see. One is the adaptive immune response to the exposure and then the second one is the innate immune response which drives the increased intraepithelial lymphocytes that we see on histology or the pathology reports that we get in the office when we diagnose people with celiac.

So how is celiac disease related to inflammatory bowel disease? Is this a slam-dunk or is this something that excites those of us who are interested in both diseases? I thought perhaps the best way to look at this is to look at the genetic predisposition in both diseases and review briefly their epidemiological data out there, and then look at the immune pathways in both conditions and then at the end of that have a look at the summaries side by side and see if this is clear association or there are many more things we don’t know about.

So NOD-2 CARD 15 is now old and has been described for several years. And the fact that people have that does not mean you have Crohn’s Disease, we know it’s just a predisposition. More recently as Dr. Ruggiaro was talking to us about there are several susceptibility loci which have been identified from GWAS studies which predisposes people to inflammatory bowel disease. And I think Dr. Duer and others in this lab here at UPMC have been the pioneers in this field. If you go to the other side of the slide in people with celiac disease this genetic predisposition has been clearly
defined. And so we know the HLA and the non-HLA susceptibility genes which I mentioned earlier on.

Now I guess when you think of diseases being common or being related to each other it makes sense to look at one disease and see do you have a higher incidence of the other in those people compared to the general population, and then flip the issue again and study it the other way around as well. This study comes from the Italian IBD multicenter study that was done in 2009. And so what they did was from January 2002 to December 2004 they collected data from 22 centers which treat people with IBD. So everybody who showed up with IBD was included in the study. Half of them had Crohn’s Disease and all of them had serological tests done for screening for celiac disease and they used both antiendomysial antibodies and anti-tissue transglutaminase as well. Then if you had these antibodies they asked you to sign a consent to do endoscopy and they took biopsies. So it’s important to remember that this study actually looked for histological evidence of celiac as opposed to serological evidence of celiac, which most of the studies are describing.

In their study 9 out of 1700 people had evidence of celiac disease. And if you look at that you say to yourself, well, 9 out of 1700, who cares? But remember, the _____ they use here at much, much higher and they are looking at EGD with histological evidence of celiac disease. If you compare this to the general population the numbers are much, much smaller. Then as I said, if you flip the coin and then try to look for the presence of IBD in people with celiac disease, I thought one of the more elegantly described studies was done a few years ago where they looked at 455 people with celiac
disease. Ten of them had IBD split halfway between UC and Crohn’s Disease. Skipping all the details of the study, I thought the most important thing here was if you looked at the age and sex adjusted prevalence rate, the numbers for both UC and Crohn’s Disease were significantly higher than what you see in the general population. Some people argued after this study that perhaps since they are both related to mucosal immunity it shouldn’t surprise any of us at all. But clearly it tells us that there are more people who seem to have both diseases than what you would expect in the general population.

So focusing on celiac disease we know there is an antigen which activates intestinal inflammation. Then it causes some damage which leads to all the things that we are aware of, but you must have a genetic susceptibility to this before you develop the damage. So we’ve described the HLA factors already, but it is important to notice that it provokes a TH1, TH1 response which leads to proinflammatory cytokines which generates the damage about what happens in here. I thought the most telling factor about this is once you remove the stimulating antigen this inflammatory cascade which you start goes back to normal. So if people stop getting exposed to this antigen within a matter of weeks you can regrow your intestinal villi without any of the damage that you see in the other diseases.

If you switch to IBD, we are not sure yet what the antigenic stimulant is as we know in celiac disease. Some people have described this as the microflora from the intestinal lumen. And this in conjunction with an impaired innate immune system stimulates once again TH1 ______ activity and
TH17 in people with Crohn’s Disease, and then if you look at ulcerative colitis the response is mediated through TH2. The difference here is that once their stimulation starts and then people have the IBD you can control them with symptoms and they are flat in remissions, but if you follow them over time they never go back to normal off medicines, and only a very small proportion of them do that.

So continuing IBD there were old reports about possible microbacteria related bacs that may be related to this or the measles study. Now we know that perhaps all of these are not necessarily relevant. We also know that people who grow up in less hygienic conditions or where they are much more likely to be exposed to organisms in their environment are less likely to develop IBD, and some people have argued that perhaps that’s why we don’t see the same numbers in sub-Saharan Africa and perhaps in the Indian subcontinent as well. There is a study that raises several eyebrows where a group of 7 people were exposed to the eggs of the worm. I think once you get over the fact the harder to convince people to swallow this, the important thing to remember is that they were able to lead to a downregulation of this aberrant intestinal inflammation that we described. And remember, once they inflammatory cascade starts unlike celiac disease since we don’t know what starts it, it doesn’t revert back to normal.

Now on the flip side of this argument, which looks interesting, other people have looked at a possible involvement of SNPs in chromosome 4q27 in the region containing IL2 and IL21 which play a significant part in IBD. They concluded rather differently and said 3 of the 5 disease celiac
disease risk markers, if you had those you were less likely to develop ulcerative colitis. They couldn’t make any comments about UC. But this sounds almost counterintuitive to the argument I’ve been trying to develop. In my mind what this tells us is that we are not sure what the immune related mechanism is yet, or it hasn’t been well defined as in other things. So putting all this together in one slide, in one disease, which is inflammatory bowel disease, you stimulate a certain aberrant inflammatory reaction and then it continues for a long time unless you give them medicines to try and suppress that. This might be that these groups may still be exposed to this initial antigenic stimulus since we don’t know exactly what it is maybe we are not able to knock it off completely as we are in celiac disease. The pathways of mucosal damage are similar in both diseases. In my mind I think it is because TH1 has been shown to play a part in both celiac and in ulcerative colitis and people with much more information in immunological studies will tell you that perhaps all of them are related along the same way. For now I guess the arguments that these are interesting ideas for both conditions is there a prognostic significance that if you have celiac disease or in some way we can manipulate your immune system from the understanding we have in celiac disease will that affect the cause of the way your IBD shapes out? Clearly at this point we can’t draw any specific conclusions and further studies are needed.

So what’s new in celiac disease? When we admit people who come in with acute diarrheal illnesses it’s important for all of us as GI physicians, physician extenders or anyone who cares for people in hospital to remember that there is an entity called celiac crisis. It presents identically to an acute diarrheal illness but clearly in the background these guys have a history of celiac disease. If we
don’t pay attention to them there is a significant risk of high morbidity in these people and we treat them with supportive therapy, steroids and sometimes _______ nutrition as well. Two symptom based questionnaires have been developed by the group from Harvard over the past couple of years. The CSI has been used as a surrogate marker for disease activity in the studies that they’ve done and they tell us that this might perhaps serve as a standard tool for future evaluation similar to what you have in CDAI for ulcerative – I mean for Crohn’s Disease. The CDAT also is a tool that has been used to assess people who are adhering to their glutin free diet that is prescribed for them.

So what tests should we do when people show up in the office and we have a clinical suspicion of celiac disease? For screening you could either use an IGA anti-TGG or an IG antiendomysial, most centers are using both simply because the anti – the IGA anti-TGG is about 99% sensitive and about 98% specific. Antiendomysial is almost 100% specific but is only about 94% sensitive, so clearly these are very high numbers and you are not likely to miss anyone that comes in in that. In the past people have argued that if you suspect somebody is not adhering to their glutin free diet one of the tests you could do is anti-tissue transglutaminase antigen, that is – I’m sorry antibody, that is still one of the things you want to do but you can also test for antigliadin antibodies in these groups of individuals and this has become much more relevant since the newest kid on the block is something called the deaminated antigliadin antibody.

I guess the one that hasn’t hit the clinical scene yet is something called an antiactin antibodies which is an antibody formed to the cytoskeleton from the intestinal cells. It is said to mirror what your
biopsies would show if you were to have endoscopic biopsies, and people have argued that perhaps a combination of the antiactin antibodies and the deaminated antagglutinin antibodies may be the wave of the future and not everyone with celiac disease may need an endoscopy with a biopsy.

Lymphoma is one of the words that scares anybody with celiac disease and perhaps in people with IDD who are exposed to the treatments we have as well. The ability to stain for CD3, CD8 and CD56 helps us to distinguish which groups of people may have that in both type 1 enteropathy associated T-cell lymphoma and in people with refractory celiac disease type 2 who develop lymphomas as well.

The next slide is a quick summary of some of the Phase I and Phase II trials out there about the newer medications. Now clearly this is interesting but has not reached the point where it’s in clinical practice just as yet. So can we stop this reaction before the wheat is exposed to the intestine, or can we give them something that inhibits this tissue transglutaminase or even if we miss all those areas, is it possible to use DQ2 inhibitors as well? And once again we don’t know the answer just yet.

In summary, I guess the relevant things to think about is there is an increase in prevalence of people with celiac disease by serological markers and in the past it was thought that 1% of individuals in northern Europe would test positive for that. The number is now the same in the US which a much higher incidence in first degree relatives as well. The most recent paper that generated a lot of
discussion was there was a reported increase in mortality in people who tested positive for celiac serology and were followed over time. However it is important to also document that other studies have not confirmed the same, and even if they die they don’t die from complications related to celiac disease. It is also interesting to bear in mind that both conditions have an antigenic trigger which is well defined in celiac but perhaps not as well understood in IBD as it is in celiac, and then over time we may be able to learn from the experience in celiac disease in some of the research for the pathways of defining antigenic trigger in IBD. Thank you very much.

Coming in from the bullpen to finish up here for probably about no more than about 10 minutes, I’m going to keep it as close as possible as I can. Again, I’m Mark Dinga, Dietician, I actually have celiac disease, I was diagnosed about 10½ years ago and I counsel patients with celiac disease really on a weekly basis, sometimes 2 to 3 per week. So it really is a privilege to speak to all of you today and again there is a lot of information here. I will be available after the next speaker, so if anybody has any other specific questions. So I’m going to talk a little bit about nutrition. And I am not going to go through every bullet of information, it’s there, like I say I’m available. And so I’m going to try to pick out the key points.

And these 6 recommendations came out of NIH’s Celiac Disease Consensus Statement, and really the first one, not being biased or anything like that, but just because of the intricacies of the diet and just because of the other play of other dietary restrictions potentially we really need to consult with a skilled dietician. But I’m going to add to that. A skilled dietician, correct, just as you are all skilled
out there, but someone, a dietician that’s experienced with this, that is very, very important. A couple of other things here, access to an advocacy group. We know that the patient will end up adapting a lot better if they have that support and also be more compliant. And we’ll talk about a few of those others as we go through.

As Kofi mentioned, again the offending grains, we are talking about wheat, rye, barley, their derivatives, their cross-breeds and specifically the protein fractions which I’m not going to get into, but again those are the toxic proteins. And so I threw a couple of the nos in there and just something as simple as patients come to us and maybe the first thing that I haven’t seen them before and they are still having difficulties after a year and the first thing you hear when you get the food history that they are eating Rice Krispies. Well, Rice Krispies have malt flavoring in and such, so just a little side thing. But really out of these the important one is that so-called crumb. And from the evidence that we have, and you’ll see on the next slide, that we know that that so-called smallest amount can trigger this inflammatory response. And the point I want to get across and I think really one of the important aspects of this discussion is that that little bit that a person thinks well, maybe I got that when I was at a restaurant or someone else prepared the food for me, and guess what, I didn’t get sick. Well, we can’t go by that. And the person has to understand that that cascade of events is starting to happen and that immune response is happening even though they might not feel the symptoms. And so that’s very, very important. Oatmeal, we could talk for about 2 hours on oatmeal, but right at this point in time regular oatmeal we say no. There are pure uncontaminated
research type oats that are out there that are acceptable, but we like folks to wait at least probably 6 months until they do that and then we monitor them clinically and serologically.

So how much is too much? At this point there is still no safe threshold out there, nothing has changed in all of these years that I’ve certainly been diagnosed, we are getting better at it, this 20 parts per million of glutin is proposed, but there is still not a final decision on that in regards to the food labeling. That was supposed to take place a couple of years ago and it still hasn’t happened. Food manufacturers are using this level but it’s again there is no final decision on that and there is no real definition for glutin free, so Dr. Katavsi who does a lot of work and cohort of Dr. Pisano did this small study a few years back. It was a 3 month trial of providing glutin and they found at the 50 milligram level that there were mucosal changes, and so to just give you a little idea how much that would be, now we are not talking much more than probably an 8th of a teaspoon of flour. And they actually saw some changes, villous changes even in one patient at 10 milligrams. So you know we are talking about very small amounts.

We are never going to get to the point on a food label that we are going to see milligrams of glutin like we see grams of saturated fat and so on, so that’s really not going to happen. And really the responses into how little amount is variable, and so those are other aspects of you know how do you figure that out, it’s a tough one. This food allergen labeling and consumer protection act, this helped us a lot back in 2006 that the law requires for the FDA controlled products, that’s not USDA, USDA is meat, poultry and eggs. But for most of the shelve items that they have to identify the top 8
allergens and of course wheat as being one of those. So we pretty much have made a lot of progress in that regard, but you know the patient still has to look for other derivatives of the rye, the barley, the malt and the oats. So we are getting there.

So as we know, the gluten free diet is the medicine, there’s no medicine behind that. I know there are some wonderful researchers working on that, maybe we’ll get something out of this division one day and then I don’t have to worry about teaching one more person about a gluten free diet. But it is lifelong, as of today this is lifelong. You know we could say that zero tolerance, we could say that 100% gluten free, to think that I’m not getting minute amounts, that’s ridiculous, I am. But hopefully I am covered. But that’s the point then the emphasis, there is no other way around this. There is no degree of this. And so the statements that are out there, whether by us as health professionals or maybe the next celiac patient that maybe didn’t learn the proper way, this little bit you’ll grow out of it, you could cheat sometimes, that doesn’t play. I go by evidence, that’s the evidence and really we are sending the wrong message, it is not an acceptable statement.

So where do you shop? You know what do you eat? That’s the statement, even after all these years, if I’m talking to someone. You know celiac disease comes up every day. It never fails, it comes up and I, I try to promote that also. And so where do you eat? What do you buy? You know where do you shop? Well guess what, you know, it’s regular foods, it’s foods that you know we are all eating every day. And again we want everybody to be very positive about this. There is so much more that I can eat that I can’t eat. So what’s wrong with salmon and some brown rice and broccoli for tonight’s
dinner and a salad and if you want a glass of wine, that’s fine also. I mean it’s beef, it’s chicken, it’s fish, it’s turkey, it’s veal, it’s milk, it’s yogurt, it’s fruits and vegetables, it’s rice, it’s potatoes, it’s you know maybe lipid wise maybe not butter, but oils and nuts. So it’s regular foods. And then if the person wants the glutin free bread and the crackers and the cereals, certainly it’s out there. And you know they are going to pay for it, there’s no question about it, but if we can educate them about the best choices and the decisions that they want to make, if they want to eat those particular food items.

In regards to nutritional needs and meeting the basic requirements, whether I’m working with a diabetic, whether I’m working with a cardiac patient, whether I’m working with a celiac, that’s the basic background; but we are going to talk about some other comorbid conditions. Importantly here, I don’t know what you might be providing in your offices, but this is just not a two sheet here you go, here is the diet. That does not work. If you do have the information we want to make sure that it’s up to date, that it’s you know evidence based, there is so much information on the internet, it’s just unbelievable. There is very good information out on the internet and the people to sift through that is very difficult, to meld all of that information together is very, very difficult and so you really want to make sure that you get them to a skilled clinician. This visit doesn’t take place, this education doesn’t take place in 15 minutes, 20 minutes, ½ hour, 45 minutes, it just doesn’t happen. I mean I’m going to implicate myself or whatever, but I mean an hour and a half’s worth of time. I could sit here and be real pretty and say okay, we are going to come in today and then we are going to follow-up in a month or 3 weeks. And you know a lot of times that doesn’t happen. So sometimes we have to grab them, we have to get them and we have to put all of this information together.
So the bottom line is you know proper education leads to better outcomes and certainly with compliance. And absolutely, absolutely we need to have that family member there, significant other and so on. It’s very wise of all of us to screen for these particular deficiencies in regards to iron, folic acid, we could add B12 to this, we could add zinc to this not only from a screening standpoint but what I do, what we do from a dietary standpoint and whether these folks need to be supplemented.

Gastrointestinally we know all the classic symptoms and how we have to deal with that from a nutrition standpoint, lactose being one of them. I typically, I mean if I have to I’ll restrict them. If we don’t have that lactase activity as part of the blunting of the villi and so on, but you know just so they are not drinking a whole glass of milk. We may restrict it initially but over the course of a couple of months that really should go away, but we certainly address it, other comorbid conditions and so anyways – I got the sign. But anyways, in regards to comorbid, you know here you have this diabetic now they are absorbing, they are following the diet they way they should whether they are Type I, Type II, their blood sugars need to be addressed. Over the course of time you get a basic lipid panel, over the course of time their blood lipids are going to increase over time, so we have to make adjustments for that.

So Kofi talked about family screening of the disease, the prescriptions, the prescription drugs, the over the counter need to be checked for glutin. There is some ideas or suggestions for some serologic testing, but one, one very important point, when your patient comes back into you, they are
diagnosed with celiac and they are symptomatic gastrointestinally, their iron indices aren’t improving, their LFTs are still up because maybe that was the reason why they were diagnosed, number one check for glutin. That’s the number one thing. We might find it automatically. I can’t tell you how many patients have been consuming the communion host, just you know not even thinking and so please check that. And of course you could check that TTG.

Cross-contamination, another very, very specific area that needs to be talked about in dining out, just simple things like that, I don’t know your background but that knife going into the peanut butter going onto the regular toast, that knife going back into the peanut butter, it’s cross-contaminated. That’s one example. That person can’t take the burger off the bun, can’t do it, it’s contaminated. I could go on and on and on. There’s the communion host.

And finally what a wonderful talk by Dr. Szeghy in regards to this aspect that I think we neglect big time. We take care of all the medical side, the nutritional side, maybe exercise but we don’t take care of this. And it’s so, so crucial and the education really helps this in regards to that person improving their health outcomes and certainly their compliance. So I’ll end it with this, if there’s any questions at the break I’d be very happy to speak with you all. Thank you.