Good morning, everybody, it’s great to see a lot of very familiar faces and friends both from the university, from industry and from the community, so welcome to our program. You’ll notice in my syllabus that I give a full disclosure on how I put my talks together because underneath my title it gives I should shorter to 20 to 25 minutes and we get these talks for those that speak a lot about 6 months in advance, so I always put a placeholder of how much time I have. And I have an embarrassing story that about a week ago in Chicago at a big conference, 2000 people, I’m asked to come up on stage and I had 15 minutes allotted, and they said now for the next 45 minute Dr. Regueiro is going to be speaking. So I was able to fill the time fortunately, but these things happen. So in the next 25 minutes I plan to discuss hot topics in inflammatory bowel disease, and my intention is to really try to make this as practical as possible and really put it in context of clinical practice and what you see in your practices every day.

So Dr. Binion already mentioned biologic loss of response, this is a huge issue in our practices now that we have four monoclonal antibodies and several more on the way. Deep remission, the question that we are asked every day by our patients, after a colonoscopy that looks entirely normal do I really need to continue these medications long term? Postoperative Crohn’s disease I’ll focus on that a bit, Dave Binion already mentioned that surgery is still common although it’s decreased we still see this at a fairly high rate. And then just very practically I’ll give you an overall what I consider scorecard on new medications in the future, not to list the 125 that are in trial that you may never see in your practice but the 2 or 3 that I think may be out in the near term.
So what do we do about patients who lose response to anti-TNF? And I think we are really in the era of optimizing our current therapies. So we go with the horse that got us there, meaning if it’s working how can we optimize that before switching? Time and time again and you’ve all seen this, we have patients who come into our office who have been on 3 anti-TNFs and then they are saying now what do I do? And the first one worked very well. So I get a little bit concerned that we quickly change from one to another and essentially burn the bridges on our options going forward. So when we consider optimization and I’m really going to focus on anti-TNFs but you can really put this to any, any biologic monoclonal antibody that’s going to come out will look like this. Dave already mentioned in this talk that there are patients who do not respond to certain medicines, probably because genetically that cytokine is not important to them.

So what are the definitions when you hear these talks at DDW and ACG you hear us say primary failure, secondary failure. And if you imagine on the Y axis as the Crohn’s disease activity index, the line horizontally at 150 is what we have defined subjectively as remission. I will start by saying I think the CDI score should be thrown out, done away with, but nonetheless for right now this is a score by which under that the patient does well. A primary nonresponder and you see these in your practices are patients that you start on a treatment and they have zero response at all. So this probably represents 20 to 40% of our anti-TNF patients never get a response to treatment. The secondary failure are what we see most commonly, right. These are people you put on an anti-TNF they do great, they say this is the best I’ve ever been. But then at some point they start to come out of that
remission and come back by saying you know before my infusion, before my injection it was a week, now it’s 2 weeks, now I’m really not responding to the treatment the way that I would like to.

So the first question to ask is why are these people not responding to the treatment? Why are they losing response? And I think this is important and Trip Barry and David Binion mentioned that there are other mechanisms beyond inflammation as a loss of response. So the first thing to know is the patient having active ulcerative colitis or Crohn’s? Sometimes these patients will have symptoms that might be C-Diff, bile salt diarrhea and a number of other things. But assume for a minute that this is inflammation and they are truly losing their response, so what do we do next and how do we look at this? And this is again an expanded version of what Dave has shown you, don’t focus on the whole slide but look at the right hand side. So when you look at the anti-TNF agents, Infliximab, Adalimumab are listed on this, Certolizumab you probably can include as well and look out at 5 years, about 50% of people at 5 years lose response. That means 50% of people maintain response, so it’s about a 50/50 proposition and over a period of time there is about a 10% loss of response per year. How do we optimize these treatments? This is really where I think we are headed now with if you will personalized optimization of treatments going forward, and this will probably be true for most monoclonal antibodies coming out. So now we have the ability with Infliximab and shortly to come with Adalimumab measurement of antibodies against the drug but also levels. So let’s consider a clinical vignette in a patient that we saw.
So this is a 33 year old who has active Crohn’s disease, has done extremely well for about 5 years. Initially had been on 6 Mercaptopurine and then self-discontinued it. They just didn’t like the way they felt on the 6 MP, still continued to do well but now before the infusions he starts to lose response. You send off the level and his Infliximab concentration level is low, meaning he’s clearing the drug very quickly but his antibody is very high, so the patient is starting to form antibodies against the drug. What would you do? So think about this, I’m not going to pick on anybody, but would you increase the dose or shorten the interval? Do you switch to another anti-TNF? What about adding back the immunomodulator now and then ultimately do we switch out of the class completely to an Adalimumab like agent?

So this study had been done actually at the Mayo Clinic looking at patients who are on Infliximab. Like I said, Adalimumab will probably have commercially available assays soon, we don’t have those yet. But what these slides shows are the clinical outcomes in patients who are developing an antibody against Infliximab, and I think we are going to see this with the others as well. So in the red bar these are patients that switch from Infliximab to another anti-TNF. The yellow bar is looking at patients who either increase the dose of Infliximab or shorten the interval. And probably intuitive is that if a patient is forming antibodies against the drug, giving them more of that drug may not work, probably won’t work. And what they found is that actually switching from one anti-TNF to another worked in 92% of the time.
There have been studies on this. So there is a GAIN study look at switching Infliximab to Adalimumab, and I won’t go through all the details but the purple in this is Adalimumab, the white is placebo and you can see that at a short time period recovery of response is fairly high with Adalimumab. Similarly with the Certolizumab, the third anti-TNF that came out, switching from Infliximab to Certolizumab works in a higher percentage of patients than those that don’t switch.

So now let’s consider another scenario, so that’s if you form antibodies. You see a patient, you send off the assay and that’s called immunogenicity, they start to form antibodies to the drug. Well a different patient, 33 year old who continues their 6 MP with the Infliximab starts to lose response, very similar scenario, they tell the infusion nurses you know at 6 weeks, now at 5 weeks I’m not feeling well, it just doesn’t seem to be working as well as it had before. You send off levels on that patient and their Infliximab level is low, just like the first case, but their antibody levels are low as well, so they are more quickly clearing the drug. One thing I will mention, with all of the anti-TNFs and all monoclonal antibodies we make a big deal out of antibodies, yes they are important, however three may be other mechanisms by which people clear drugs. So in this case, in somebody who is clearing the drug more quickly and doesn’t have antibodies the yellow is looking at the clinical outcome in patients who increased their Infliximab, didn’t switch to Adalimumab or Certolizumab but simply increased their Infliximab, so now this is an optimization of treatment that can be done just simply by measuring some of the these antibodies.
What don’t we know about loss of response? Unfortunately I think we probably know less than we know about why people lose response, but I think the future probably is going to be around checking these levels. If you form antibodies to a biologic can they become overcome by an immunomodulator? One thing I’ll mention is that there are a lot of patients despite our best efforts who are on monoclonal – or sorry monotherapy with an anti-TNF. We are starting to look at in our group here adding back an immunomodulator to see if we can overcome immunogenicity. I have zero data, but I will tell you anecdotally that I have patients who I have put on Methotrexate or one of the immunosuppressives, Azathioprine, 6-MP and we’ve been able to regain response. So that’s an interesting possibility in the future about overcoming antibody formation.

And then one of the questions Dave Binion mentioned already that many patients on monotherapy lose response, but all of us in this room have patients who are 7, 8, 9, 10 years out on a single agent doing well. Why are they doing well? Why are some patients doing well and others lose response at such a high rate? So this second question that you are probably asked weekly or daily, can I stop my treatment? Do I really have to continue these medications long term? So Kofe Clark who is a fellow with us and I last year published a study looking at all of the available data on stopping treatment, and I’m sorry to say that there is not much out there, but I’ll give you what’s out there and I’ll give you my clinical impression on what we can do about stopping treatment.

So one option is you have somebody on dual therapy, Azathioprine with an anti-TNF and one option is to stop the Azathioprine and continue the anti-TNF. The other is you stop the anti-TNF and you
continue the Azathioprine. We don’t have much data on stopping drugs completely, so we don’t have much evidence based data on that. Most of the data so far are in Infliximab, most of the published data are in Infliximab. So what are the data on stopping Azathioprine, 6 MP and continuing monotherapy with Infliximab? And really these are the two studies, probably the two best studies on this topic.

And just to briefly recap the Van Assche studies. So these are probably like patients you see, patients in remission on Infliximab with Azathioprine. So all patients were on remission for at least 6 months, they were then either continued on their Azathioprine with their Infliximab, or discontinued with their Azathioprine and just continued Infliximab alone. And these Kaplan Meier curves that you see time and time again from the loss of response studies, they all look about the same that over time about 50% of people lose response. What’s interesting is that from a clinical standpoint the efficacy from a response standpoint was no different in patients who continued the immunomodulator or stopped. There was no difference between the two groups. However a word of caution, and this was brought up in the first lecture, what was seen though is the C reactive protein levels, a marker of inflammation, started to go up higher in people who stopped Azathioprine with Infliximab. So that was number one. Number two is that the Infliximab trough levels started to drop, and at this DDW there is going to be a presentation by this group where you are going to start to see separation in response, meaning that yes the trough levels are low first, clinically people are doing well but now that the group has 3 or 4 years of data we are seeing a separation.
Then there was a similar study that looked the same thing, 48 patients in remission, dual or combination treatment, all of the patients in this study stopped the Azathioprine, they continued the Infliximab, and no surprise the Kaplan Meier curves looked about the same, interestingly in this group about ¾ of the patients continued to do well off of the Azathioprine. Am I saying that there are patients who do well with monotherapy? Yes, I have, these are the dirty little secrets we don’t tell, but I have about 30 to 40% of my patients on monotherapy biologics, some not by my choice, some by the practical reality of the patients. And those patients are doing very well. However immunogenicity is a problem in many of these patients.

The second scenario, what about stopping the anti-TNF and continuing the immunomodulator? So there have been most of these studies again looked with Infliximab and I’ll just present the Waugh study here which essentially took 48 patients on combination treatment who stopped their Infliximab, 3/4 or 2/3 of the patients were on Azathioprine, 6 MP and about a third were not. And again the Kaplan Meier curves, the loss of response looks about the same, about 50% of the patients withdrawn from Infliximab had a relapse, 2/3 by 7 years had a relapse.

This is probably the best study, and if you are to remember one study on withdrawing Infliximab this is it, this is the Louis study that was published last year in Gastroenterology and I think probably represents the best prospective study. So what this group did is they took 115 patients in remission for at least one year on Infliximab and Azathioprine. They had to have been off steroids for at least 6 months and then they stopped the Infliximab and continued the Azathioprine. Bottom line is about
50% of the patients relapsed within a year. Interestingly something we don’t talk about much, they were able to regain response by adding back the Infliximab. So you know patients come in and they say well if I stop my Infliximab, I stop my Adalimumab, if I stop my Certolizumab I can’t go back on that treatment. Well in this study it’s interesting that 88% were able to restart Infliximab and do well, probably because they were on an immunomodulator. And this is just the Kaplan Meier curve. So these Kaplan Meier curves kind of get burned into your brain as all looking about the same in terms of loss of response.

Who possibly can stop treatment? And I’m about to, to debate this with Bill Sanborn at American College of Gastro, this should be interesting because he’s a proponent of continue forever and I’m going to have to take the side in stopping treatment, so I’m trying to creatively come up with ideas, so if anybody has any please let me know because that’s going to be an interesting debate. But nonetheless I think maybe this is the patient group that we can target, they don’t have signs of inflammation, whether it be sero-markers, mucosal evidence of disease, they don’t have signs of inflammation. But these are the bottom line numbers that I tell my patients. Patients that come in and they say can I stop treatment I say at a year it’s probably about 50/50 that you are going to recur. At about 5 years it’s about 75% chance if you stop your treatment you are going to have a recurrence, and I think the evidence based data bears that out.

So I’m going to switch gears now into the postoperative prevention strategies in looking at these patients and what happens when you see a patient with surgery. So all of us as gastroenterologists
and I’ll probably offend surgeons if they are in the room, are used to having the surgeons take care of
the problem surgically but then 2 to 4 weeks later they show back up in your office and surgeon said
to the patient you are clear, go back to your gastroenterologist, they’ll take care of you now. And then
you are left with all right what am I going to do now in a patient who has just had Crohn’s surgery?
And we still know that about 2/3 of our Crohn’s patients have surgery. I’m not going to focus on
ulcerative colitis as much as far as postop, I’m happy to in the discussion but still about a third of
patients with UC will have surgery as well.

So this is a very important slide and I borrowed this from Bouguereau who was kind enough to lend
me this slide on the natural course of postop Crohn’s, but I would submit that this probably
represents the understanding of all of Crohn’s and I would also submit possibly of all autoimmune
diseases. And let’s just consider the postop model for a minute, okay. So on the left hand side of the
arrow project this is where people have surgery. So you have a patient that you send to the surgeon,
they have a ileocecal resection, for that second they are cured, assume they have no disease anywhere
else. What happens one week after surgery if you biopsy the normal neoterminal ilium above the
anastomosis, it looks normal but histologically there is already Crohn’s that’s recurring. It makes
sense, genetically and immunologically you haven’t changed anything. One year after surgery 70 to
90% of people start to have ulcers. Within 5 years they are starting to get this tissue destruction and
damage that’s evident on radiograph and low and behold by 5 years 2/3 of the patients come in with
symptoms and in this group about half of these people will require another surgery. That’s the story
of Crohn’s.
Well think for a minute forget surgery, forget surgery, you see in your practices newly diagnosed Crohn’s patients probably on a regular basis. You do a colonoscopy and a CT and you see these horrible changes and you say there is no way this just happened today, this has been going on for a long time. What we’ve learned from the postoperative model is that patients recur but without symptoms, they are clinically silent until they develop a complication that requires another surgery. Why do I think that there is still going to be potentially a high percentage of patients with Crohn’s who will need surgery? It’s because by the first time they are showing up in your office for the first diagnosis the damage is too far gone in many of these patients. And I think Dave mentioned we shouldn’t look at surgery as a failure, we should look at surgery in groups of patients as a combined approach to treating Crohn’s disease. So the postoperative model – in rheumatoid arthritis they can’t cut out the joints, psoriasis you can’t cut off the skin, Crohn’s we have the ability to start over again and look at the natural course of postop Crohn’s.

So what would you do – I’m going to actually probably skip through these cases in the effort of time, but I’m happy to talk about them and I have the answers in the syllabus, but how do you manage postoperative Crohn’s? So there are a lot of different medicines available for postop Crohn’s and I’ve summarized about 325 slides on one table right here looking at placebo versus 5 ASA, Budesonide, Nitroimidazole, that’s Metronidazole or Imidazole and then Azathioprine, 6 MP. And if you look at green the endoscopic recurrence rates were not dissimilar between all of these
treatment and placebo. There were a couple of Azathioprine, 6 MP studies that looked positive, but there were also a couple that looked negative.

What about postop anti-TNF? There’s been an enormous amount of hype over this recently and I’m afraid that we may be responsible for some of this, and I will stop by saying this study on 24 patients was never ever intended to be the pivotal study on postop Crohn’s, so I get a little bit worried with when I go to conferences and hear certain things. But nonetheless this was a proof of concept study that has led to a larger study called the PREVENT trial that I think we need more data from when we look at this. But nonetheless this was a study and imagine your patient goes to surgery and within 4 weeks the patient was randomized to either Infliximab or placebo and at one year you do a colonoscopy and you score the colonoscopy. And on the colonoscopy above the anastomosis you say there is either no disease or there is minimal disease, a score of 0 or 1. We consider that remission. This is not a validated score but this is the best we have. Recurrence more than 5 ulcers, more severe inflammation a 3, or they start to stricture, so endoscopic remission versus endoscopic recurrence.

And the bottom line from the study and placebo is in red, yellow is Infliximab, what we found from an endoscopic recurrence a score of 2, 3 or 5 we saw very large separation. Interestingly this wasn’t just a separation between a score of 1 and a 2, which you could say that’s not a big deal. Most of the Infliximab patients were 0, most of the placebo were 3 or 4. Now granted we had a higher risk group of patients in this. But this is one small study, I would argue we should not change practice based on this. Now there have been 4 other studies that have been published or in process of being published.
In the light blue there are 3 are anti-TNF with Infliximab, in the white it’s Adalimumab postop, and what you see is you see trends that look about the same. So this is endoscopic recurrence at 1 year after starting treatment. So 0 to 10% recurrence in 4 studies, one study 21%. So these are remarkable findings compared to some of the other treatments that we’ve had available to date. And we now know that stating anti-TNF early in course may change the post or change the natural course of disease.

So these are medical treatment studies, SONIC, the STEP UP, TOP DOWN, the REACH study, CHARM and ACCENT 1, and when you look at postop starting treatment before there is evidence of disease we probably see the highest rates in terms of mucosal healing and progression of disease long term.

So my approach, and I’ll just show you the algorithm and then I’ll probably just end with the new treatment slide and then we’ll get on to the next lecture. This is how I look at my patients in the postoperative management of Crohn’s disease. And I’m somewhat embarrassed to say we did not coin this the Pittsburgh Protocol but this has actually come up at some of the international lectures that I’ve attended. But this is the way that I would look at Crohn’s. This is not validated, we are in the process of validating this. I split them into low risk for recurrence, moderate risk for recurrence and high risk. You will see 2 of the 3 arms I do not recommend starting an anti-TNF agent. So the low risk for recurrence group, the one on the left hand side in green, these are patients that you see who have had a short stricture for a number of years, come to their first surgery without a lot of
inflammation. I would argue don’t put them on any treatment postoperatively. These are patients who probably don’t need anything but a colonoscopy within a year to make sure there is no recurrence. The moderate risk group is probably what you see more commonly, these are patients with longer inflammatory strictures or stenosis that cause an obstruction who come to surgery. These are patients I would recommend an immunomodulator postoperatively if they haven’t been on one. Probably the group that we would target for anti-TNF is the high risk group, penetrating or perforating disease. Dave Binion mentioned multiple surgeries, 2, 3, 4 surgeries. Smokers, which is a little bit controversial that we found that we were tabled over, smoking, which I don’t recommend to my patients, but smokers and possibly patients who have truly failed immunomodulators, been on Azathioprine or Methotrexate come to surgery despite this. This is the PREVENT study, this is the study that we are looking at and hopefully we’ll know more about.

So in you syllabus these are just the answers to the clinical questions that I look at, and I’m just going to skip to the last slide looking at new treatments. And I’ll tell you the three that I would look at as potentially going to be hitting the market in the future.

So the three that are probably closest to FDA approval is Ustekimumab, also known as Stelara, that’s used for psoriasis and it comes as IV or sub-Q. This is blocking IL1223 and this interestingly seems to work well in people who have lost response or have been refractory to anti-TNF. So we might have a valuable medication in Ustekimumab. Vedolizumab is given IV, it’s an alpha 4 beta 7, unlike alpha 4 which is Natalizumab. The advantage is potentially, and I think we need to wait, but
potentially doesn’t cross the CNS and these rates of PML should be low or hopefully nonexistent. And then finally Golimumab is the last which is another anti-TNF given subcutaneously and I think that will be approved soon.

So current hot topics, I didn’t talk about mucosal healing, but optimization of current medications I do think that combining surgery and medicines are important, promising new medicines I already mentioned there are 3, but there are many others in your syllabus that I didn’t cover and then Dave Binion already mentioned I think the future really relies on personalized treatment, understanding the person, the genetics, the immune system of that person and then ultimately treating. So I’d like to thank my group, this is the IBD Center, many are here today and a nice photo to end. So thank you very much for your attention.