(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 08 19 22 ***"Epic Builders"*** – Esteban Figueroa, MD from the University of Virginia

- Well, welcome everyone to the grand rounds today we're excited to hear from our very own Esteban Figueroa.
- 00:14:24residency.
- 00:14:27And for heading back to east coast.
- 00:14:30Is training.
- 00:14:32Day, we also served as the chief fellow is a member of both the gold humanism and alpha alpha side and impressive feat.
- 00:14:44That I'm not at all tell us about our better about.
- 00:14:47survival younger used by active about the local, regional levels, having been invited to speak and dozens of conferences, including in research focuses on the diagnosis and management of inflammatory bowel disease.
- 00:15:01Testimony destination.
- 00:15:04Europe they liked as a fellow it's been a great teacher and the research Center has a faculty Member and he was a very bright future.
- 00:15:11Welcome
- 00:15:29So today's talk about.
- 00:15:37The two review the turn of the etiology and pathophysiology as best we understand it.
- 00:15:43God is he getting that getting the actions for the therapy w's and treating this condition.
- 00:15:49The recent changes in our practices.
- 00:15:52To the.
- 00:15:55Innovations that said.
- 00:16:00Before we get into the new will start a little bit of the old so anyone in this room thought that more bonnie's disease has a nice ring to it you're probably on to something because.
- 00:16:10Giovanni, but teach them or Gandhi was probably the first person to characterize crohn's disease clinical case and 1761 describes a young.
- 00:16:22Male 20th died after many months of fever abdominal pain and diarrhea and on pathology notice trends neuroinflammation and Liam, and this is all to land brett's into this call what.
- 00:16:39you're saying.
- 00:16:40Is a British decision.
- 00:16:44London is.
- 00:16:46The first and coined the term culture politesse I use this reports 59 this case reports title the morbid conditions of this banks and again similar stories and 43 year old female.
- 00:17:01abdominal pain.
- 00:17:04To eventually the way on and on autopsy notices and colonic inflammation.
- 00:17:12The disease crohn's disease comes from world pro, who is a physician of Mount Sinai he only eats.
- 00:17:22For.
- 00:17:25A case series which entitled the regional really is a pathologic entity published in 1932 and October issue of JAMA to mount Sinai so just to review again we have crohn's disease on your left side of your screen, which can involve anywhere from the rectum to know classically Liam.

- 00:17:48characterized by that information up to describe it for donnie fighters, on the other end is struggling and rectum is in a uniform pattern molding anywhere from website into and clinical correlation.
- 00:18:01Also, do not forget that this is not strictly the best comedy festival manifestations that much classically or more commonly recorded sessions from patients food skin complaint complaint.
- 00:18:19And there's a strong correlation with primary.
- 00:18:24phenotype.
- 00:18:34is changing so.
- 00:18:36About 3 million cases and then the United States, you go back to the 1990s by RON 2 billion so we're probably sort of Plateau face.
- 00:18:45For instance, increasing prevalence there's a Bible old age distribution in terms of onset of this cheesy so classically segments or decades of life, then a later.
- 00:18:55He six and seven decades, would you see that there's also a rising trend and this disease coming out of the developing world, so you look at this graphic that first coin term for Samuel world and at&t benign you fast forward 100 years and the western world predominant disease so.
- 00:19:14People of Western European descent Nazi June.
- 00:19:18and rapid increase during that industrial revolution, we see a second curve here where there's another incidents and the developing country so Southeast Asia parts of northern Africa really seeing an upward search.
- 00:19:33I thought this was very interesting when I first learned about this is that you see you're the first case of also politeness was reported in China 60 years ago, essentially, so now you're the one of the places the world has the most cases, just to that size, population.
- 00:19:53Allocation diagnosed with crohn's disease come in and I usually go through this figure compensation, so this is a seminal study up France.
- 00:20:04publish in early 2000s, and this is a retrospective and introspective cohort study of over 2000 locations that follow them a time of diagnosis up to 20 years later, so we can see is that.
- 00:20:18Initially diagnosed.
- 00:20:22At this time, here we have 2000 patients 80% of those patients purely just have to worry about these information they don't have.
- 00:20:32complications like structuring penetrating complications some patients do present with it so about 20% at index diagnosis, or have a complicated horseman heart surgery.
- 00:20:45Patients over 20 years more and more the.
- 00:20:50First recurring.
- 00:20:53entry to more and more proportion of patients are getting a proper patient preparation these.
- 00:21:00are just running.
- 00:21:03Information you get this transfer on our tissue, then you get us to gnosis or structure now you have.
- 00:21:09A pristine dilation with transmissible inflammation and then you have a perforation so there's a microprocessor official a or intra abdominal abscess.
- 00:21:18And really once you get to structuring and penetrating disease, you need surgery, so, if you look at the end of this study only 37 of those initial 2000 patients are surgery free.
- 00:21:29After 20 years so 80% of patients, requiring surgery we've probably bent this curve, a little bit with our therapies, since the last 20 years but still rings true.
- 00:21:40Also, have colitis, on the other hand, classically more milder course I would say, less likely to need surgery left side is sort of the classic picture, where it's sort of limited to the clinic fletcher.
- 00:21:53Do you tell patients, there is a risk of progression So if you have limited practice there's about a 10 to 30% chance during your disease course that you might have extension.

- 00:22:02About 10 to 15% of patients will have an aggressive disease phenotype and about you know, half of patients, over the course of their disease will need some sort of round, you see related hospitalization.
- 00:22:14And again 10 years human risk for collecting me which, on the good side, this is curative roster potus is lower so 10 to 15% lifetime risk essentially for collected me.
- 00:22:28Patients always asked me Doc why Why do I have this disease now you know it was something I did wasn't my lifestyle my my diet, what can I do to change it, and the truth of it is we're still learning a ton.
- 00:22:39This is a very complicated auto inflammatory condition and we're really just scratching the surface, but the current sort of framework or schema is that is sort of four components.
- 00:22:50versus is clearly a genetic disposition or predisposition interestingly enough inflammatory bowel disease is one of the few diseases that has the most gene I'm genome wide association studies or snips with risk levels characterized so there's over 300 of those.
- 00:23:07Clearly, an environmental exposure, if you remember to that that slide with the you know incidents increasing in the developing world.
- 00:23:13Our genetics on a population wide haven't changed over the last six years, but clearly our environment has and that has led to sort of this upswing and prevalence and incidents of this disease.
- 00:23:24interesting things of born out of this are many hypotheses there's the hygiene hypothesis, and that you know we're just living in a more sterile environment.
- 00:23:31we're not training our immune system to sort of you know recognize good from bad, as well as we did you know hundred 200 years ago.
- 00:23:39So sort of protective risk factors that have come out or sort of large family size growing up on a farm having a pet drinking unpasteurized milk all things you probably get around Charlottesville interestingly enough so good thing we're living here.
- 00:23:54Other things like you know smoking clearly risk factor for a more aggressive phenotype for crows, these are the enough seems to be somewhat protected for all sort of colitis you know medicine exposures antibiotic oral contraceptives all potential risks, whether your breasts better not.
- 00:24:10All these pretend to be some sort of impact on developing this disease, like I said there used to be a predisposition of sort of this Western European.
- 00:24:20risk of developments, disease and interesting enough, you would see.
- 00:24:23extremes of latitude where you would see hot pockets of inflammatory bowel disease would you know that these patients.
- 00:24:29Are vitamin D deficient in vitamin D plays an important role in our immune regulation so there's a thought process that also plays a role so depending on where you live on Planet Earth.
- 00:24:39microbial despite gnosis this is sort of a term that's come about in the last 10 to 15 years.
- 00:24:44And you know, this is a you know, a disease of the intestines our intestines have incredible amount of microbes in it, you know they outnumber our cells in our body millions and millions to one.
- 00:24:54And we just scratched the surface we're just characterizing bacteria and we know that there's many more things at play.
- 00:25:01And then, at the end of it, the crux of this is that it's a maladaptive immune response so your body, you know you carry all these risk factors these.
- 00:25:09predispositions and then some insult happens you take ibuprofen or you get an infection and you have an acute inflammatory response.
- 00:25:16And, but normal immune response eventually shut that off, but what happens in inflammatory bowel disease is, you have a.
- 00:25:24inability to reverse those inflammatory signals and you transition into a chronic inflammatory state and that's what you actually need to diagnose this condition is on history pathology you need to see signs of chronic inflammation.

- 00:25:36If you don't see it you can't label it as inflammatory bowel disease.
- 00:25:42To the genetic CBD are very complicated, this is a poly genetic disease, the only exception is sort of rare very early onset inflammatory bowel disease, which happens in young children and thats related to the ios 10.
- 00:25:54mutation So the first sort of well-known characterization was this nod to risk illegal and not to, as you can see down here is plays a role in your microbial sensing so.
- 00:26:06If it plays a role in sort of your interest in presenting cells that live at the interfaces the mucosal and the luminous contents of all the bacteria that live in your gut.
- 00:26:15And it's sort of feeding information of like this is bacteria that's living inside of me, and if that goes awry, then you might start you know.
- 00:26:22labeling things that are host bacteria that are supposed to be normal as bad and mounting an inflammatory response.
- 00:26:29I will 10 is another well-known risk illegal again like I mentioned its associated with very early onset valid as the inflammatory bowel disease, and we have i'll tend knockout mice so.
- 00:26:40 I'll 10 plays a role in sort of immune regulation and so it's actually down regulates the inflammatory pathways, and so what we see in these ios 10 knockout mice if they're born and within three to four months they develop a spontaneous autoimmune colitis.
- 00:26:57 I'll 23, which is an interleukin again involved in inflammatory pathway along this teach 17 pathway, this is.
- 00:27:07going well, characterized and psoriasis and inflammatory bowel disease, so we see that there's a some risks in this I'll 23 receptor and as an early target for therapy for inflammatory bowel disease.
- 00:27:17Again, we see that I'll 23 receptor knockout mice are actually resistant to an induced autoimmune colitis and experimental mice models.
- 00:27:28But genetics doesn't explain everything like I said you look at concordance studies and identical twins only 50% of identical twins will both develop crohn's disease even less open plan for also quietest so clearly this isn't the whole picture.
- 00:27:46So this concept of despite gnosis so healthy gut bacteria and what's unhealthy we've learned a lot so earlier studies really just began with.
- 00:27:5516 s right our rivals RNA sequencing and just characterizing what bacteria live inside of our gut we're getting much more information in terms of what kind of metabolic.
- 00:28:07byproducts are these bacteria producing what a sort of the other viral and fungal pathogens that live inside of our gut and how do they play a role in mean regulation we do look at this.
- 00:28:21So that I have 10 knockout mice that was predisposed to developing autoimmune colitis if you raise them in a sterile environment a germ free environment they don't develop the disease so clearly this is part of the pathogenesis.
- 00:28:34We do see in sort of these early studies of patients that do and don't have inflammatory bowel disease there's a clear.
- 00:28:40signal difference in terms of the composition of bacteria, you know they have less biodiversity what we've seen is that they have less of these firmicutes.
- 00:28:48firmicutes is Latin for firm for strong scan so gram positive so there's six.
- 00:28:53cell wall bacteria and what they are doing is what we learned is that they're providing some essential nutrients to the health of our gut lining so they make these short chain fatty acids, so this SL a's.
- 00:29:05That help a talk to our immune system and interact with our T regulus Teresa cells which down regulate.
- 00:29:14immune pathways they also help produce this music layer this protective music layer that basically provides a barrier between our gut lining and our.

- 00:29:25immune system and all the pathogens that live inside of our gut and so when you lose those you lose some of these protective mechanisms, and you have more closer interaction.
- 00:29:36And then we see that there's also this increase in these pretty good bacteria So these are gram negative bacteria.
- 00:29:41They have life with poly saccharine and, as we all know from Medical School that's a potent and do serve immune system your lps.
- 00:29:48So, again there there's clearly a signal for healthy and unhealthy gut bacteria, and this is clearly modulated by many environmental and host factors.
- 00:29:57And it's extremely complicated and dynamic, so you can't just say like one point in time, this is literally changing on a day by day basis.
- 00:30:05And it's very complicated and we're just learning about it, and again we're This is just bacteria and we are learning more and more that you know viruses and fun guy also play an important role in this.
- 00:30:20So we'll switch on to you know how have we leveraged our knowledge of how this disease occurs and targeting it with our therapies, so I think most people in this room are familiar with the tnf alpha pathway.
- 00:30:31We target this with our anti tnf agents, so this includes infliximab which goes by the brand name remicade at elim averages humira.
- 00:30:39it's used across multiple auto inflammatory conditions, not just inflammatory bowel disease.
- 00:30:44But it's a very potent and do serve our immune system so recruits a lots of components of both the innate and active immune and adaptive immune system we think it's a very important for some of that fibrosis and that laying down of that collagen that relates to structuring.
- 00:31:02complications in our crohn's disease patients and then it also is a potent sort of cell signaling molecule for these.
- 00:31:11intracellular adhesion molecules or addressing which will touch base on later, which are another potential target for inflammatory bowel disease.
- 00:31:20So obviously this is affecting a wide swath of our immune system anti tnf therapy has been great, but it carries side effects are.
- 00:31:28opportunistic infections associations with lymphoma and other malignancies so it's well welcome that we've in the last five to 10 years have other options to talk with our patients.
- 00:31:43So in 2014 we had the first sort of add specific biologic therapy, so this was beetle ISM and it goes by the branding and tiptoe and it's called an Anti integrity.
- 00:31:55And so you probably learned about this in Medical School so we have our integrity and our addressing so our integrity sort of live on the surface of our circulating lymphocytes.
- 00:32:03And you can think of an address and it's almost like the zip code of the immune system, it has specific logins that it binds to and it tells you.
- 00:32:11immune system target this and Oregon I have inflammation in my gut send it to my gut don't send it to my nervous system and what we've seen is that we can specifically target gut selective.
- 00:32:24integrity and addresses, so there was a backstory that for multiple sclerosis there's a drug called natalie's a map or tie Sabri.
- 00:32:33It was an integral it was an alpha for specific integrity, so you can see here before, as part of this mucosal associated sailor adhesion molecule but.
- 00:32:43alpha for was also part of an integrity that targeted the central nervous system so that drug was used for multiple sclerosis.
- 00:32:49And inflammatory bowel disease, but you may remember, one of the really rare but tragic.
- 00:32:56complications is P amp l so progressive multifocal Luca and soft encephalopathy, which is associated with the JC virus.

- 00:33:03So, now that we have a gut selective option that safety profiles much more favorable and that's what a so in the interview is specific to that alpha or beta seven integrity.
- 00:33:15We have some investigation molecules which are coming out that target alpha E beta seven, and so the additional benefit is not only is alpha.
- 00:33:25beta seven targeting sort of the homing of our inflammatory response it's able to interact with this cat here in here and that's part of sort of the retention.
- 00:33:36it's telling your inflammatory cells you're not done yet don't leave my intestines inflammation still needs to be going on again that's part of that pathways that not only.
- 00:33:45Is the inflammatory response going to the test, if we have a difficulty, turning it off in or if I'm proud of it, so this is a really promising alternative pathway and really exciting that we have some therapies that may be addressing that in the near future.
- 00:34:00Next, we have the aisle 1223 pathway, so this is about 2018 that was approved for crohn's disease and the shortly after ulcerative colitis.
- 00:34:10So, as you remember 23 receptor pathways That was a very attractive target early on in our discoveries of the pathogenesis of inflammatory bowel disease.
- 00:34:20And they discovered this molecule ustekinumab that was able to target it, but it targeted at this P 47 units so, which is a shared sub unit So these are both.
- 00:34:30inflammatory cytokines so i'll as a more potent stimulation of the Th one signaling pathway of proven Fleming pro inflammatory pathways.
- 00:34:40Whereas i'll 23 is more specific towards this teach 17 pathway, which we think is the more important pathway and inflammatory bowel disease and also in psoriasis.
- 00:34:51And so you initially got sort of a two for one deal with ustekinumab and you know this was a very.
- 00:35:00exciting drug it's a narrower immunosuppressant so less of a potent immunosuppressant compared to anti tnf so really we have about 10 years of safety data now.
- 00:35:11Really, no strong signal for concerning opportunistic infections or malignancies and again it treats psoriasis right up arthritis so there's some other things that can treat as well.
- 00:35:22Most recently, about two months ago this drug raising kids map came to market, so it is an aisle 23 specific agent so it's hitting that p90x, so this is only getting the.
- 00:35:34pathway, and this was very exciting because it's similar enough to use to Kenya mad that I think the safety profile is going to be very similar and favorable for our patients.
- 00:35:44And again it's really targeting that main path of it we think is a main driver pathogenesis and inflammatory bowel disease.
- 00:35:54Next, we have the jack Stat pathway, and the molecules that affect this or the jak inhibitors.
- 00:36:01I think we had a Milo fibrosis talked a few weeks ago that use this as well, so the just to review the jack stack pathway is sort of a cell signaling pathway that drives numerous functions both pro inflammatory and anti inflammatory and I met a few pieces.
- 00:36:18So these genius kinase they sit at the surface of the cell and geniuses the Roman god of duality has two faces So these are all you know hetero timers and Homer diners and when they bind to their target login.
- 00:36:35They come close together, and then it sets off basically a kinase and phosphorylation cascade these jack families, they interact with the step proteins family.
- 00:36:46So it's Nice and medicine, when the name of the drug or the protein kind of fits with its function so Stat stands for signal transduction.
- 00:36:53An activator of transcription so goes to the cell nucleus up regulates the necessary genetic information to you know up regulate inflammatory pathways down regulates on in certain cases, and even medical uses.

- 00:37:11So the benefit of this is that the jack inhibitor that was approved and zell jan's or type of setting up it's a nonspecific jack inhibitor so it kind of hits all the Jacks.
- 00:37:23And what we saw from that is that, as you can imagine, from jack to you know P Vera or poly sighting of area.
- 00:37:29There was a signal for increased risk of DVD and P with that drug so it carries a black box.
- 00:37:35warning, we really saw that mainly and our patients older than age 50 and that carried one or more cardiovascular risk factor again, this is probably more of a broader immunosuppressant compared to beat Elizabeth and used to can you haven't risen kusa mab so we're seeing more sort of.
- 00:37:52opportunistic infections like or herpes zoster a reaction or reactivation.
- 00:37:59there's a new, more selective jack inhibitor called uber to sitting up or invoke this came out earlier this year.
- 00:38:08it's also used in other inflammatory conditions and that's more of a generic one specific genius kindness inhibitor which again seems more promising potentially because it might limit some of these more concerning adverse effects that we saw with COPA sit.
- 00:38:28In line with another one is a, this is another small molecule this targets pathway called this finger seen one phosphate signaling pathway really interesting, so this is a pathway that's also been used in multiple sclerosis to this.
- 00:38:44pathway involves finishing one phosphate and that's this signaling molecule right here, you see, and you can imagine it the analogous.
- 00:38:53phrase I use is like think of is breadcrumbs that are telling your lymphocytes to egress out of the lymphocytes and go into circulation.
- 00:39:02And target those sites have inflammation and they're interacting with those downstream addressing to kind of home and to where inflammation is problematic, with our auto inflammatory diseases.
- 00:39:15To Zanna MOD basically binds to these cellular receptors on your circulating lymphocytes and it sequesters them inside of your lymphocytes.
- 00:39:24Interestingly enough, this doesn't affect your memory T cells so it's not as potent immunosuppression that you think just based on the mechanism action.
- 00:39:32there's been a similar drug called spin gola that's been used in multiple sclerosis for a longer time, so we do have some more safety data.
- 00:39:40Behind this and it seems like it's fairly well tolerated there's no real strong signals for malignancies or severe opportunistic infections again more akin to maybe some of these viral reactivation like herpes zoster.
- 00:39:55And then the other things, you should know is that these s one phosphate receptors there's five subtypes.
- 00:40:03they're widely expressed in the body so there's also expression and cardiac micro sites that are part of the conductive pathway.
- 00:40:09And our new sites in our lungs and, of course, the central nervous system and are you know lymphoid oregon's so rosanna MOD is a nonspecific inhibitor of these receptors so it's hitting all of these, so the potential.
- 00:40:25implications of this is that there may be some breda Cardio what we've seen in the clinical trials it's it's very minimal about one to two beats per minute, but.
- 00:40:32advocate not using it in patients with pre existing part Blocker or conduction abnormalities.
- 00:40:37So this is fairly recently approved about last late last year for all striplight is still being investigated for crohn's disease.
- 00:40:44And seems to be very promising because, again, more and more studies in terms of more specific subtype receptor subtypes to kind of limit that side effect profile.

- 00:40:56So we'll kind of change gears a little bit so we've talked about all these therapies, that we have at our disposal now and it's how great it is to have options for our patients.
- 00:41:05But we really had a change in our practice patterns in the last five years in terms of timing of starting these advanced therapies positioning them.
- 00:41:14How are we measuring success in our patients in terms of like what is a successful end goal when we start therapy and then i'll touch base on a couple innovative exciting things that are coming to the forefront of our field, right at the end.
- 00:41:29So when I was in Medical School this triangle on the left is what we were taught about inflammatory bowel disease is that this step up pathway you kind of start with you know your lower tier medications more favorable side effect, but maybe not as potent.
- 00:41:42And then you step up, based on how the patients responding, but really done away with that so.
- 00:41:47About five years ago is really a paradigm shift and adult management inflammatory bowel disease, where.
- 00:41:51we've no longer done this we've kind of taken a page out of the rheumatoid arthritis literature, where we try to want to start our best therapies upfront early on in the disease to help improve long term outcomes their patients.
- 00:42:02So the way we look at it now is that at time of diagnosis we're really wrist ratifying our patients sort of based on patient and disease specific factors of.
- 00:42:11Are they likely to have a high risk phenotype or a low risk, you can type so some high risk features include young age of diagnosis extensive in atomic and involvement deep alterations at endoscopy or index presentation requiring hospitalization or steroids.
- 00:42:28periodontal disease and groans and for those patients we're starting our therapies in our advanced therapies up front, on the other side if there's.
- 00:42:37A low risk patient so like I said that elderly onset inflammatory bowel disease tend to be more of an indolent course or they have limited anatomic disease like illegal isolated Elio involvement.
- 00:42:48or even sometimes on screening colonoscopy will diagnose patients they never even knew that they had inflammatory bowel disease those patients, we might take a little bit watching way to approach or starting some of our lower risk therapies and just seeing how they do.
- 00:43:05To a part of this paradigm shift really occurred around kind of two components one was this this study and crohn's disease, called the calm study.
- 00:43:13This was published in 2017 and what this was is that it took early crohn's disease patients so that's patients within six months of diagnosis that never been on sort of advanced therapy.
- 00:43:23They treat them with a steroid burst up front, which is pretty similar to how this would occur in real life, and then they randomize them.
- 00:43:31To kind of two groups so at the top was sort of standard of care where you kind of just.
- 00:43:36bait made treatment decisions based on how the patient was doing so this click the cta is has crohn's disease activity index basically a composite score symptoms of the patient.
- 00:43:46Are they feeling good or not, and then, if they were using prednisone and if they did that, then they would escalate therapy in this tight control group.
- 00:43:54They use obviously symptoms of prednisone but they incorporated stool cow protection, which is a school biomarker for inflammation and C reactive protein.
- 00:44:03And they follow these patients over a year, and what you saw was at the end of the study a couple of interesting things a the tight control group did better.
- 00:44:12Be there was a clear difference in how you're treating these two patients, so at the top is sort of the more aggressive combination therapy every week injection with humira.

- 00:44:23More patients in that tight control group that we're using additional information on how to make treatment decisions ended up on the therapy that they probably need it and they got there sooner.
- 00:44:32I mean these patients on the Left reply, no different because there's a randomized control trials so there's probably some under treatment going on.
- 00:44:39And what we also saw is like we kind of knew this already we had seen that the patient says they're doing well, about a third of the time when you scope them you still find significant information on there, and asked up.
- 00:44:49And this study confirm that, by looking at C reactive protein and soon called protecting there's clearly patients that were doing Okay, but still had significant inflammation and weren't being treated in that sort of control group.
- 00:45:02Even more interesting so long term follow up with this study so about five years now, they looked at patients that have.
- 00:45:08achieved this concept called deep remission so they were able to get clinical remission so they felt well systematically.
- 00:45:14And then, when they scoped them they achieve mucosal healing their colon looked healthy and almost couldn't tell that they had inflammatory bowel disease, if you achieve both of those you get deeper mission.
- 00:45:24Patients that achieve deeper mission and they followed them out, you know almost three to four years you see the separation is that the top group is that the deep remission group.
- 00:45:34 they're much more likely to stay in remission and not have progression or disease or relapse years out, whereas this red group the people that.
- 00:45:43Maybe they just got clinical remission but they still had some inflammation on their scope you're probably going to have some sort of flair progression or disease down the road so again, a new target to kind of to tell our patients that we're gonna try to treat to.
- 00:45:59We also have new information on how to position these drugs like what is the best drug for this patient in front of me, based on numerous clinical factors.
- 00:46:07We still think that, for our highest risk of diabetes patients the best one is probably our oldest drug infliximab in combination with methotrexate and is the therapy and we call that combination therapy.
- 00:46:20But interestingly enough, in the last couple years we've had to really seminal studies so this first one is the varsity study.
- 00:46:26which was conducted in ulcerative colitis patients when they called biologic naive, so they never been on any sort of advanced therapy.
- 00:46:34And this was a head to head trauma, so this is very rare and clinical trials, where they compared the dualism APP that integration with a very safe safety profile with humira an Anti Tina.
- 00:46:45And what they saw was that vandalism actually was better and a lot of the categories in terms of clinical our mission and his comic response only really difference was the asteroid free.
- 00:46:56clinic or mission there wasn't a significant difference, so this route, was really pivotal because it allowed us to tell patients at diagnosis.
- 00:47:03You don't have to start this news scary drug I mean it's hard to convince patients sometimes to commit to therapy that you read the sort of insert and there's all this laundry list of bad things that can happen to them.
- 00:47:13So this is really a paradigm changing the crohn's disease correlate to this is the CV trial, which was recently published.
- 00:47:21So this looked at a similar patient population So these are bio naive patients they've never been on advanced therapy and they looked at a randomized them either ustekinumab or key marrow.
- 00:47:33And this was basically no difference, no significant difference between the two groups so.

- 00:47:39You know, you can look at that, as a glass half full or half empty, in my opinion, what I take from this is that it's basically you have an option for either one.
- 00:47:47there's no clearly superior agent in this particular patient population.
- 00:47:51biggest caveats of obviously both of these is that they didn't allow for dose optimization which doesn't fully reflect what we do in clinical practice, so I will often shortened intervals kinda like that calm study.
- 00:48:02Where they shorten intervals for humira to get better outcomes that was we're not allowed in these trials so and you weren't allowed to shorten intervals for interview or still are, they still are either.
- 00:48:16And then recently we've really codified this concept of like we cannot just use patient's symptoms as a treatment.
- 00:48:22metric so the strike consensus is basically a conglomerate conglomeration of all the experts and they came together and they said.
- 00:48:30Basically, this is how you should think about your treatment targets inflammatory bowel disease, you should have a short term medium term and long term targets.
- 00:48:37And when you have a patient come in your first target is obviously make them feel better so symptomatic response that's a short term target if you're able to achieve that.
- 00:48:45Then you should really focus on some of these medium term targets like normalization of some of these biomarkers and pediatrics you know get them back on that growth curve.
- 00:48:54And, in the long term, you know we want that mucosal healing on endoscopy that deeper mission improvement in quality of life and sort of getting that functionality back.
- 00:49:04They did touch on some interesting potential future goals, which you know, we would like to you know have validated, but you know.
- 00:49:12Do you get more bang, for your buck for transmissible healing on the imaging an ultrasound if you get that in our current disease patients do they do better.
- 00:49:19What about on all sort of colitis when we you know we scoped them.
- 00:49:22They look normal, but when you buy it there's still some residual mild chronic inflammation But what if you normalize that does that improve outcomes that's still to be determined and that's Obviously we need to assess that through the lens of cost effectiveness.
- 00:49:36So a little bit of a downer So when I have a patient come in and they're you know reading about this disease and all the treatment options, they tell me.
- 00:49:44Is it really only have about a 40% chance of responding to this drug and unfortunately that's the case we sort of hit a therapeutic ceiling and our and this field and what this.
- 00:49:55image is showing you is is a list of all the sort of seminal kind of clinical trials, going back to the very first with infliximab early 2000s and the left side is remission and the treatment group and the right side is remission and the placebo group.
- 00:50:10is long term remission and, as you can see, really nothing is getting over 30% essentially.
- 00:50:19You have to take this with a grain of salt, a lot of these newer trials patients that are being enrolled in these have been refractory to other medicine so that's why infliximab looks so great it's like it was the first one on the market.
- 00:50:28No one's been on anything when they got enrolled to that, but still, this is true, and you know this is a hard pill to swallow for our patients.
- 00:50:39Make that even more disappointing is that cost of it is astronomical so estimated cost to society or $30 billion just in the US due to loss of productivity healthcare utilization.
- 00:50:51And we're seeing more and more concerning shift away from like things like surgery and hospitalization er usage, to the therapies and these therapies are eye watering no one infusion itself can be upwards of $20,000 and they're getting you know six cities, a year essentially.
- 00:51:07So clearly room for improvement in terms of.

- 00:51:11Treating our patients, but I think the future is bright, I think, a couple things are really promising which will touch base on is I think we're really going to.
- 00:51:18push through this therapeutic ceiling and the near term.
- 00:51:21kind of a kind of like what we've seen in oncology like they've done great inroads in terms of orders of magnitude improvement and have some diseases that been historically very difficult to treat.
- 00:51:30And there's a couple ways, so one is you know why all these mechanisms they all act so different, why do they all have the same sort of 30 to 40% remission.
- 00:51:40response, maybe we're just starting the drug too late in the disease like at time of diagnosis you're just reading missed your window.
- 00:51:48So there's a lot of interest in sort of this preclinical face of the disease, like if you interact, then, are you going to get better outcomes for our patients.
- 00:51:56You know that goes along with early diagnosis there's really as I'm seeing a lot more Community ordered stool protections by PCP which I think is great like that's a really great thing to see because it's going to start capturing and eliminating that delayed diagnosis.
- 00:52:11better understanding of the pathogenesis like I think we still have a long way to go a lot of our our therapies are again they're treating numerous different auto inflammatory conditions so once we get sort of more IB specific drugs I think we're going to push through the ceiling.
- 00:52:26You know classifying the phenotype like Why is some groans only illegal Why is some periodontal Why is no some patients never gets trickier and disease, like we're going to have to better classify this, and this is going to come with sort of molecular.
- 00:52:38classifications, which I think is a little bit further out in the horizon.
- 00:52:43And then I think you know new combinations a new trial designs are really going to push this through this as well you know I'm tasked with a lot of our clinical trials here university Virginia.
- 00:52:53And there's more and more trials that are again having that active competitor arm and also combination therapy so it's really exciting one that's combining an Anti tnf with an.
- 00:53:01Anti l 23 because that 23 has a pretty favorable safety profile so it's not as concerned for overly immune suppressing the patient and we're going to see what the results of that trial like that could be a drastic improvement over outcomes.
- 00:53:16Some other things are really interesting I get this question all the time with patients like what about diet, what can I do to eat better and make my disease better.
- 00:53:25The data behind this is better for crohn's and it's basically limited to the pediatric population, so this seminal study this crohn's disease exclusion diet with partial internal nutrition.
- 00:53:38was conducted about five years ago, what this did was there was already been existing literature that if you just gave a pediatric.
- 00:53:46Patient exclusive internal feeding give them a to feed nothing else in the mouth six weeks, you can actually get endoscopic response and clinical responsiveness patients.
- 00:53:55So obviously that's not a very well tolerated thing right they can't probably convince a kid to do that for a long time.
- 00:54:01So with this study looked at is they said well let's get a nutritionist and design a diet, called the crohn's disease.
- 00:54:07Exclusion diet and maybe supplement it with a formula called module and which kind of mimic some of that exclusive internal nutrition eliminating some of the.
- 00:54:15You know, food, preservatives that we think are a role in pathogenesis of crohn's disease eliminating some of these sort of process things.
- 00:54:22And what this study showed, is that you know hey, not only was the combination of this partial nutrition, with the crohn's disease exclusive better tolerated.

- 00:54:33You know, it still had some meaningful cleaning meaningful clinical effects they looked at a bacterial composition using 16 s represent RNA sequencing and saw that you actually were able to change the bacterial composition, with this strategy, so this is really exciting.
- 00:54:51But again, limited to a pediatric population tends to be more mild again.
- 00:54:56And the correlate to this and adult population is this, you know dying CD study so.
- 00:55:01Specific carbohydrate diet is it's very similar to that CD diet essentially you're just going towards whole food, avoiding preservatives, you know universal allowance of fruits and vegetables, but maybe eliminating some of the starchy vegetables.
- 00:55:14But then they compared that diet to something that a lot of patients are familiar with the Mediterranean diet and what we saw here was that essentially they're the same there really wasn't any significant difference between the two diets.
- 00:55:29So a couple caveats here, so this is, you know.
- 00:55:32Again, like I mentioned clinical symptoms don't always correlate with endoscopic activity, they did not you know scope these patients to sort of prove that there is a meaningful improvement and in this topic findings.
- 00:55:43Only a minority of patients had abnormal fecal car protecting that enrollment so again, this is a more mild crohn's patients that are in these studies, but.
- 00:55:51This is a you know something I can tell the patients is that look, we are not ready for prime time, but if you really want to try something there's at least two or three options on the table and you choose what's best for your lifestyle.
- 00:56:05So what about periodontal crohn's so like I said that's a high risk feature that's extremely highly morbid condition.
- 00:56:10 there's some really exciting stuff coming out with this so just to review, so a period or chrome involves either period i'll abscess or more commonly at fistula.
- 00:56:19And you can break it down into a simple official or a complex so simple is on the left.
- 00:56:24And you can see that it just traverses and it spares this inner and external sphincter muscle.
- 00:56:29And a surgeon can basically just come in here and unruh fat and do a lot of me kind of flayed open and then it heals by secondary intent.
- 00:56:36You obviously can't do that with a complex fistula because you can be violating the sphincter muscles and then patients at risk for and continents so typically what's done is that they play some see Tom which is basically a rubber band.
- 00:56:48To keep that track open so that another abscess doesn't form and then more branching and then you have even a worse fistula and you kind of use that, in combination with really trying to get that inflammation under control.
- 00:57:00So what we've seen is that there was a study in Europe, called the admire crohn's disease study.
- 00:57:05And they used adipose derived stem cell therapy and surgeons basically curators that fish to the track and then injected stem cells all along.
- 00:57:13And what you saw was a remarkable difference in terms of success, compared to you know placebo sham injection and so.
- 00:57:22This is typically something that's about 20% success rate with our therapy, with a surgeon a seat on and then optimizing biologic therapy.
- 00:57:30We were seeing upwards of 50 even 60%.
- 00:57:34So we've actually replicated the study in the US, and we were a participant here at uva we've closed enrollment so we're going to see the results of that, but I think this is really something that's going to come to.
- 00:57:42clinical practice probably within the next couple of years and it's extremely exciting.

- 00:57:48So precision medicine, I think you know we already use this to certain degree, like when we start a patient on a thigh appearing we're getting tpm T enzyme activity to kind of you know.
- 00:57:57Risk stratified potential toxicities, but I think more interesting things are coming.
- 00:58:01So there's a really interesting cohort called the gem cohort that stands with genetics environmental microbial cohort.
- 00:58:07This is patients that don't have inflammatory bowel disease but have a first degree relative that habit so they're considered an at risk population.
- 00:58:15And they're conducting many studies and two that are really interesting is that there's one is an altar politeness what they've done is they.
- 00:58:24Looked at these patients and what they saw was they're doing sort of again shotgun manager know Max metabolism mix in vitro as a as a lot of different things, and what they saw is that.
- 00:58:37Of the patients that develop ulcerative colitis there was a phase where they were still asymptomatic but you saw an increase in this bacterial prolific activity.
- 00:58:47And so maybe this is a marker for pre-clinical ulcerative colitis again, this is a small cohort it needs to be externally validated amongst different populations again.
- 00:58:58Many of our studies are limited to sort of these Western European descent populations and we need to be able to extrapolate this findings to other population groups but interestingly, not nonetheless.
- 00:59:09yeah there's the correlate to the currency, so the same cohort.
- 00:59:13 And crohn's disease, they saw that there's a signal for increase intestinal permeability that leaky gut you know thing that you see everyone talking about and see all over the Internet.
- 00:59:22or there's some truth to it, so what they saw in this study, they took that same at risk population and they had him drink a.
- 00:59:28mixture of men at all and lactose and lactose is a laxative it's not poorly absorbed so really shouldn't be absorbed systemically but you could measure, a fraction airy excretion in the urine.
- 00:59:39And detect sort of like a metric for how permeable is your gut and what they saw was if you had an elevated urinary fraction of black fellows you're more likely to develop groans down the road.
- 00:59:52And so again Maybe this could be a marker for that preclinical face and an opportunity to intervene earlier, and you know really change long term outcomes for patients.
- 01:00:04 there's been some interesting studies is sort of like akin to oncology where you know you're sampling you're looking at the genetic.
- 01:00:11makeup of the disease and really saying this drug for this, you know biomarker and so two studies have been done they're pretty interesting so you've looked at membrane brown bounty enough, and if patients.
- 01:00:25Have a high expression of Member membrane bound tnf your response rate to anti tnf therapy was 92% if you didn't have your response rate was 15% so really wide discrepancy and response rates to again only to anti tnf therapy, but promising nonetheless.
- 01:00:47And alpha or beta seven which again that's that target for realism and that got selective integrity inhibitor.
- 01:00:52So they looked at a you know lymphocytes expression of that integration and the way they did this is they actually stained or they attached foreseen to interview, so they could see.
- 01:01:03After patient got started on therapy they take samples of their gut look under a microscope and see how much this foreseen staying interview is bound to the new Cosa.
- 01:01:13And what you saw was is that if you had expression.
- 01:01:18 you're much more likely to respond so again wildly discrepant sort of response rate so we're getting to the point where we may be able to.
- 01:01:25get a patient get some information to say what's the best therapy based on precision medicine few other interesting thing correlates so this trend one.

- 01:01:36And angst and m are also predictors of non-responsive tnf so Trent one is sort of.
- 01:01:45Express on circulating lymphocytes so it's a whole blood test, you can do and inversely correlated to high expression of trim one less likely to respond to in touch enough.
- 01:01:56Or the correlate is August at Nam if you do have expression ivanka set them on the new Cosa you can biopsy and stand for this protein much more likely to respond to therapy.
- 01:02:08And then again like I mentioned clinical trials are really starting in bend a lot embed a lot of these sort of company diagnostic tests into they're designed to really see how can we predict, who are responders and non-responders.
- 01:02:22So, to conclude, you know I think new drugs are here, you know it's an exciting time we're still figuring out how to position them but we're starting to me earlier disease and kind of borrowing a book out of rheumatoid arthritis literature.
- 01:02:36You know feeling well, is no longer acceptable like we need to have a conversation of what our targets for their patients.
- 01:02:43and obviously that first year is clinical our mission, but we have.
- 01:02:47second and third tier goals that we should target and at least have a conversation what our options on the table to achieve those targets, maybe we're already maxed out on therapy and we're only able to achieve clinical our mission.
- 01:02:56But you know, we should have this concrete goals and conversations with our patients.
- 01:03:01died, I think, is going to come to the forefront we're gonna learn more and more about this and I think a really attractive potential population is that sort of pre clinical you know inflammatory bowel disease is like is that a way we could.
- 01:03:11impact the the outcome of this disease i'm starting earlier, you know diet begins at the early stages, by.
- 01:03:19And then you know I think we are going to break through that therapeutic ceiling, many of those things I just discussed so.
- 01:03:24Hopefully, in five years time, I can give you this lecture again, and you know we'll have a really exciting things to talk about so thank you for your attention and I hope you enjoy the talk.
- 01:03:48Thank you yeah Thank you so much for that talk.
- 01:03:52A question for you and your research in the next maybe one or two years what's getting you excited about what you're heavily involved in what you see from coming out from your research yeah great question so.
- 01:04:05One of the things that's really been a problem for the longest time is.
- 01:04:09So biologic therapy, so a lot of patients, even physicians kind of get the concept confused a biologic is just the size of the therapy so it's just a molecular size over then 5000 kilotons a small molecule is small enough to be absorbed by your mouth and your intestinal barrier.
- 01:04:27All our therapies have traditionally been biologics and what we've seen is that some patients, we can never get their their drugs therapeutic they're just leaking they're spilling the drug.
- 01:04:36And even when we match those they're still not getting the drug levels that we want and small molecules you don't have to worry about that so I'm really excited about.
- 01:04:45You know, new incoming wave of advanced therapies that involve small molecules because I think that's really going to address an unmet need that we've been seeing for a very long time yeah great question.
- 01:04:57And I think combination, you know novel combinations of different mechanisms, I think that's another exciting thing to come.
- 01:05:04So I know there's a big push towards machine learning and artificial intelligence and GI and I was.
- 01:05:11wondering if that has shaped your practice and how you see that evolve in the future yeah so currently nothing that would say shapes my practice, but if you think about it, we use imaging.

- 01:05:23And endoscopy for a large portion of our jobs, and that is ripe for machine learning that is just data points.
- 01:05:31That you could push through an algorithm, and so I think, where some of these things are moving is sort of having a more objective standardized way of interpreting.
- 01:05:39You know inflammation so I score moderate my colleague says that's mild.
- 01:05:45But if you train them machine learning, it can be the same every time and that might drive more sort of objective measurements and improve sort of you know trial design and measuring outcomes.
- 01:05:56yeah I think that's where that most will be as sort of a on the history logic endoscopy and imaging forefront yeah you know, on a lighter note, is it true that ustekinumab was named such because it's a subcutaneous antibody that you stick in your so.
- 01:06:14I don't know how they named them but that's a pretty good I've never heard that Nice.
- 01:06:25Well, as much as.
- 01:06:27I find a strategy of testing actually interviewing on your pre-clinical populations pretty Tom interesting from you know for this goal if.
- 01:06:36He said breaking through the ceiling wonder if you could elaborate a little bit on that just in terms of what like path of physiologic changes.
- 01:06:44 they're seeing for those populations, if they are indeed preclinical and then second i'm wondering.
- 01:06:50For interventions for those populations are they using the same drugs, you know that you hit here, or are they using kind of different molecular mechanisms.
- 01:06:59yeah so good question so your first part of your question yeah that preclinical phase, I think we are seeing sort of.
- 01:07:05Some of this change in your microbiome the this leaky gut phenomenon it's all sort of tightly wound is like a lot of these risk levels.
- 01:07:13They play a role, like your type barrier junctions arm regulated on the genetic level so some of that might be, what is the chicken or the egg.
- 01:07:21But some of these things that are common is that yeah some sort of gut permeability changing.
- 01:07:27microbiome signals changing and then some low level inflammation so that angst at them, they also looked at patients.
- 01:07:35That hadn't developed groans and they saw that there was a two fold increase in aqua sat Nam expression prior to development of clinical symptoms, so you know all the above, and then you know novel mechanisms for therapy and that preclinical phase, not that I have seen honestly.
- 01:07:53there's just more and more different mechanisms and there's you know five to six, you know that we're currently being investigated they're completely different pathways and inflammatory pathways that are being targeted.
- 01:08:06yeah just had a couple of questions, the first one bring know you know this immune T cells.
- 01:08:16What condition is in a second one yeah.
- 01:08:22Okay yeah great question so unclear it's probably numerous different targets so for about 15 years ago there was a seer logic panel that you could order that might.
- 01:08:35be a predictive diagnostic tool for patients, some of the things that came out of that were like antibodies to sacrifice the service yeah.
- 01:08:44So, like a yeast so some of these like anka so there's it's there is no clear target at this time that we know of it's probably numerous different ones also probably explains why there's.
- 01:08:56Different predilections to extra intestinal manifestations probably some serious shared antigen for the you know ocular manifestations, with some sort of gut.

- 01:09:05antigen that's being driven you know the process, so we still not clear, but it's probably a numerous and clearly some sort of shared antigen with our microbes and then our body is most likely, the current hypotheses.
- 01:09:19And secondly, you know, I was quite surprised, you know with this shift in immune therapy, you know from getting out of Imran and middle criterion all those drugs and then switching to.
- 01:09:35And the cytokines and take the entire p.
- 01:09:39Because.
- 01:09:42The current thinking I'm wondering whether it is really right and whether it only applies to a certain subset of patients.
- 01:09:52And there might be other patients where besides T cells, there could be others immune cells, having a role in in in.
- 01:10:06combat you know inflammatory bowel disease, so the current therapy is mostly focused on T cells, but could.
- 01:10:15Other sales like NK cells or macrophages yeah also have a heavy role yeah and this this old treatments could be taking care of those cells.
- 01:10:30yeah no that's a great point yeah I think there's probably some truth to that because I think we still reserve anti tnf for our most severe patients and we're also using combination therapy.
- 01:10:41And anti tnf does hit both lymphocytes but also involved with you know macrophage and mana site recruitment and persistence so.
- 01:10:50There, there is probably some on targeted a component, with some of these more narrow disease.
- 01:10:56drugs and that's why I think is really promising for combination therapy of like we're going to hit two pathways at the same time and cover all our bases.
- 01:11:05But yeah we still, this is still pretty poorly understood the real detailed molecular level what's driving this disease and most likely.
- 01:11:15we're going to have five to six subtypes of inflammatory bowel disease in the coming years, with different sort of targets and pathogenesis and sell T cell and versus macrophage.
- 01:11:28used to be an old thinking of basically crohn's disease verse also Clyde this was basically that distinction, whether it was a T cell mediated process or not and we've, the more you learn the less you know I mean it's basically gotten muddier essentially if we learn more.
- 01:11:42and have a look at grand slams in in this condition enzymes no Green times.
- 01:11:51Like a like granular site enzymes you're saying yeah I'm.
- 01:11:57Not not off the top of my head there's.
- 01:12:01there's a lot of sort of.
- 01:12:04probiotic and modulation of the like the bacteria and then still sort of main drivers of inflammatory cell signaling so either through that you know jack inhibitor pathway that's a pretty ripe area or other cytokines nothing on the sort of the enzyme and enzyme level.
- 01:12:26Excellent questions everybody.