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

**TRANSCRIPT - GR 12 10 21 *"Going Against the Grain: An Overview of Celiac Disease" –* Dennis Kumral, MD from the University of Virginia**

* 00:14:00Please join me in welcoming Dr Dennis Kumal across the cliches custom newsletters so well intended for college for his undergraduate studies and neuroscience account and then attended the records.
* 00:14:13wr jms for about school Dr Kumar came here to Charlottesville for his internal medicine residency year, even completed his training with the gastroenterology division down the road and then joined our GI faculty after that.
* 00:14:30Since he joined the Faculty in 2019 he has had an active role in the Inpatient and outpatient work in the division, including times many industries who work with our GI doctor
* 00:14:39doctor Kumar is a clinical research interest in seeing activities, with a focus on outcomes diagnosis and management.
* 00:14:46roles and interesting quality improvement in this area of care.
* 00:14:49Dr Kumar has a joint venture with Dr site and UVA pediatrics department to develop a ti celiac Disease Registry, in order to expand our research for pregnant this area.
* 00:14:59Dr Kumar is also an invite and peer reviewer at the American Journal of gastroenterology on the topic of celiac.
* 00:15:05through all of these managers and many more not addressed here, Dr Kumar has already left his mark at the institution that he called his residency home and I'm certainly a much more important, too, but that'll have done a curveball coming to the lectern 2pm grand rounds.
* 00:16:20that's perfect alright well, thank you for the invitation it's my privilege to give this talk today, I remember being our resident and during grand rounds in Pin hall and.
* 00:16:30Usually somebody would walk in at the last minute and sort of rub up on the lights and they sort of turn off right in the middle of.
* 00:16:37That, if you have to.
* 00:16:40Learning objectives for today we're just going to go over basically a big overview of celiac disease so we'll talk about the diagnosis and management.
* 00:16:47And some potential not dietary therapies that might be available in the future.
* 00:16:52No disclosures to report so I'm going to start with a brief history lesson about celiac disease, this is a condition that's been known for.
* 00:17:00Years and dates back to the ancient Greeks actually are a taste of kemet Nokia and 50 ad actually first described celiac disease.
* 00:17:10And the word celiac actually comes from the Greek word co Leah which means abdomen or other descriptions of like a celiac artery and celiac plexus that are in the abdomen that actually don't have anything to do with this diagnosis, but.
* 00:17:24Artists describe this patient that he said at the stomach be retentive of food and if a pastor on digested and crude nothing I sent into the body we call such a person celiac so he was sort of referring to people with severe mental absorption and this description.
* 00:17:42was basically a you know, a while past before and other sort of description of celiac disease came in the 1800s, and this was a pediatrician in London, Dr Samuel.
* 00:17:54Jones gee who i'll kind of SAVE reading this paragraph, because he just kind of described somebody that's having really bad diarrhea and.
* 00:18:02How absorption probably stay out area, but this was like the sort of lecture that brought back celiac disease and sort of people started thinking about this diagnosis again.
* 00:18:13So that in the 1920s, there is a pediatrician by the name of Dr Cindy hos from the United States, but he actually had studied some.
* 00:18:22Patients in Puerto Rico they found that the dwellers who eat much bread suffer from celiac spruce while farmers who live largely on bananas never.
* 00:18:33So it was his impression that celiac disease can be treated by going on, by banana diet and yet recognize that it was wheat and gluten that was actually the trigger for the condition, but he started treating.
* 00:18:45kids with celiac disease, when a high basically banana diet and this poor child has to eat all these bananas to try.
* 00:18:56It actually works, because they were accidentally cutting out live in there, eating a lot of bananas, they were also eating meat, vegetables and it was accidentally gluten free.
* 00:19:05Unfortunately, some of these children later grew up and sort of went back to eating gluten and then got sick later in life.
* 00:19:12And sort of the final sort of history slide here is that this was in the 1940s and 1950s.
* 00:19:19When there was a year after World War Two there was a famine in the Netherlands and we're finding bread and finding week was actually very difficult, so people didn't really have wheat in the diet anymore.
* 00:19:31And then, Dr William deck was a pediatrician and Netherlands notice that previously kids were dying from celiac disease.
* 00:19:39mortality rate of about 25% but then during World War Two they were actually doing a lot better and then he recognized that it was actually gluten how much was found in wheat.
* 00:19:50Was the trigger and that was how they then later on starting to gluten free diet.
* 00:19:55You always hear the word cx brew just just search for your knowledge that's broom comes from the Dutch word which also I guess it's brown something like spruce and it means inflammation of the mouth or brush and that's usually associated.
* 00:20:10With this diagnosis and there are other causes of spruce as well and tropical fruits and things that are aren't actually celiac disease.
* 00:20:18So this show this slide to suggest, and since the 1920s quite a bit has been discovered in regards to the pathogenesis of celiac disease diagnosis, as well as management and we'll sort of go into that in the upcoming slides here.
* 00:20:34So, to define celiac disease for Tommy gastroenterologist and i'm talking to you about this condition, because the primary.
* 00:20:42target of injury is the small mouth, but we should recognize that it is really a multi system disorder and there are symptoms that are outside of the GI tract as well.
* 00:20:52As we've mentioned, and, as you may know, it's triggered by gluten, which is the main storage protein in grains and we will talk a little bit more about that in the upcoming slides.
* 00:21:01And it's actually a genetic condition and presents in people that have the right genes for celiac disease.
* 00:21:08So on the slide is a busy slide but what I want to show you is that these are the different types of symptoms and the various definitions we celiac disease.
* 00:21:17draw your attention to the middle column so previously these words typical and atypical to sort of describe the different presentations you'll see that.
* 00:21:26You know balancer action diarrhea weight loss failure to thrive sort of fall into this category.
* 00:21:31We don't really use this term typical anymore instead reserve the term classic because this is the presentation that.
* 00:21:38In that you know 1800s they were describing when people haven't present with severe about malnutrition and i'll show you in a couple of slides that that might not be the more common presentation, then non classic presentation of celiac disease.
* 00:21:51These are the folks that come in with iron deficiency and then work up and haven't been able to explain it and then someone thinks of celiac elevated trans-am cases that are unexplained can be related with this.
* 00:22:02Patients can have constipation infertility osteoporosis, is a common reason, where somebody might have early osteoporosis, and then we find that they have celiac disease, and these are just some some of the non classical symptoms.
* 00:22:16And then there are conditions that are very strongly associated with celiac disease, one of them being dermatitis or performance.
* 00:22:25So this is a PR riddick extremely itchy rash that develops on the extensive surfaces, like the elbows knees and smallest around the buttocks.
* 00:22:34And that is actually a skin manifestation of celiac disease and people that have dermatitis repetitive warmness.
* 00:22:42almost certainly also have some interrupt with the associated with celiac disease and often it gets better with going on a gluten free diet.
* 00:22:48type one diabetes is strongly associated with celiac disease due to some of the shared genetics.
* 00:22:56And we get a lot of referrals from the undercurrent clinic about patients with type one diabetes, there we later diagnosed with celiac and there are a number of other conditions that are associated so here's a slide that sort of shows us right I’m thinking my pointer and some maybe.
* 00:23:15My appointment, this is the slide that shows why we shouldn't say typical typical because the non-classical warm have celiac disease.
* 00:23:24Those with constipation osteoporosis and diagnosis, but don't really have diarrhea that made that accounts for 50% of patients with celiac disease.
* 00:23:33And the folks that had the mountains option symptoms that's only a quarter and here's the tricky part another.
* 00:23:38about another quarter of patients have no symptoms at all so they're only picked up because they underwent some sort of screening tests that show that they have celiac so it's hard to convince these folks to also follow up with pre diabetes, they never had any symptoms, to begin with.
* 00:23:55So this brings us to the conversation about the Celia iceberg, and so this is the concept, where those that actually have symptoms of celiac disease and are dying.
* 00:24:05Or the tip of the iceberg and there's quite a few people that have undiagnosed celiac disease and sort of walking around with it right now and don't know.
* 00:24:13And then there are those that have potential celiac disease, they have the right genetic susceptibility but right now, they have normal need kosta and they make this condition later in life.
* 00:24:23So that discuss the epidemiology conditions, a global.
* 00:24:28condition it's about 1.4% pool prevalence around the world, so about one and 100 people in the world have celiac disease that's true for the United States, where it's about 0.8 to 1%.
* 00:24:41There are some countries in Scandinavia like Finland, where the prevalence is higher about 2.4% and then there are certain areas of the world like in
* 00:24:50northern India menchov region it's very common we have quite a few patients in our clinic that come from countries like Afghanistan and Iraq, where they also have celiac disease very commonly.
* 00:25:02There are other parts of the world where it's very common and that would be sub Saharan Africa, for instance, for this condition is not very common.
* 00:25:10Why, why is this difference in the world there's you know difference in genetics.
* 00:25:17There are differences in environmental patterns that we consumption and the age of we introduction in different cultures and then charlton GI infections may play a role and we'll talk about that in a few slides.
* 00:25:29The mean age of diagnosis is 38 years, so we do see it in the adult population but it's actually seeing.
* 00:25:36People as old as 60 and we have some people that are diagnosed in their 70s and that always begs the question of whether or not it's a new diagnosis, or if they've.
* 00:25:45Had this condition for years, and it was some clinical and not picked up until later in life.
* 00:25:51Like other autoimmune conditions it's more common in women than men, and this part of us may be that women may see care more than men do.
* 00:25:59And that may probably play a role, but there may also be an increase in the incidence and females, and then i'm similar to why, why is this.
* 00:26:09One thing to show here's the incidence of celiac disease, this is showing us from the 1950s 1980s really sort of picked up the diagnosis sometime in the 1990s 2000s and then sort of leveled off since then.
* 00:26:23Part of this may be increased awareness of the diagnosis their blood tests that will discuss that are available and make it easier to diagnose that condition.
* 00:26:32But there are likely changes and week processing and how much week people eat, as well as the age that they started which may play a role.
* 00:26:42So this was an interesting study it's done for my air force base and.
* 00:26:47wyoming where they had banks blood serum from condense the 1940s and 1950s and then they kind of started for study later on and for future studies and so what they did is they tested these these banks here and they found that you know the 9000 or so 14 of them are point 2%.
* 00:27:09Now, are looking at love that's been sitting from the 19 52% of celiac disease and they compare them to age managed cohort from around the Mayo clinic.
* 00:27:21One cohort or folks that we're currently the same age as the cadets work when their blood was bank and the second cohort were people that were born the same.
* 00:27:32year as the cadets and in both of those cohorts the diagnosis of celiac disease was greater about fourfold greater, and so this study seem to suggest that it's hard to say that it tested to increase awareness and.
* 00:27:46celiac disease there might really be something that's making it more common and blaming it on a genetic shift is difficult to say over just 50 years, though I think diversity has changed in the country, since that time.
* 00:27:59And again brings back the idea of environmental reasons, maybe playing a role.
* 00:28:04So, like it a lot of musicians there's the old environment genetics and new industry regulation, causing the underlying physiology so regarding that environmental factors and suppose a very interesting study coming from Scandinavia, so what they found the.
* 00:28:26In Sweden, there was a significant increase in patients with celiac so they wanted to see compared to neighboring country, Denmark.
* 00:28:34Or the celiac disease was not as common looking at factors that may be playing a role and what they found is that if they compared the Danish infant diet.
* 00:28:44live in was a lot less a part of the diet that in the Swedish and been diet, where they had 4400 milligrams of Colombian ingestion whereas Danish kids had 100 milligrams of gluten ingestion so.
* 00:28:58They thought that maybe early exposure to live in a tribute system, maybe one of the contributors to this increase in diagnosis in Sweden.
* 00:29:09Another study about environmental factors I mentioned childhood infections so.
* 00:29:14reovirus is a virus that's in the same group as rotavirus which rotavirus causes a lot of childhood infection so reovirus is actually asymptomatic and, in fact, children and other repositories symptoms.
* 00:29:27But when they looked at a mouse model.
* 00:29:30Of infecting the MICE with reovirus they actually were able to show that there was a loss of tolerance to live in and.
* 00:29:37It seemed to make that even the MICE didn't have any symptoms when they gave them live in the MICE that were infected with reovirus tend to have a celiac disease like phenotype.
* 00:29:46And then the same study actually at the University of Chicago look at their celiac disease cohort and here chose they looked at.
* 00:29:53antibody titers reovirus antibodies which usually are not really part of clinical practice, but in this study, they measured them.
* 00:30:01and controls that didn't have celiac disease was pretty rare to have reovirus antibody titers.
* 00:30:06Then, compared to the folks with celiac disease that either had active celiac disease or those that were actually being treated on a gluten free diet.
* 00:30:14Can reovirus titers require higher in the people that have celiac disease, so they thought that maybe this innocuous virus that otherwise doesn't cause any symptoms repeated infections can be causing celiac disease.
* 00:30:29So we talk more about what gluten is so this is from a.
* 00:30:33Little search about living they'll find that is poisonous danger that you know you get a T-shirt gluten is the devil.
* 00:30:40Or you can you know by thousands of books about gluten free living and gluten free diet and then I even came across this guy who apparently gluten free diet and turned out like this stuff actually sure it's the same person when you look at it closely.
* 00:30:55It might work if you want to try so we'll talk about what gluten is actually an actuality so just to review.
* 00:31:04When you think about a cereal grain, there is a brand, which is the outer Shell contributes to the fiber component.
* 00:31:11there's the German playing embryo and as part of the endo sperm, which is where blue and actually is included again it's the protein prominent of the material and it's a combination of.
* 00:31:26Two different printing components, one is called completed the other ones called a lieutenant.
* 00:31:31These two components combined in a business environment of water and they formed this mesh like structure that you can see down here, and this is what we refer to it.
* 00:31:42And it's important for baking because when you want something to rise, when you want breads horizons living that actually captures and traps that carbon dioxide and also gives know this to me elastic texture i'm good and is an important part of making.
* 00:32:01But when you look at the three different grains so that are troublesome for folks with celiac disease it's week that we think about most commonly, but we also have to remember that barley and Rye also contain gluten.
* 00:32:14And all three of these grains are derived from the same tribe, and when you look at the neighboring Dr that's.
* 00:32:21Suppose are actually not it'll contain gluten and technically there OK, for both with celiac disease.
* 00:32:29But a lot of places don't just mail or farm one sort of grain handle farm you know oats one year than they might turn over a new week the next year and.
* 00:32:37Also, the places that process these Greens sometimes so work on all of them, so a lot of times folks can be contaminated with gluten I thought this was an interesting story.
* 00:32:49cheerios is actually made with whole grain oats doesn't contain any but.
* 00:32:55They didn't previously have a gluten free designation until when I’m there are administrators and R amp D or family member was diagnosed with celiac disease, and I think i'm more interested in.
* 00:33:05Actually, making the product within frame and so they figure that it's too expensive to go with just certified gluten free oats because that would those the you know size of the process of the cheerios is huge and it would cost.
* 00:33:19A lot more money to buy the consumer, so they developed a mechanical Senator where they actually can see this.
* 00:33:27Brain has a different shape than we in barley and Rye and they're able to sort of sift out the other grains just sort of make.
* 00:33:34Their product codes and now they're able to carry this creek designation.
* 00:33:39And so, these are some of the sources of the in which you all, are all probably familiar with and places around Charlottesville where you can go consume it in.
* 00:33:48But we should also consider hidden sources of in on the right side here, you know processed meats, you know the patient might be eating just meets, but if it's in a marinate that contains week they're consuming gluten.
* 00:34:02taken years and I’m also fires and certain foods, even an ice cream may have jelling agents that have wheat and.
* 00:34:09Things like butter seasonings so I saw some all contained glue him, and then there are some medications, in particular, these are.
* 00:34:16Typically, not prescription meds but supplements that patients might have GI symptoms and sort of have celiac disease and reach for a dietary supplement and unknowingly be consuming as or as a result.
* 00:34:30So this is the art of living that's a problem it's called the 33.
* 00:34:36Large fragment.
* 00:34:3833 peptides that basically doesn't get very well digested by any of the enzymes in the intestine and it passes through the intestines pretty much intact and, unfortunately, is a trigger for the immune response and when.
* 00:34:54celiac disease so here we'll talk about the get into the genetics of celiac disease, but surely familiar with those are two gene complexes to Hla YouTube and dq eight are.
* 00:35:07The ones that folks have to have to have celiac disease, these are found in chromosome stakes they're part of the mhc complex.
* 00:35:14Complex of genes that make these hetero timers on antigen presenting cells, and so the body decides, something is you know friendly or low and then something external to it, or if it's an invader and celiac disease patients must have the.
* 00:35:35But about 30% 30 to 40% of the general population actually has these genes so it's not enough just to have the genes to have celiac disease, but if you don't have the genes you can't have celiac disease.
* 00:35:49And this is an important slide and comes from a nice New England journal review that's a little data now 2007 but just to go over the pathophysiology and i'm going to just kind of walk you through this so you somebody and just live in.
* 00:36:04live in a sort of broken down, but that blade and fragment that I showed you there's not completely get processed and it goes through the small bowel.
* 00:36:14into the southern area where it actually comes in contact with an important enzyme called tissue transport Chamonix and tissue transfer emanates does this thing where it actually going back to this.
* 00:36:27slide before here is tcg it takes the glade and peptide and it does something called DM a nation, and it makes the glade and peptide more negatively charged, so that you can more neatly fine into these Hla dq to the QA heterozygous.
* 00:36:44This is on the surface of the antigen presenting so now, this is where the inflammatory process starts this complex interacts with T cells and patients with celiac disease and all the cytokines get released, including things like I’ll to and I’ll.
* 00:37:01And, as a result and causes all this damage celiac disease Phyllis atrophy interest Philippa psychosis.
* 00:37:10And I’m going to ship the end will start to come back to that discussion about of is in a little later, too, but we're going to shift to more of a clinical aspect about who we should.
* 00:37:19Consider testing for celiac disease and this comes from the acg guidelines which are from 2013 and they're a little bit dated and I believe they're supposed to be undergoing a revision.
* 00:37:29In the upcoming years but obviously in step one of those patients that have mal absorption symptoms, they get today should be tested for celiac disease.
* 00:37:38Chronic diarrhea weight loss data Rhea Donnelly bloating anybody who has a family.
* 00:37:43Member first degree relative with celiac disease and called you and said underlying genetic condition so anybody with a family member who definitely has symptoms of celiac disease should be tested.
* 00:37:55Think about it and unexplained libertarians emanates elevations when you've already gone through all the other tests.
* 00:38:01And then we talked about type one diabetes, they should be tested, but I think that going back to the slide that I showed you earlier, I think it's more comprehensive that you have to think about celiac disease and all of these.
* 00:38:11presentations and if you don't test for for probably missing people that have it.
* 00:38:17And this is one of the most important sort of points I want to make, and this whole talk is that all the blood tests, as well as endoscopy tested for celiac disease have to be done when patients are still eating gluten.
* 00:38:29This is a common problem, and I know part of it is you know takes a while, sometimes getting the GI clinic and.
* 00:38:34we'll start going gluten free where they see us and for all the tests are done then often the diagnosis for meeting question on for years.
* 00:38:43So we'll talk about one work we'll talk about endoscopy which I don't recommend is just if somebody gets better from eating gluten free diet, there is a condition called non celiac.
* 00:38:54gluten intolerance or non-celiac non celiac gluten intolerance and those patients they don't have celiac disease, but they have GI symptoms when they eat.
* 00:39:04gluten and it may be that it's more of a Fahd maps that are in, week and it's actually possibly not even within that they're reacting to so a.
* 00:39:12lot of people might feel better going on a gluten free diet, but they may not have celiac disease, and there are online food sensitivity tests that.
* 00:39:20In general, we just don't recommend for any of our patients in GI because they don't have a lot of rigorous data in the back of them.
* 00:39:27Just to briefly mention I talked about iga strategies and those are the gold standard and celiac disease.
* 00:39:33But there are folks that have something called selective iga deficiency, and this is where the buyer doesn't make any iga.
* 00:39:40And it's actually more common in celiac disease patients has two to 3% of celiac disease patients may have selective I jade efficiency.
* 00:39:48Really pretty rare in the general population, we have a patient in our clinic but celiac disease looks like the.
* 00:39:55Efficiency and previously, the guidelines would recommend that you should send an total iga level on anybody when you're testing for celiac make sure.
* 00:40:03That you're not missing this condition, but our lab at uva will actually reflex to a celiac hygiene panel if they find that the patients total iga is less than seven so.
* 00:40:15From a cost effectiveness perspective, you do not have to check in separate iga level and patients when you're screening them celiac disease.
* 00:40:23And this is a slide that kind of goes over the alphabet soup of all these different terminologies and all of them have different acronyms so that the box.
* 00:40:31drawn here is to drink bring your attention to the two that are most important and we'll go over them in detail.
* 00:40:37But the tissue transfer contaminates iga, otherwise known as tg and the DMA ugly an iga, otherwise known as bgp and if any of you order a celiac iga screen, these are the two tests that we're tracking.
* 00:40:50And so, also to sort of talk about a little historical perspective of the different tests, the first one that came along with the anti gay lead and antibody a, otherwise known as a GA this was developed in 1980.
* 00:41:03that's you know, one of the reasons why perhaps that diagnosis really picked up in the 1980s and 1990s, because now there is a blood test, where you can actually screen patients.
* 00:41:12Other than having to do a biopsy on all of them, initially, and it has a not a bad sensitivity and specificity around 80 to 90%.
* 00:41:20Of the issue is that these are the screening test and low probability populations it's actually false positives out number two positives tend to one so.
* 00:41:29it's one of the reasons why this test sort of fell out of favor and we can't even order it anymore UDA.
* 00:41:34Patients sometimes to have been diagnosed 1015 years ago and bring us these lab tests, the second test was that no musial antibody also an iga antibody this was developed also the 1980s, has a pretty good.
* 00:41:49specificity and sensitivity, but it's a little more bit more cumbersome have a test there's technician has to do a technique called.
* 00:41:57Indirect immuno fluorescence so it's a little more Labor intensive and it costs more, and so a uva we can actually order this test directly, but you can put it in as a.
* 00:42:08Mayo clinic send out if you are interested in the reason to draw it, I would say is that there's discordance between some of your other strategies and histology and you sort of need a tiebreaker test.
* 00:42:20The tests that we use here and I’m describing what acg guidelines.
* 00:42:25For tissue transfer terminates this came in 1996 97 and remember I talked about tissue transfer contaminates earlier is this enzyme that helps the emanate the ugly.
* 00:42:35side, this is the antibody against that enzyme, and so the interesting thing is that this.
* 00:42:41antibody is a good marker of celiac disease but we don't actually think that this is the antibody that causes the problems in patients with celiac disease it's likely.
* 00:42:50Just sort of a marker and then kind of coexist with the condition, but the antibody myself, although you can measure very easily to diagnose and trends nobody's Celia it doesn't actually cause the damage that we see in the patients.
* 00:43:05I would really recommend that you consider doing the iga version, and one thing I think if I can impart on do is sort of forget about sending a big screen on all these people that are iga sufficient.
* 00:43:16Because if somebody has a normal tissue and transport tammany iga and they have a mildly elevated tissue transplant families, I GG it's more often than not a false positive and.
* 00:43:28So I would just try to stay with the iga version of this test last one is the dominated lead and.
* 00:43:37Then somebody ggv is also part of our typical panel at uva, this is a newer antibody that was found in the 2000s, I would really ask for this I wish we could have the lab maybe remove it from the.
* 00:43:50original panel, and I wish we could just use tissue transplant candidates alone, because I think the value of this test is in patients that are iga efficient.
* 00:44:00And it's really good the ipg dominated gladden peptide is really good to monitor celiac disease and those patients.
* 00:44:06Because we often see this scenario where their tissue transfer contaminates I J is normal, but they have a mildly elevated the emanated clean and peptide.
* 00:44:15And then they're sent our clinic and to find out, they have celiac disease.
* 00:44:19But the point at the bottom here is that only 16% of patients that have a positive theme, the emanated Glynn antibody and a negative tissue trans with tammy is actually end up having.
* 00:44:29Seal actually end up doing a lot of HIV, AIDS, for these patients and oftentimes finding that they don't have celiac disease.
* 00:44:36So I’m just a summary there's a summary slide of the testing algorithm and I just want to draw your attention to this one scenario here tissue transfer contaminate iga is negative.
* 00:44:46Total iga is normal for some reason you really think your patient has celiac disease, they have type one diabetes of your mouth absorption is no other explanation.
* 00:44:56This is where you would might want to go and still do an endoscopy and sort of take biopsies to sort of find out if they have celiac because there's.
* 00:45:03Rarely, a condition called zero negative celiac disease there's recently impatient admitted to the medicine service that we think has zero negative celiac disease.
* 00:45:11So sometimes they don't make the antibodies but you know you rule out other reasons for wanting, and it looks like it's celiac and maybe there are these conditions where the auto antibodies doesn't come into circulation, and so what a spot.
* 00:45:24In most patients that have kind of a medium probability or are low probability if your answer ology tests are negative I often don't think you need to definitely do the biopsy in those patients, you can kind of roll them out with astrology.
* 00:45:39Just a word on false positives and false negatives reasons for false negatives would be you know, this is a common one, they have celiac disease but they started a gluten free diet, for they came and got tested so that can cause a false negative test.
* 00:45:51There is a deficient that one hopefully wouldn't happen here again because we screen for that at the lab.
* 00:45:56or they said really mile and around with the sort of early stage caught it really early in the test isn't positive yet, but if you check again in a year or two it'll be positive, and we have a patient in our clinic that was.
* 00:46:07of that sort of scenario false positives are pretty rare in the case where you have a tissue transplant candidates that's markedly elevated.
* 00:46:16I have read that other autoimmune conditions like primary biliary Colin Jost or crohn's disease has been associated with this haven't seen that connective tissue disorders, because false positives and then the literature, they also mentioned advanced heart failure cirrhosis has causes.
* 00:46:33A lot sort of bloodwork test again going back to we talked about the genetics of celiac, but this is the.
* 00:46:39Talking about why to order the blood tests, so the reason or the blood test would be a patient is on a gluten free diet, you want to try to figure out if they have or do not have celiac.
* 00:46:50And they absolutely do not want to do a gluten challenge they don't want to go back on will.
* 00:46:54send this patient if you check a genetic test, you can essentially if it's negative, you can rule out celiac disease and pretty confidently tell them if they don't have this condition.
* 00:47:04Another reason to do it would be to screen for family members so first degree relative of celiac you might order the genetic test, because if it's positive.
* 00:47:13Then you're going to have to you know check strategies every few years of the kids if it's negative the kids don't have to worry about.
* 00:47:20Having Celia and when you order the panel at uva it does give you this it's called Celia gene is the name of the gene test.
* 00:47:28Is a little bit expensive I’ll more new so it's not something to retain the order, but it is for certain circumstances.
* 00:47:34And it gives you this have reached out about how common how increase the risk might be going from about 30 times increased almost you know impossible to have, if you have the negative genes.
* 00:47:47So I’ll skip this, this is a summary of the diagnostic algorithm and then start to get to the next part about the endoscopic evaluation so.
* 00:47:57As of now, the guidelines do recommend that we do an endoscopy to make the diagnosis is based on how biopsy.
* 00:48:05However, in pediatrics and Europe, they have a guideline where they say that if the transmit tammany says 10 times the upper limit of normal and there's positive.
* 00:48:13Indonesia antibody can make the diagnosis of celiac disease.
* 00:48:17that's not the current standard of care in the US for adults, so we do recommend doing a biopsy we recommend doing it when they're still on a gluten containing diet, this is the problem that I usually have somebody gets serology.
* 00:48:28Six months eight months later, I see them in GI clinic and they are already been on a gluten free diet, for all that time and we never got a biopsy.
* 00:48:36So in that case we send them to ask them to do a gluten challenge, which would mean eating one to two slices of wheat bread.
* 00:48:43For two to six weeks to being a minimum and up to six weeks before during the endoscopy and trying to secure the diagnosis.
* 00:48:51These are the things that we see on endoscopy, this is a patient and their Dalton them with very modular because I didn't include a normal slide, but it should kind of look very fluffy like a carpet.
* 00:49:01With the bill I’m projecting that you can see in the sky quickly and this patient has sort of lost that another patient has this very cobblestone.
* 00:49:08appearance to their new item here we see some features that are visible and the Guatemalan folds and the last one is a patient that has really severe atrophy and mucosal flattening, and this is most a pattern script on them, and this patient very refractory celiac disease.
* 00:49:26This is just to show you I don't think he don't expect you to know this, but the pathologist will make the diagnosis, based on Sunday.
* 00:49:33march classification they're going to look for a village blunting so here, you can see the Villa or along here the Villa are shortened the crypt skin longer in celiac disease.
* 00:49:43And you have all these lymphocytes that activated and attack the small balance of the pathologist to look for these characteristics when they make the diagnosis for us.
* 00:49:54We really consider celiac disease and people that have this March three and we sort of suspect other ecologies if they just have March, one which has increased lymphocytes without vilest blunting.
* 00:50:05So i'll move on to the management part of the talk.
* 00:50:10So you know I wish I could tell you about a lot of new medicines and i'll talk about some that are maybe coming in the future, but.
* 00:50:17The honestly, the only treatment, we have is a gluten free diet so strict lifelong gluten free diet is the management for celiac disease and.
* 00:50:25it's easy just to tell somebody that and hand them a handout and tell them to follow it, but it's really hard to do in practice, and so this is the best employed with the direction of.
* 00:50:36Actual registered dietician who knows about celiac disease.
* 00:50:40And some of the nuances of the gluten free diet, you know I talked about foods that contain gluten earlier but all even draw your attention to like dairy, which often you know doesn't contain live in.
* 00:50:50Patients with celiac disease, because of their interrupted the may have lactose intolerance and.
* 00:50:56As a result, you know they may go gluten free they're drinking milk and having diarrhea and getting frustrated, so we actually asked them to sort of avoid dairy initially to until the valve starts to heal.
* 00:51:07This is just an example of actual gluten free beer that's made from non-wheat or barley green.
* 00:51:14Those are things that are okay wine and liquor usually cider Okay, but here is barley and wheat, so I usually shouldn't be consumed.
* 00:51:23Until that registered dietitian should know you know not just any money I should be somebody who has experience in celiac disease, and we do have our fortunate to have somebody Mallory foster.
* 00:51:35Those are registered dietitian and she has a lot of expertise of celiac disease, he can educate our patients in the clinic.
* 00:51:41Because they need to go over what are the foods that have in what are foods that are naturally gluten free help with label reading, which is very difficult.
* 00:51:50Cross contact and the kitchen is a huge problem for patients with celiac disease and the dietitian can also help with treatment of some nutrient deficiencies as well.
* 00:52:01And so the gluten free diet, although it's accessible, more so than it used to you'll see a lot more options for gluten free like.
* 00:52:09You know reading and talking to people that have celiac for years, they say that they always have to previously order everything online they couldn't go to the supermarket and just pick up gluten free foods that's changed, but unfortunately it's still really expensive.
* 00:52:23And UK studies show that gluten free bread was 400 times more expensive than wheat bread.
* 00:52:29And this, I just took off the way Wegmans website here in Charlottesville, and so we bred goes for 349 or, if you look at the small print as point one five.
* 00:52:39cents per point one 515 cents an ounce, whereas the comparable gluten free bed is bread is 39 cents and house ounces twice as expensive to buy gluten free bread.
* 00:52:50and cost is a big factor 50% of patients in a survey said that the cost of the gluten free diet was really an impact on their life, and this is something that they have to follow for their entire lives.
* 00:53:03So to go over.
* 00:53:06More of the management, so there are you know regulations from the FDA coming back to 2004 where food that contains wheat has to have this sort of.
* 00:53:18Designation contains we on it and that's because of allergies and kids often can have a week as one of their allergens, so it wasn't really keeping celiac disease in mind, but more for allergies.
* 00:53:30So a lot of foods that do have wheat if they're packaged good you'll see that it says contains wheat and sort of highlighted on the back of the label, but the same is true for barley and Rye.
* 00:53:39Another point is that since 2013 any food that is labeled gluten free has to have less than 20 parts per million gluten, so this is a little confusing so food that's gluten free may still have gluten in it, but it's just a really small concentration.
* 00:53:56So I wanted to start give some context, so one slice of wheat bread has 3500 milligrams of gluten.
* 00:54:04So 10 milligrams of living per day is the amount of gluten that's thought somebody was celiac disease can consume before they have reactivation have they're going to wrap it up.
* 00:54:14So 10 milligrams of living is like chrome of bread basically have a piece of bread and so, then when you at the bottom here, if you think on the.
* 00:54:24image, if you think of a gluten free bread one ounce of a gluten free bread has about Point five seven milligrams of gluten since actually really small amount.
* 00:54:34So for somebody to be able to get to 10 milligrams a day if they were eating just gluten free bread, it has to consume 17 and a half slices of gluten free bread so.
* 00:54:44gluten free bread has a little pre packaged goods have gluten but it's this small concentration 20 parts per million.
* 00:54:51And the other thing is that restaurants, do not have to carry this designation, so a restaurant tells you that they're having.
* 00:54:59A free product that's sort of the honor system there's nobody checking or nobody regulating that set us apart place to arrest patients often gate gluten is what they say when they consume it unknowingly.
* 00:55:11So we ask our patients to be very vigilant when they're eating out specifically, so this is a food label modernization act of 2021 seven this year it's a bill that's going to be presented in.
* 00:55:25Congress and the Senate and what they want to do is besides just for celiac disease, there are some you know foods that label themselves that's like healthy or nutritious and I sort of want to make this more standardized so what that means.
* 00:55:38But um as it applies to celiac disease patients, we talked about how barley and Rye aren't sort of highlighted on the back of the package and.
* 00:55:46They would like it to me anything that has any gluten would really be like labeled as having gluten in it, so that our patients can more easily know what to avoid.
* 00:55:56And the part about gluten free wouldn't change, but the big thing would be that patients can more easily look on the back of the label and figure out if something has gluten and I think they have like a civil penalty of like $10,000 if the company that makes the product as a follow.
* 00:56:14So last couple of points here about the management so surveillance so once somebody is diagnosed to go on a gluten free diet.
* 00:56:22We find that their symptoms if they had any tend to get better pretty quickly usually within a month.
* 00:56:29They said specifically like the symptom that gets worse if they get gluten is always nasza so that seems to be a very common one, if they have probably because the cytokines that get released when they.
* 00:56:39eat live in and they had symptoms against better to tell if they didn't have any symptoms, so that it's hard to track them.
* 00:56:46The tissue transfer contaminates gets better usually within six months there's a good trend down.
* 00:56:52And within a year, it should be normal, but if it was really high To start with, sometimes it takes a lot longer to normalize that we don't often do an endoscopy.
* 00:57:01To check for healing it's not part of the guidelines that's because of the histology takes a long time to heal sometimes two years before there's any improvement.
* 00:57:11I won't go through this in detail, but just want to show you guys that these are the.
* 00:57:15micronutrients that we sort of scan for and look for in our patients iron fully be 12 environment year my standard panel that I check and I expect that these will get better with improvement.
* 00:57:27After going on the gluten free diet zinc copper basics and sort of save these are patients that present with a more mal absorption on presentation.
* 00:57:37And then last side I’m monitoring, this is a busy slide but all I want to do is point out to you here is that.
* 00:57:43You know, we don't just to make a diagnosis and send them off it's good for somebody including I’m happy to follow them but also you know from internal medicine, this is also part where.
* 00:57:52You all can help out is to see these patients and regular intervals, usually within three to six months after diagnosis, they should be checked in to see if their symptoms are improving it's a good time to repeat a server ology around them.
* 00:58:07within that period, we expect that they're getting better and if they're not necessarily go to the bottom algorithm here, where they have to see a dietitian again and find out if there's ingestion that they're not aware of.
* 00:58:18I usually see them, then, and like an annual interval for follow up.
* 00:58:22And one thing I didn't mention is the Dexter scan there's a question mark next to this, this is from the acg guidelines, whether or not to do it.
* 00:58:29The more updated European guidelines that came out of the past year they recommend the decks a scan for anybody diagnosed with celiac disease over the age of 35.
* 00:58:38And then they say that in the younger folks if they have a profound vitamin D deficiency to consider a Texas, and so we mentioned earlier osteoporosis, is a big problem in this population so that's.
* 00:58:48Something that in primary care can also be incorporated into their management or we can do it in the celiac clinic.
* 00:58:55And so, this is the last part of the talk as we're sort of wrapping up here is to talk about what are some possible options for treatments that may be coming out in the future and.
* 00:59:06i'll say that none of these are actually improved yet and all sort of still in study phases, but to talk about this goes back to our pathophysiology slide that we went over earlier.
* 00:59:17So one of the options would be here the you know, looking at lead in fragments that are being adjusted let's say somebody is on a gluten free diet and they can.
* 00:59:25they're having a tough time following and exactly they're still getting live in both he had an enzyme you can take at the time of ingestion to try to break up that 33 Amor that doesn't.
* 00:59:36digest very well, that would be something that you know, can help, and I said this medication called Latin root nieces and it's a lumen.
* 00:59:44illumination and it's been studied in some early studies and seems to help with some symptoms specifically and people that struggle with.
* 00:59:52Ongoing gluten ingestion but not ready for approval, yet the other option would be what if you can make it so that these.
* 01:00:01The gluten couldn't get through the membrane and there was the tight junctions here we're tighter, for instance, and that's what la Raza time does.
* 01:00:10sort of modulation tight junctions to try to make it can't pass and that's also been studied and seems to having an effect and then continue to have gluten ingestion despite the gluten free diet and then this one over here is called.
* 01:00:30And so it's an aisle 15 Blocker So the idea is what if they still are getting live in in how about we turn off the cytokines response and see if that helps reduce their symptoms and.
* 01:00:41isn't a face to study and they're actually there's a lot of ads for their recruiting at various centers to try to see if it'll improve symptoms and.
* 01:00:49they're not requiring a globe and challenge so they're trying to see patients that are honest celiac disease and are just still having issues with gluten ingestion.
* 01:01:00And so, then I’ll talk about the one I think that's most promising is a tissue transfer contaminates to inhibitor, and so this was actually published this past year and the New England Journal of medicine.
* 01:01:11And so it goes back to the idea that tissue trans contaminates is that enzyme that makes creating.
* 01:01:18The emanates it so it can bind better to that antigen presenting cell So what if we try to block this enzyme tissue tissue transfer contaminates such that.
* 01:01:28The gluten is now no longer binding as well with this antigen presenting cell and as a result, this whole inflammatory cascade can be turned off and that's what this drug zed 1227.
* 01:01:40So this was a study that was based out of Norway and they had 159 patients confirmed celiac disease, they even my book in challenge and the gluten challenge was a three Graham biscuit that hadn't lived in in it.
* 01:01:55is sorry was a biscuit that three grams living in it, so they continued on a gluten free diet and all they did was add have basically one biscuits today.
* 01:02:03And they took three different doses of 10 5100 milligrams is oral tablet.
* 01:02:08And the what they showed, is that all three of these doses seem to work, and I think it's better illustrated here.
* 01:02:14They looked at the ratio of villas hi to crib death ratio and they found that there really wasn't a change like patients that.
* 01:02:22took this drug and had live in their bill I didn't get shorter, but here was the placebo group there, you can see, the trend is downwards their bill I are getting shorter and they're actually having more.
* 01:02:34So this was a setup phase two study preliminary trial, it was very promising one of the most promising sort of studies that have come out for medical treatment for celiac disease.
* 01:02:45But here's the challenge it was only three grams of gluten per day so it's like I said, like a slice of bread or biscuit per day so.
* 01:02:52What we don't know is that you know traditional American diet might contain thousands of gram grams of gluten so.
* 01:02:59it's probably not going to be a medication, if it comes out in the future, you can just put your patient on and let them eat whatever they want.
* 01:03:06it's probably going to work better for somebody who's already on a gluten free diet and it's going to be that sort of safety net to sort of prevent them from having issues with getting unknown gluten ingestion.
* 01:03:18And so i'll wrap up here with that with take home points I want you to remember the non classical presentations of celiac disease.
* 01:03:25I want you to please remember that all testing and except for the gene testing and all the blood work and biopsies needs to be done while the patient son gluten.
* 01:03:35gluten free diet obviously has to be lifelong and we'll see what comes in the future for more dietary therapy and.
* 01:03:41The last thing i'll say is that you know we're hoping to build larger celiac disease practice, you know as was mentioned at the beginning.
* 01:03:49of your sentence is a pediatrician pediatric gastroenterologist to his interest and celiac disease and.
* 01:03:56With her we like to try to improve the research friend you here as well, so if you have patients that you are.
* 01:04:03diagnosed or have celiac for years, and you want to have us check in with them and see how things are going we're happy to see them if you have new.
* 01:04:11diagnoses and you're having trouble getting them into clinic just send me a message I’m happy to get those patients and stop there, thank you.
* 01:04:24Excellent wrong young.
* 01:04:30Yes, so on the three to six month all of that being diagnosed record.
* 01:04:37Breaking serology is I was just wondering what we can expect to see once someone has gone change their diet.
* 01:04:44yeah so that's great question, so the question is repeating Sir orgies and the initial interval so really we want to see a trend down so different for every patient.
* 01:04:53i'll tell you like folks that have a diagnosis, the lab at uva reads up to 2000, I think, and if it's above two pounds and just says, greater than 2000.
* 01:05:02So i've had people like that were three months later, the test is still like 1800 or 1500.
* 01:05:08i've also had patients, where they were diagnosed in their astrology was our upper limit of normal is 15 and it was like 21 it was diagnosed.
* 01:05:16So it really depends on how hydrology was, but what we want to see is that it is on an improvement trajectory and if it's not.
* 01:05:24It probably indicates that they're still ingestion and then do the tricky part about astrology is it's really one of the only biomarkers we have sort of monitor the disease.
* 01:05:36But there are cases where people have been biopsy later that's what I was trying to mention on the biopsy things that.
* 01:05:43Sometimes the others are all is perfectly normal and a year later, you go biopsy they started ramping up there no symptoms are inefficiencies and crew everything looks like it's going good but.
* 01:05:54histology doesn't look great, so I would caution against, and I know you guys aren't included in these will we get patients from other.
* 01:06:01Practices where this happens, like six months in and do another gnostic be a year end to do another MSP and then pathologist says mile those one thing.
* 01:06:10And then they get referred to us for something to evaluate for refractory together we try to go into today but that's a whole different diagnosis Square.
* 01:06:17Also really six and 20 prior to the end and such so All I would say to us and you know we expected improvements and it doesn't improve kind of talk to them about where they're getting they're probably getting gluten not known about it.
* 01:06:34yeah what other people with your screen goes period people with confirmed celiac disease.
* 01:06:41Have spontaneous resolution of symptoms, or is it rather than if they continue to be exposed to it will just continue to be symptomatic yeah so a good question, so these symptoms to your question is is symptoms resolved spontaneously, and some people.
* 01:06:57I think that you know it's definitely the gluten free diet is what helps resolve symptoms and many of our patients.
* 01:07:04I don't know about resolving spontaneously what I’ll say is like people, some people do not get better on gluten free diet.
* 01:07:10And then, in those cases there are alternative diagnoses that we have to consider some.
* 01:07:15symptoms didn't get better and they're astrology is improved everything else got better than we think about things like cboe is that, as a problem lactose intolerance is that a problem.
* 01:07:26There are these Members have celiac disease I didn't show you guys but audio muted and around with the I think there's a patient right now admitted to the hospital they're worrying about possibly having autoimmune or apathy.
* 01:07:38You know, drug effects there's a drug called banner car almost certain that can cause these sort of pictures of your patients not getting better Those are the things to think about outside of celiac disease.
* 01:07:54question in the chat and what is considered a true positive Tiki any degree that family.
* 01:08:01yeah most I would say most muscle literature suggests two to three times the upper limit of normal of your lab This is where we run into trouble with my personal opinion, in terms of some of the.
* 01:08:14Other leaders in this area, say that the tissue train the tenants iga if it's above 50 you can still bring somebody in and celiac so take 16 and they get a biopsy and it looks like celiac disease that patient has celiac disease.
* 01:08:28The ones where their tissue transportation is greater than two to three times normal we really feel confident that we're going to have the diagnosis.
* 01:08:36The question is, when we don't do like file, so if somebody comes to me and it had the labs and their tissue trans contamination 17.
* 01:08:44may make gluten free and they don't want to try biopsy, this is the one where it's like tricky because they are not two or three times the.
* 01:08:50Normal we never proved that maybe it was a false positive I usually tell those people like you know it's up to you, if you want to stay gluten free that's fine we'll manage you we call it like a potential improbable celiac disease.
* 01:09:03I think it's a problem in the future more drugs are available on Wednesday drugs are available, probably going to want to have.
* 01:09:11Confirmation before they're going to get that drug.
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**Unknown Speaker**

01:09:15Is.

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**UVA Chiefs**

01:09:18Just for practice.

* 01:09:20When we explain iron deficiency anemia do you always buy it for celiac or not, because I’m always.
* 01:09:27So good question narrow about whether or not the biopsy and unexplained iron deficiency anemia so you're right actually.
* 01:09:35There was a recent acg guideline, or maybe it's a GA I think guideline about iron deficiency, and they actually say that you should not biopsy because it's like less cost effective than running astrology.
* 01:09:47But I do often biopsy because it's like when just for us to get her all just were in there, doing the procedure.
* 01:09:53It makes more sense to me to just get a number biopsies then to like TV all right, like once you're done you're going to go to the lab we're going to astrology.
* 01:10:00over my cost effectiveness perspective I think that's just technology costs and things are so much they.
* 01:10:06Have a GA guideline from a blast or maybe as a guide and statement of you by I usually biopsy i'll be honest it's not like.
* 01:10:13I don't think of it every time I’ll be very clear like you know it's not like every patient that we work up Brian deficiency.
* 01:10:19That we do it, but I think we probably should think about it because we probably get an GI those anemia cases were just thinking it's a GI bleed.
* 01:10:27And we don't find anything and then lot of times, maybe don't think about testing for celiac and we probably should because some of them might have that.
* 01:10:39standard for labs to be checking the iga or report outside of uva.
* 01:10:44Yes, I would say in reverse check the iga with astrology if you're outside uva and you don't know if your lab screens for it, yes, you should.
* 01:10:54acg guidelines say check the total iga along with serum tissue transmits database, but since our lab will screen partitioning for hygiene efficiency, I think here it's.
* 01:11:06The cost effectiveness perspective, you don't need to and there's like one study like that that looked at on.
* 01:11:11It was not complete iga deficiency of patients that I forget the exact number for the minimum cut off for iga, but I think it's also 15 if I’m not mistaken, and then.
* 01:11:22Like folks that have idea of efficiency or undetectable So if you have mild idea deficiency there wasn't really an issue with the screening labs for celiac disease so.
* 01:11:32For that reason I don't recommend jumping in here, I used to check it and then I realized like nobody I call the ladder talk to them about it they're like oh yeah we screen for it.
* 01:11:41And if you ever do have like I have patient as a deficiency like when we order if you by accident orders Celia iga.
* 01:11:48screen for them he'll just kind of like Apollo reply to the last thing like random processor was still less than detectable so, then they automatically will put an ID order for you.
* 01:12:04Just.
* 01:12:06did a lot of research into negative predictive values like the normal albumin level if along with like iron i'm just thinking from the standpoint of they're not absorbing to have like vitamin deficiency, should that be the normal the normal and if it isn't marvel.
* 

**Unknown Speaker**

01:12:21Especially.

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**UVA Chiefs**

01:12:24The question.

* 01:12:25level and celiac isn't in a negative predictive value of a normal human right, so I don't I don't know the answer, but maybe something your fellowship.
* 01:12:38Or maybe.
* 01:12:42Just do one more pictures attached so, are there any epigenetic changes associated with feeling.
* 01:12:50yeah.
* 01:12:52epigenetic changes slowly most appealing, the main thing is, I think folks that are diagnosed owner, so those that are in their 50s 60s 70s, they really have this slower sponsor phenotype.
* 01:13:04And might just be because they had the diagnosis for much longer, I told you, the averages.
* 01:13:09So that people have seven years I don't have to send us but usually it's seven years before time diagnosis so somebody starts having celiac disease it's not picked up for seven years on average.
* 01:13:20And folks that were diagnosed in their 70s, they might have had it for 20 years and not known about it so.
* 01:13:25I think that's the main factor that I know of, and I have a few patients, where I really struggle with this, because they are referred to me with.
* 01:13:34Again outside gastroenterologist found persistent millis blunting trans contaminates normal all the symptoms are better it's like What do you do with this patient and.
* 01:13:44Besides doing there's something that had mentioned.
* 01:13:46Besides the gluten free diet there's the living contamination elimination diet and all it means is that you basically eat nothing like package that's quote unquote gluten free all the things that have like up to 20 parts per million of live.
* 01:14:00You just eat like fruits and vegetables and things that are like naturally free because some of these people that are slow responders.
* 01:14:07Perhaps they're just really sensitive to low doses of gluten so we have a few patients that we've recommended that but I struggle with them and I don't I’m.
* 01:14:16The again that condition called refractory celiac is reserved for people who are really sick and mountains or getting and have empathy most of the folks that we see are in that.
* 01:14:26Presentation they just kind of have empathy and they're doing great the enzymes are normal, so it is an area that struggles.
* 01:14:35Just the last year.
* 01:14:38I can't help myself to ask what on that list of things, is it played out the potential yeah you know, are there any like plan case reports to people I don't know yeah.
* 01:14:49I don't personally have yeah there, I have to look into this now that you've asked about this, but it always comes up so like play doh is comes up on that list I don't know of any case reports of Plato, causing.
* 01:15:01unknown yeah this case reports are related to talk about this and I mentioned a little bit that almost our pan is the case before the odd thing about.
* 01:15:10All this stuff share the interesting story about that was the patients were getting into the Mayo clinic with this like refractory spruce.
* 01:15:18And they just weren't getting better and then the main client moment happen the hypotension because they were really mountain malnourished and.
* 01:15:26The hydrated main thing would stop their blood pressure meds and then they start getting better like dramatically, and then they eventually found out that it wasn't celiac disease, but it was almost our town was the trigger and said.
* 01:15:38You always have to sort of think of that as causes of celiac disease that causes a better empathy as well.
* 01:16:24No, I just said.
* 01:16:27it's pretty appropriate timing of spending my.